DOI: 10.1093/jnci/djs477 JNCI Journal of the National Cancer Institute Advance Access published November 1, 2012

ARTICLE

International Multicenter Tool to Predict the Risk of Nonsentinel Node Metastases in Breast Cancer

Tuomo J. Meretoja, Marjut H. K. Leidenius, Päivi S.Heikkilä, Gabor Boross, István Sejben, Peter Regitnig, Gero Luschin-Ebengreuth, Janez Žgajnar, Andraz Perhavec, Barbara Gazic, György Lázár, Tibor Takács, Andras Vörös, Zuhair A. Saidan, Rana M. Nadeem, Isabella Castellano, Anna Sapino, Simonetta Bianchi, Vania Vezzosi, Emmanuel Barranger, Ruben Lousquy, Riccardo Arisio, Maria Pia Foschini, Shigeru Imoto, Hiroshi Kamma, Tove F. Tvedskov, Niels Kroman, Maj-Brit Jensen, Riccardo A. Audisio, Gabor Cserni

Manuscript received May 18, 2012; revised September 19, 2012; accepted September 30, 2012.

Correspondence to: Tuomo J. Meretoja, MD, PhD, Helsinki University Central Hospital, Breast Surgery Unit, PO Box 140, FI-00029 HUS, Finland (e-mail: tuomo.meretoja@fimnet.fi).

Background Axillary treatment of breast cancer patients is undergoing a paradigm shift, as completion axillary lymph node dissections (ALNDs) are being questioned in the treatment of patients with tumor-positive sentinel nodes. This study aims to develop a novel multi-institutional predictive tool to calculate patient-specific risk of residual axillary disease after tumor-positive sentinel node biopsy.

Methods Breast cancer patients with a tumor-positive sentinel node and a completion ALND from five European centers formed the original patient series (N = 1000). Statistically significant variables predicting nonsentinel node involvement were identified in logistic regression analysis. A multivariable predictive model was developed and validated by area under the receiver operating characteristics curve (AUC), first internally in 500 additional patients and then externally in 1068 patients from other centers. All statistical tests were two-sided.

Results Nine tumor- and sentinel node–specific variables were identified as statistically significant factors predicting nonsentinel node involvement in logistic regression analysis. A resulting predictive model applied to the internal validation series resulted in an AUC of 0.714 (95% confidence interval [CI] = 0.665 to 0.763). For the external validation series, the AUC was 0.719 (95% CI = 0.689 to 0.750). The model was well calibrated in the external validation series.

Conclusions We present a novel, international, multicenter, predictive tool to assess the risk of additional axillary metastases after tumor-positive sentinel node biopsy in breast cancer. The predictive model performed well in internal and external validation but needs to be further studied in each center before application to clinical use.

J Natl Cancer Inst

Axillary treatment of breast cancer patients is undergoing a paradigm shift, with the main question under scrutiny being how to treat the axilla of a patient with tumor-positive sentinel node biopsy (SNB). Since the introduction of SNB as a procedure to stage the axilla of breast cancer patients, the gold standard of treatment has been completion axillary lymph node dissection (ALND) for all cases with metastasis in the sentinel node (SN) or when the identification of SNs has failed.

Since then, many centers have developed their own predictive tools to identify patients with low risk of additional axillary metastases in whom completion ALND could be omitted (1–16). With a growing body of literature, many centers have abandoned completion ALND in patients with a low risk of nonsentinel node metastases (17). The results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial further shook the completion ALND concept by showing that even a subset of patients with macrometastases in their SN do not benefit from completion ALND in terms of recurrence rate or overall survival (18,19).

Some centers have abandoned predictive tools altogether after the results of the ACOSOG Z0011 trial were published. However, vivid discussion continues on the generalization of the ACOSOG Z0011 results because the study only included patients who had undergone breast-conserving surgery followed by whole-breast radiation (18,19). Furthermore, contradicting results have been published recently, including the current analysis of the Dutch MIRROR cohort study, which showed an increased 5-year regional recurrence rate in patients with micrometastases in their SN and no completion ALND performed (20).

Most of the current predictive tools estimating the likelihood of additional axillary metastases after tumor-positive SNB have been developed from single-institution patient series and thereafter validated in other centers. Current predictive tools have also

been developed to identify patients with low risk of residual disease, rather than those with high risk, and tend to perform worse in a high-risk setting (21).

In light of the ACOSOG Z0011 trial, this study aims to examine factors associated with a high risk of additional axillary metastases and to identify such high-risk patients for whom completion ALND might be warranted. This study further aims to develop a novel international and multi-institutional predictive tool to calculate a patient-specific risk of residual disease. Finally, we aim to validate the novel predictive tool first internally and then externally in various institutions.

Methods

Original Patient Series

Five European centers collected retrospective data, each on 200 consecutive women with invasive breast cancer with one or more tumor-positive SNs and a completion ALND, contributing a total of 1000 patients who were operated on between January 2004 and January 2011. Patients with macrometastasis, micrometastasis, or isolated tumor cells/clusters (ITC) in their SN were included. Patients who had neoadjuvant treatment or previous axillary surgery were excluded. These data were originally collected to assess the impact of differences in the SNB procedure and pathology practices on the performance of existing predictive models for nonsentinel node involvement (22). Although the tools performed well in the institution in which they were developed, subsequent validation produced less-satisfactory and variable results. Hence, we decided to develop a novel predictive tool with emphasis on high-risk patients (22).

The participating centers in the collection of this original patient series were Bács-Kiskun County Teaching Hospital, Kecskemét, Hungary; Helsinki University Central Hospital, Finland; Medical University of Graz, Austria; Institute of Oncology, Ljubljana, Slovenia; and University of Szeged, Hungary.

The collected data were based on known risk factors for additional axillary metastases after tumor-positive SNB (1–15). Primary tumor-specific variables included pathological tumor size, multifocality, histological and nuclear grade, histological type (ductal, lobular, mixed, or other), estrogen and progesterone receptor status, human epidermal growth factor receptor 2 (HER-2) status, and presence of lymphovascular invasion. Lymph node–specific variables included the number of tumor-positive and tumor-negative SNs and nonsentinel nodes, method of detection of the SN metastasis, size of the largest SN metastasis (ITC vs micrometastasis vs macrometastasis) (23), and presence of extra-capsular extension of the SN metastasis. The method of detection of the SN metastases was categorized as intraoperative (frozen section/imprint cytology), paraffin standard staining, serial sectioning, or immunohistochemistry. Patient, tumor, and lymph node characteristics from different centers are given in Table 1.

Surgical techniques and pathological work-ups of the primary tumors and the axillary specimen were conducted according to each center's protocols (22).

Internal Validation Patients

Additional consecutive patients with similar inclusion and exclusion criteria to the original series were gathered from each center to form an internal validation series. The surgical treatment and methods of pathological assessment were similar to the original patient series. Data were collected on 500 additional patients who had surgery between 2003 and 2011.

External Validation Patients

Eight different centers, mainly from Europe but also from Japan, participated in the external validation of the predictive tool. Each external validation center provided consecutive patient series with similar inclusion criteria to the original series. The number of patients included from each center was not restricted because the performance of the predictive tool was examined separately in each center in addition to pooled performance. Altogether, 1068 patients were included in the external validation (Supplementary Data 1, available online).

The participating centers in the collection of the external surgically treated validation patient series were Lariboisiere Hospital, Paris, France (patients surgically treated from 2007 to 2011); Lancashire Teaching Hospitals, Chorley, United Kingdom (2006 to 2011); Azienda Ospedaliera Universitaria San Giovanni Battista di Torino, Turin, Italy (2005 to 2011); Careggi Hospital and University of Florence, Italy (2003 to 2009); Sant'Anna Hospital, Turin, Italy (2010 to 2011); Bellaria Hospital, University of Bologna, Italy (2009 to 2011); Kyorin University Hospital, Tokyo, Japan (2007 to 2010); and Copenhagen University Hospital, Denmark (2010 to 2011).

Statistical Analyses

A univariate analysis of the original patient series was conducted to examine individual risk factors for additional axillary metastases after tumor-positive SNB. Distribution of continuous variables (patient age, prevalence of nonsentinel node metastases in each center's patient series, histological size of the primary tumor, number of negative and positive SNs harvested) was analyzed using the Mann–Whitney *U* test, and the χ^2 test was used for categorical variables (multifocality of the primary tumor, lymphovascular invasion in the primary tumor, estrogen and progesterone receptor status, HER-2 status, nuclear and histological grade of the primary tumor, histology of the primary tumor, detection method of the SN metastasis, and extra-capsular extension of the SN metastasis). All statistical tests were two-sided with *P* values less than .05 considered significant.

All variables with a *P* value less than .1 in the univariate analysis were included in a logistic regression analysis using a backward stepwise likelihood ratio method. Variables with a *P* value less than .05 were included in the final predictive model.

The resulting multivariable predictive model was then validated both internally and externally by the independent patient series. Discrimination of the model was assessed by area under the receiver operating characteristic curve (AUC), and the calibration of the model was assessed by the Hosmer–Lemeshow goodness-of-fit test. Sensitivity and specificity of the model was determined for various cutoff values.

IBM SPSS Statistics version 20 (SPSS Inc., Chicago, IL) software was used to conduct the statistical analyses.

Ethical Considerations

The patient series were gathered retrospectively with no influence on patient therapy. Institutional review boards and ethical committees

Table 1. Patient, tumor, and lymph node characteristics in the original patient series of 1000 patients*

Patient, tumor and lymph node characteristics	Center A: Bács-Kiskun	Center B: Helsinki	Center C: Graz	Center D: Ljubljana	Center E: Szeged
Patient enrollment period	2005–2010	2010	2010–2011	2005–2008	2004–2010
Patient age, mean (SD), y	58 (12)	59 (11)	57 (13)	58 (10)	56 (11)
Histological size of the primary tumor, mean (SD), mm	20 (14)	21 (18)	18 (9)	22 (11)	22 (11)
Multifocal primary tumor, no. (%)	57 (29%)	47 (24%)	30 (15%)	53 (27%)	19 (10%)
Lymphovascular invasion in the primary tumor, no. (%)	76 (38%)	52 (26%)	51 (26%)	80 (40%)	57 (29%)
Estrogen receptor positive, no. (%)	178 (89%)	189 (95%)	161 (81%)	181 (91%)	152 (76%)
Progesterone receptor positive, no. (%)	157 (79%)	146 (73%)	152 (76%)	156 (78%)	149 (75%)
HER-2 positive, no. (%)	17 (9%)	23 (12%)	26 (13%)	20 (10%)	33 (17%)
Nuclear crade of the primary tumor, no. (%)					
Grade 1	15 (8%)	24 (12%)	45 (23%)	4 (2%)	10 (5%)
Grade 2	79 (40%)	101 (51%)	91 (46%)	124 (62%)	76 (38%)
Grade 3	106 (53%)	75 (38%)	64 (32%)	72 (36%)	114 (57%)
Histological grade of the primary tumor, no. (%)					
Grade 1	48 (24%)	50 (25%)	20 (10%)	27 (14%)	21 (11%)
Grade 2	85 (43%)	89 (45%)	91 (46%)	104 (52%)	100 (50%)
Grade 3	67 (34%)	61 (31%)	64 (32%)	69 (35%)	79 (40%)
Histology of the primary tumor, no. (%)					
Ductal	143 (72%)	149 (75%)	160 (80%)	168 (84%)	169 (85%)
Lobular	21 (11%)	31 (16%)	15 (8%)	21 (11%)	13 (7%)
Mixed	10 (5%)	4 (2%)	21 (11%)	9 (5%)	4 (2%)
Other	26 (13%)	16 (8%)	4 (2%)	2 (1%)	14 (7%)
Detection method of the sentinel node metastasis, no. (%)					
Intraoperative analysis (frozen section/ imprints)	98 (49%)	178 (89%)	111 (56%)	52 (26%)	Not done
Paraffin standard staining	56 (28%)	5 (3%)	4 (2%)	49 (25%)	189 (95%)
Paraffin immunohistochemistry	30 (15%)	17 (9%)	33 (17%)	88 (44%)	11 (5%)
Serial sectioning	16 (8%)	Not done	52 (26%)	11 (6%)	Not done
Size of the sentinel node metastasis, no. (%)					
Isolated tumor cells	1 (1%)	42 (21%)	19 (10%)	1 (1%)	5 (3%)
Micrometastasis	56 (28%)	43 (22%)	54 (27%)	62 (31%)	29 (25%)
Macrometastasis	143 (72%)	115 (58%)	126 (63%)	137 (69%)	166 (83%)
Extracapsular extension of sentinel node metastasis present, no. (%)	90 (45%)	54 (27%)	43 (22%)	53 (27%)	36 (18%)
Sentinel nodes harvested, mean (SD), no.	1.9 (1.0)	2.4 (1.4)	1.8 (1.2)	1.8 (1.0)	1.9 (1.0)
Nonsentinel nodes harvested, mean (SD), no.	12 (5)	19 (6)	15 (6)	17 (6)	10 (5)
Nonsentinel node positive patients	79 (40%)	55 (28%)	70 (35%)	53 (27%)	70 (35%)

* HER-2 = human epidermal growth factor receptor 2.

were consulted in each center as required, and no ethical objections were raised. All patient information was gathered anonymously.

Results

In the original patient series, 327 (32.7%) patients were found to have additional axillary metastases in their completion ALND. This proportion varied between centers from 27% to 40%. Variables associated with additional metastases in univariate analysis with a *P* value less than .1 were prevalence of nonsentinel node metastases in each center's series, size of primary tumor, multifocality, lymphovascular invasion, HER-2 status, histological and nuclear grade, SN metastatasis detection method, SN metastasis size, extracapsular extension of the SN metastasis, and number of tumor-negative and -positive SNs (Table 2).

Prevalence of nonsentinel node metastases in each center's series, primary tumor diameter, multifocality, lymphovascular invasion, HER-2 status, SN metastasis size, extracapsular extension of the SN metastasis, and number of tumor-negative and -positive SNs remained statistically significant risk factors in the logistic regression analysis (Table 3). The Hosmer–Lemeshow test produced a *P* value of .58, indicating that the multivariable model fits and calibrates well for the patient population. The AUC for the original patient series was 0.756 (95% confidence interval [CI] = 0.725 to 0.787), suggesting good discrimination. The following mathematical model was produced from the logistic regression analysis to predict the presence of additional axillary metastases, with p denoting the probability of nonsentinel node metastases:

$$\mathit{logit}\,(p) = -6.391 + 0.036 \times a + 0.321 \times b + 0.420 \times c - 0.594 \times d - 0.216 \times e + 0.278 \times f + 0.021 \times g + 1.274 \times h + 0.655 \times i$$

The letters in the equation denote the variables: a = prevalence of nonsentinel node metastases in patient series (percentage of patients); b = lymphovascular invasion (1 if present, 0 if not); c = multifocality (1 if multifocal, 0 if not); d = HER-2 status (1 if positive, 0 if negative); e = number of negative SN; f = number of positive SN; g = histological size of the primary tumor in millimeters; h = SN metastasis size (1 if ITC, 2 if micrometastasis, 3 if macrometastasis); and i = extracapsular extension of SN metastasis (1 if present, 0 if not). The predictive model is given as a supplementary Excel file calculator (Supplementary Data 2, available online) and at the website of the Breast Surgery Unit of Helsinki University Central Hospital (http://www.hus.fi/breastsurgery/predictivemodel).

Each patient's information from the internal and external validation patient series was then introduced into the multivariable equation to perform validation of the predictive model. AUC values with confidence intervals for each center are given in Table 4, and receiver operating characteristic curves are given in Figure 1. The prevalence of nonsentinel node metastases ranged from 20.8% to 36.0% between centers in the internal validation series and from 30.2% to 53.0% in the external validation series. Similarly, the AUC values ranged from 0.458 to 0.841 in the internal validation series between different centers and from 0.577 to 0.949 in the different external validation centers. Overall, internal validation of the predictive model yielded an AUC of 0.714 (95% CI = 0.665 to 0.763), whereas the external validation AUC was 0.719 (95% CI = 0.689 to 0.750) (Table 4).

The model generates a probability of additional metastases, which can be termed a risk estimate score, and the sensitivity and specificity of the predictive model may be calculated for any given cutoff value of the risk estimate score. For example, when applied to the external validation series, our model has a sensitivity of 67.6% and a specificity of 65.8% for a cutoff value of more than 50% of the risk score. The sensitivity and specificity of the model in the external validation series for different cutoff values are: greater than 10% risk (98.2% sensitivity and 7.5% specificity), greater than 20% risk (89.4% sensitivity and 31.6% specificity), greater than 30% risk (83.1% sensitivity and 43.9% specificity), greater than 40% risk (70.3% sensitivity and 61.6% specificity), greater than 60% risk (27.3% sensitivity and 91.4% specificity) and greater than 70% risk (12.4% sensitivity and 97.2% specificity).

Calibration of the predictive model was examined by grouping patients in each series into quintiles according to the predicted probabilities of additional metastases. A calibration plot was acquired by plotting the mean predicted probability of each quintile against the actual proportion of patients with additional metastases in each quintile (Figure 2).

Discussion

Our predictive model is presented in the form of a multivariable equation that produces the probability of additional axillary metastases. Most of the previous models were given in the form of scores or nomograms that were always approximations of the original mathematical model (1–15). In the contemporary era, we feel that the predictive equation is the most appropriate form because it produces the most accurate prediction and can be easily incorporated into various platforms, including computers and mobile devices. Moreover, by producing a probability of additional metastases, our predictive model is not tied into specific cutoff points because the thresholds for clinical decision making may well change in the future and increasingly become more patient specific.

The present model performed relatively well both in the internal and external validation. In fact, the model performed equally or even better in the external patient series than it did in the internal setup in terms of AUC. Furthermore, the model performed well in both low-risk (up to 10% risk) and high-risk (60% risk and over) conditions, as illustrated by the calibration plot (Figure 2). Other predictive models may not calibrate equally well, as shown by previous validation studies (15,24). In fact, we have recently validated four previous nomograms with the original patient series of this study with resulting AUC values of 0.640 to 0.686 and relatively poor performance in high-risk (>50% risk) settings (21).

The baseline prevalence of additional axillary metastases in our original patient series (32.7%) is substantially lower than that of the external validation series (42.2%). Such baseline differences may be relatively customary and may account for poor performance of previous predictive tools in other centers. In fact, our model is the first predictive tool to incorporate each center's baseline prevalence of nonsentinel node metastases as a coefficient in the equation to calibrate the model.

The exclusion criteria for this study were intentionally minimal to produce a heterogeneous patient population closely resembling real-life patient material. Furthermore, the methodology of the

Table 2. Univariate analysis comparing patients with additional metastases in axillary lymph node dissection to those with no additional metastases in the original patient series*

Patient, tumor, and lymph node characteristics	No additional metastases in ALND, n = 673	Additional metastases in ALND, n = 327	All patients, N = 1000	*P*
Patient age, y				.35
Mean (range)	57.4 (26–86)	58.1 (27–87)	57.6 (26–87)	
Standard deviation	11.2	11.8	11.4	
Prevalence of nonsentinel node metastases in each center's patient series				
Mean (range)	32.6% (27.0%–40.0%)	33.7% (27.0%–40.0%)	33.0% (27.0%–40.0%)	<.001
Standard deviation	4.8	4.8	4.9	
Histological size of the primary tumor, mm				<.001
Mean (range)	19.3 (0.4–81.0)	23.1 (0.5–200.0)	20.6 (0.4–200.0)	
Standard deviation	10.1	17.4	13.1	
Multifocality of the primary tumor, no.				.003
No	552	242	794	
Yes	121	85	206	
Lymphovascular invasion in the primary tumor, no.				.001
No	484	200	684	
Yes	189	127	316	
Estrogen receptor status, no.				.93
Negative	94	45	139	
Positive	579	282	861	
Progesterone receptor status, no.				.94
Negative	162	78	240	
Positive	511	249	760	
HER-2 status, no.				.04
Negative	583	298	881	
Positive	90	29	119	
Triple negative, no.†				.48
No	622	298	920	
Yes	51	29	80	
Triple positive, no.‡				.50
No	633	311	944	
Yes	40	16	56	
Nuclear grade of the primary tumor, no.				.01
Grade 1	78	20	98	
Grade 2	320	151	471	
Grade 3	275	156	431	
Histological grade of the primary tumor, no.				.003
Grade 1	130	36	166	
Grade 2	310	159	469	
Grade 3	233	132	365	
Histology of the primary tumor, no.				.37
Ductal carcinoma	539	250	789	
Lobular carcinoma	62	39	101	
Mixed	29	19	48	
Other	43	19	62	
Detection method of the sentinel node metastasis, no.				<.001
Frozen section analysis	258	181	439	
Paraffin standard staining	199	104	303	
Paraffin immunohistochemistry	154	25	179	
Serial sectioning	62	17	79	
Size of the sentinel node metastasis, no.				<.001
Isolated tumor cells	64	4	68	
Micrometastasis	215	30	245	
Macrometastasis	394	293	687	
Extracapsular extension of sentinel node metastasis, no.				<.001
No	544	180	724	
Yes	129	147	276	
Number of negative sentinel nodes harvested				<.001
Mean (range)	0.7 (0–11)	0.5 (0–5)	0.7 (0–11)	
Standard deviation	1.1	0.8	1.0	

(Table continues)

Table 2 (Continued).

Patient, tumor, and lymph node characteristics	No additional metastases in ALND, n = 673	Additional metastases in ALND, n = 327	All patients, N = 1000	*P*
Number of positive sentinel nodes harvested				<.001
Mean (range)	1.2 (1–5)	1.4 (1–5)	1.3 (1–5)	
Standard deviation	0.5	0.8	0.6	

* Mann–Whitney *U* test used for continuous variables and χ^2 test for categorical variables. All statistical tests were two-sided. HER-2 = human epidermal growth factor receptor 2.

† Triple negative = estrogen receptor, progesterone receptor, and HER-2 status all negative.

‡ Triple positive = estrogen receptor, progesterone receptor, and HER-2 status all positive.

Table 3. Binary logistic regression analysis using backward stepwise likelihood ratio method in the original patient series*

Variable	Coefficient	Standard error	Wald	*P*	Odds ratio (95% CI)
Prevalence of nonsentinel node metastases in patient series	0.036	0.015	5.340	.02	1.036 (1.005 to 1.068)
Lymphovascular invasion in the primary tumor	0.321	0.159	4.100	.04	1.378 (1.010 to 1.881)
Multifocality of the primary tumor	0.420	0.181	5.397	.02	1.522 (1.068 to 2.169)
HER-2 status	−0.594	0.248	5.732	.02	0.552 (0.340 to 0.898)
Number of negative sentinel nodes	−0.216	0.086	6.327	.01	0.806 (0.681 to 0.954)
Number of positive sentinel nodes	0.278	0.118	5.596	.02	1.321 (1.049 to 1.664)
Histological size of the primary tumor, mm	0.021	0.007	9.897	.002	1.021 (1.008 to 1.034)
Size of the sentinel node metastasis	1.274	0.184	47.907	<.001	3.552 (2.492 to 5.127)
Extracapsular extension of sentinel node metastasis	0.655	0.163	16.074	<.001	1.925 (1.398 to 2.652)
Constant	−6.391	0.764	69.989	<.001	0.002

* Reporting two-sided *P* values. CI = confidence interval; HER-2 = human epidermal growth factor receptor 2.

Table 4. Performance of the predictive model in internal and external validation*

Patient series	No.	Nonsentinel metastases	AUC (95% CI)	Bonferroni corrected CI (99.4%) for AUC	Sensitivity	Specificity
Original patient series	1000	327 (32.7%)	0.756 (0.725 to 0.787)	0.713 to 0.800	38.5%	89.2%
Internal validation series	500	155 (31.0%)	0.714 (0.665 to 0.763)	0.646 to 0.783	36.8%	90.1%
Center A	100	36 (36.0%)	0.692 (0.586 to 0.797)	0.545 to 0.841	41.7%	85.9%
Center B	134	43 (32.1%)	0.760 (0.675 to 0.844)	0.642 to 0.880	39.5%	89.0%
Center C	42	15 (35.7%)	0.841 (0.706 to 0.976)	0.650 to 1.000	46.7%	92.6%
Center D	200	56 (28.0%)	0.686 (0.600 to 0.771)	0.565 to 0.805	32.1%	91.7%
Center E	24	5 (20.8%)	0.458 (0.176 to 0.740)	0.069 to 0.868	0	94.7%
External validation series	1068	451 (42.2%)	0.719 (0.689 to 0.750)	0.676 to 0.762	51.4%	79.4%
Center F	100	53 (53.0%)	0.762 (0.669 to 0.856)	0.629 to 0.892	62.3%	85.1%
Center G	137	51 (37.2%)	0.747 (0.663 to 0.831)	0.625 to 0.861	62.7%	75.6%
Center H	67	30 (44.8%)	0.577 (0.440 to 0.715)	0.389 to 0.775	23.3%	83.8%
Center I	153	64 (41.8%)	0.715 (0.635 to 0.795)	0.603 to 0.827	51.6%	71.9%
Center J	43	13 (30.2%)	0.949 (0.886 to 1.000)	0.866 to 1.000	84.6%	93.3%
Center K	100	47 (47.0%)	0.702 (0.598 to 0.805)	0.557 to 0.847	48.9%	83.0%
Center L	200	64 (32.0%)	0.673 (0.591 to 0.756)	0.556 to 0.789	56.2%	72.1%
Center M	268	129 (48.1%)	0.731 (0.672 to 0.792)	0.648 to 0.817	44.2%	86.3%

* Sensitivity and specificity calculated for a cutoff value of greater than 50% risk estimate score. AUC = area under the receiver operating characteristics curve; CI = confidence interval.

preoperative nodal assessment, such as the use of axillary ultrasound, and the pathological nodal assessment varied considerably between centers, accounting for differences. A high-quality, preoperative, axillary ultrasound blocks a high proportion of women with macrometastases from the SNB procedure, thereby also lowering the proportion of women with additional nonsentinel node metastases.

Differences between the centers both in internal and external validation are apparent, considering the variation of the AUC values in Table 4. These may partly be due to small patient series from some centers, accounting for both very high (external validation Center J; AUC = 0.949) and very low (external validation Center H; AUC = 0.577) AUC values. These are most likely statistical variations that will be leveled with a higher number of patients. On the other hand, the alteration between centers may represent real methodological or population-wise differences, and further validation of the model with reasonably large patient series is of crucial importance before adoption into clinical use.

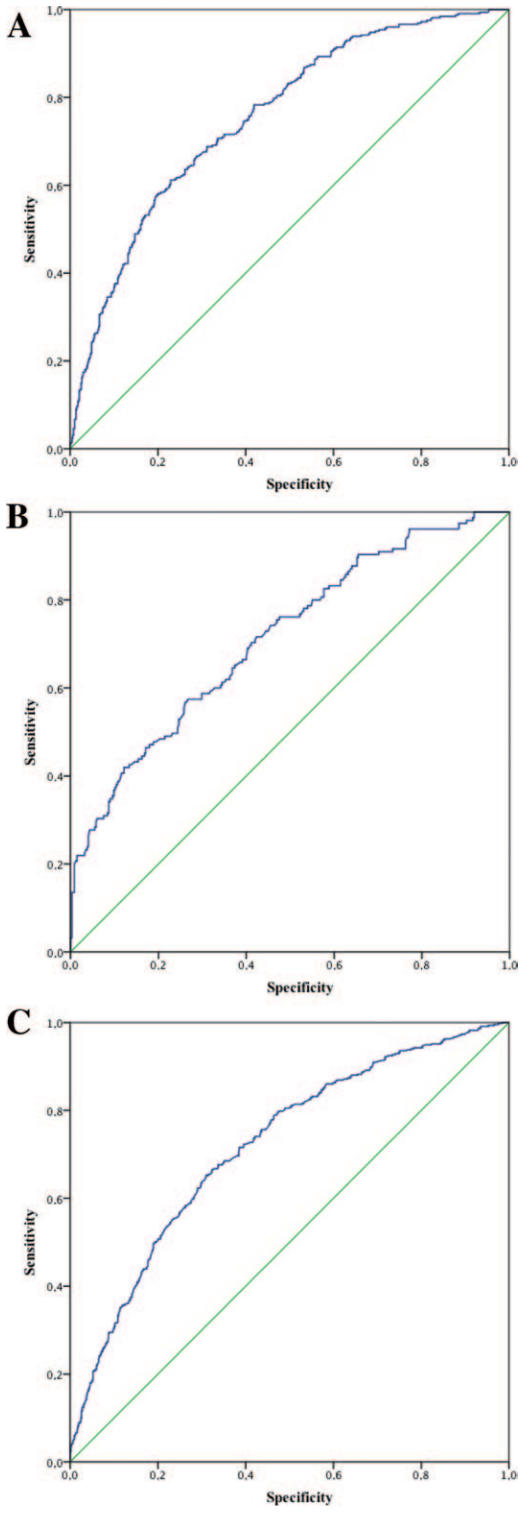

Figure 1. Receiver operating characteristic curves for the original patient series (**A**), the internal validation patient series (**B**), and the external validation patient series (**C**).

Although the present model produces simply the percentile probability of residual disease, the sensitivity and specificity of the model were tested, as an example, for a cutoff value of more than 50% risk score in Table 4. In the wake of the ACOSOG Z0011 trial, such a high cutoff value was chosen because it is being substantially higher than those of previous models (1–16) and also considerably higher than the 27% risk of the ACOSOG patient series (18,19). Our model had a reasonably good sensitivity and specificity at this cutoff point, both in the internal and external validation series.

Nine variables were statistically significant in the logistic regression analysis and were incorporated into our predictive model. The prevalence of nonsentinel metastases is a center- or patient series–specific variable, which is a unique feature in the present model. Most of the other variables included in the model have been found to predict the risk for additional axillary metastases in previously published models (1–15), except for HER-2 status. HER-2 status stood out as an independent factor from estrogen and progesterone receptor status because both triple-negative and triple-positive combinations had similar distributions across the two groups in univariate analysis. The biological explanation behind this phenomenon remains unclear. The implications of HER-2 status on recurrences and survival have been extensively studied (25,26), but the detailed effects of steroid receptor and HER-2 status on axillary lymph node and especially nonsentinel node involvement have not been described in the literature. Triple-positive breast cancer has been shown to lead to highest incidence of tumor-positive lymph nodes in multivariable analysis (27) between different phenotypes, but this study did not find an association between nonsentinel node metastases and triple-negative or triple-positive phenotypes.

Our model includes SN metastasis size as a factor in the predictive equation. In fact, the distinction between ITC, micrometastasis, and macrometastasis as the SN finding greatly affects the probability of additional metastases. Some of the previous models do not take the SN metastasis size into consideration (1,7,11), whereas some models are specifically designed for only ITC or micrometastases (9,15,16).

The ACOSOG Z0011 trial suggested that omitting completion ALND after tumor-positive SNB does not increase regional recurrence rate nor decrease survival rate in general. The prevalence of additional axillary metastases was 27% on the ALND arm of the randomized ACOSOG trial, suggesting a comparable residual disease rate in the SNB-only arm. However, the study only included women having undergone breast-conserving surgery followed by whole-breast radiotherapy including the axilla through a tangential field. The prevalence of nonsentinel node metastases in our unselected patient series was considerably higher than in the ACOSOG trial (33% in our original series, 31% in the internal validation series, and 42% in the external validation series). A meta-analysis of more than 8000 patients reported an additional axillary metastases rate as high as 53% after a tumor-positive SNB (28).

Many factors affect the baseline prevalence of axillary metastases in a given patient population. These include the method of preoperative nodal assessment and many primary tumor-specific factors, such as tumor diameter, which also determines whether a patient undergoes breast-conserving surgery or mastectomy. Therefore, the patient selection of the ACOSOG Z0011 trial may have led to a lower baseline prevalence of nonsentinel node metastases, and the results may not be generalizable to patients with a higher risk of additional metastases than the 27% reported in that study. Moreover, a substantial proportion of patients undergoing mastectomy do not receive radiotherapy and may be at a higher risk of regional recurrence than patients undergoing breast-conserving surgery and radiation (29,30).

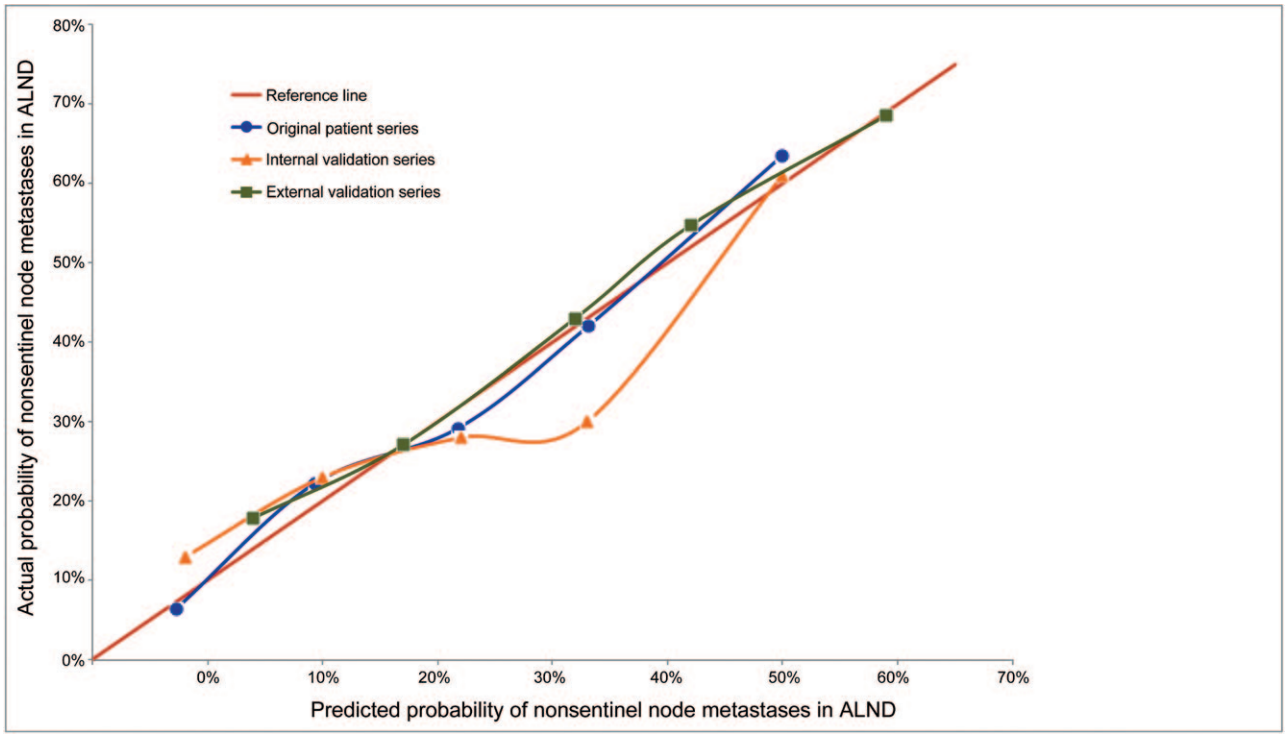

Figure 2. Calibration plot for the predictive model applied to the original patient series, internal validation series, and external validation series, split to quintiles. ALND = axillary lymph node dissection.

Although most axillary recurrences have been reported to occur in the first 5 years after ALND (31), the metastatic tumor load to the axilla is believed to be considerably lower in the SNB era than in the period prior to it. Therefore, the presentation of recurrences may need a longer time than the 6.3 years of median follow-up reported to date (19), despite the fact that at present there is not even a trend toward a decreased survival without completion ALND in the ACOSOG Z0011 trial.

The whole paradigm of axillary treatment of breast cancer patients is changing, but the future may well be multidirectional. In addition to completion ALND, axillary radiotherapy may also be a future option in the treatment of patients with tumor-positive SN. The European Organisation for Research and Treatment of Cancer AMAROS trial (32) is comparing axillary radiotherapy to completion ALND in a randomized set-up, but the final results have not yet been published. Patient-specific prediction of residual axillary disease may become even more relevant in the future because the treatment options of the axilla are under scrutiny. One implication of the ACOSOG Z0011 trial and also of the AMAROS trial is the diminishing role of intraoperative SN analysis and the adaptation of pathology methods to the clinical context (ie, to potential treatment options). Many previous predictive models include SN detection method or the use of frozen section analysis as a factor in the model. These models may become obsolete with possible abandoning of intraoperative SN analysis.

Our study also has limitations. The heterogeneity of our patient series probably reduces the performance of the predictive model in specific subgroups of patients. The subgroup of patients for whom predictive models are especially needed in the future is, however, unclear. Our novel predictive model may perform well in everyday practice with the average patient, but care needs to be taken in special cases with, for example, very large tumors or tumors representing rare histological types. Another limitation of this study is the variance in the patient enrollment times between different centers. This may have a negative impact on the performance of the new model.

We present a novel, international, multicenter, predictive tool to assess the risk of additional axillary metastases after tumor-positive SNB in breast cancer. In the era of changing paradigm, our tool seems to be able to also identify high-risk patients. The predictive model performs well in internal and external validation patient series, but on the basis of our previous results (21,22), it needs to be validated in each center before its application in clinical practice.

References

1. Van Zee KJ, Manasseh DM, Bevilacqua JL, et al. A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. *Ann Surg Oncol.* 2003;10(10):1140–1151.
2. Hwang RF, Krishnamurthy S, Hunt KK, et al. Clinicopathologic factors predicting involvement of nonsentinel axillary nodes in women with breast cancer. *Ann Surg Oncol.* 2003;10(3):248–254.
3. Farshid G, Pradhan M, Kollias J, Gill PG. A decision aid for predicting non-sentinel node involvement in women with breast cancer and at least one positive sentinel node. *Breast.* 2004;13(6):494–501.
4. Saidi RF, Dudrick PS, Remine SG, Mittal VK. Nonsentinel lymph node status after positive sentinel lymph node biopsy in early breast cancer. *Am Surg.* 2004;70(2):101–105; discussion 105.
5. Barranger E, Coutant C, Flahault A, Delpech Y, Darai E, Uzan S. An axilla scoring system to predict non-sentinel lymph node status in breast cancer patients with sentinel lymph node involvement. *Breast Cancer Res Treat.* 2005;91(2):113–119.
6. Degnim AC, Reynolds C, Pantvaidya G, et al. Nonsentinel node metastasis in breast cancer patients: assessment of an existing and a new predictive nomogram. *Am J Surg.* 2005;190(4):543–550.

7. Chagpar AB, Scoggins CR, Martin RC, et al. Prediction of sentinel lymph node-only disease in women with invasive breast cancer. *Am J Surg.* 2006;192(6):882–887.
8. Pal A, Provenzano E, Duffy SW, Pinder SE, Purushotham AD. A model for predicting non-sentinel lymph node metastatic disease when the sentinel lymph node is positive. *Br J Surg.* 2008;95(3):302–309.
9. Houvenaeghel G, Nos C, Giard S, et al. A nomogram predictive of non-sentinel lymph node involvement in breast cancer patients with a sentinel lymph node micrometastasis. *Eur J Surg Oncol.* 2009;35(7):690–695.
10. Kohrt HE, Olshen RA, Bermas HR, et al. New models and online calculator for predicting non-sentinel lymph node status in sentinel lymph node positive breast cancer patients. *BMC Cancer.* 2008;8:66.
11. Cho J, Han W, Lee JW, et al. A scoring system to predict nonsentinel lymph node status in breast cancer patients with metastatic sentinel lymph nodes: a comparison with other scoring systems. *Ann Surg Oncol.* 2008;15(8):2278–2286.
12. Gur AS, Unal B, Ozbek U, et al. Validation of breast cancer nomograms for predicting the non-sentinel lymph node metastases after a positive sentinel lymph node biopsy in a multi-center study. *Eur J Surg Oncol.* 2010;36(1):30–35.
13. Perhavec A, Perme MP, Hocevar M, Besić N, Zgajnar J. Ljubljana nomograms for predicting the likelihood of non-sentinel lymph node metastases in breast cancer patients with a positive sentinel lymph node. *Breast Cancer Res Treat.* 2010;119(2):357–366.
14. Coufal O, Pavlík T, Fabian P, et al. Predicting non-sentinel lymph node status after positive sentinel biopsy in breast cancer: what model performs the best in a Czech population? *Pathol Oncol Res.* 2009;15(4):733–740.
15. Meretoja TJ, Strien L, Heikkilä PS, Leidenius MH. A simple nomogram to evaluate the risk of nonsentinel node metastases in breast cancer patients with minimal sentinel node involvement. *Ann Surg Oncol.* 2012;19(2):567–576.
16. Tvedskov TF, Jensen MB, Lisse IM, Ejlertsen B, Balslev E, Kroman N. High risk of non-sentinel node metastases in a group of breast cancer patients with micrometastases in the sentinel node. *Int J Cancer.* 2012;131(10):2367–2375.
17. Galimberti V, Cole B, Zurrida S, et al. Update of International Breast Cancer Study Group trial 23-01 to compare axillary dissection versus no axillary dissection in patients with clinically node negative breast cancer and micrometastases in the sentinel node. Paper presented at San Antonio Breast Cancer Symposium; December 2011; San Antonio, TX.
18. Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg.* 2010;252(3):426–432; discussion 432–433.
19. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA.* 2011;305(6):569–575.
20. Pepels MJ, de Boer M, Bult P, et al. Regional recurrence in breast cancer patients with sentinel node micrometastases and isolated tumor cells. *Ann Surg.* 2012;255(1):116–121.
21. Cserni G, Bori R, Maráz R, et al. Multi-Institutional comparison of non-sentinel lymph node predictive tools in breast cancer patients with high predicted risk of further axillary metastasis [published online ahead of print July 14, 2012]. *Pathol Oncol Res.* 2012;doi: 10.1007/s12253-012-9553-5.
22. Cserni G, Boross G, Maráz R, et al. Multicentre validation of different predictive tools of non-sentinel lymph node involvement in breast cancer. *Surg Oncol.* 2012;21(2):59–65.
23. Sobin LH, Wittekind Ch, eds. *TNM Classification of Malignant Tumours*. 6th ed. New York: Wiley-Liss; 2002.
24. Coutant C, Olivier C, Lambaudie E, et al. Comparison of models to predict nonsentinel lymph node status in breast cancer patients with metastatic sentinel lymph nodes: a prospective multicenter study. *J Clin Oncol.* 2009;27(17):2800–2808.
25. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science.* 1987;235(4785):177–182.
26. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proc Natl Acad Sci U S A.* 2003;100(14):8418–8423.
27. Van Calster B, Vanden Bempt I, Drijkoningen M, et al. Axillary lymph node status of operable breast cancers by combined steroid receptor and HER-2 status: triple positive tumours are more likely lymph node positive. *Breast Cancer Res Treat.* 2009;113(1):181–187.
28. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. *Cancer.* 2006;106(1):4–16.
29. van Wely BJ, Teerenstra S, Schinagl DA, Aufenacker TJ, de Wilt JH, Strobbe LJ. Systematic review of the effect of external beam radiation therapy to the breast on axillary recurrence after negative sentinel lymph node biopsy. *Br J Surg.* 2011;98(3):326–333.
30. Meretoja TJ, Leidenius MH, Heikkila PS, Joensuu H. Sentinel node biopsy in breast cancer patients with large or multifocal tumors. *Ann Surg Oncol.* 2009;16(5):1148–1155.
31. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* 2005;366(9503):2087–2106.
32. Straver ME, Meijnen P, van Tienhoven G, et al. Role of axillary clearance after a tumor-positive sentinel node in the administration of adjuvant therapy in early breast cancer. *J Clin Oncol.* 2010;28(5):731–737.

Funding

T. J. Meretoja was supported by grants from the Helsinki University Central Hospital Research Fund, the Academy of Finland and the Emil Aaltonen's Foundation.

Note

The funders did not have any involvement in the design of the study; the collection, analysis, and interpretation of the data; the writing of the article; or the decision to submit the article for publication.

Affiliations of authors: Breast Surgery Unit (TJM, MHKL) and Department of Pathology (PSH), Helsinki University Central Hospital, Helsinki, Finland; Department of Surgery (GB) and Department of Pathology (IS, GC), Bács-Kiskun County Teaching Hospital, Kecskemét, Hungary; Department of Pathology (PR) and Department of Obstetrics and Gynecology (GL-E), Medical University of Graz, Graz, Austria; Department of Surgical Oncology (JZ, AP) and Department of Pathology (BG), Institute of Oncology, Ljubljana, Slovenia; Department of Surgery (GL, TT) and Department of Pathology (AV, GC), University of Szeged, Szeged, Hungary; Department of Breast Surgery, Lancashire Teaching Hospitals, Chorley, United Kingdom (ZAS, RMN); Breast Unit Azienda Ospedaliera Universitaria San Giovanni Battista di Torino, Department of Biomedical Sciences and Human Oncology, University of Turin, Turin, Italy (IC, AS); Section of Pathological Anatomy, Department of Medical and Surgical Critical Care, University of Florence, Florence, Italy (SB, VV); Department of Gynecology and Obstetrics, Lariboisiere Hospital, Paris, France (EB, RL); Department of Pathology, O.I.R.M. -Sant'Anna Hospital, Turin, Italy (RA); Section of Anatomic Pathology at Bellaria Hospital, Department of Biomedical Sciences and Neuromotory Disorders, University of Bologna, Bologna, Italy (MPF); Department of Breast Surgery (SI) and Department of Pathology (HK), Kyorin University School of Medicine, Tokyo, Japan; Department of Breast Surgery (TFT, NK) and Danish Breast Cancer Cooperative Group (M-BJ), Copenhagen University Hospital, Copenhagen, Denmark; Department of Surgery, St Helens Teaching Hospital, St Helens, United Kingdom (RAA).