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CLINICAL TRIAL

Ljubljana nomograms for predicting the likelihood of non-sentinel lymph node metastases in breast cancer patients with a positive sentinel lymph node

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Abstract Several tools for predicting the likelihood of non-sentinel lymph node (non-SLN) involvement in SLN-positive breast cancer patients have been created so far. The aim of our study was to create and validate different nomograms for predicting the likelihood of non-SLN involvement that would be applicable in different institutions and that would also include the results of the preoperative US examination of the axilla. From January 2000 to January 2009, 534 breast cancer patients underwent axillary lymph node dissection (ALND) due to metastatic SLN at our institution. Using logistic regression results three nomograms differing in the inclusion of the results of intraoperative examination of SLN were created. The nomograms were validated using bootstrap methods. In all three nomograms, US examination of the axilla was a powerful independent variable. Other variables included (different in different nomograms) were tumor size, lymphovascular invasion, metastasis size in SLN, number of negative and number of positive SLNs. Mean absolute error and mean area under the ROC curve equals to 0.016 and 0.77 for the first, 0.023 and 0.75 for the second and 0.014 and 0.79 for the third nomogram. Three nomograms for predicting the likelihood of non-SLN metastases including the results of the preoperative US examination of the axilla were created at our institution. They differ in the inclusion of the results of intraoperative examination of SLNs and are thus applicable in different institutions. The validation results seem promising and omission of completion ALND might be considered in patients with the probability of having non-SLN metastases of 10% or less.

Keywords Breast cancer · Sentinel lymph node · Prediction of non-sentinel lymph node metastases · Nomogram

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Introduction

Breast cancer surgery has gradually become more conservative, from radical mastectomy as the only surgical option in breast cancer patients in the late nineteenth and early twentieth century to breast conserving surgery and sentinel lymph node (SLN) biopsy, which are standards of care in selected patients nowadays.

SLN biopsy has been proven to accurately stage lymph nodes in breast cancer patients with less morbidity and better quality of life as compared with the standard axillary lymph node dissection (ALND) [1, 2]. In the case of a positive SLN, completion ALND (cALND) is routinely performed because of the possibility of non-SLN involvement. In such cases, cALND may offer additional prognostic and/or therapeutic benefit. However, in more than 50% of SLN-positive patients, the SLN has been shown to be the only lymph node affected by cancer [3]. Therefore, it would be important to identify patients who have no additional lymph nodes affected by cancer in order to avoid unnecessary ALND and its sequels.

In order to avoid unnecessary ALND, different tools for predicting the likelihood of non-SLN metastases in breast cancer patients with a positive SLN have been developed [4–10]. Most of them were created based on the data of the single institution with specific patient population and

protocols (for example specialities in surgical procedures, intraoperative examination of SLNs, pathological assessment of SLNs, etc). Therefore, it is not surprising that they often perform poor when validated outside the institution they were developed [11, 12]. The most widely validated is the prediction tool created by van Zee et al. from the Memorial Sloan Cattering Cancer Center (MSKCC) [10]. Because of interinstitutional differences in intraoperative examination of SLNs, they created two nomograms, one with and the other without frozen section information. As a result, one nomogram may be used in institutions where frozen section is performed and the other in those where it is not, which widens the applicability of their tool. However, MSKCC nomograms have an important weaknesses—they do not include the information on preoperative US examination of axillary lymph nodes, which is known to be an important predictor of non-SLN involvement when SLN is positive [12–14].

The aim of our study was to create and validate a tool for predicting the likelihood of non-SLN involvement that would include the information on the preoperative US examination of axillary lymph nodes.

Patients and methods

From January 2000 to January 2009, 2188 SLN biopsies in patients with invasive breast cancer were successfully performed at the Institute of Oncology Ljubljana. Of those, 1360 (62%) were free of tumor cells, and in 143 (7%), only isolated tumor cells (ITC) were found at the definite histology. Metastases were detected in 685 (31%) cases. cALND was performed in 549 patients. Of those, 15 (3%) have ITC, 133 (24%) micrometastasis and 401 (73%) macrometastasis in SLN. In 136 patients, cALND was not performed due to various reasons (comorbidities, inclusion in multicenter studies, patient preference).

In the present study, overall 534 patients were included. The inclusion criteria were as follows:

1. invasive breast cancer,
2. clinically negative axillary lymph nodes,
3. SLN biopsy successfully performed,
4. at least one metastasis (micro or macro) in SLN and
5. cALND performed

Fifteen patients who have ITC detected in SLN and who underwent cALND were excluded from the study, because cALND in patients with ITC-positive SLNs is no longer indicated as a routine procedure [15].

Clinical and pathological data of patients were prospectively collected. The data include age, tumor type, tumor size, tumor grade, location of the tumor, ER, PR and Her-2 status, lymphovascular invasion, number of removed SLNs, number of positive and negative SLNs, number of all lymph nodes removed, number of all positive lymph nodes, number of non-SLNs affected by micrometastases and macrometastases, metastases size of SLNs, perinodal invasion of metastases in SLNs, results of the touch imprint cytology (TIC) and results of the US of the axilla.

Three models for predicting the likelihood of non-SLN metastases have been created and validated:

1. First model—the nomogram suitable for our institution and other institutions where intraoperative examination of SLNs is not routinely performed in patients with low risk for SLN involvement ($n = 534$): the model consider the results of intraoperative examination of SLNs, where it was performed and the metastasis size where it was not performed.
2. Second model—the nomogram suitable for institutions where intraoperative examination of SLNs is not performed ($n = 534$): the results of intraoperative examination of SLNs were not included in this analysis.
3. Third model—the nomogram suitable for institutions where intraoperative examination of SLNs is standardly performed ($n = 460$): patients with SLNs, which were not examined by intraoperative examination, were excluded from this analysis.

The clinicopathological characteristics of patients are shown in Table 1.

Preoperative US examination of axillary lymph nodes

At the Institute of Oncology Ljubljana, preoperative US of axillary lymph nodes in combination with FNAB is a routine (but not obligatory) examination in clinically lymph node negative breast cancer patients.

The preoperative US examination of the axillary lymph nodes was performed by experienced radiologists, using a linear-array transducer with range 12–15 MHz (Power Vision 8000 model SSA-390A; Toshiba, Otawara, Japan).

Lymph node was considered US suspicious if one of the following criteria were met:

- the longitudinal-transverse axis ratio of the lymph node <1.2,
- lymph node hilus not seen or
- the cortex thickness larger than 3 mm

In all patients with US suspicious lymph nodes, US-guided FNAB with a 21-G needle was performed, and two smears were prepared. In the case of a positive cytologic result, patients proceeded to the immediate ALND, in the opposite case, the SLN biopsy was performed. The details of preoperative US examination of axillary lymph nodes are described elsewhere [16].

Table 1 Clinicopathological characteristics of patients

		First and second model	Third model
No. of patients		534	460
Age		Mean 55; median 54; range 25–87	Mean 54; median 53; range 25–87
Tumor size (mm)		Mean 20.0; median 18; range 3–80	Mean 20.8; median 19; range 3–80
No. of LNs removed per patient		Mean 18.7; median 18; range 5–61	Mean 18.7; median 18; range 5–39
No. of positive LNs per patient		Mean 2.8; median 1; range 1–29	Mean 2.8; median 2; range 1–29
No. of SLNs removed per patient		Mean 2.1; median 2; range 1–9	Mean 2.1; median 2; range 1–9
No. of positive SLNs per patient		Mean 1.3; median 1; range 1–5	Mean 1.4; median 1; range 1–5
SLN metastases size	Macrometastases	401/534 (75%)	351/460 (76%)
	Micrometastases	133/534 (25 %)	109/460 (24%)
Proportion of positive SLNs per patient	>0% and <100%	257/534 (48%)	213/460 (46%)
	100%	277/534 (52%)	247/460 (54%)
Non-SLNs metastases	Non-SLNs positive	180/534 (34%)	159/460 (35%)
	Non-SLNs macrometastases	160/534 (30%)	143/460 (31%)
Tumor type	IDC[a]	453/534 (85%)	393/460 (85%)
	ILC[b]	67/534 (13%)	55/460 (12%)
	Other	14/534 (3%)	12/460 (3%)
Grade	1	96/534 (18%)	74/460 (16%)
	2	258/534 (48%)	224/460 (49%)
	3	180/534 (34%)	162/460 (35%)
LVI[c]		197/534 (37%)	180/460 (39%)
Hormonal status	ER+	463/534 (87%)	398/460 (87%)
	ER−	71/534 (13%)	62/460 (13%)

[a] Invasive ductal carcinoma

[b] Invasive lobular carcinoma

[c] Lymphovascular invasion

SLN biopsy

On the morning of surgery, 30–60 MBq of ^{99m}TC-labelled nanocolloid (Nanocol®) in 0.2 ml saline, divided in two doses, was injected peritumorally at two sites. Static and dynamic lymphoscintigraphy was then performed. Hot spots in the regional lymph node basins were marked on the skin. After the induction of general anesthesia, 1 ml of blue dye (Blue Patente V; Laboratorie Guerbet, Aulnaysous-Bois, France) was injected peritumorally at the same two sites. SLN excision was guided by a hand-held gamma probe (Navigator GPS System, USSC, Watertown, Massachusetts, USA) and/or by the blue-stained afferent lymphatic channels. The excised SLN was measured for ex vivo radioactivity. Additional hot nodes were removed until the background radioactivity was less than 10% to the hottest ex vivo SLN.

In the palpable breast cancers, excised SLNs were standardly examined by the TIC. The cytopathologist examined the imprints and diagnosed them as negative, suspicious or positive. In the case of a positive result, the surgeon performed immediate cALND. In the case of non-palpable breast cancer, TIC was performed only if the SLN seemed clinically suspicious.

All slices of SLNs were formalin fixed and embedded in paraffin. The slides were examined with H&E staining. For all negative SLNs, serial sections were evaluated with H&E and immunohistochemistry (IHC)-stained levels at 250 μm. IHC staining was performed using commercially obtained monoclonal anticytokeratin antibody, clone MNF 116 (Dako, Glostrup, Denmark). All non-SLNs were sectioned transversely at 2–3 mm and entirely embedded. One section was examined with one H&E staining per paraffin block.

The details of SLN procedure are described elsewhere [17].

Statistical analysis

A logistic model was fitted to the data to evaluate the predictive ability of the covariates. Nomograms were created to assist in future predictions, and the area under the ROC curve was calculated. The models were validated using bootstrap methods [18]. The optimism was described by estimating the mean absolute error and the bias-corrected value of the area under the ROC curve. Performance of the nomograms is illustrated using a bootstrap

calibration curve. The *P* values (two-sided) under 0.05 are considered statistically significant. The statistical analysis was performed at the Institute of Biomedical Informatics using statistical software R for Windows version 2.6.2.

Results

The intraoperative examination of SLNs was performed in 460 patients. The remaining patients ($n = 74$) had non-palpable tumors; the SLNs in those patients (according to the policy at our institution) were thus not examined by intraoperative examination. Three models were calculated.

First model—the nomogram suitable for our institution and other institutions where intraoperative examination of SLNs is not routinely performed in patients with low risk for SLN involvement

534 patients were included in the calculation of the first model. In patients with SLNs, which were not examined by intraoperative examination (patients with non-palpable tumors), metastasis size was used in the calculation instead of the results of intraoperative examination of SLNs (74 patients).

The results of multivariate logistic regression are shown in Table 2. A nomogram created based on this multivariate model is shown in Fig. 1. The area under the ROC curve equals to 0.78. The proportions of patients with non-SLNs metastases for various predicted probability groups were calculated, the smoothed line through them is given in Fig. 2. In particular, there were 80 (15.0%) patients with less than 10% probability for non-SLNs involvement and 10 of them (12.5%) actually had non-SLNs metastases (8 macrometastases and 2 micrometastases).

The model was validated using the bootstrap validation method with 500 repetitions. The bias-corrected smoothed curve of the actual versus predicted probabilities is given in Fig. 2. The mean absolute error equals to 0.016. The average area under the ROC was 0.77.

Second model—the nomogram suitable for institutions where intraoperative examination of SLNs is not performed

534 patients were included in the calculation of the second model. The results of intraoperative examination of SLNs were not included in this analysis.

The results of multivariate logistic regression are shown in Table 3. A nomogram created based on this multivariate model is shown in Fig. 3. The area under the ROC curve equals to 0.76. The proportions of patients with non-SLNs metastases for various predicted probability groups were calculated, the smoothed line through them is given in Fig. 4. In particular, there were 64 (12.0%) patients with less than 10% probability for non-SLNs involvement and 6 of them (9.4%) actually had non-SLNs metastases (4 macrometastases and 2 micrometastases).

Table 2 First model—results of multivariate logistic regression testing the association of each variable with the likelihood of non-SLN metastases

	Coefficient	SE	*P* value
Intercept	−1.856	0.340	<0.001
Tumor size	0.408	0.106	<0.001
TIC/FS/MetSize = positive (vs. negative)[a]	1.477	0.253	<0.001
TIC/FS/MetSize = suspicious (vs. negative)[b]	0.774	0.579	0.182
TIC/FS/MetSize = not performed/micro (vs. performed/negative)[c]	0.332	0.616	0.590
TIC/FS/MetSize = not performed/macro (vs. performed/negative)[d]	1.093	0.392	0.005
US axilla = normal (vs. not performed)	−0.963	0.227	<0.001
US axilla = suspicious (vs. not performed)	−1.004	0.342	0.003
LVI = present (vs. absent)	0.488	0.214	0.023
No. of neg SLN = 1 (vs. No. = 0)	−0.347	0.234	0.139
No. of neg SLN = >1 (vs. No. = 0)	−1.155	0.322	<0.001

Tumor size pathological tumor size in centimeters; *TIC/FS/MetSize* touch imprint cytology/frozen section/metastasis size in SLN; *US axilla* results of preoperative US examination of axillary lymph nodes, *LVI* lymphovascular invasion, *No. of neg SLN* number of negative SLN

[a] TIC or FS performed and positive (vs. performed and negative)

[b] TIC or FS performed and suspicious (vs. performed and negative)

[c] TIC or FS not performed, micrometastasis found in SLN (vs. TIC or FS performed and negative)

[d] TIC or FS not performed, macrometastasis found in SLN (vs. TIC or FS performed and negative)

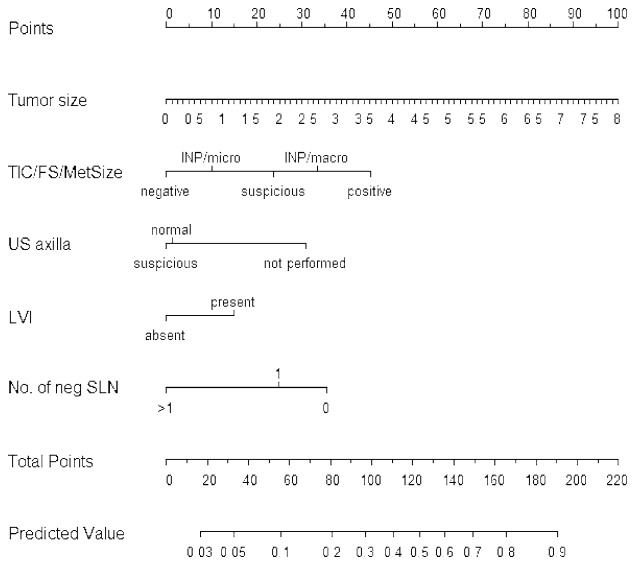

Fig. 1 The first nomogram—suitable for our institution and other institutions where intraoperative examination of SLNs is not routinely performed in patients with low risk for SLN involvement. *Rows* 2 through 6 represent variables. Vertical line should be made between each variable and the *uppermost row* (Points). In this way, the effect of each variable is determined by a defined number of points, which should be summed and located in *row* 7 (Total Points). Vertical line should be made between the *row* 7 and 8 (Predicted Value) to get the predicted probability of non-SLN metastasis. Tumor size—pathological tumor size in centimeters; TIC/FS/MetSize—results of touch imprint cytology (TIC) or frozen section (FS), when they were performed and the information on SLN metastasis size (MetSize), when TIC or FS were not performed: INP/micro—imprint (or FS) not performed, micrometastasis found in SLN; INP/macro—imprint (or FS) not performed, macrometastasis found in SLN; US axilla—results of preoperative US examination of axillary lymph nodes; LVI—lymphovascular invasion; No. of neg SLN—number of negative SLN: >1—more than 1 negative SLN, 1—one negative SLN, 0—no negative SLN

The model was validated using the bootstrap validation method with 500 repetitions. The bias-corrected smoothed curve of the actual versus predicted probabilities is given in Fig. 4. The mean absolute error equals to 0.023. The average area under the ROC was 0.75.

Third model—the nomogram suitable for institutions where intraoperative examination of SLNs is standardly performed

460 patients were included in the calculation of the third model. Patients with SLNs, which were not examined by intraoperative examination, were excluded from this analysis.

The results of multivariate logistic regression are shown in Table 4. A nomogram created based on this multivariate model is shown in Fig. 5. The area under the ROC curve equals to 0.79. The proportions of patients with non-SLNs metastases for various predicted probability groups were calculated, the smoothed line through them is given in Fig. 6. In particular, there were 75 (16.3%) patients with less than 10% probability for non-SLNs involvement and 8 of them (10.7%) actually had non-SLNs metastases (6 macrometastases, 2 micrometastases).

The model was validated using the bootstrap validation method with 500 repetitions. The bias-corrected smoothed curve of the actual versus predicted probabilities is given in

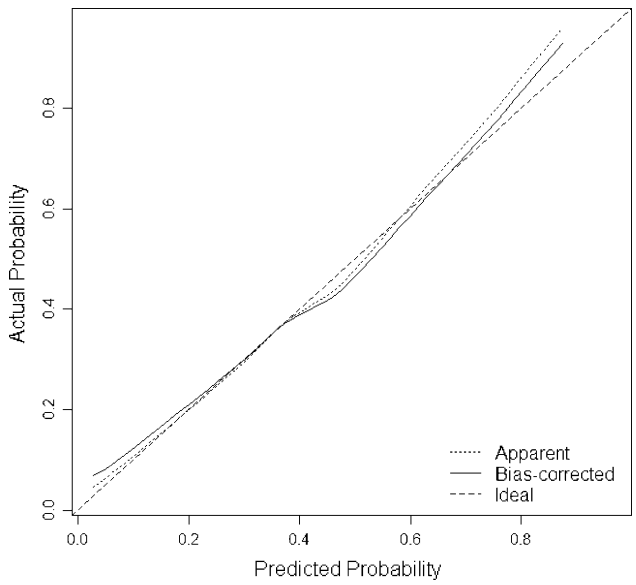

Fig. 2 Calibration plot for the first nomogram—the actual versus the predicted probabilites. The *dashed line* presents the line of equality, the *dotted line* depicts the observed situation on our sample and the *solid line* presents the bias-corrected line using the bootstrap validation procedure

Table 3 Second model—results of multivariate logistic regression testing the association of each variable with the likelihood of non-SLN metastases

	Coefficient	SE	*P* value
Intercept	−1.809	0.354	<0.001
Tumor size (cm)	0.401	0.101	<0.001
MetSize (macro vs. micro)	0.980	0.275	<0.001
US axilla = normal (vs. not performed)	−1.069	0.222	<0.001
US axilla = suspicious (vs. not performed)	−1.012	0.334	0.003
LVI = present (vs. absent)	0.549	0.209	0.009
No. of neg SLN = 1 (vs. No. = 0)	−0.379	0.229	0.098
No. of neg SLN = >1 (vs. No. = 0)	−1.100	0.319	<0.001
No. of pos SLN = >1 (vs. No. = 1)	0.451	0.220	0.041

Tumor size pathological tumor size in centimeters, *MetSize* metastasis size in SLN: micro—micrometastasis, macro—macrometastasis; *US axilla* results of preoperative US examination of axillary lymph nodes, *LVI* lymphovascular invasion, *No. of neg SLN* number of negative SLN, *No. of pos SLN* number of positive SLN

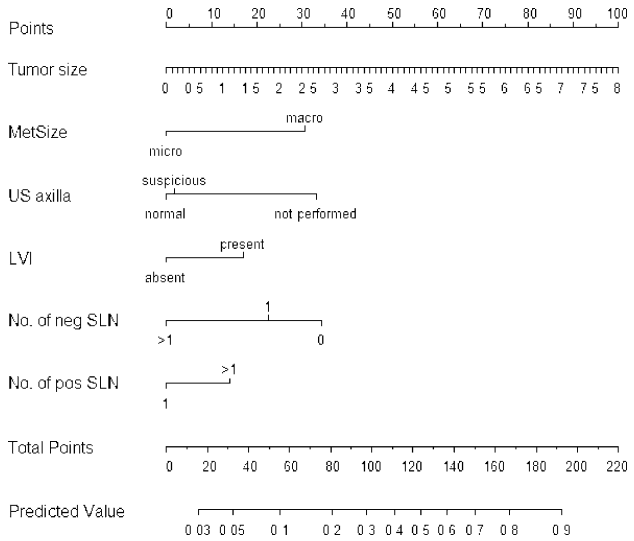

Fig. 3 The second nomogram—suitable for institutions where intraoperative examination of SLN is not performed. *Rows* 2 through 7 represent variables. Vertical line should be made between each variable and the *uppermost row* (Points). In this way, the effect of each variable is determined by a defined number of points, which should be summed and located in *row* 8 (Total Points). Vertical line should be made between the *row* 8 and 9 (Predicted Value) to get the predicted probability of non-SLN metastasis. Tumor size—pathological tumor size in centimeters; MetSize—metastasis size in SLN: micro—micrometastasis, macro—macrometastasis; US axilla—results of preoperative US examination of axillary lymph nodes; LVI—lymphovascular invasion; No. of neg SLN—number of negative SLN: >1—more than 1 negative SLN, 1—one negative SLN, 0—no negative SLN; No. of pos SLN—number of positive SLN: 1—one positive SLN, >1 more than one positive SLN

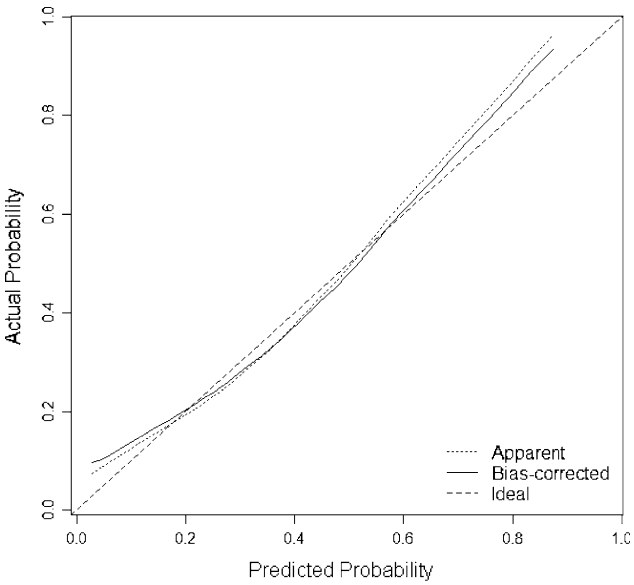

Fig. 4 Calibration plot for the second nomogram—the actual versus the predicted probabilites. The *dashed line* presents the line of equality, the *dotted line* depicts the observed situation on our sample and the *solid line* presents the bias-corrected line using the bootstrap validation procedure

Table 4 Third model—results of multivariate logistic regression testing the association of each variable with the likelihood of non-SLN metastases

	Coefficient	SE	*P* value
Intercept	−1.675	0.349	<0.001
Tumor size (cm)	0.346	0.107	0.001
TIC/FS = positive (vs. negative)	1.415	0.257	<0.001
TIC/FS = suspicious (vs. negative)	0.646	0.588	0.272
US axilla = normal (vs. not performed)	−1.144	0.249	<0.001
US axilla = suspicious (vs. not performed)	−1.170	0.359	0.001
LVI = present (vs. absent)	0.460	0.232	0.048
No. of neg SLN = 1 (vs. No. = 0)	−0.444	0.256	0.083
No. of neg SLN = >1 (vs. No. = 0)	−1.370	0.367	<0.001
No. of pos SLN = >1 (vs. No. = 1)	0.477	0.245	0.052

Tumor size pathological tumor size in centimeters; *TIC/FS* results of touch imprint cytology (TIC) or frozen section (FS), *US axilla* results of preoperative US examination of axillary lymph nodes, *LVI* lymphovascular invasion, *No. of neg SLN* number of negative SLN, *No. of pos SLN* number of positive SLN

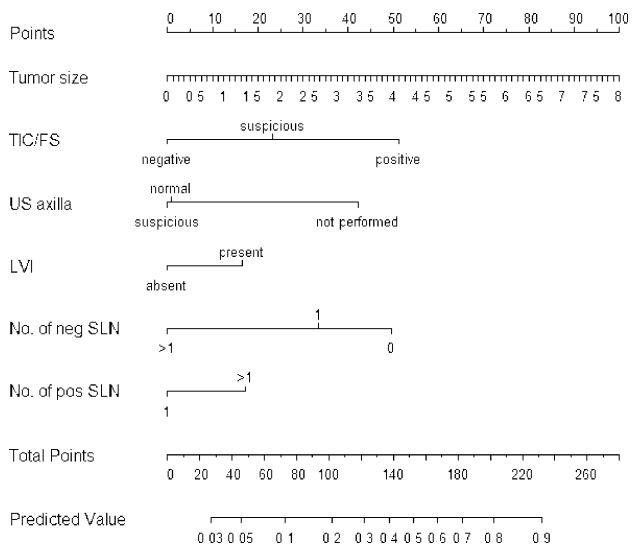

Fig. 5 The third nomogram—suitable for institutions where intraoperative examination of SLNs is standardly performed. *Rows* 2 through 7 represent variables. Vertical line should be made between each variable and the *uppermost row* (Points). In this way, the effect of each variable is determined by a defined number of points, which should be summed and located in *row* 8 (Total Points). Vertical line should be made between the *row* 8 and 9 (Predicted Value) to get the predicted probability of non-SLN metastasis. Tumor size—pathological tumor size in centimeters. TIC/FS—results of touch imprint cytology (TIC) or frozen section (FS); US axilla—results of preoperative US examination of axillary lymph nodes; LVI—lymphovascular invasion; No. of neg SLN—number of negative SLN: >1—more than 1 negative SLN, 1—one negative SLN, 0—no negative SLN; No. of pos SLN—number of positive SLN: 1—one positive SLN, >1 more than one positive SLN

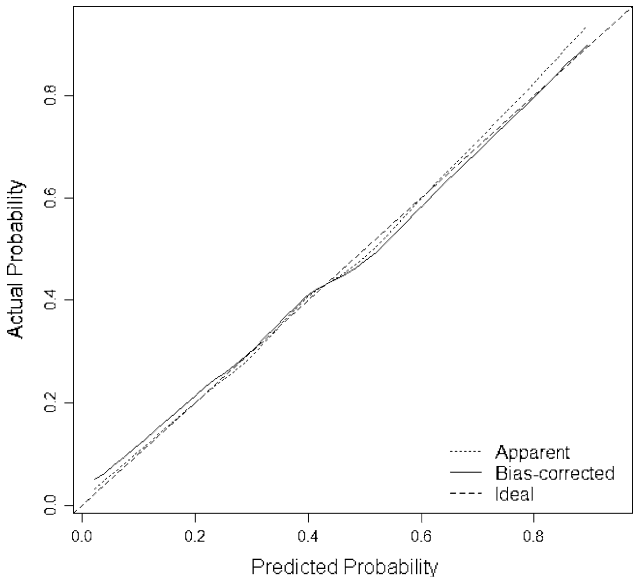

Fig. 6 Calibration plot for the third nomogram—the actual versus the predicted probabilites. The *dashed line* presents the line of equality, the *dotted line* depicts the observed situation on our sample and the *solid line* presents the bias-corrected line using the bootstrap validation procedure

Fig. 6. The mean absolute error equals to 0.014. The average area under the ROC was 0.79.

36 patients have less than 10% probability of having non-SLN metastases according to all three nomograms. None of them have non-SLN macrometastases and 2 of them have micrometastases in one non-SLN.

Discussion

The SLN biopsy has been proven to reliably identify lymph node metastases in breast cancer patients [2]. About 50% of patients with metastasis in SLN have additional metastases in non-SLNs [3]. Therefore, standard treatment in patients with metastatic SLN remains cALND or radiotherapy of the axilla [19]. However, not all patients with metastatic SLN have an equal possibility for non-SLN metastases. For example, is it necessary to further treat the axilla in patients with micrometastatic SLN, small tumors (<1.5 cm), more than two negative SLNs and preoperatively normal US examination of axillary lymph nodes? Furthermore, there is increasing number of older SLN-positive patients with many comorbidities or patients that are extremely unwilling to undergo further treatment of the axilla. A tool for predicting non-SLN metastases would be of great value in such cases for patients and clinicians.

Van Zee et al. from MSKCC created a nomogram for predicting non-SLN metastases in SLN-positive breast cancer patients. The authors concluded that the nomogram easily and accurately calculates the likelihood of having additional, non-SLN metastases for an individual patient [10]. However, many authors who validated the nomogram found several pitfalls, as for example, inclusion of the method of detection of SLN metastasis, which varies considerably among institutions. Furthermore, we found that the nomogram performed poorly when patients were grouped according to the information on the preoperative US examination of axillary lymph nodes. Namely, the nomogram overestimated the probability of non-SLN metastases in patients with preoperatively US uninvolved or US suspicious, but fine needle aspiration biopsy (FNAB) negative axillary lymph nodes. On the other hand, the nomogram underestimated the probability of non-SLN metastases in patients with preoperatively unperformed US of axillary lymph nodes [12]. This is not surprising, since US in combination with US-guided FNAB preoperatively detects metastases in axillary lymph nodes in 13% of SLN candidates at our institution [14]. The remaining patients with US negative axilla represent a distinct subgroup of patients with lower total axillary tumor burden and lower probability of non-SLN metastases when SLN is affected by cancer [14]. Based on these data, we created three new nomograms that also include the information on the preoperative US examination of axillary lymph nodes, which turned out as one of the most powerful variables. Surprisingly, the likelihood of non-SLN metastases is almost the same in patients with suspicious (but FNAB negative) as compared to those with normal US examination of axillary lymph nodes. However, patients with suspicious (but FNAB negative) US represent what is left of the entire US suspicious group after the patients with FNAB-positive result were already selected. Therefore, patients with suspicious (but FNAB negative) US have small tumor burden in axillary lymph nodes (ie, to small to be detected with US-guided FNAB), which explains our results.

The nomograms were created for different institutions, depending on the use of the intraoperative examination of SLNs. They have been developed based on the results of TIC as a method of intraoperative examination of SLNs. Thus, one might argue that our nomograms are not applicable for institutions, where frozen section is used instead of TIC. However, studies directly comparing frozen section with TIC showed that sensitivities of both methods are comparable [20, 21]. Furthermore, Lambert LA et al. who validated MSKCC nomogram (which uses frozen section), showed that TIC seems to be an acceptable substitute for frozen section as a nomogram variable [22]. We, therefore, believe that vice versa—substitution of frozen section for TIC—is also an acceptable option for our nomograms.

The first nomogram was created for our institution, where intraoperative examination of SLNs is performed only in selected patients; the second nomogram is suitable

for institutions where intraoperative examination of SLNs is not performed and the third one where it is standardly performed. At our institution, intraoperative examination of SLNs is not routinely performed in patients in whom the positive result is less likely (patients with non-palpable tumors). As a result, the decision of performing or not performing the intraoperative examination of SLNs carries additional information. For this reason, we cannot simply use the second nomogram, when intraoperative examination of SLNs is not performed and the third one, when it is performed. Instead, the first nomogram should be used, which considers the information on intraoperative examination of SLNs, when it was performed and the information on SLN metastasis size, when it was not performed. Our opinion is that the first nomogram could also be used in other institutions with similar policy regarding the use of intraoperative examination of SLNs.

The SLN metastasis size, which is known to be strongly associated with non-SLN metastases [23–27], was statistically significant only when the results of intraoperative examination of SLNs were not available (the first model in patients in whom intraoperative examination of SLNs was not performed and the second model). It is known that TIC is less likely positive, when tumor burden in SLNs is small and is thus a surrogate of SLN metastasis size [17, 28]. In addition, patients with only clinically uninvolved axillary lymph nodes have larger tumor burden in SLNs than those with ultrasonically uninvolved axillary lymph nodes [14]. Information on US examination of axillary lymph nodes is thus another surrogate of SLN metastasis size. It is, therefore, not surprising that SLN metastasis size was not statistically significant, when both surrogates of SLN metastasis size were already included in the model.

The validation results of our nomograms as defined by the bootstrap corrected area under the ROC curve seem promising (first nomogram 0.77, second nomogram 0.75 and third nomogram 0.79). The calibration curves showed that they are accurate through the entire range of probabilities, and the mean absolute calibration error is lower compared to other prediction tools [11]. We identified 12–16% of patients with the probability of having non-SLN metastases of less than 10% and found actual presence of non-SLN metastases in the expected range 10 (2 micrometastases)/80 (12.5%), 6 (2 micrometastases)/64 (9.4%) and 8 (2 micrometastases)/75 (10.7%) for the first, second and the third model, respectively. Interestingly, none of them have macrometastatic disease in non-SLNs if the probability was less than 10% according to all three nomograms. Many of the low risk patients did not undergo cALND and were thus not included in the study. Therefore, the proportion of patients with the probability of having non-SLN metastases of less than 10% according to our nomogram is expected to be higher than calculated in this study. Identifying those patients is important since most surgeons would omit the cALND when the probability of non-SLN metastases is below 10% [29]. Our opinion is that the risk of clinically evident axillary disease is very low in those patients. Namely, it is known that the false negative rate for SLN biopsy is between 5 and 10% [3, 30, 31]. However, the axillary recurrence rate in patients with a negative SLN biopsy and no further treatment of the axilla is far lower. A meta-analysis of 14 studies ($n = 3802$) reporting for axillary recurrence after negative SLN and no further treatment of the axilla showed a median axillary recurrence rate of 0.3%. The median follow-up in those studies was 47 months [31]. Thus, considering SLN false negative rate of 5–10%, only 3–6% of patients with residual disease in the axilla will have axillary recurrence after 47 months. If we decide not to further treat the axilla when the probability of non-SLN metastases according to the nomogram is 10% or less, about 100 out of 1,000 such patients will have residual disease in the axilla. Taking into account data on axillary recurrence after negative SLN, we can expect clinical manifestations in only 3–6 (0.3–0.6%) of those patients. Furthermore, six series ($n = 583$) of selected SLN-positive patients who did not undergo cALND reported similar axillary recurrence (0.5% at a median follow up of 31 months) [32–37]. These rates seem acceptably low and it is very unlikely that they would ever reach 10%, the level at which local recurrence have a detectable impact on survival according to the latest Early Breast Cancer Trialists Collaborative Group overview [38]. Therefore, we believe that in patients with the possibility of having non-SLNs metastases of 10% or less omission of the cALND is a reasonable option. However, other factors such as patient's age and comorbidities, effectiveness of adjuvant therapy, delay in receiving adjuvant chemotherapy if cALND is performed and nonetheless patient's preferences should be considered besides the nomogram result and arbitrary defined cutoff value at which cALND might be omitted.

In conclusion, three nomograms for predicting the likelihood of non-SLN metastases, differing in the inclusion of the results of intraoperative examination of SLNs, were created at the Institute of Oncology Ljubljana. The nomograms include the information on the preoperative US examination of the axilla, which turned out as a powerful independent variable. The validation results for all three nomograms seem promising. Omission of cALND might be considered in patients with the probability of having non-SLN metastases of 10% or less, but further validations elsewhere are needed before the widespread use of the nomograms. Also, the nomogram results should be carefully discussed with the patient and other factors considered before final decision regarding further treatment of the axilla is made.

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