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Predicting Non-Sentinel Lymph Node Status After Positive Sentinel Biopsy in Breast Cancer: What Model Performs the Best in a Czech Population?

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Abstract Several models have previously been proposed to predict the probability of non-sentinel lymph node (NSLN) metastases after a positive sentinel lymph node (SLN) biopsy in breast cancer. The aim of this study was to assess the accuracy of two previously published nomograms (MSKCC, Stanford) and to develop an alternative model with the best predictive accuracy in a Czech population. In the basic population of 330 SLN-positive patients from the Czech Republic, the accuracy of the MSKCC and the Stanford nomograms was tested by the area under the receiver operating characteristics curve (AUC). A new model (MOU nomogram) was proposed according to the results of multivariate analysis of relevant clinicopathologic variables. The new model was validated in an independent test population from Hungary (383 patients). In the basic population, six of 27 patients with isolated tumor cells (ITC) in the SLN harbored additional NSLN metastases. The AUCs of the MSKCC and Stanford nomograms were 0.68 and 0.66, respectively; for the MOU nomogram it reached 0.76. In the test population, the AUC of the MOU nomogram was similar to that of the basic population (0.74). The presence of only ITC in SLN does not preclude further nodal involvement. Additional variables are beneficial when considering the probability of NSLN metastases. In the basic population, the previously published nomograms (MSKCC and Stanford) showed only limited accuracy. The developed MOU nomogram proved more suitable for the basic population, such as for another independent population from a mid-European country.

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Introduction

Metastatic involvement of the sentinel lymph node (SLN) in breast cancer implies the possibility of additional metastases in non-sentinel (NSLN) lymph nodes. Thus, positive axillary SLN has been a traditional indication for axillary lymph node dissection (ALND). This surgical procedure is inconvenient for the patient and may be associated with late complications ranging from common mild sensory dysfunctions to severe disabling symptoms such as lymphoedema. One- to two-thirds of SLN-positive women have NSLNs that are free of cancer and these patients would not benefit from further axillary surgery. It seems reasonable, therefore, to omit ALND in women who are expected to have a very low risk of additional NSLN metastases. Such practice has been previously reported [1, 2] and shows promising results. However, a simple method to assess the probability of NSLN involvement and to identify patients where ALND may be unnecessary is lacking.

Several models have been proposed to predict the status of the NSLNs in patients with positive sentinel lymph node biopsy (SLNB). They are all based on clinicopathologic variables that refer to the primary tumor and the SLN. The complexity of the models ranges from simple prediction rules and scoring systems to nomograms, which are generally considered the most refined tools for such prediction. The most widely studied prediction tool is the nomogram using eight variables developed at the Memorial Sloan-Kettering Cancer Center (MSKCC) in 2003 [3]. In the original MSKCC populations (the training set and the test set), the area under the receiver operating characteristics (ROC) curve (AUC) reached 0.76 and 0.77, respectively. The model was subsequently validated in different groups of patients. In some series it showed excellent accuracy (AUC > 0.8) [4, 5] or good accuracy (AUC=0.7–0.8) [4, 6–9]; however, some studies did not confirm such encouraging results [10–15]. A substantial drawback of the MSKCC nomogram is the use of the method of metastasis detection as one of the variables. As the histopathological processing is not standardized and varies from one institution to another, the model may sometimes be unusable. Its lower applicability led several investigators [4, 13] to use modifications that differed only slightly from the original, whereas, in 2008, authors from Stanford University proposed a considerably different model [16] (hereafter referred to as the Stanford nomogram/model). This model uses only three variables rather than eight, and one of these is the size of the SLN metastasis. The metastasis size can be considered a more standardized substitute for the method of detection, as smaller metastases require more detailed analysis of the SLN, whereas larger metastases are generally discovered during intraoperative assessment of a single section.

So far, none of the predictive tools has been established for general use. The recommendation of the American Society of Clinical Oncology (ASCO) Expert Panel is to perform routine ALND for patients with macrometastases (>2 mm) and micrometastases (>0.2 mm and ≤2 mm) found in the SLN. [17] As the SLN with only clusters of isolated tumor cells (ITC) of <0.2 mm is classified as pN0 [18], it can be inferred that patients with only ITC in the SLN are not recommended an ALND. This recommendation actually simplifies the need for an ALND to a single variable—the size of the largest tumor focus in the SLN, with a threshold of 0.2 mm. There are, however, data suggesting that even ITC in the SLN may be associated with a considerable risk of NSLN involvement. [19] On the other hand, many patients with larger metastases (micro- and macrometastases) have NSLNs that are free of cancer. Some surgeons reflect these facts and use multivariate predictive models in their clinical practice to estimate the risk of NSLN metastases as a basis for an individual decision about ALND.

The primary aim of this study was to assess the performance of two previously mentioned models (MSKCC, Stanford) in the patient population of the Masaryk Memorial Cancer Institute, Brno, Czech Republic (hereafter referred to as MOU) and to develop an alternative model of the best overall predictive accuracy in this population.

Methods

Study Populations and Data Collection

There were two independent patient populations involved in the study: the "basic" MOU population and the validation "test" population. The basic population was formed by all SLN-positive breast cancer patients who underwent SLNB in MOU in the years 2001–2007 and fulfilled the following criteria: concurrent partial or total mastectomy for primary invasive breast cancer, no prior neoadjuvant therapy, a minimum of one tumor-involved SLN in the ipsilateral axilla, and ALND completed within several weeks after the SLNB (330 patients). All patients were preoperatively classified as cN0 [18] by clinical examination and ultrasonography. SLN identification was performed using a technique combining blue dye and radioisotope. Surgical specimens were fixed in formalin and embedded in paraffin. Sentinel nodes were cut into halves and one hematoxylin and eosin (H&E) slide from each half was viewed. If this examination was negative, serial sections were prepared and examined by H&E

staining and cytokeratin immunohistochemistry (IHC). Clinical data collected prospectively in a SLN database included: age, primary tumor stage (pT) and tumor type. Other parameters added retrospectively from the histopathological reports included: the pathological size of the primary tumor in millimeters, the number of positive SLNs, the number of negative SLNs, the number of NSLNs, the number of positive NSLNs, tumor grade according to the Nottingham grading system, nuclear grade, lymphovascular invasion, histopathological multifocality of the primary tumor, the method of detection of the SLN metastasis, the size of the largest SLN metastasis in millimeters, extranodal extension, mitotic index, estrogen receptor status, progesterone receptor status, and HER-2/neu status. In some patients, the last three variables were not available. All SLN metastases were re-classified according to the sixth edition of the TNM Staging System [18] as isolated tumor cells / micrometastasis / macrometastasis. The study protocol was approved by the local ethics committee of MOU.

The validation data were derived from 383 SLN-positive breast cancer patients from the Bács-Kiskun County Teaching Hospital, Kecskemét, Hungary, operated on between 1997 and 2008. At this institution, SLNB was performed with either a blue-dye-guided method or a combined dye- and radio-guided method as described earlier. [20] SLNs were subjected to complete step sectioning and cytokeratin IHC as reported earlier. [21] An ALND was performed either on a routine basis (n=100), or after the finding of a positive SLN. Only SLN-positive patients with an ALND yielding at least six NSLNs were considered, and patients with neoadjuvant therapies or unknown tumor sizes were excluded. Only variables that were relevant for the developed predictive model were collected from the test population.

Although analyzed separately as a group, patients with only ITC in the SLN were considered SLN-positive for the purpose of the study.

Data Analysis

The basic characteristics of patients and their parameters were summarized using frequency tables and descriptive statistics (median, average, minimum, and maximum). Association of the considered clinicopathologic variables with NSLN status was assessed by univariate analysis using the Fisher exact test or the chi-square test for categorical data. For calculation of the probability of additional NSLN metastases according to the MSKCC and Stanford nomograms, the web calculators available on the Internet [22, 23] were used. An alternative nomogram was developed for the basic study population by means of multivariate logistic regression analysis. Possible multicollinearity between considered variables was verified using the variance inflation factor. The discriminative power of all three nomograms was measured by using the area under the ROC curve, and its 95% confidence intervals (CI) calculated according to Hanley and McNeil [24]. In addition, the performance of the three above-mentioned nomograms was studied in the low-probability area, i.e. on patients with low risk of NSLN metastases. The groups of patients with maximum 5%, 10%, and 15% values of predicted risk were chosen, and the number of actual NSLN-positive cases in each respective group was listed. Statistical analyses were performed with the R system for statistical computing, and Statistica for Windows 8.0 (StatSoft, Inc.).

Results

Characteristics of the Basic Population and Association of Clinicopathologic Variables with the Incidence of NSLN Metastases

The median patient age was 57 years (range 22–84), median histopathological size of the primary invasive carcinoma was 1.7 cm (range 0.3–6.5), median number of harvested SLNs was 1 (range 1–14, mean 1.7), and median total number of lymph nodes removed at the completion of ALND was 13 (range 5–32, mean 13.6). Additional NSLN metastases were found on final pathology in 99 cases. Clinicopathologic variables and their association with the probability of NSLN metastases on univariate analysis are listed in Table 1. Variables that showed a significant association with the incidence of NSLN metastases in the multivariate logistic regression analysis included: size of SLN metastasis (P<0.001), primary tumor size (P=0.023), and multifocality (P=0.042).

Prediction of NSLN Involvement in the Basic Population with Existing Nomograms and the Development of the MOU Nomogram

The AUC for the MSKCC nomogram in the basic population was 0.68 (95% CI: 0.61–0.75). The AUC for the Stanford nomogram in the basic population was 0.66 (95% CI: 0.59–0.73).

To develop a model of the best overall predictive accuracy in the basic population, all available clinicopathologic variables were considered. Some were used even if they were not individually significant, yet all of them contributed to the best performance of the model. The final predictive model comprised seven variables: the size of the largest SLN metastasis, multifocality, primary tumor size, extranodal extension, the proportion of positive SLNs, lymphovascular invasion, and tumor type. Based on this model, a nomogram (MOU nomogram) for

Table 1 Clinicopathologic variables and their association with the incidence of additional NSLN metastases on univariate analysis in the basic population; only variables used in the MOU nomogram are listed

Variable	Category	Number of NSLN-positive cases/number of all cases in the category	Significance (*P* value)
Size of SLN metastasis			<0.001
	ITC	6/27	
	Micrometastasis	13/117	
	Macrometastasis	80/186	
Primary tumor size			<0.001
	≤2 cm	57/231	
	>2 cm	42/99	
Extranodal extension			<0.001
	No	68/266	
	Yes	31/64	
Multifocality			0.034
	No	79/285	
	Yes	20/45	
Proportion of the positive SLNs (from all harvested SLNs) (%)			0.041
	<50	4/25	
	50	18/80	
	>50	77/225	
Lymphovascular invasion			0.087
	No	51/195	
	Yes	48/135	
Tumor type			0.174
	Ductal	65/234	
	Lobular	19/45	
	Mixed	13/39	
	Other	2/12	

predicting positive NSLNs was developed and is summarized in Box 1.

***Box 1**. MOU nomogram for prediction of additional NSLN metastases*

To predict the likelihood of positive NSLN add up the corresponding numbers:

- size of SLN metastasis (mm)[a] × 3.33
- +15.2 if multifocality is present
- +12.9 if primary tumor size is >2 cm
- +8.8 if extranodal extension is present
- +8.5 if the number of positive SLNs is equal to number of negative SLNs
- +18.3 if the number of positive SLNs is greater than the number of negative SLNs
- +4.2 if lymphovascular invasion is present
- +1.9 if there is mixed histology
- +5.8 if there is lobular histology
- = total score

[a]*If only ITC are present, the size of SLN metastasis is considered zero*

The likelihood of a minimum one positive NSLN as a function of the total score is shown in Box 2.

Box 2. *The likelihood of additional NSLN metastases as a function of total score*

- Total score = 0 → likelihood = 0.054
- Total score = 14 → likelihood = 0.10
- Total score = 23 → likelihood = 0.15
- Total score = 30 → likelihood = 0.20
- Total score = 36 → likelihood = 0.25
- Total score = 58 → likelihood = 0.50
- Total score = 80 → likelihood = 0.75
- Total score = 102 → likelihood = 0.9
- Total score = 117 → likelihood = 0.95

The AUC of the proposed model in the basic population reached 0.76 (95 % CI: 0.70–0.82). The ROCs of all three models (MSKCC nomogram, Stanford nomogram, MOU nomogram) are shown in Fig. 1. The predictive accuracy of the nomograms according to ≤5%, ≤10%, and ≤15% predicted probability levels is shown in Table 2.

Validation of the MOU Nomogram and the Stanford Nomogram in the Test Population

In the test population, the median histopathologic size of the primary invasive carcinoma was 1.9 cm (range 0.1–16.0), and median number of harvested SLNs was 1 (range 1–7, mean 1.7). Additional NSLN metastases were found on final pathology in 158 cases. The association of relevant variables with the incidence of NSLN metastases on univariate analysis is showed in Table 3.

The AUC for the MSKCC nomogram could not be validated in the test population since some of the requisite variables were not available (method of metastasis detection, nuclear grade). The AUC for the Stanford nomogram in the test population was 0.66 (95% CI: 0.60–0.73). The AUC for the MOU nomogram in the test population was 0.74 (95% CI: 0.68–0.80). The ROCs of the two models (Stanford nomogram, MOU nomogram) are shown in Fig. 2.

The predictive accuracy of the nomograms according to ≤5%, ≤10%, and ≤15% predicted probability levels in the test population is shown in Table 2.

Discussion

According to the ASCO guidelines published in 2005, completion ALND is not recommended if only ITC are found in the SLN. The probability of additional NSLN metastases in these ITC cases has been regarded as low. [17, 25] However, more recent studies have shown that the distinction between ITC and micrometastasis is often difficult and of limited prognostic significance. [26, 27] Depending on the interpretation of the TNM definition, the incidence of NSLN metastases in patients with SLN ITC may even exceed 10%. [28] In the basic population of the

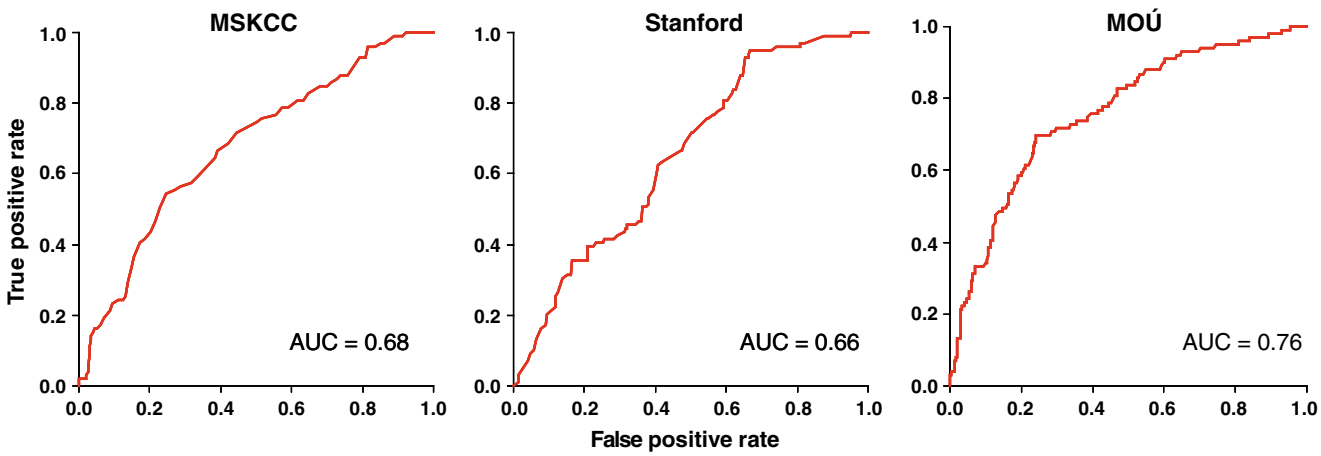

Fig. 1 ROC curves constructed for the MSKCC nomogram, the Stanford nomogram, and the MOU nomogram in the basic population

Table 2 Performance of the nomograms according to ≤5%, ≤10%, and ≤15% predicted probability levels; listed is the number of NSLN-positive cases / number of all cases in the category

	Basic population			Test population	
	MSKCC	Stanford	MOU	Stanford	MOU
Probability ≤5%	0/2	0/0	0/0	0/4	0/0
Probability ≤10%	1/21	3/47	2/21	8/44	2/23
Probability ≤15%	3/37	6/84	7/77	14/67	8/62

present study, 27 patients with ITC underwent ALND, and six of these had positive NSLN. These data indicate that the absence of SLN metastasis greater than 0.2 mm may fail as a sole predictor for SLN-only disease. Thus, additional clinicopathologic variables should be taken into account when considering the omission of ALND.

The applicability of any particular predictive model depends on which variables are available at the time of the decision about ALND. In this study, clinicopathologic characteristics based on the final histopathology were used since intraoperative biopsy was not performed in most patients from the basic population. If the decision regarding whether or not to proceed to completion ALND were taken intraoperatively, the options for predicting the probability of NSLN metastases would be restricted.

In the basic population, both the previously published nomograms (MSKCC, Stanford) showed comparable overall accuracy (AUC=0.68 and 0.66, respectively), which, however, proved substantially worse than the accuracy in their original populations. We proposed another nomogram that better fits MOU patients. Its AUC reached 0.76, which is similar to the performance of the MSKCC nomogram in the MSKCC population.

Nomograms intended for prediction of overall probability are tailored to the populations they were derived from and proposed for; thus their potential for general use should not be overestimated. Any model showing excellent accuracy in some populations may have only limited predictive value in others. Therefore, clinical discussion about the probability of NSLN metastasis and possible omission of ALND in a SLN-positive patient should be supported by knowledge of the actual performance of the respective model in the appropriate patient population.

Although the characteristics of the basic and test populations of this study differ in some respects, the performance of the MOU nomogram in these two populations was very similar (ROC=0.76 vs. 0.74). It confirmed the anticipation that the validity of the proposed MOU nomogram is not limited only to the basic population of this study. It may be useful in other populations as well.

Both previously published nomograms assessed in the present work have their limitations. The overall applicability of the MSKCC nomogram is somewhat limited due to the use of a rather MSKCC-specific parameter: the method of metastasis detection, which is obviously dependent on the pathology protocol used for investigation of the SLNs. Although the whole of the test population could not be evaluated for the predictive accuracy of the MSKCC nomogram due to lack of data, part of it was previously used for the validation of this nomogram [10], with an AUC of 0.73 and an actual NSLN involvement rate of 14% in the lowest risk decile (the expected rate was 0–8%). [29] The Stanford nomogram uses only three variables: tumor size, metastasis size, and lymphovascular invasion. All of these should be available in common clinical practice. Nevertheless, should any of these three variables be of poor individual predictive value in a population, a substantially lower accuracy of the Stanford nomogram would be expected. In the basic and the test populations of this study, lymphovascular invasion was not significantly associated with the incidence of NSLN metastases, which could be the main reason for the lower accuracy of the Stanford nomogram in both populations. Models using more parameters may keep their accuracy even if some of the individual factors would be of no predictive value alone. The proposed MOU nomogram uses seven clinicopathologic variables, all of which should be reported on a routine basis; thus the model should be relatively reliable and applicable in common clinical practice.

A possible drawback of nomograms may result from the aspiration to achieve the best overall predictive accuracy as assessed by the AUC. In clinical practice the aim is to omit ALND and prevent its potential morbidity in minimum-risk women. Therefore, predictive tools are expected to perform well in the low-probability areas where even models that are considered to be accurate overall on the basis of the AUC value can fail. The low probability levels (≤5%, ≤10%, and ≤15%) listed in Table 2 imply this assumption. The probability levels investigated are not proposed as possible cut-offs for omission of ALND but are intended to show concrete numbers of patients in the "low-risk" areas and their actual rates of NSLN metastases. In clinical practice, the decision about ALND should be individualized on the basis of all possible pros and cons of the completion surgery. The probability of NSLN metastasis constitutes an important component of such decision making.

Based on the results of this study, we have confirmed that the size of the largest tumor focus in the SLN alone may not be sufficient as a predictor of minimum risk of further metastases. In order to assess the risk of NSLN

Table 3 Clinicopathologic variables and their association with the incidence of additional NSLN metastases on univariate analysis in the test population; only variables used in the MOU nomogram are listed

Variable	Category	Number of NSLN-positive cases/ number of all cases in the category	Significance (*P* value)
Size of SLN metastasis			<0.001
	ITC	0/21	
	Micrometastasis	18/83	
	Macrometastasis	140/279	
Primary tumor size			0.002
	≤2 cm	74/215	
	>2 cm	84/168	
Extranodal extension			<0.001
	No	71/230	
	Yes	87/153	
Multifocality			0.705
	No	144/352	
	Yes	14/31	
Proportion of the positive SLNs (from all harvested SLNs) (%)			0.005
	<50	6/28	
	50	25/80	
	>50	127/275	
Lymphovascular invasion			0.217
	No	103/264	
	Yes	55/119	
Tumor type			0.999
	Ductal or other	141/342	
	Lobular	5/12	
	Mixed	12/29	

involvement more exactly, additional clinicopathologic variables should be taken into account. In the basic population, the previously published nomograms (MSKCC and Stanford) showed only limited accuracy; the developed model fits MOU patients better. In addition, the MOU nomogram was shown to have good accuracy on an independent dataset of patients from another mid-European country, which implies its possible usefulness for further populations. The proposed MOU nomogram should enrich the family of models available to date.

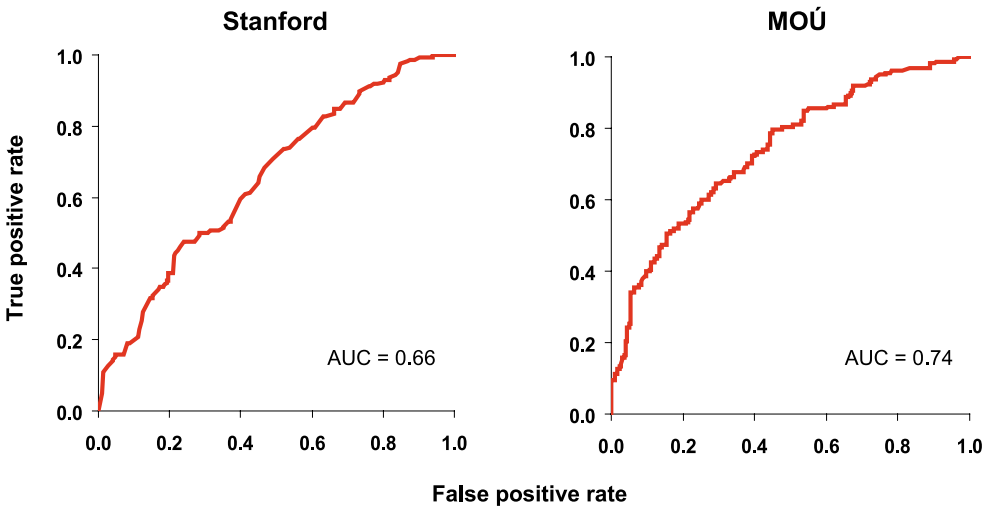

Fig. 2 ROC curves constructed for the Stanford nomogram, and the MOU nomogram in the test population

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