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ORIGINAL ARTICLE – BREAST ONCOLOGY

Good Prediction of the Likelihood for Sentinel Lymph Node Metastasis by Using the MSKCC Nomogram in a German Breast Cancer Population

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ABSTRACT

Background. The sentinel lymph node (SLN) procedure could be omitted in cases of accurate prediction of very high or very low probability of SLN metastasis in early breast cancer patients. We evaluated a breast cancer nomogram, an online tool provided by the Memorial Sloan–Kettering Cancer Center (MSKCC), that predicts the likelihood of a positive lymph node.

Methods. Data from 545 patients with successful SLN biopsy were collected, including 118 patients with a positive sentinel lymph node. Histopathological assessment of the SLN included hematoxylin and eosin staining and/or immunohistochemistry. Predictive accuracy was assessed by calculating the area under the receiver–operator characteristic (ROC) curve.

Results. In our collective tumor size, histology, lymphovascular infiltration, multifocality, Her-2-neu positivity, and nuclear grade correlated with the probability of SLN metastasis. The ROC of the validated nomogram in our breast cancer population revealed a value of 0.78 compared with 0.75 in the original publication.

Conclusion. The MSKCC nomogram is a useful tool in our population of breast cancer patients. However, variations in the pathological assessment of the SLN between breast cancer centers worldwide might be an impediment to widespread application of the nomogram.

Many studies have shown that sentinel lymph node (SLN) biopsy accurately detects metastases to axillary lymph nodes (ALN) in breast cancer patients.[1–3] In patients with negative SLN, axillary lymph node dissection (ALND) can safely be avoided, thereby reducing postoperative morbidity and costs of longer hospital stay.[4,5]

However, side-effects of SLN biopsy without consecutive ALND are not negligible: In a prospective multicenter comparison of intermediate morbidity and mortality in 635 patients receiving either SLN biopsy alone or with completion by ALND, 10.9% of the patients within the group of SLN biopsy alone ($n = 431$) complained about numbness, 8.1% about arm/shoulder pain, and 7.7% about breast pain.[6] In the preoperative phase with the patient, these morbidity numbers need to be reflected, especially in cases of patients with a very low probability of a positive SLN.

Reviewing the data of previous studies on the SLN technique, the likelihood of having cancer cells spread to the SLN depends on: tumor size, lymphovascular invasion, patient age, histological type, multifocality, Her-2/neu status, and tumor grade.[7–14] Although these factors for lymph node metastasis seem to be well established, it has to be noted that most of the data of these studies was collected retrospectively without additional validation. Furthermore, the magnitude of each prognostic factor's influence varies and accurate information on an individual's probability of having a positive SLN can only be gained by the combination of these factors.

Bevilacqua et al. from the Memorial Sloan–Kettering Cancer Center (MSKCC) developed a model that predicts the presence of SLN metastasis. The nomogram is based on retrospective data of the MSKCC (a multivariate analysis with nine variables associated with SLN metastasis: age, tumor size, type, location, lymphovascular invasion, multifocality, nuclear grade, and estrogen and progesterone receptor status), which was prospectively validated on 1,545 sequential SLN biopsies. It achieved a receiver–operating characteristic (ROC) curve of 0.75, indicating a rather good prediction and discrimination. The authors

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conclude that, since all nine variables included in the nomogram can be assessed before admission to the SLN procedure, each woman treated at the MSKCC can now "estimate their individual likelihood of having SLN metastasis" before the operation.[15]

Although this MSKCC SLN nomogram is presumably clinically less important than the previously MSKCC non-SLN (NSLN)-nomogram, the fact that this tool is worldwide freely accessible to patients and physicians on the MSKCC website (http://www.mskcc.org/mskcc/html/15938.cfm) certainly increases its significance.[16] The authors mention, and we gained comparable impressions from our local German breast cancer population, the increased use of Internet sites as a source of information about the disease and its prognosis. Since the prognostic value of the axillary lymph node status is generally known to the well-informed patient, many women might use the web tool for further information about the probability of having a positive SLN. In some cases, the thereby informed European patient might reject the proposed SLN procedure due to very low or very high probability of SLN metastasis based on data in a US breast cancer population.

In order to estimate the future impact of the MSKCC nomogram on the preoperative informed consent with patients in our Breast Cancer Center we performed a validation study of this online tool for the prediction of the likelihood of SLN metastasis.

MATERIALS AND METHODS

The research protocol was approved by the local oncological review board of the Medical School of Freiburg, Germany. Data for this study was collected from 577 patients who underwent breast-conserving surgery or mastectomy with SLN biopsy. The inclusion criteria for SLN biopsy were as follows: histologically proven breast cancer, negative axillary lymph nodes on palpation and sonography, and informed consent for sentinel lymph node procedure. Exclusion criteria were: neoadjuvant chemotherapy, failed SLN mapping, inflammatory breast cancer, ductal carcinoma in situ (DCIS), no informed consent, clinically suspicious axillary lymph nodes, pregnancy or lactation, allergies against nanocol or blue dye, and previous operation of the axilla. Thirty-two patients were excluded because of lacking follow-up-data or failed SLN detection.

For SLN mapping either radioisotope (97.5%) or blue dye (2.5%) technique was used. Both techniques have been described elsewhere in detail.[17,18] For radioisotope technique, ^{99m}Tc-nanocol was injected subcutaneously around the tumor and lymphoscintigraphy was performed 1 day prior to surgery. Intraoperatively, SLN were detected by using a handheld gamma probe. Any lymph node with radioactivity was regarded as SLN and sent for immediate intraoperative pathological evaluation by hematoxylin and eosin (H&E) frozen section.

The pathological assessment started with the transversal dissection of lymph nodes between 5 and 7 mm (lymph nodes >7 mm were sliced in 2–3-mm slices. Lymph nodes <5 mm were assessed as a whole). Intraoperative evaluation was stopped if a macrometastasis was detected. The frozen tissue was then fixed in formalin and embedded in paraffin blocks for multilevel histological assessment (250-μm levels). If at this point no metastasis was detected, the SLN was declared free of metastasis at intraoperative frozen section. For final pathological diagnosis immunohistochemistry staining was required. ALND was performed in any case of tumor detected intraoperatively or after final pathological workup. The remaining SLN material was further analyzed by hematoxylin and eosin (H&E) staining and immunohistochemistry (IHC). Also in cases of micrometastasis and tumor cell clusters a secondary ALND was indicated. The tumor stage was classified according to International Union against Cancer (UICC) classification. Hormone receptor and Her-2/neu status were determined by immunohistochemistry. A Her-2/neu score of +++ was classified as positive.

Data from all patients were entered into a database including each patient's personal data, data on surgery, tumor, SLN, NSLN, data on adjuvant treatment and date of recurrence, time of follow-up, and nomogram-specific data (see above).

One hundred eighteen patients (of 545 patients meeting the inclusion criteria of our study) were SLN positive. Of these, 98 patients underwent ALND with at least ten lymph nodes removed from the axilla. Standard of care by completion via ALND with at least ten nodes after positive SLN, however, was not performed in the remaining 20 patients, including some with micrometastasis and isolated tumor cells (ITC). These patients received radiation of the axilla. Four hundred twenty-seven patients were SLN negative. Of these, 125 underwent ALND during our initial training period, when the SLN technique was introduced at our institution.

Statistical analyses were conducted with SPSS12.1. For numeric data, values are expressed as mean and median values ± standard derivation (SD). Numeric data was analyzed with Student's *t*-test if normally distributed, and equality of variances are given. If not, the Mann–Whitney test was used for comparison of data. Categorical data was analyzed with the chi-squared test or with Fisher's exact test.

To measure the nomogram's discrimination, a receiver–operating characteristic (ROC) curve was constructed. ROC curves compare sensitivity versus specificity across a

range of values for the ability to predict the dichotomous outcome. Overall accuracy of the nomogram was expressed by the area under the ROC curve (AUC). The AUC under the ROC provides a useful parameter for comparing the nomogram's predicted probability with the actual outcome, thus measuring the accuracy.[19]

Further information on the methods of development and internal validation of the MSKCC nomogram are available on the above Internet site and the corresponding publication.[15]

RESULTS

Collective Assessment

The overall descriptive clinical and histopathological characteristics of patients with SLN biopsy ($n = 545$) are shown in Table 1. Adjuvant treatment of these patients included chemo- (52%), radio- (72%), and endocrine therapy (72%).

SLN Metastasis

Tumor size, histology, lymphovascular infiltration, multifocality, Her-2-neu positivity, and nuclear grade correlated with the probability of SLN metastasis (Table 2).

One hundred eighteen of the 545 patients (22%) had at least one positive SLN (characteristics in comparison with the collective of the MSKCC are shown in Table 1). One hundred seventy-eight positive SLN were obtained (mean 1.51 SLN per patient). Of the 118 SNL-positive patients, 16 (13.5%) had isolated tumor cells (ITC) in the SNL, whereas 60 (50.8%) and 28 (23.7%) had macro (>2 mm) and micrometastasis (≤2 mm), respectively. In 14 patients the size was not specified.

Data on Survival and Recurrence

Overall survival (OS) in the whole cohort ($n = 545$) during the mean follow-up time of 32.5 months was 97.6%, and disease-free survival (DFS) was 93.6%.

During the median follow-up time, within the group of SLN-negative patients receiving no ALND ($n = 302$), nine recurrences (3.0%) were observed: five local recurrences at the breast, one axillary recurrence, and three distant metastasis.

Among the 118 SLN-positive patients, 18 recurrences (15.2%) were observed: 4 local recurrences at the breast and 14 distant metastasis. Three patients with distant metastasis died within the follow-up time. No axillary local recurrence was observed in this group.

Among the patients receiving ALND after negative SLN ($n = 125$), eight recurrences occurred (6.4%) during follow-up time, including three local recurrences at the breast, two axillary recurrences, and three distant metastasis.

The MSKCC Nomogram in Our Collective

Clinical data collected for MSKCC nomogram included: age, tumor size, tumor type, lymphovascular invasion, tumor location, multifocality, and estrogen and progesterone receptor status. In comparison with the population of the original publication of the MSKCC nomogram our collective showed no major differences (Table 1).[15]

In order to assess the accuracy of the nomogram in our collective, actual probabilities were plotted against the calculated probabilities for each decile of the patients. The cutoff value for each decile was three patients. The trend line differed only slightly (Fig. 1). The calculated ROC value was 0.78 (Fig. 2).

Twenty-six patients (4.77%) of our collective were included in the group with the least probability of a positive SLN predicted by the nomogram (≤10 decile). One patient in this group was diagnosed with a micrometastasis (<2 mm) in the SLN in the final pathological assessment (false-negative rate 0.04).

DISCUSSION

Validations of worldwide free accessible online devices that predict an individual's clinical outcome are obligatory. To our knowledge, this is the first external validation of the MSKCC nomogram on the likelihood of SLN metastasis in early breast cancer.

The overall findings of this study support the predictive accuracy of the MSKCC nomogram in our cohort with a statistically significant ROC *c*-statistic value of 0.78. The *c*-statistic value is a measure of the overall discrimination of a model. Generally, a model that performs with ROC measurements of 0.7–0.8 is considered good, whereas values of 0.81–0.90 are considered excellent.[20]

Nomograms provide prognostic information based on the combination of variables that allow an individualized prediction of outcome. Within the last years, nomogram performances have been improved due to their validation in larger datasets and with longer follow-up periods. In daily clinical work, in many types of cancer, nomograms have become more popular because of their simplicity and easy graphical representation when it comes to considering treatment choices and assessments of risk.

In breast cancer, nomograms have been published for the prediction of the likelihood of non-SLN (NSLN) metastasis in early breast cancer patients. These

TABLE 1 Comparison of descriptive characteristics of the two validation groups for the SLN nomogram of the MSKCC, New York and UFK, Freiburg

Variable	UFK, Freiburg retrospective group ($n = 545$)		MSKCC, New York validation group ($n = 1{,}545$)	
	n	%	*n*	%
Age (years)				
Median (range)	58.7 (29–91)		56 (25–90)	
<40	27	4.9	191	11.7
41–69	427	78.3	1.066	69
≥70	91	17	298	19.3
Tumor size				
T1mic	8	1.5	51	3.3
T1a	45	8.3	199	12.9
T1b	77	14.1	362	23.4
T1c	250	45.8	624	40.4
T2 ≤ 3 cm	120	22	215	13.9
T2 > 3 cm	34	6.2	80	5.2
T3	9	1.6	14	0.9
Tumor location				
UOQ	251	46.1	879	56.9
LOQ	91	16.7	211	13.7
UIQ	106	19.4	264	17.1
LIQ	44	8.1	135	8.7
Central	43	7.9	NA	NA
Histologic grade				
I	64	11.7	97	6.3
II	332	60.9	375	24.3
III	146	26.8	810	52.4
Lobular	114	21	166	10.7
Lymphovascular invasion	115	21.1	340	22
Multifocality	165	28.6	390	25.2
Estrogen receptor positive	407	74.6	1,186	76.8
Progesterone receptor positive	362	66.4	858	55.5
HER-2-neu positive	208	38.1	NA	NA
SLN positive	118	21.6	579	37.5
Method of SLN metastasis detection				
IHC	16	3.5	57	3.7
Serial H&E	37	6.2	118	7.6
Routine H&E	–	–	75	4.8
Frozen section	65	11.9	329	21.3

IHC immunohistochemistry, *H&E* hematoxylin and eosin, *SLN* sentinel lymph node, *UOQ* upper outer quadrant, *UIQ* upper inner quadrant, *LOQ* lower outer quadrant, *LIQ* lower inner quadrant

nomograms were developed at US breast cancer centers (MSKCC, Massachusetts General Hospital, Stanford Hospital, Mayo Clinic) and have also been validated at different European institutions.[16,21–26] Interestingly, in contrast to US validations of the nomogram developed at MSKCC, the results in Europe are rather heterogenous, with ROC curves ranging from 0.58 to 0.72, raising the question of the comparability of SLN mapping procedures, pathological assessments of SLN, and tumor biologies in other than US breast cancer populations.[27,28]

With respect to SLN mapping procedures, our technique included radioisotope marking in 97.5% of cases, which is also the method of choice in the vast majority of publications on the SLN in breast cancer.

Concerning pathological assessment of SLN, considerable heterogeneity has been reported by Cserni et al., not

TABLE 2 Clinicopathologic correlation in patients with SLN metastasis

Variable	SLN negative	SLN positive	*P*-value
Number of patients	427	118	
Primary tumor size (mean in mm)	16.5	20.82	<0.001
Age (mean in years)	59	58	0.28
Histology			<0.001
Ductal	265 (62%)	79 (67%)	
Lobular	81 (19%)	35 (30%)	
Other	81 (19%)	4 (3%)	
Nuclear grade			0.015
I	59 (14%)	5 (4%)	
II	255 (60%)	77(65%)	
III	110 (26%)	36 (31%)	
Primary tumor location			0.079
UOQ	185 (44%)	66 (57%)	
UIQ	91 (22%)	15 (13%)	
LOQ	71 (17%)	20 (17%)	
LIQ	38 (9%)	6 (5%)	
Central	34 (8%)	9 (8%)	
ER positive	323 (76%)	90 (76%)	1.0
PR positive	289 (68%)	76 (64%)	0.509
Her-2/neu pos (score +++)	143 (34%)	52 (44%)	0.039
Lymphovascular invasion positive	58 (14%)	57 (48%)	<0.001
Multifocality	117 (27%)	48 (41%)	0.007

ER estrogen receptor, *PR* progesterone receptor, *UOQ* upper outer quadrant, *UIQ* upper inner quadrant, *LOQ* lower outer quadrant, *LIQ* lower inner quadrant

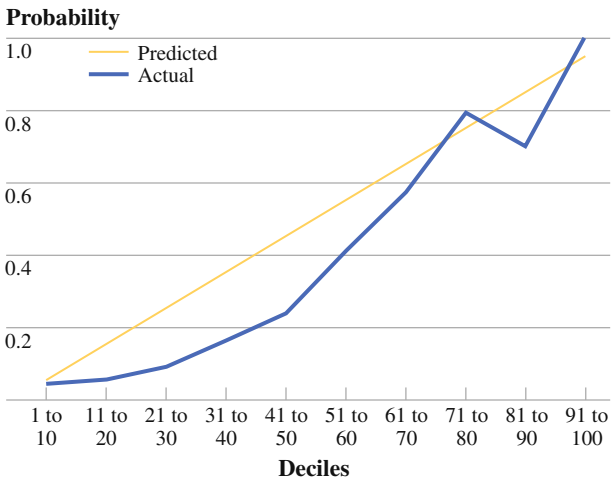

FIG. 1 Comparison between predicted and actual probability for SLN metastasis in the Freiburg collective ($n = 545$)

only between the USA and Europe, but also among European countries. These authors report the results of a survey of the European Working Group for Breast Screening

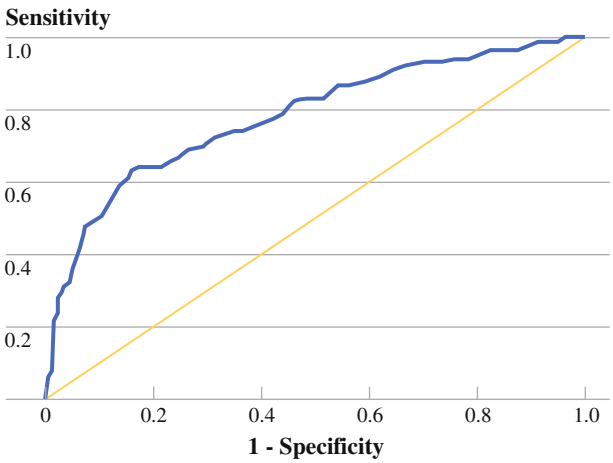

FIG. 2 Receiver–operating characteristic (ROC) curve calculation for the MSKCC nomogramm applied to the Freiburg collective ($n = 545$)

Pathology among 240 institutions routinely dealing with SLN evaluations in breast cancer. One hundred twenty-three different protocols relating to SLN assessment were found among the 240 laboratories. The number of levels per single SLN was heterogeneous and 12% of the institutions investigated only one level of the SLN.[29,30] Furthermore, the role of micrometastasis in the SLN (in our study defined as SLN positivity, $n = 28$) is still under debate. A comparison of the many studies on SLN and NSLN is seriously hampered by this obvious heterogeneity. Differences in tumor biology did not seem to limit the application of the nomogram in our collective. The collective of UFK Freiburg ($n = 545$) and the validation group MSKCC New York City ($n = 1{,}545$) are remarkably similar (Table 1).

In contrast to the validations of the MSKCC NSLN nomogram, which have shown a degradation as the model is transferred from US to European populations, we hereby report the usefulness of a US-population-based SLN nomogram in a German breast cancer population. As a consequence, we will now use the nomogram for patients with very low risk of SLN metastasis ($\leq$10 decile) after histopathological confirmation and clinical examination. We consider the MSKCC nomogram to be useful in this, albeit small, subgroup of patients.

The influence of the freely accessible, online-based SLN nomogram on the shared decision making is not negligible as patients and physicians increasingly go online to use information for decision support. Therefore, a critical assessment of this tool in Breast Cancer Centers is mandatory. Although our data is encouraging for broader use of the nomogram, we advise caution against its application as an alternative to SLN biopsy. To date, only the SLN technique has proven to have little morbidity in

combination with high accuracy for prediction of axillary status in early breast cancer patients. Therefore, the nomogram provides only a clinical accessory in the preoperative discussion between the clinician and the low-risk breast cancer patient.

We recommend the application of the European guidelines on SLN biopsy and refer to the German guidelines for achieving a more homogenous assessment of SLN.[31,32]

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