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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

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Abstract

Objective: In the study, our aim was to evaluate the predictability of four different nomograms on non-sentinel lymph node metastases (NSLNM) in breast cancer (BC) patients with positive sentinel lymph node (SLN) biopsy in a multi-center study.
Methods: We identified 607 patients who had a positive SLN biopsy and completion axillary lymph node dissection (CALND) at seven different BC treatment centers in Turkey. The BC nomograms developed by the Memorial Sloan Kettering Cancer Center (MSKCC), Tenon Hospital, Cambridge University, and Stanford University were used to calculate the probability of NSLNM. Area under (AUC) Receiver Operating Characteristics Curve (ROC) was calculated for each nomogram and values greater than 0.70 were accepted as demonstrating good discrimination.
Results: Two hundred and eighty-seven patients (287) of 607 patients (47.2%) had a positive axillary NSLNM. The AUC values were 0.705, 0.711, 0.730, and 0.582 for the MSKCC, Cambridge, Stanford, and Tenon models, respectively. On the multivariate analysis; overall metastasis size (OMS), lymphovascular invasion (LVI), and proportion of positive SLN to total SLN were found statistically significant. We created a formula to predict the NSLNM in our patient population and the AUC value of this formula was 0.8023.
Conclusions: The MSKCC, Cambridge, and Stanford nomograms were good discriminators of NSLNM in SLN positive BC patients in this study. A newly created formula in this study needs to be validated in prospective studies in different patient populations. A nomogram to predict NSLNM in patients with positive SLN biopsy developed at one institution should be used with caution.

Keywords: Breast cancer; Sentinel lymph node; Non-sentinel lymph node; Nomogram

Introduction

Axillary staging is an important part of breast cancer (BC) surgery, since axillary lymph node metastasis remains an important prognostic factor in BC patients. At present, sentinel lymph node (SLN) biopsy is accepted as a standard approach for clinically axillary negative BC patients. Completion axillary lymph node dissection (CALND) is recommended if the SLN is positive. Non-SLN metastasis (NSLNM) is detected in 35–50% of SLN positive patients.[1,2] Several institutions have developed nomograms

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to identify patients with a sufficiently low risk of NSLNM to avoid CALND.[1–4] The Memorial Sloan Kettering Cancer Center (MSKCC) nomogram[5] was published in 2003 and has been internationally accepted and commonly used for the prediction of NSLNM. However, a limitation of this nomogram such as it is not applicable when all the pathological parameters are not known to have been reported.[6–10] Even if the accuracies of the nomogram were validated in some European countries; patient characteristics and treatment approach were not similar in different populations.

Three additional nomograms from France,[11] England,[12] and Stanford–USA[13] have been developed and published. These nomograms are less complex than the MSKCC using three pathology parameters instead of eight, but is not widely accepted as of yet. The axillary staging in clinically negative BC has being evaluated by SLN biopsy in Turkey since 1998 in several BC treatment centers. The common approach of evaluating the SLN is intraoperative frozen section and if it turns positive, immediate CALND is the preferred method in Turkey. The NSLNM rates are 45–50% in the Turkish BC population; close to the world average.[14] The aim of the Turkish Federation of Breast Disease Associations Protocol MF08-01 study is to evaluate the available breast nomograms to predict NSLNM and to determine the variables on NSLNM in the SLN positive BC patients in the Turkish population.

Patients and methods

We retrospectively reviewed BC patients who underwent SLN biopsy at seven different BC treatment centers in Turkey. Six hundred and seven SLN biopsy positive patients who had CALND were evaluated. The patients who received neoadjuvant chemotherapy were excluded from the analysis.

Sentinel node biopsy

All patients underwent SLN biopsy using isosulphan blue dye alone ($n = 377$) or in addition to a technetium Tc 99 m sulfur colloid technique ($n = 230$). The technique was performed as described previously in the literature.[14] In order to assess sentinel node metastases, frozen section was done in 593 of 607 patients (93%) and the detection method of SLN metastases was frozen section in 574 patients, routine haematoxylin–eosin (HE) in 21 patients, and serial section haematoxylin–eosin (SSHE) in 12 patients. Micrometastasis was defined as tumors between 0.2 mm–2 mm and macrometastasis as >2 mm.

Variables

The variables documented included: pathologic size of the tumor in centimeters, nuclear grade and tumor type [invasive ductal carcinoma (DC) grade I, DC grade II and DC grade III or invasive lobular carcinoma], the number of positive SLNs, the number of negative SLNs, the method of detection of SLNs [frozen section (FS), routine haematoxylin–eosin (HE), serial section haematoxylin–eosin (SSHE) and immunohistochemistry (IHC)], estrogen receptor status, lymphovascular invasion (LVI), overall metastatic tumor size [the largest size of SLN metastasis in millimeters (OMS)], micrometastasis, and multifocality of the tumor.

Nomograms

The probability of NSLNM was determined using the four published nomograms. The online version of the MSKCC nomogram at www.mskcc.org/nomograms was utilized including tumor size, grade, the number of positive SLNs, the number of negative SLNs, the method of detection of SLNs, estrogen receptor status, LVI status, and multifocality of the tumor.

The Tenon scoring system, developed by Barranger et al. at the Tenon Hospital,[11] was applied to our dataset. Three parameters are used for this scoring system (0–7 points): histological tumor size, macro or micrometastasis in SLN, and the proportion of involved SLNs among all removed SLNs. Patients with scores of ≤ 3.5 (constituting the median score) had a 97.3% chance of having negative NSLNM and the chance of having negative NSLNM is 94.7% in patients with a score of ≤ 4 in Barranger et al.'s original paper.[11]

The formula developed by Pal et al. at Cambridge University[12] utilizes grade, OMS, and the proportion of involved SLNs among all removed SLNs. In our study, in order to standardize OMS, we accepted OMS = 2 mm if the largest metastatic tumor size was smaller than 2 mm.

The final nomogram, recently developed by Stanford University,[13] employs tumor size, status of LVI, and the largest size of SLN metastasis. Stanford nomogram calculations were done by using the online version of this method (http://wwwstat.stanford.edu/~olshen/NSLNcalculator/).

Statistical analysis

The likelihood of having positive NSLNM based on the factors was evaluated by use of χ^2 test. Stepwise multiple logistic regression analysis was used to estimate a predictive model for NSLNM. Three factors were found to contribute significantly to the logistic regression model. The areas under (AUC) the receiver operating characteristic curve (ROC) were used to describe the performance of the diagnostic value of each nomogram. A ROC curve plots sensitivity (''true positive rate'') against 1-specificity (''false positive rate''). The best possible prediction method would yield a point in the upper left corner or coordinate of the ROC space representing 100% sensitivity and 100% specificity. For perfect validation of a model the ROC value has to be one which requires a perfect match between the two dataset which is not feasible. A model with a ROC of 0.5 is equal to the toss of a coin. A model with a ROC of 0.7–0.8 is considered good, whereas a ROC of 0.81–0.9

Table 1
Descriptive characteristics of study group ($n = 607$)

Characteristics of the patients'	*n* (%)
Age (year)	
≤50	355 (58.4)
>50	252 (41.6)
Pathologic tumor size (cm)	
≤2	276 (45)
2–5	319 (53)
5<	12 (2)
Tumor type	
Ductal	529 (87.1)
Lobular	78 (12.9)
Nuclear grade	
1	41 (6.8)
2	330 (55.2)
3	226 (38.0)
Lymphovascular invasion	
Yes	326 (53.8)
No	280 (46.2)
Estrogen receptor status	
Positive	441 (73.2)
Negative	161 (26.8)
SLN detection method	
SSHE	12 (2.1)
Routine HE	21 (3.4)
Frozen	574 (94.5)
Frozen done	593 (97.6)
Frozen not done	14 (2.4)
Number of positive SLN	
1	490 (80.7)
2	85 (14.1)
3	23 (3.8)
4	4 (0.6)
≥5	5 (0.8)
Number of negative SLN	
0	317 (52.3)
1	164 (27.1)
2	79 (13.1)
3	29 (4.6)
4	10 (1.6)
≥5	8 (1.3)
Proportion of positive SLN/total SLN	
<0.5	181 (29.8)
0.5≤–<1	109 (17.9)
1	317 (52.3)
Micrometastasis	
Yes	42 (17.6)
No	500 (82.4)

(SLN, sentinel lymph node; SSHE, serial section haematoxylin–eosin, HE; haematoxylin–eosin).

has excellent discrimination.[9,15] Stata Statistical Software: Release 10 was used for statistical analysis (StataCorp. 2007, TX). All *p* values were two-tailed, and a value less than 0.05 was considered to be significant.

Results

General characteristics

The mean patient age was 50.4 ± 12.3 (range 24–87) years (Table 1). The mean tumor size was 25 ± 12 mm (range 2–100 mm). Multifocality was present in 21% ($n = 126$) of patients. The mean SLN number was 2 (1–11) and the mean number of positive SLN was 1 (1–7). The mean OMS was 15 ± 9 mm (2–41). We could not reach the OMS of 108 patients, nuclear grade of 10 patients, LVI status of 1 patient, and estrogen receptor status of 5 patients. There was no information if the metastasis of SLN was micrometastasis or macrometastasis in 65 patients. The MSKCC nomogram was applied to 596 patients, the Cambridge model to 495 patients, the Tenon model to 537 patients, and the Stanford model to 538 patients with considering the missing variables. Two hundred and eighty-seven patients (47.2%) had positive axillary NSLNM. The mean number of dissected axillary lymph nodes was 15 ± 6 (range 2–40), and the mean number of involved NSLNM was 2 ± 4 (range 0–26).

AUC values of the nomograms

The overall predicted probabilities of the MSKCC nomogram, Cambridge model, Tenon model, and Stanford model; as measured by the AUC are shown in Fig. 1. The AUC values were 0.700, 0.711, and 0.730 for MSKCC nomogram, Cambridge model, and Stanford model, respectively. The AUC value of Tenon model was 0.582.

The results of univariate and multivariate analysis

Tumor size, total SLN number, SLN detection method, proportion of positive SLN to total SLN, OMS, micrometastasis of SLN, LVI, and multifocality were found statistically significant on NSLNM with univariate analysis. The multivariate analysis was performed on the data with the parameters which were found to be significant in univariate analysis. After a multivariate analysis of LVI, OMS, and the proportion of positive SLN to the total number of SLN were statistically significant variables on NSLNM

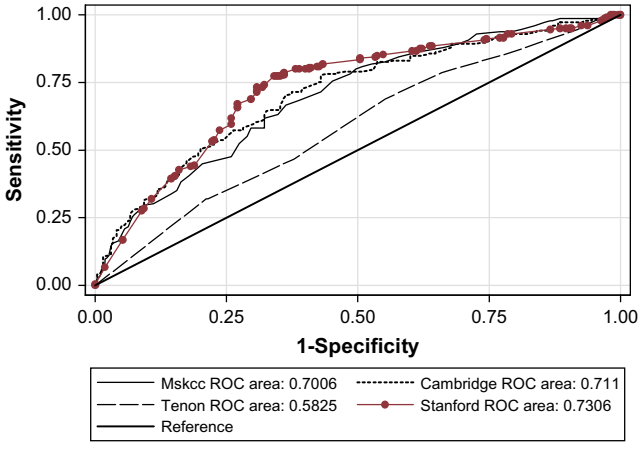

Figure 1. ROC curves and AUC of the study population for MSKCC, Cambridge, Stanford, and Tenon nomograms.

Table 2
Multivariate analysis of the study group ($n = 607$)

	OR	Std err	Z	P	[95% conf. interval]
LVI	6.34	1.41	8.29	0.000	4.10–9.82
OMS	1.10	0.01	7.80	0.000	1.08–1.13
Proportion of +SLN/Total SLN	2.44	0.87	2.50	0.012	1.21–4.93

OR: odds ratio; Std err: standard error; LVI: lymphovascular invasion; OMS: overall metastasis size (the largest size SLN metastasis); SLN: sentinel lymph node.

metastasis (Table 2). The most important factor was the positivity of LVI with a 6.34 (95% CI = 4.10–9.82) odds ratio.

The formula for predicting the NSLNM positivity in SLN positive BC patients was designed based on the multivariate analysis (Fig. 2). Using our formula as an example on a patient with OMS = 2 mm, the proportion of positive SLN among total SLN was 0.5, and positive LVI the prediction of NSLNM would be 52%, and it would be 11% if a patient with OMS = 2 mm, proportion of positive SLN among total SLN was 0.1, and negative LVI. Our created formula to predict the NSLNM in our patient population and the AUC value of this formula was 0.8023, which is considered to be a good discriminator (Fig. 3). Table 3 shows the parameters that are included in the current nomograms and our formula.

Discussion

The worldwide performance of the nomograms

The MSKCC nomogram was published in 2003 and validated in several studies.[7–10,12,13,16–20] The AUC values of the MSKCC nomogram in 15 validation studies were higher than 0.70 except in five studies.[9,10,12,16,17] The MSKCC nomogram was validated by the Stanford group, but was not by the Cambridge group with 0.77 and 0.68 AUC values, respectively. In our multi-center study, the MSKCC nomogram predicted the NSLNM probability successfully in the Turkish BC population. The most important difference between our study and Van Zee's study was the detection method of SLN. Van Zee et al.[5] performed the FS method 66% for the retrospective group, 73% for the prospective group, and detected SLN metastasis by FS in 47% of the patients. In our study group, the FS method was performed on 97.6% of the patients and SLN metastasis was detected by the FS method in 94.5% of the patients.

$$p = \frac{1}{1 + \exp\{3.46 - 0.10 \times OMS - 0.90 \times P - 1.85 \times L\}}$$

Figure 2. The formula we created for predicting non-sentinel lymph node metastases. (p: predictability, OMS: Overall metastasis size, P: proportion of positive SLN number among total SLN number, L: lymphovascular invasion).

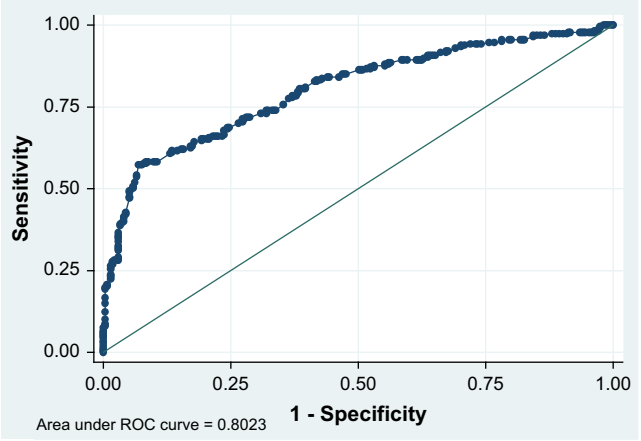

Figure 3. ROC curve and AUC of our patients using our formula.

The Cambridge and Stanford models[12,13] for predicting the NSLNM probabilities in SLN positive BC patients were published in 2008. On the basis of their results, the Cambridge group and the Stanford group developed their own scoring models. The Cambridge model has not been validated yet by the other institutes. The validation study for the Stanford model was presented by the Mayo Clinic at the San Antonio Breast Cancer Symposium 2008.[21] The AUC value for the Stanford model was 0.72 in this study and authors concluded that the Stanford nomogram appears to perform as well, but not better than the MSKCC. They also concluded that further validation in other patient populations is needed prior to widespread utilization of this nomogram. In our study, we used the Stanford and Cambridge models for validation. Although our patient group was different from the Cambridge's and Stanford's patient groups by means of OMS and micrometastasis, the Cambridge model and the Stanford model predicted successfully the probability of NSLNM in the Turkish BC population with 0.71 and 0.73 AUC values, respectively.

Factors limiting the worldwide application of the nomograms

The differences in the performance of the four nomograms observed in the present and the previous study[22] are mainly due to variations in the methods used for histopathological assessment of the sentinel nodes, number of dissected SLN, and having age and micrometastasis as variables. The number of nodes harvested as SLN as well as the intraoperative assessment of SLN metastases vary between the centers. A nomogram usually performs best at the center where it has been developed, but needs to be validated outside of the facility. Based on our results, our own model is superior to the four pre-existing nomograms when it is applied to the Turkish breast cancer patients. However, this model has to be validated before application in routine clinical practice.

Table 3
The parameters included in the current nomograms and our formula

	MSKCC	Tenon	Cambridge	Stanford	Turkish
Tumor size	+	+		+	
Grade	+		+		
Number of positive SLNs	+				
Number of negative SLNs	+				
The method of detection of SLNs	+				
Estrogen receptor status	+				
LVI status	+			+	+
Multifocality of the tumor	+				
Macro or micrometastasis in SLN		+			
Proportion of +SLN/total SLN		+	+		+
OMS			+		+
Largest size of SLN metastasis				+	

LVI: lymphovascular invasion; OMS: overall metastasis size (the largest size SLN metastasis); SLN: sentinel lymph node.

The statistically significant parameters for NSLNM in our patient group

We determined three statistically significant parameters on NSLNM in SLN positive BC patients in our study after multivariate analysis (LVI, OMS, and proportion of the positive SLN among total SLN). The highest odds ratio (6.34, 95% CI = 4.10−9.82) was for LVI status of the tumor with those analyses. In a large series with 1228 patients; SLN metastasis size, peritumoral vascular invasion, and the number of positive SLN were found as statistically significant parameters.[23] Recently, very similar results with our study were found by another study from Japan.[24] Jinno H, et al. found that the LVI status and the number of positive SLN numbers were statistically significant parameters on NSLNM in SLN positive BC patients. LVI was confirmed previously as the most important factor with the tumor size for axillary status in BC patients.[25,26] LVI was also used as one of the parameters with two different nomograms (MSKCC and Stanford) which were validated in our study.

The formula which was developed in our study is very similar to the Cambridge model. Both formulas use OMS and proportion of the positive SLN among total SLN as parameters. The limitations of our study group with the OMS and micrometastasis were that we were missing some data and the size of micrometastasis. OMS was accepted as equal 2 mm if it was smaller than 2 mm when we put it in the calculation.

The clinical value of the nomograms

Nomograms do not predict the probability of NSLNM perfectly in SLN positive BC patients, but is more valuable than clinical judgment. There are two studies which compared the clinical judgment and nomograms to predict NSLNM.[27,28] It was shown that the AUC value of MSKCC nomogram was higher than the AUC value of clinical judgment. The cutoff value for nomograms is another problematic issue when using nomograms. Poirier et al.[17] stated that Canadian surgeons would prefer omitting CALND in a patient when the nomogram result is less than 10%. Park et al.[29] observed a gradual and significant decline over time in the rate of CALND when the patient had lower nomogram results. We and other authors believe that nomograms for predicting the non-sentinel lymph node metastases after a positive sentinel lymph node biopsy have value as practical tools for clinicians in the clinics to consult the patient for further treatment options and nomograms have been used since 2003 widely for this reason.

Conclusions

The MSKCC nomogram, Cambridge formula, and Stanford nomogram were good discriminators of NSLNM in SLN positive BC patients for the Turkish population. A newly created formula depending on three factors (OMS, LVI, and proportion of positive SLN among total SLN) needs to be validated in prospective studies in different patient populations. The Turkish Federation of Breast Disease Associations recommends: a) a nomogram to predict NSLNM in patients with positive SLN biopsy developed at one institution should be used with caution; b) must be validated before using it for the population, and c) more than one validated nomograms may be used together while consulting patients.

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Conflict of interest

The authors state that they have no conflict of interest.

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