RESEARCH ARTICLE

Validation of Three Breast Cancer Nomograms and a New Formula for Predicting Non-sentinel Lymph Node Status

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Abstract

Background: The aim of the study was to evaluate the available breast nomograms (MSKCC, Stanford, Tenon) to predict non-sentinel lymph node metastasis (NSLNM) and to determine variables for NSLNM in SLN positive breast cancer patients in our population. Materials and Methods: We retrospectively reviewed 170 patients who underwent completion axillary lymph node dissection between Jul 2008 and Aug 2010 in our hospital. We validated three nomograms (MSKCC, Stanford, Tenon). The likelihood of having positive NSLNM based on various factors was evaluated by use of univariate analysis. Stepwise multivariate analysis was applied to estimate a predictive model for NSLNM. Four factors were found to contribute significantly to the logistic regression model, allowing design of a new formula to predict non-sentinel lymph node metastasis. The AUCs of the ROCs were used to describe the performance of the diagnostic value of MSKCC, Stanford, Tenon nomograms and our new nomogram. Results: After stepwise multiple logistic regression analysis, multifocality, proportion of positive SLN to total SLN, LVI, SLN extracapsular extention were found to be statistically significant. AUC results were MSKCC: 0.713/Tenon: 0.671/Stanford: 0.534/DEU: 0.814. Conclusions: The MSKCC nomogram proved to be a good discriminator of NSLN metastasis in SLN positive BC patients for our population. Stanford and Tenon nomograms were not as predictive of NSLN metastasis. Our newly created formula was the best prediction tool for discriminate of NSLN metastasis in SLN positive BC patients for our population. We recommend that nomograms be validated before use in specific populations, and more than one validated nomogram may be used together while consulting patients.

Keywords: Breast cancer - sentinel lymph node - nomogram - axillary dissection - non sentinel lymph node metastasis

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Introduction

Breast cancer, which accounts for 28% of female cancers and approximately 14% of cancer-related deaths, is the most common cancer type in females. According to the statistics from 2004-2008, a woman's risk of the lifetime probability of being diagnosed with an invasive breast cancer has increased from 1/13-1/8 (Jemal et al., 2010).

Axillary lymph node involvement is the most important prognostic factor in patients with breast cancer. In the case of axillary lymph node involvement, not only the treatment modality will be changed, but also the life expectancy will decrease (Chen et al., 2010). Nowadays, sentinel lymph node (SLN) biopsy is considered as the standard approach in patients without clinical diagnosis of axillary metastasis. Complementary axillary dissection is performed as a continuation of standard therapy in patients with sentinel lymph node (SLN) metastasis. However, studies have revealed that 40-70% of the patients with SLN metastasis undergoing complementary axillary dissection do not have an additional non-SLN metastasis (Van Zee et al., 2003; Chen et al., 2010)

After the above-mentioned determinations, studies have been conducted in many centers in order to create models that are capable of predicting the risk of non-SLN metastasis in patients with SLN metastasis. Van Zee et al. (2003) developed a nomogram based on the records of the Memorial Sloan-Kettering Cancer Center (MSKCC) using a retrospective analysis method. They also tested the nomogram prospectively, and found the area under the receiver operating characteristic (ROC) curve to be 0.77 (Van Zee et al., 2003). Validation studies were performed in many centers after the nomogram was published. However, obtaining different results in different patient populations have led the researchers in other centers to

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seek new nomograms.

Barranger et al. (2005) retrospectively reviewed the data from the Hospital Tenon in Paris city of France and developed a new nomogram (Barranger et al., 2005). In England, Pal et al. (2008) applied the MSKCC nomogram to their patients in 2008 and found the AUC of the ROC curve to be 0.68. Based on this result, they found the MSKCC nomogram not suitable for their patients and published the Cambridge nomogram (Pal et al., 2008). Kohrt et al. (2008) from the Stanford University School of Medicine evaluated the MSKCC nomogram using their own data and reported the AUC of the ROC curve to be 0.62. Depending on this finding, they concluded that the MSKCC nomogram was not suitable for their patients, and they published the Stanford nomogram with an AUC of the ROC curve of 0.74 (Kohrt et al., 2008).

In our clinic, 41% of the patients with SLN metastasis, which was detected on SLN biopsy between July 2008 and August 2010, did not have non-SLN metastasis. The present study aimed to evaluate the efficacy of mostly accepted three nomograms, the MSKCC, Tenon and Stanford nomograms, in our patient population.

Materials and Methods

Files of the patients who underwent surgical procedure with the diagnosis of primary breast cancer in the Dokuz Eylul University Hospital between July 2008 and August 2010 were retrospectively reviewed. Among 289 patients who underwent successful SLN biopsy, 170 patients with positive SLN biopsy were included in the study. Patients who were thought to have clinical axillary lymph node metastasis, those with distant metastasis, and those who received neoadjuvant therapy or have >T3 tumor were excluded from the study.

During SLN evaluation; formalin-fixed paraffin embedded tissue sections of all the sentinel and nonsentinel lymph nodes were examined after frozen section diagnosis. Four deeper levels of 4 μm sections from formalin-fixed parafin-embedded tissue blocks of lymph nodes with 25 μm intervals each, were performed. The first, third, and fourth sections were examined with hematoxylin-eosin (H&E) staining, whereas the second section was reserved for IHC. IHC of the lymph node sections were carried out by streptavidin biotin peroxidase method using AE1/AE3 (1:100 dilution, MS-343, Neomarker, USA), which is a monoclonal antibody cocktail reactive with cytokeratins.

Diagnosis was established by frozen imprint in 165 patients, whereas it was established by further analyses [hematoxylin and eosin (H&E) staining, serial section examination, immunohistochemistry (IHC) assay] in 5 patients.

The age of all patients was recorded. The following tumor characteristics were recorded: location, type, size, grade, multifocality, the Scarff-Bloom-Richardson (SBR) grade, nuclear grade, mitotic grade, histologic grade, ratio and type of intraductal component, lymphocytic infiltration status, presence of elastosis, presence of invasion to lymph vessel, blood vessel, skin or fascia, estrogen receptor (ER) and progesterone receptor (PR) status, and ER and PR staining intensities. The method used in the detection of SLN, and the number of positive and negative SLNs were determined; proportion of SLN was calculated. Capsular invasion status and size of metastasis were recorded for SLN metastasis.

Nomograms

The MSKCC nomogram, which was published in 2003 by Van Zee et al. (2003), is the first known nomogram. This nomogram includes the following nine variables: presence or absence of frozen examination, tumor diameter, histologic and nuclear grade of tumor, lymphovascular invasion (LVI), multifocality, ER status, method of detection of SLN, number of positive SLNs, and number of negative SLNs. In that model, 702 patients with SLN metastasis were evaluated retrospectively, and the relation of each variable with SLN metastasis was assessed by a multivariate logistic regression analysis. A calculation chart showing the score of each variable was created (Figure 1). The authors then validated the method by prospectively applying this calculation chart to another group comprising 373 patients. A ROC curve was drawn for this method, and the AUC was reported to be 0.77 (Van Zee et al., 2003; www.mskcc.org/applications/nomograms).

A new scoring system, which was developed in Tenon Hospital in France by Barranger et al. (2005), was published in 2005. They found that non-SLN metastasis was correlated with the tumor size, presence of macrometastasis, method of detection of SLN metastasis, number of positive SLN, proportion of positive SLN, LVI status, and size of SLN metastasis. Based on these data, "the Tenon axilla scoring system" was developed. This scoring system is based on the following three variables: 1) ratio of number of positive SLN to the total number of dissected SLN, 2) presence of macrometastasis, 3) histological tumor size.

The likelihood of non-SNL metastasis in breast cancer patients with SNL involvement is calculated obtaining a score between 0 and 7 with these variables (Table 1). A score of <3.5 indicates the absence of non-SLN metastasis with a probability of 97.3% (Barranger et al., 2005).

In 2008, Kohrt et al. (2008) developed a new nomogram, namely the Stanford nomogram, in which 13 parameters were evaluated. Eight of these parameters (tumor size, AJCC T score, tumor grade, ER status, PR status, presence of LVI, size of SLN metastasis, method

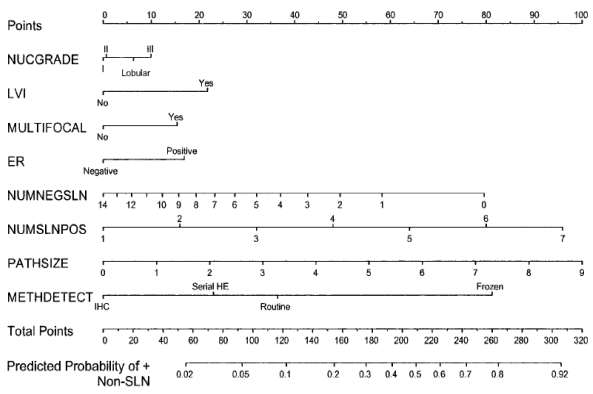


Figure 1. Calculation Chart

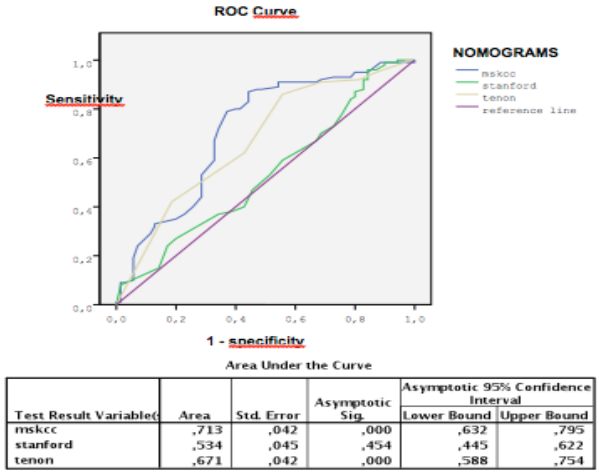
of detection of SLN metastasis) were found significant in univariate analysis. Based on multivariate analyses, they concluded that only three of these parameters (tumor size, presence of LVI, and size of SLN metastasis) could be used to predict non-SLN metastasis (www3-hrpdcc.stanford.edu/nsln-calculator).

The study patients were divided into two groups as those without non-SLN metastasis and those with non-SLN metastasis. Calculations were performed for each patient according to the MSKCC, Tenon and Stanford nomograms.

All statistics including the ROC curve analysis were performed using the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA) version 15.0. The efficacies of MSKCC, Tenon and Stanford nomograms were evaluated using ROC curves. A ROC curve was drawn, and an AUC was calculated for each nomogram (an AUC of the ROC curve between 0.7 and 0.8 was considered good, an AUC of the ROC curve between 0.8 and 0.9 indicated that the nomogram had excellent discrimination, and an AUC of the ROC curve of 0.5 indicated that there is no discrimination).

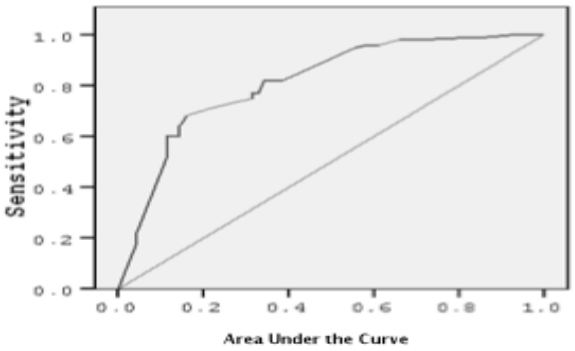
Statistical analysis

In univariate analysis, the Student's t-test, one-way analysis of variance (ANOVA), Mann-Whitney U test and Chi–square test were performed, where appropriate, to detect the factors influencing non-SLN metastasis. A p value <0.05 was considered statistically significant. Based on these analyses, statistically significant parameters (Table 2), as well as the parameters defined as significant in the other nonograms including tumor size, tumor grade, number of positive SLN, lymphovascular invasion, micro/macrometastasis of SLN, were assessed. Logistic regression analysis was used for multivariate analysis, and odds ratio (OR) values were assessed.



Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
mskcc	,713	,042	,000	,632	,795
stanford	,534	,045	,454	,445	,622
tenon	,671	,042	,000	,588	,754

Figure 2. Receiver Operating Characteristic (ROC) Curve. MSKCC, Tenon and stanford nomograms



Test Result Variable(s): DEU

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
,814	,034	,000	,748	,881

Figure 3. Receiver Operating Characteristic (ROC) Curve. The area under the curve (AUC) was 0.814 using our formula

Results

Calculation was performed for each of the three nomograms, and an AUC of the ROC curve was calculated to evaluate the efficacy of each nomogram (Figure 2). The AUC values of the ROC curves were found to be 0.713, 0.534, and 0.671 for the MSKCC, Stanford, and Tenon nomograms, respectively.

Results of the univariate analyses are presented in Table 2. Univariate analysis revealed significant differences between the patients with and without non-SLN metastasis in the following parameters: multifocality (p=0.001), PR status (p=0.05), PR staining intensity (p=0.022), number of negative SLN (p=0.001), proportion of metastatic SLN (number of metastatic SLN/total number of SLN; p=0.001), size of SLN metastasis (p=0046), SLN capsular invasion (p=0.001). A multivariate analysis was performed for the above-mentioned significant variables and the variables used in all of the three nomograms. The logistic regression analysis yielded Exp.(B) values for multifocality, LVI, number of positive SLN, and SLN capsular invasion (Table 3).

Table 1. Barranger's axillary scoring system (4)

Variable	Point value	p value Multivariate analysis
Macrometastasis in the SLN		0.02
No	0	
Yes	2	
Histological tumor size (mm)		0.006
≤10	0	
11-20	1.5	
>20	3	
Proportion of involved SLNs among all removed SLNs		0.03
<0.5	0	
0.5-1	1	
1	2	

*SLN: sentinel lymph node

Table 2. Significant Variables in the Univariate Analysis

Variable	p
Multifocality	0.001
PR status	0.050
PR staining intensity	0.022
Number of negative SLN	0.001
Proportion of metastatic SLNs to total SLNs	0.001
Extracapsular extension of SLN	0.001
Size of SLN metastasis	0.046

*PR: progesterone receptor, SLN: sentinel lymph node

Table 3. Results of the Logistic Regression Analysis

	B	SE	Wald	df	p	Exp(B)	95% CI	
							Lower	Upper
Multifocality	0.857	0.433	3,917	1	0.048	2,357	1,008	5,510
Proportion of metastatic SLNs to total SLNs								
	2,686	0.729	13,583	1	0.000	14,674	3,517	61,221
LVI	1,065	0.614	3,012	1	0.083	2,902	0.871	9,664
Extracapsular extension of SLN								
	2,058	0.390	27,907	1	0.000	7,830	3,649	16,801
Constant	-4,113	0.936	19,316	1	0.000	0.016		

SLN: sentinel lymph node, SE: standard error, CI: confidence interval

Table 4. Results of the Validation Studies of the MSKCC Nomogram (Adapted from the Study by Unal and Gur (11)

First author	Year	Country	n	AUC
Smidt	2005	Netherlands	222	0.78
Soni	2005	Austria	149	0.75
Dengim	2005	USA	89	0.86
Dauphine	2007	USA	51	0.63
Cripe	2006	USA	92	0.82
Lambert	2006	USA	200	0.71
Zgajnar	2007	Slovenia	276	0.72
Ponzone	2007	Italy	186	0.71
Arlan	2007	France	588	0.72
Evrensel	2007	USA	233	0.73
Klar	2008	Germany	98	0.58
Pal	2008	England	182	0.68
Gür	2010	Turkey	607	0.70
Our study	2010	Turkey	170	0.71

Discussion

Breast cancer is the most common cancer in women. Recently, conservative methods are preferred for the treatment of breast cancer to reduce the potential morbidity. SLN biopsy has been accepted as the standard therapy approach in many centers. With the use of SLN biopsy, it is possible to prevent lymphedema, nerve injury, limitation of shoulder motion, and chronic pain, which are likely to occur due to unnecessary axillary dissection (Latosinsky et al., 2008). However, review of a 15-year data has revealed that 40-70% of the patients with metastasis detected on SLN biopsy have no additional axillary lymph node metastasis (Chen et al., 2010).

Retrospectively evaluating the data of Memorial Sloan-Kettering Cancer Center, Van Zee et al. (2003) developed a nomogram (the MSKCC nomogram) in 2003, and then prospectively validated this nomogram. They found the AUC value to be 0.77. In the present study, we found the AUC value to be 0.71 for the MSKCC nomogram.

In their study, Kohrt et al. (2008) validated the MSKCC nomogram and found the AUC value to be 0.62. They developed the Stanford nomogram and reported the AUC value for this nomogram to be 0.74 (Kohrt et al., 2008). In our study, we found the AUC value for the Stanford nomogram to be 0.53.

Barranger et al. (2005) defined the Tenon nomogram in 2008 based on the data from Hospital Tenon in Paris. In the present study, we found the AUC value to be 0.67 for the Tenon nomogram.

In 2008, Pal et al. (2008) from England validated the MSKCC nomogram using their own data and found the AUC value as 0.68. They found the AUC value as 0.84 for the Cambridge nomogram, which they developed based on their own data.

In the first validation study performed in Turkey for the MSKCC, Cambridge, Stanford, and Tenon nomograms, the predictability of these nomograms were evaluated (Gur et al., 2010). In that particular study, the AUC values were determined to be 0.70, 0.73, 0.71, and 0.58 for the MSKCC, Stanford, Cambridge, and Tenon nomograms. They found the AUC value to be 0.80 for the nomogram (MF08-01) that they developed based on their own data (Gur et al., 2010).

The results of the validation studies performed for the MSKCC nomogram, which was the first nomogram, are summarized in Table 4 (Unal et al., 2008).

Tumor size is the common variable used in the MSKCC, Tenon and Stanford nomograms, whereas LVI and tumor grade are the common variables used in the MSKCC and Stanford nomograms. While the variables including number of positive SLN, number of negative SLN, method of detection of SLN metastasis, ER status, and multifocality are used only in the MSKCC nomogram, SLN micro/macrometastasis status and proportion of positive SLN are used only in the Tenon nomogram. Size of SLN metastasis is used only in the Stanford nomogram (Table 4).

The logistic regression analysis performed in the present study revealed a highest OR of 14.674 [(95% confidence interval (CI): 3.51-61.22] for the proportion of positive SLN, followed by an OR of 7.83 (95%CI; 3.64-16.80) for SLN capsular invasion, 2.90 (95%CI; 0.87-9.66) for LVI, and 2.35 (95%CI; 1.00-5.51) for multifocality (Table 3).

In the present study, when the obtained data and the nomograms were reviewed, we observed that SLN capsular invasion, which had the second highest OR in the present series, was used in none of the three nomograms. The other intriguing finding was that three of the parameters for which OR was calculated in the present series, however, were separately evaluable in the three nomograms. This was considered as the greatest inadequacy of the validated nomograms for the present series (Table 4).

Based on the data of the patients from the Dokuz Eylül University Breast Tumor Group, a risk assessment formula was developed using these outcomes. When the formula was verified for the patients in the present study, the AUC for the ROC curve was calculated as 0.814 (Figure 3).

The new formula; $p=1/[1+\exp^{-1x(4,113+MFx0,857+PrSLNx2,686+LVIx1,065+SLNkapINVx2,058)}]$

In conclusion, there is no method other than the nomograms developed to assess the likelihood of non-SLN metastasis; however, there are limitations concerning the use of these nomograms. Primarily, the best outcomes of the nomograms are obtained based on the data of the clinic, in which the nomogram was developed. In order to overcome this limitation, each step of SLN biopsy procedure should be standardized, and the nomograms should be revised with multicenter, even with

multinational, studies.

In the present study, we evaluated the MSKCC, Tenon and Stanford nomograms. We concluded that the MSKCC nomogram is in the limits of applicability, whereas the Tenon and Stanford nomograms are not available for our patients. From this point of view, based on the data of patients of the Dokuz Eylül University Breast Tumor Group, we developed a new risk assessment system, which was intended to be verified prospectively. Thus, we aimed to contribute to the large-scale scoring systems that would be developed in the future.

Efficacy of the risk assessment formula defined in the present study should be prospectively controlled both in our clinic and in other centers. In the event of obtaining adequate evidence about applicability of this new formula, a conclusion about the risk of non-SLN metastasis could be reached together with the outcomes of another nomogram, the efficacy of which has been proven (e.g. the MSKCC nomogram).

It may be suggested that, in clinical practice, these nomograms can be used in the near future to better inform the patients about their potential risks". Nevertheless, as the information on cancer biology and behavior is enhanced and stronger outcomes for the nomograms are obtained, the rate of axilla-preserving surgical procedures may increase in the future.

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