Evaluation of the Probability of Non-sentinel Lymph Node Metastasis in Breast Cancer Patients with Sentinel Lymph Node Metastasis using Two Different Methods

İrfan Başoğlu¹, Muhammet Ferhat Çelik², Ahmet Cem Dural¹, Mustafa Gökhan Ünsal¹, Cevher Akarsu¹, Halil Fırat Baytekin³, Selin Kapan¹, Halil Alış¹

¹Clinic of General Surgery, Bakırköy Dr. Sadi Konuk Training and Research Medicine, İstanbul, Turkey

²Clinic of General Surgery, Yedikule Surp Pırgıç Armenian Hospital, İstanbul, Turkey

³Clinic of Pathology, Bakırköy Dr. Sadi Konuk Training and Research Medicine, İstanbul, Turkey

ABSTRACT

Objective: The aim of this retrospective clinical study was to evaluate the accuracy and feasibility of two different clinical scales, namely the Memorial Sloan-Kettering Cancer Center (MSKCC) nomogram and Tenon's axillary scoring system, which were developed for predicting the non-sentinel lymph node (NSLN) status in our breast cancer patients.

Material and Methods: The medical records of patients who were diagnosed with breast cancer between January 2010 and November 2013 were reviewed. Those who underwent sentinel lymph node biopsy (SLNB) for axillary staging were recruited for the study, and patients who were found to have positive SLNB and thus were subsequently subjected to axillary lymph node dissection (ALND) were also included. Patients who had neoadjuvant therapy, who had clinically positive axilla, and who had stage 4 disease were excluded. Patients were divided into two groups. Group 1 included those who had negative NSLNs, whereas Group 2 included those who had positive NSLNs. The following data were collected: age, tumor size, histopathological characteristics of the tumor, presence of lymphovascular invasion, presence of multifocality, number of negative and positive NSLNs, size of metastases, histopathological method used to define metastases, and receptor status of the tumor. The score of each patient was calculated according to the MSKCC nomogram and Tenon's axillary scoring system. Statistical analysis was conducted to investigate the correlation between the scores and the involvement of NSLNs.

Results: The medical records of patients who were diagnosed with breast cancer and found to have SLNB for axillary staging was reviewed. Finally, 50 patients who had positive SLNB and thus were subsequently subjected to ALND were included in the study. There were 17 and 33 patients in Groups 1 and 2, respectively. Both the MSKCC nomogram and Tenon's axillary scoring system were demonstrated to be significantly accurate in the prediction of the involvement of NSLNs ($p < 0.05$ for each). Among all the parameters, the only one that was found to be correlated with the risk of NSLN involvement was the presence of lymphovascular invasion.

Conclusion: The MSKCC nomogram and Tenon's axillary scoring system both seem to be reliable tools for the assessment of NSLN status in SLNB-positive breast cancer in our breast cancer population. Nevertheless, the omission of ALND in SLNB-positive breast cancer cannot be yet recommended because of the lack of long-term results of current nomograms and scoring systems.

Keywords: Sentinel lymph node biopsy, lymph node dissection, axilla, breast cancer, surgery

Introduction

Breast cancer is the second most common cancer in the world with a rate of 11.9%, and the most common cancer type in women with a rate of 25%. It is estimated that 1.67 million patients will be newly diagnosed in 2012. It is the most common reason for cancer related deaths in under-developed regions, while ranking second after lung cancer in developed regions (1, 2).

The evaluation of historical development of breast cancer surgery reveals that the role of radical surgical methods that have been applied in the past were replaced by less invasive methods (3). Axillary lymph node involvement is the most significant clinical prognostic factor in the treatment of breast cancer (4). Metastases theoretically course from the primary tumor to the sentinel lymph node (SLN) or nodes and then non-sentinel lymph nodes (NSLN). Sentinel lymph node biopsy (SLNB), which was first defined by Krag et al. (5, 7) and Giuliano et al. (4, 6, 7), is a reliable and effective method applied in clinically node-negative patients for axillary staging with less morbidity than conventional axillary lymph node dissection (ALND), and has become the standard procedure for axillary staging instead of conventional ALND.

Various models have been designed to determine the risk of axillary lymph node metastases. One of these methods is the Memorial Sloan Kettering Cancer Center (MSKCC) incorporating 9 variables for nomogram calculation: tumor diameter, lymphatic invasion,

tumor histology, nuclear grade, multifocality, number of negative SLNs, number of positive SLNs, metastasis detection method (frozen, routine, serial section, immunohistochemistry), and estrogen receptor status (8). Designed for a similar purpose, the Tenon scoring system uses three variables: the size of SLN metastasis, primary tumor size, and the proportion of positive SLNs among all removed SLNs (7).

On the other hand, 20% of patients accepted as lymph node negative by routine pathological examinations develop metastatic disease (9). In studies using different techniques, the possibility of a NSLN metastasis in SLN-negative patients (false-negativity) is reported as 0-11%. This rate increases to 12-14% if isolated tumor cells are detected in SLN, and to 20-35% in the presence of micrometastasis (9). That is why, factors that may be used to predict NSLN status in the presence of SLN involvement were examined and numerous pathological factors were found to be associated with higher NSLN involvement in the presence of a positive SLNB. These parameters are evaluated in two groups; primary tumor-related factors (histological tumor type, invasive carcinoma size, histologic grade, lymphovascular invasion, and estrogen receptor status), and lymph node-related factors (metastasis detection method, metastasis size, extranodal extension, positive SLN number and negative SLN number) (7, 8, 10, 11). The MSKCC nomogram that was designed by Van Zee et al (8) and published in 2003 is the first nomogram developed for the prediction of NSLN metastasis in breast cancer patients with positive SLN metastasis.

In our study, we aimed to evaluate the predictive value and feasibility of the MSKCC nomogram and Tenon axilla scoring system that are being used to estimate the risk of NSLN metastasis in patients with positive SLN metastasis in a single-center retrospective database.

Materials and Methods

Files of patients who underwent surgery in Bakırkoy Dr. Sadi Konuk Education and Research Hospital between January 2010 and October 2013 with a diagnosis of invasive breast cancer were retrospectively reviewed. Fifty patients with successful SLNB who underwent completion axillary lymph node dissection (CALND) for positive findings were enrolled in the study. Two groups were identified as NSLN negative (Group 1) and NSLN positive (group 2) patients. All SLNBs were evaluated with intraoperative frozen section. If the cross-section was positive then ALND was performed in the same session. Those with a suspicious finding on H & E were evaluated with cytokeratin by immunohistochemistry (IHC). Patients with negative SLN biopsy, those that could not be localized with success, those with a clinically positive axilla, with distant metastases, who received neoadjuvant therapy, and who did not undergo axillary dissection were excluded from the study.

Written informed consent was obtained from patients. The Bakırkoy Dr. Sadi Konuk Education and Research Hospital Ethics Committee (Resolution No. 11/11 /2013) performed a board review.

Each patient's age, tumor size and histology, grade, presence of lymphatic invasion, multifocality, number of removed SLNs, number of positive SLNs, number of negative SLNs, diameter of the metastases in the SLN (macrometastases, micrometastases, isolated tumor cells), pathological detection method of SLN metastasis (frozen, routine,

Table 1. Tenon axilla scoring system

Variable	Score	Multi-variable analysis (p)
Macrometastasis		=0.02
Present	2	
Absent	0	
Histologic tumor diameter (mm)		=0.006
≤10	0	
11-20	1.5	
>20	3	
The ratio of number of positive SLN* to total number of dissected SLN		=0.03
<0.5	0	
0.5-1	1	
1	2	
A score of 0-7 is obtained by variables stated above with the Tenon scoring system and a probability calculation is performed. If patient score is <3.5, it is concluded that there is a 97.3% possibility that there will not be a NSLN metastasis.		
*SLN: sentinel lymph node		

serial sections, immunohistochemistry), estrogen, progesterone and Cerb-B2 receptor status, and ALND pathology results were recorded in a database file created with Microsoft® Excel 2007. The risk of each patient was calculated with the MSKCC nomogram (Figure 1) and Tenon axilla scoring system (Table 1). The ROC curve was plotted for both models and area under the curve (AUC) values were determined. Risk scores and axillary involvement were statistically evaluated, and the correlation of each variable with axillary involvement was assessed.

Statistical analysis

NCSS® (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package was used for statistical analysis. Descriptive statistical methods (mean, standard deviation) were used along with Student's t test for comparison of groups in two, and Chi-square and Fisher exact tests for comparisons of qualitative data. The ROC-AUC, sensitivity, specificity, positive predictive value, negative predictive value, LR (+) value, and accuracy were calculated for MSKCC nomogram and Tenon score. P<0.05 was considered statistically significant.

Results

The NSLN was negative in 17 patients (34%), and positive in 33 (66%). The mean age of the patients was 56.8±10.51 in Group 1, and was 50.33±12.17 in Group 2 (Table 2). The mean tumor diameter was greater in Group 2 (2.63±0.82 cm) than Group 1 (Figure 2). Accordingly, 70.5% of patients in Group 1 (n=12) had T1 tumors, while 72.7% of patients in Group 2 (n=24) had T2 tumors. In both groups, the most frequent histopathological tumor type was invasive ductal carcinoma. The majority of patients in both groups had Grade 2 tumors, more in Group 2 (Table 2).

Lymphovascular invasion (LVI) was detected in 9 patients in Group 1 (52.9%), and 31 patients in Group 2 (93.9%) (Figure 3). 16 of the tumors in Group 1 (94.12%) were unifocal, while 26 patients in Group

Figure 1. MSKCC nomogram calculation. MSKCC uses 9 variables in the nomogram: if frozen section evaluation is performed or not, tumor size, tumor histology and nuclear grade, lymphovascular invasion, multifocality, estrogen receptor status, SLN detection method, number of positive SLNs and negative SLNs.

*LVI: lymphovascular invasion; Res stat: receptor status; Neg SLN: negative sentinel lymph node; pos SLN: positive sentinel lymph node; Pat.: pathologic; nSLN: non-sentinel lymph node

2 (78.7%) had unifocal tumors, 7 (21.2%) tumors were multifocal. SLN metastasis was detected in 13 patients in Group 1 (76.5%), and in 22 patients in Group 2 (66.7%) (Figure 4).

88.2% of patients in Group 1 (n=15) had macrometastases, while all patients in Group 2 (n=33) had macrometastases. Receptor positivity for estrogen and progesterone was similar in both groups while Cerb-B2 positivity was more pronounced in Group 2 (Table 2). According to SLN (+) / total SLN rate, 35.3% of patients in Group 1 were in the range of 0.5-1, and 75.7% of patients in Group 2 (n=25) were in the range of 1 (Table 2).

The mean risk percentage for MSKCC nomogram was determined as $15.7 \pm 38.6\%$ in Group 1, and as $62.8 \pm 12.6\%$ in Group 2. The mean score for Tenon axilla scoring system was 4.9 ± 1.6 in Group 1, and 6.2 ± 1.1 in Group 2. The statistical analysis revealed a p value of 0.0001 for MSKCC nomogram, and of 0.001 for Tenon axilla scoring system, both of which were statistically significant (Table 3). ROC curves were plotted for each nomogram, and the AUC for MSKCC nomogram was detected as 0.899 and as 0.747 for Tenon axilla scoring system (Table 4).

The area under the ROC curve in MSKCC nomogram was significantly higher than the area under the ROC curve in Tenon axilla scoring system ($p=0.007$). The accuracy, positive and negative predictive value, sensitivity, specificity, and positive LR values for MSKCC nomogram and Tenon axilla scoring system are presented in Table 5.

Correlation between the variables used in both models (tumor size, histological type, grade, size of metastasis in the SLN, lymphovascular

Figure 2. Distribution of patients in Group 1 and Group 2 according to tumor size

invasion, multifocality, SLN involvement rate, estrogen, progesterone, Cerb-B2 receptor status) and age and NSLN involvement were assessed. Statistical analysis was performed separately for each variable. Among all variables, statistically significant correlation was detected only with LVI ($p=0.0001$) (Table 2).

Discussion and Conclusion

The concept in the Halsted era that breast cancer is a local disease and that radical mastectomy will decrease local recurrence and prolong survival was replaced by modified radical mastectomy in the 1940s, due to its high morbidity. The hypothesis "breast cancer is a systemic disease" was first suggested by Fisher (12) in the 1970s leading to the model of breast conservation in breast cancer surgery. In the 1970s,

Table 2. Statistical results of variables affecting NSLN metastasis risk

Variable		Metastasis (-)	Metastasis (+)		P value	
Age		56.8±10.5 (37-85)	50.3±12.2 (25-84)		0.327	
Size		2.1±1.1 (0.5-4.5)	2.6±0.8 (0.8-4)		0.075	
Total SLN*		2.3±1.6 (1-6)	1.9±1.1 (1-5)		0.583	
SLN (-)		0.9±1.3 (0-4)	0.4±0.7 (0-2)		0.054	
SLN (+)		1.3±0.7 (1-3)	1.5±0.9 (1-4)		0.255	
Total NSLN**		13.5±5.6 (6-26)	16.2±6.3 (6-30)		0.087	
Type	Ductal	14	%82.3	30	%90.9	0.748
	Ductal+Lobular	1	%5.9	1	%3.0	
	Lobular	2	%11.8	2	%6.1	
Grade	Ductal 1	4	%26.7	5	%16.1	0.338
	Ductal 2	11	%73.3	23	%74.2	
	Ductal 3	0	%0	3	%9.7	
	Lobular	2		2		
LVi†	Present	9	%52.9	31	%93.9	0.0001
	Absent	8	%47.1	2	%6.1	
Multifocality	Present	1	%5.9	7	%21.2	0.131
	Absent	16	%94.1	26	%78.8	
ER‡	ER (-)	5	%29.4	6	%18.2	0.246
	ER (+)	12	%70.6	27	%81.8	
PR§	PR (-)	4	%23.5	6	%18.2	0.459
	PR (+)	13	%76.5	27	%81.8	
Cerb-B2	Cerb-B2 (-)	14	%82.3	24	%72.7	0.648
	Cerb-B2 (+)	3	%17.7	9	%27.3	
Metastasis Size	Micro	2	%11.9	0	%0	0.111
	Macro	15	%88.1	33	%100	
SLN(+)/	<0.5	2	%11.8	2	%6.1	0.261
Total SLN	0.5-1	6	%35.3	6	%18.2	
	1	9	%52.9	25	%75.7	
*SLN: sentinel lymph node						
**NSLN: non-sentinel lymph node						
†LVI: lymphovascular invasion						
‡ER: estrogen receptor						
§PR: progesteron receptor						

several prospective trials compared mastectomy vs. breast-conserving surgery (BCS). The 20-year follow-up results of the NSABP-B06 and Milan studies reported there was no statistically significant difference between the mean survival of patients who underwent mastectomy or BCS, with a significantly higher local recurrence rate in the BCS group (13, 14).

Current guidelines recommend completion axillary lymph node dissection (CALND) in case of detection of SLNB metastases (15, 16). However, NSLN positivity in SLN positive patients has been reported in the literature as 35-70% (5). Whether CALND should be performed or not in SLN-positive patients is one of the present debates

in breast cancer surgery. In the literature, several article and centers proposed that CALND was not valuable, that low-volume nodal metastases could be treated with systemic adjuvant chemotherapy and/or full breast radiation therapy that is being applied to many patients, and that approximately 50% of SLN metastasis-positive patients undergo unnecessary CALND in fact without harboring any NSLB metastasis (17, 18). In addition, it is emphasized that in a selected group of patients with nodal metastasis, more aggressive chemotherapy regimens and chest wall and axillary radiotherapy can be applied (19).

On the other hand, opponents advocate CALND based on the presence of NSLN metastasis in approximately 50% of SLN-positive pa-

Figure 3. Distribution of NSLN negative and NSLN positive patients according to LVI

*LVI: lymphovascular invasion

Table 3. MSKCC nomogram and Tenon axilla scoring system statistical results

	Group	Group 2	p value
MSKCC*	%38.6±15.7	%62.8±12.6	0.0001
Tenon Score	4.9±1.6	6.2±1.1	0.001

*MSKCC: Memorial Sloan Kettering Cancer Center

Table 4. AUC values for MSKCC nomogram and Tenon axilla scoring system

	AUC	SE	CI %95
MSKCC*	0.899	0.043	0.781-0.966
Tenon Score	0.747	0.069	0.604-0.859

AUC: Area under the curve; SE: Standard error; CI: Confidence interval

*MSKCC: Memorial Sloan Kettering Cancer Center

tients, providing some therapeutic effect as well as local control (18, 20), providing important prognostic information by revealing the exact number of metastatic lymph nodes in the axilla, and guiding the decision for chemotherapy and axillary radiotherapy (21, 22).

The ACO-SOG Z0011 Phase 3 randomized study did not report a statistically significant difference in overall survival, disease-free survival and local recurrence between SLNB and CALND group after a 6.3-year median follow-up (23, 24). In their study on 1960 SLN-positive patients, Park et al. (25) detected 2% axillary recurrence in the group with SLNB, and 0.4% in the SLNB + CALND group after 23 and 30 months of follow-up, respectively which was statistically significant ($p=0.004$).

It is difficult to predict the NSLN metastasis status for a single patient with the literature data. The risk estimations for any characteristics vary considerably from study to study. These differences may be attributable to relatively small population of patients participating in the study or differences between the populations in terms of other factors affecting the risk. Additionally, it is difficult to apply risk estimations to various patient characteristics simultaneously, due to the generally preferred one-variable methods in the literature (8).

Figure 4. Number of SLN with metastasis in NSLN negative and NSLN positive patients

*SLN: sentinel lymph node **NSLN: non-sentinel lymph node

Therefore, nomogram and scoring systems aimed at estimating NSLN involvement have been designed by many researchers in order to identify patients with SLN involvement without NSLN involvement, decrease unnecessary CALND in this patient group, and increase the quality of life (7, 8, 10, 11).

The MSKCC nomogram that has been developed based on a retrospective group of 702 patients by Van Zee et al. (8) was confirmed in a prospective group of 373 patients. The AUC for the retrospective group was found as 0.76 and as 0.77 for the prospective group. In the literature, there have been several studies evaluating the accuracy of the MSKCC nomogram. The AUC was detected as 0.786 by Cho et al (5,26), as 0.724 by Alran et al (5, 27), and as 0.58 by Klar et al (5, 28). In our study, the AUC for MSKCC nomogram was determined as 0.899.

This wide variation between the studies is thought to be due to differences in age, tumor size, tumor grade, histologic type, SLN mapping techniques, SLN histopathological evaluation and staining techniques, and differences in positive and negative SLN rates and micrometastases (5).

Numerous limitations have been identified for the MSKCC nomogram. The nodes removed by CALND were only examined by routine pathological analysis. It has been reported that the proportion of patients with NSLN metastasis could increase if the NSLNs were examined by serial sectioning and IHC (8).

Another factor limiting the MSKCC nomogram is lack of data on nodal metastasis size. The AJCC Cancer Staging Manual included metastasis size as a determining factor for stage (hence prognosis) in the 6th and 7th editions. However, in most cases, due to differences in the distribution pattern of malignant cells in the nodes, size specification is challenging. Another potential weakness in the data used in the MSKCC study is not performing CALND in selected patients at a low predicted risk of NSLN metastasis, therefore exclusion from the model. Finally, evidently this model is not perfect. The area under the ROC curve in the first model was 0.77 in the prospective population. This means that if two women were randomly chosen and one of these women had at least one positive NSLN and all NSLNs were negative in the other, the nomogram is 77% likely to predict a higher likelihood for the positive woman (8).

Table 5. Accuracy, sensitivity and specificity values for MSKCC nomogram and Tenon axilla scoring systems

	Accuracy	Sensitivity	Specificity	PPV	NPV	+LR
MSKCC	>56	75.76	88.24	92.6	65	6.44
Tenon score	>4.5	90.91	47.06	76.9	72.7	1.72

PPV: Positive predictive value; NPV: Negative predictive value; +LR: Likelihood ratio; *MSKCC: Memorial Sloan Kettering Cancer Center

Figure 5. The ROC curve for MSKCC nomogram and Tenon axilla scoring system

MSKCC: Memorial Sloan Kettering Cancer Center

Developed by the Tenon Hospital, the risk estimation in axilla scoring system based on the results of multivariate analyzes is expressed as percentages. Unlike other studies, this model provides a risk score in the range of 0-7. In their own group assessment, the likelihood of having negative NSLN was 97.3% in patients with a score equal to or lower than 3.5 (7). However, not including an important parameter for prediction of NSLN metastasis risk, extracapsular extension of SLN metastasis, is defined as the main limitation to this scoring system. The authors applied CALND to all patients in this subgroup, and these patients were excluded from the study.

There have been many studies in the literature evaluating the accuracy of Tenon scoring system. The AUC ranged from 0.58 to 0.70 (29). The AUC for Tenon's scoring system for this study was found to be 0.747.

The purpose of nomograms is not to tell physicians exactly what to do but to help them discuss the risks with the patient and make a joint decision for a better treatment (30). Park et al (25) evaluated 287 patients with SLN positivity without ALND. They reported that 15% of patients declined surgery despite the surgeon's advice, while in 85% the surgeons and the patient made a joint decision not to proceed with ALND, and that there was no difference in MSKCC nomogram score distributions between the two groups. The evaluation of pre- and post- nomogram periods showed that the rate of ALND in SLN-positive patients has significantly decreased after introduction of the nomogram (25).

Performance of nomograms varies by patient groups or centers to which they apply. These differences are related to differences in the methods used for SLN histopathological evaluation, dissected number

of SLNs, as well as inclusion of parameters such as age and micro-metastases. The number of nodes accepted as SLN and intraoperative assessment methods for SLN metastasis may vary among centers. Therefore, nomograms show the best performance where they were first developed in and need evaluation and confirmation to be used in other centers (31).

In our study, parameters used in MSKCC nomogram and Tenon axilla scoring system to identify NSLN metastasis in SLN-positive patients, and other parameters affecting NSLN metastasis were statistically evaluated.

Within these parameters, LVI positivity was the only parameter found to be statistically significant in assessing the risk of NSLN metastasis. Primary tumor size, number of positive SLNs, total number of removed SLNs, the proportion of the number of positive SLNs to the total number of SLNs, tumor type and grade, estrogen and progesterone receptor status, multifocality and SLN metastasis size were not found to be statistically significant parameters to evaluate the risk of NSLN metastasis.

Currently, the only tool that evaluates NSLN metastasis in SLN metastasis positive breast cancer patients is nomograms. Nomograms provide the most reliable and relevant result in the centers they are designed at. The low number of cases used in studies generating nomograms limits their general use. In our study on fifty patients, the MSKCC nomogram and Tenon axilla scoring system were found to be statistically valid in the calculation of NSLN metastasis risk, but new studies are needed in this area.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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