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# The Gulf Journal of Oncology

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Assessment Of An Existing And Modified Model For Predicting Non Sentinel Lymph Node Metastasis In Breast Cancer Patients With Positive Sentinel Node Biopsy

M. Al-Masri¹, G. Darwazeh¹, M. El-Ghanem¹, B. Hamdan¹, M. Sughayer²

¹Department of Surgery, King Hussein Cancer Center, Amman, Jordan.
²Department of Pathology, King Hussein Cancer Center, Amman, Jordan

Abstract

Summary

The Memorial Sloan Kettering Cancer Center (MSKCC) breast nomogram has been validated in different populations. In this study, the nomogram was validated for the first time in a Middle East population sample. Although our sample was found to have significant differences from the dataset from which the model was derived, the nomogram proved to be accurate in predicting non sentinel axillary lymph node metastasis.

An attempt to use the proportions of involved sentinel lymph nodes instead of absolute numbers of positive and negative sentinel lymph nodes, yet using the same online calculator to predict the probability of non sentinel axillary lymph node metastasis, improved the accuracy, specificity, negative predictive value, and false negative rate.

Background

Axillary clearance is the standard of care in patients with invasive breast cancer and positive sentinel lymph node biopsy. However, in 40-60% of patients, the sentinel lymph nodes are the only involved lymph nodes in the axilla. The Memorial Sloan Kettering Cancer Center (MSKCC) breast nomogram serves to identify a subgroup of patients with low risk of non sentinel lymph node (NSLN) metastasis, in whom axillary lymph node dissection (ALND) could be spared, and thereby, preventing the unwarranted associated morbidity.

Methods

The MSKCC nomogram was applied on 91 patients who met the criteria. A modified predictive model was developed by substituting proportions of positive and negative SLN for their absolute numbers. The accuracy was assessed by calculating the area under the receiver-operator characteristic (ROC) curve.

Results

The MSKCC nomogram achieved an area under the ROC curve of 0.76. The area under the curve for the modified predictive model was 0.81. The specificity, negative predictive value, and false negative were 30%, 71%, 20% (MSKCC model) and 55%, 84%, 17% (modified model) at 20% predicted probability cut-off values.

Conclusion

Although differences existed in characteristics of our breast cancer population, and in the methods of sentinel lymph node metastasis detection, the MSKCC model proved to be accurate. An attempt to replace the number of positive and negative SLNs with proportions in the MSKCC model raised the accuracy but did not achieve statistical significance (p = 0.09).

Keywords

Breast cancer, Sentinel lymph node, Non sentinel lymph node, Axillary clearance, Predictive model.
Introduction

Axillary lymph node dissection and positive sentinel lymph node (SLN) biopsy is the standard of care in patients with early breast cancer. Meanwhile, in 40% to 60% of patients, the SLNs were the only positive lymph nodes in the axilla. These patients underwent axillary lymph node dissection (ALND) and were exposed to the risk of potential morbidities without benefit.

Many predictive models were developed to identify the subset of patients with a positive sentinel lymph node (SLN) biopsy in whom non-sentinel axillary lymph node (NSLN) involvement is unlikely. In these patients, ALND could be omitted and thereby preventing the unnecessary associated morbidity, higher costs of treatment, and longer period of hospitalization.

Memorial Sloan-Kettering Cancer Center (MSKCC) nomogram was the first and the most widely validated model in different breast cancer populations. The accuracy of this nomogram, assessed by calculating the area under the receiver-operator characteristic (ROC) curve, was .76 when applied to the MSKCC dataset.

Many predictive models were subsequently developed with improved accuracy, but since these models incorporate variables not reported in routine pathological assessment of sentinel lymph nodes, the MSKCC nomogram remains the most widely applicable nomogram.

The MSKCC nomogram was validated on different populations with areas under the curve (AUC) ranging between .58 and .84. This might be explained by inter-institutional variation in methods of SLN mapping, removal, and pathological assessment, or other differences in tumor characteristics among different breast cancer populations; therefore, the nomogram should be validated in the target population as well as the institution performing the procedure before it can be adopted. The purpose of this study was to validate the MSKCC nomogram in a regional cancer center patient population in Jordan, and to assess a modified model of the MSKCC nomogram.

Materials and methods

Patients

King Hussein Cancer Center (KHCC) institutional review board approval was obtained to review the medical records of 369 breast cancer patients who underwent SLN biopsy during the period from July 2005 to September 2010 at KHCC. One hundred and eleven patients had a positive SLN biopsy. The inclusion criteria were: primary invasive breast cancer, clinically negative axilla or negative ultrasound guided FNA in clinically palpable axillary lymph nodes, no previous systemic therapy, positive sentinel lymph node biopsy, and ALND with at least 10 lymph nodes retrieved. The MSKCC nomogram was applied on 91 patients. 20 patients were excluded; 7 patients refused to undergo completion ALND, 9 patients had neoadjuvant chemotherapy, and 4 patients had missing data.

Surgery and pathology

SLNs were identified intra-operatively using both blue dye and radioactive colloid. Lymph nodes that stained blue, were radioactive, or were palpably suspicious, were considered sentinel lymph nodes and sent for immediate intraoperative frozen section pathological evaluation. All lymph nodes sent were submitted for examination. Each lymph node was bisected and imprinted for cytology analysis. Frozen section examination was performed on both halves in nodes measuring less than 1 cm in maximum diameter, while only one half was examined in larger nodes. Three levels sectioned at intervals of 100μm were obtained from each half. Permanent sections using haematoxylin and eosin (HE) were prepared from the remaining SLN material. Only one level was performed unless suspicious cells were detected by the pathologist. Immunohistochemistry was only used to confirm the presence of tumor in suspicious areas with isolated atypical cells on routine exam. Serial HE was not routinely performed on SLNs.

Applying different models

MSKCC nomogram (Model A)

The MSKCC nomogram developed by Van
Zee et al.\(^{(7)}\) incorporates eight variables to estimate the risk of non SLN metastasis; The primary tumor size, tumor type and nuclear grade (ductal grade 1, ductal grade 2, ductal grade 3, lobular), method of SLN metastasis detection (frozen section, routine HE, serial HE, Immunohistochemistry (IHC)), lymphovascular invasion (present or absent), multifocality (unifocal or multifocal), number of positive SLNs, and number of negative SLNs. These variables were used to validate the MSKCC nomogram in our sample. This method was referred to as Model A.

**The modified predictive model (Model B)**

This method uses the proportion of positive and negative SLN instead of the absolute number of positive and negative SLNs in the MSKCC nomogram. The proportions were calculated by dividing the number of positive and number of negative SLN on the total number of SLNs removed. The MSKCC nomogram uses a scale of 1-7 for the number of positive SLNs, and a scale of 0-14 for the number of negative SLNs. The proportion of positive and proportion of negative SLNs for each patient was multiplied by the upper limit of its corresponding scale; 7 and 14 respectively, and used in the MSKCC calculator.

The predicted probability of non sentinel axillary lymph node metastasis in both models was calculated using the MSKCC nomogram calculator available at the institution’s website (http://www.mskcc.org/nomograms).

**Verifying the method used for model B**

As the formula for model A was not available, the following three models were generated from our data to verify our method used in model B:

- Model 1: Logistic regression test was applied on our data using the same variables incorporated in the MSKCC nomogram. This model represents model A.

- Model 2: The formula generated by Model 1 was used, but numbers of positive and negative SLNs were replaced by proportions in the same manner applied for model B and mentioned previously.

- Model 3: Logistic regression test was applied on the same variables used in the MSKCC model except that the percentage of positive SLN was used instead of the number of positive and number of negative SLNs.

Correlation between Model 2 and Model 3 was performed to assess if the two methods provide similar estimates.

**Statistical analysis**

The data collected for each patient included: Data specific for the nomogram (Age at diagnosis, pathological size of invasive tumor, tumor type, nuclear grade, presence of lymphovascular invasion, multifocality, estrogen receptor status, method of SLN metastasis detection, and number of positive and number of negative SLNs), and non sentinel axillary lymph node biopsy result.

Normally distributed numeric data was expressed using means ± standard deviations, minimum, and maximum. Numeric data was tested for normal distribution using Kolmogorov-Smirnov test and was analyzed using Student’s-t-test. Equality of variances was tested with Levene’s test. Categorical data was analyzed using the Chi-Square test or Fisher’s-Exact test. Sample models were built using logistic regression test, and correlation between these models was assessed using Pearson correlation tests and bootstrapping based on 1000 samples. The accuracy of the nomogram was assessed by calculating the area under the ROC curve. The ROC curves of both models were compared using Hanley and McNeil method. Predicted probabilities at cut-off values of 20% or less were compared with the actual status of the NSLN for model A and model B. The specificity, negative predictive value (NPV), and false-negative values were calculated for both models. Statistical analyses were conducted using SPSS 18.0 (SPSS, Chicago, IL).

**Results**

In this study, 91 patients had positive SLNs and underwent ALND. The mean pathological tumor size was 2.77 ± 1.57 cm. The mean number of SLN retrieved was 3.8 ± 1.7 (range, 1-7) of which, on average 1.6 ± 1.1 (range, 1-6)
<table>
<thead>
<tr>
<th>Characteristics of the study population</th>
<th>KHCC (n = 91)</th>
<th>MSKCC (n = 373)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50</td>
<td>55 (60.0)</td>
<td>157 (42.1)</td>
<td>.002</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>36 (40.0)</td>
<td>216 (57.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Pathological size (cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 0.5</td>
<td>2 (2.2)</td>
<td>13 (3.5)</td>
<td>.005</td>
</tr>
<tr>
<td>0.6 - 1.0</td>
<td>6 (6.6)</td>
<td>49 (13.1)</td>
<td></td>
</tr>
<tr>
<td>1.1 - 2.0</td>
<td>28 (30.8)</td>
<td>166 (44.5)</td>
<td></td>
</tr>
<tr>
<td>2.1 - 3.0</td>
<td>29 (31.9)</td>
<td>93 (24.9)</td>
<td></td>
</tr>
<tr>
<td>3.1 - 5.0</td>
<td>20 (22.0)</td>
<td>41 (11)</td>
<td></td>
</tr>
<tr>
<td>&gt; 5.1</td>
<td>6 (6.6)</td>
<td>11 (2.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor type and nuclear grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ductal, I</td>
<td>5 (5.5)</td>
<td>11 (2.9)</td>
<td>.68</td>
</tr>
<tr>
<td>Ductal, II</td>
<td>43 (47.3)</td>
<td>175 (46.9)</td>
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<tr>
<td>Ductal, III</td>
<td>30 (33.0)</td>
<td>129 (34.6)</td>
<td></td>
</tr>
<tr>
<td>Lobular</td>
<td>13 (14.3)</td>
<td>58 (15.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphovascular invasion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>49 (53.8)</td>
<td>219 (58.7)</td>
<td>.41</td>
</tr>
<tr>
<td>Yes</td>
<td>42 (46.2)</td>
<td>154 (41.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Multifocality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>77 (84.6)</td>
<td>241 (64.6)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Yes</td>
<td>14 (15.4)</td>
<td>132 (35.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Estrogen receptor status</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Negative &lt;10%</td>
<td>19 (20.9)</td>
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<td>Positive</td>
<td>72 (79.1)</td>
<td>290 (77.7)</td>
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</tr>
<tr>
<td><strong>Method of detection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frozen Section</td>
<td>82 (90.1)</td>
<td>273 (73.2)</td>
<td>&lt; .001</td>
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<td>Routine</td>
<td>9 (9.9)</td>
<td>23 (6.2)</td>
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</tr>
<tr>
<td>Serial HE</td>
<td>0 (.0)</td>
<td>40 (10.7)</td>
<td></td>
</tr>
<tr>
<td>Immunohistochemistry IHC</td>
<td>0 (.0)</td>
<td>18 (4.8)</td>
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<tr>
<td><strong>Number of positive SLN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>60 (65.9)</td>
<td>265 (71)</td>
<td>.25</td>
</tr>
<tr>
<td>2</td>
<td>20 (22.0)</td>
<td>75 (20.1)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3 (3.3)</td>
<td>21 (5.6)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5 (5.5)</td>
<td>8 (2.1)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2 (2.2)</td>
<td>3 (.8)</td>
<td></td>
</tr>
<tr>
<td>≥ 6</td>
<td>1 (1.1)</td>
<td>1 (.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Number of negative SLN</strong></td>
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<td></td>
</tr>
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<td>17 (18.7)</td>
<td>132 (35.4)</td>
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<tr>
<td>4</td>
<td>9 (9.9)</td>
<td>22 (5.9)</td>
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</tr>
<tr>
<td>≥ 5</td>
<td>12 (13.2)</td>
<td>27 (2.2)</td>
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</tr>
</tbody>
</table>

Table 1: Characteristics of the study population

Calculated using Chi-square and Fisher’s exact test.
Values are n (%).
HE = Hematoxylin & eosin; IHC = Immunohistochemistry; SLN = Sentinel lymph node.
SLN were positive and 2.2 ± 1.7 (range, 0-6) SLN were negative. The mean number of lymph nodes retrieved from ALND was 21.5 ± 8.7 (range, 8-55).

Table 1 shows the descriptive characteristics of the study population. Our population significantly (p value ≤ 0.02) differed from the MSKCC population regarding the age at time of diagnosis, the pathological size if invasive tumor, the presence or absence of multifocality, and the method of SLN metastasis detection. The characteristics of the primary tumor and SLN for those with and without NSLN metastasis are shown in Table 2. Non sentinel lymph node (NSLN) metastasis was found in 35 patients (38.5%), whereas in 56 patients (61.5%) the SLN were the only axillary lymph nodes involved.

The ROC curve for model A and model B is shown in Fig. 1. The area under the ROC curve was .76 (95% CI, .66-.84) for model A; and

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>Non sentinel axillary lymph nodes biopsy result</th>
<th>P value</th>
</tr>
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<td></td>
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<td>Negative (n=56)</td>
<td>Positive (n=35)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>≤ 50 years</td>
<td>35 (62.5)</td>
<td>20 (57.1)</td>
</tr>
<tr>
<td></td>
<td>&gt; 50 years</td>
<td>21 (37.5)</td>
<td>15 (42.9)</td>
</tr>
<tr>
<td>Pathological size of invasive cancer</td>
<td></td>
<td>2.68 (1.38)</td>
<td>2.92 (1.83)</td>
</tr>
<tr>
<td>in centimeters&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor type and nuclear grade</td>
<td>Ductal, I</td>
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<td>2 (5.7)</td>
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<td>10 (28.6)</td>
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<td></td>
<td>Lobular</td>
<td>6 (10.7)</td>
<td>7 (20.0)</td>
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<tr>
<td>Presence of lymphovascular invasion</td>
<td>No</td>
<td>32 (57.1)</td>
<td>17 (48.6)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>24 (42.9)</td>
<td>18 (51.4)</td>
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<tr>
<td>Multifocality</td>
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<td>51 (91.1)</td>
<td>26 (74.3)</td>
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<td>5 (8.9)</td>
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<tr>
<td>Estrogen receptor status</td>
<td>Negative &lt;10%</td>
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<td>9 (25.7)</td>
</tr>
<tr>
<td></td>
<td>Positive ≥10%</td>
<td>46 (82.1)</td>
<td>26 (74.3)</td>
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<tr>
<td>Method of SLN metastasis detection</td>
<td>Frozen Section</td>
<td>48 (85.7)</td>
<td>34 (97.1)</td>
</tr>
<tr>
<td></td>
<td>Routine</td>
<td>8 (14.3)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Number of positive SLN&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>1.23 (0.54)</td>
<td>2.17 (1.40)</td>
</tr>
<tr>
<td>Proportion of positive SLN&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>0.35 (0.20)</td>
<td>0.72 (0.28)</td>
</tr>
<tr>
<td>Number of negative SLN&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>2.96 (1.65)</td>
<td>1.06 (1.11)</td>
</tr>
<tr>
<td>Proportion of negative SLN&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>0.65 (0.20)</td>
<td>0.28 (0.28)</td>
</tr>
</tbody>
</table>

Table 2 : Characteristics of primary tumor and SLN for those with and without NSLN metastasis

Values are n (%) unless otherwise indicated.

<sup>a</sup> Values are mean (standard deviation).

SLN = Sentinel lymph node
NSLN metastasis in which ALND can be safely omitted and thereby, preventing the possible associated complications. The first nomogram was developed by Van Zee et al. at MSKCC (7).

In comparison to the MSKCC breast cancer population, our sample showed significant (p value ≤ 0.02) differences in terms of age at diagnosis, pathological size of invasive tumor, and focality of the tumor. Tumors occurred at a younger age with the majority of our patients being younger than 50 years. The pathological size of invasive component of the tumor was larger than 2 cm in more than 50% of our population. This is most likely due to the late presentation of our patients, which could be explained, in-part, by the absence of a national screening program.

According to our institution’s protocols, SLN biopsy is a staging procedure, and all lymph nodes with radioactivity, stained with blue, or palpably suspicious at time of lymph node retrieval should be considered sentinel nodes and sent for intra-operative frozen section analysis, and post operative routine histopathological analysis. This explains the large mean number of SLN retrieved in comparison to other institutes. All retrieved SLNs are submitted for intraoperative frozen section analysis followed by routine examination using HE. Serial HE was not performed as opposed to MSKCC, and IHC was only used to confirm the presence of tumor in suspicious cases with atypical cells during routine exam.

Although all these discrepancies existed, the MSKCC model still proved to be accurate in predicting the probability of NSLN metastasis in which ALND can be safely omitted and thereby, preventing the possible associated complications. The first nomogram was developed by Van Zee et al. at MSKCC (7).

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Although all these discrepancies existed, the MSKCC model still proved to be accurate in predicting the probability of NSLN metastasis in our breast cancer patients with positive SLN biopsy. The area under the ROC curve was 0.76, similar to that achieved when the model was applied on the prospective MSKCC dataset.
Several studies have shown that the size of SLN metastasis is highly predictive of NSLN status (23-26). The proportion of involved SLNs is one of the measures of the tumor burden and overall metastasis in the positively involved SLNs, and has been shown to be an independent predictor of NSLN status (26). The MSKCC nomogram incorporates both, the number of positive, and the number of negative SLNs as measures of the size of SLN metastasis, and thereby, predictors of NSLN metastasis. Since these factors are used as independent variables, and absolute numbers of positive and negative SLNs are used, the current model does not reflect the proportion of SLNs involved by disease. For example, if the current nomogram was applied on a patient with unifocal invasive ductal carcinoma with the following characteristics: Size of invasive component 2 cm; nuclear grade 2; positive lymphovascular invasion; and positive estrogen receptor, and she had 2 positive and 2 negative SLNs detected by means of frozen section, the resulting score would be 49%. If the same patient had 3 positive and 3 negative SLNs, the predicted probability would be 55%. Meanwhile, both cases would have a similar score (53%) if model B was used as they both have the same proportion (50%) of SLNs involved.

This observation becomes more prominent when the total number of SLN removed is relatively small. This could be explained by the fact that any change in the number of positive or number of negative SLNs will have a large effect on their respective proportions since the denominator (total number of SLNs) is small. In other words, when the total number of SLNs removed is small, the proportions will be sensitive to any change in the number of positive or negative SLNs. This might, in-part, explain why the nomogram showed lower performance when the mean number of SLNs removed was low in some studies (5, 11, 15). Another possible explanation is that larger numbers of SLNs removed are more representative samples of the axilla although several studies had larger mean numbers of SLNs retrieved while the accuracy of the nomogram was relatively low (10, 12).

Since the total number of SLN retrieved varies among patients and institutes, the proportion of involved SLNs is a more precise measure of the size of SLN metastasis. Accordingly, we attempted to replace the number of positive and the number of negative SLNs with their respective proportions in the MSKCC nomogram. This raised the accuracy of the predictive model, and improved the specificity, sensitivity, and negative predictive value (Table 3), though not reaching a statistically significant value (p value = 0.09). This could be due to the large mean number of SLN removed, which attenuated the effect of replacing the absolute numbers by proportions.

To verify our method, different models were generated using our sample. Model 2, which represents the modified predictive model (Model B), was compared to the model generated by incorporating the percentage of positive SLNs and excluding the number of positive and number of negative SLNs (Model 3). The correlation between the predicted probabilities of the two models was 0.94 (95% CI, 0.90-.97). This means that the method applied for replacing the absolute numbers of positive and negative SLNs by their proportions in model B does represent the percentage of SLNs involved by malignancy.

In conclusion, The MSKCC nomogram, apart from being the first predictive model for NSLN metastasis, is widely validated in different populations as it incorporates variables routinely reported in standard SLN pathology reports, and is available in the form of an online calculator. To our best knowledge, this is the first study to validate the MSKCC model in our region, and although differences existed between our breast cancer population and the population from which the model was derived, and despite the discrepancies in the method of SLN detection, the MSKCC nomogram was accurate in predicting the likelihood of NSLN metastasis in our breast cancer population.

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References


