# Efficacy of Breast Cancer Nomograms and Factors Related to Non-Sentinel Lymph Node Metastasis in Breast Cancer: A Cross Sectional Study

# Meme Kanseri Nomogramlarının Etkinlikleri ve Non-Sentinel Lenf Nodu Metastazı Üzerinde Etkili Faktörler: Kesitsel Bir Çalışma

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**Abstract**
Sentinel lymph node (SLN) biopsy for breast cancer was accepted and implemented worldwide. Many researchers found that 50-70% of patients with positive SLN biopsy have no further non-sentinel lymph node (NSLN) metastasis. Memorial Sloan Kettering Cancer Center (MSKCC) and Stanford nomograms are the two online calculators to identify patients who have low risk for NSLN metastasis. Aim to validate MSKCC and Stanford nomograms and to investigate which patient characteristics are effective on NSLN metastasis. Between May 2003 and June 2008 patients who underwent SLN biopsy due to breast cancer enrolled to the study. Patient clinicopathologic features and NSLN status were recorded. NSLN metastasis risks were calculated by MSKCC and Stanford nomograms. The relations between the risk scores and NSLN status, NSLN status and patient features were investigated. Results: The AUC values for MSKCC and Stanford nomograms were 0.651 (p=0.004) and 0.631 (p=0.001) respectively. Mean age of the patients were 51.4 (30-85); mean tumor size were 2.70 cm (0.7-8.5). Micrometastasis, macrometastasis and SLN involvement proportions were found statistically significant for NSLN metastasis. Age, tumor size, histology, grade, lymphatic invasion, multifocality and estrogen receptor status were found statistically insignificant. Both MSKCC and Stanford nomograms weakly predicted NSLN metastasis in our patient group. Although the value of the nomograms seems to be diminished after Z011 study, if improved, they can help physicians and patients to decide whether ALND is beneficial in preventing and controlling loco-regional or systemic disease recurrence.
**Keywords:** Axillary metastasis, breast cancer, breast cancer nomogram, sentinel lymph node, SLN biopsy

**Özet**
Meme kanserinde sentinel lenf nodu (SLN) biyopsisi dünya çapında kabul edilmiş ve uygulanmakta olan bir yöntemdir. Pozitif SLN biyopsisi saptanmış olan hastalarda %50-70 oranında non-sentinel lenf nodu (NSLN) metastazı saptanmamaktadır ve gereksiz aksiller diseksiyon yapılmaktadır. Memorial Sloan Kettering Kanser Merkezi (MSKKM) ve Stanford nomogramları NSLN metastazı düşük riskli olan hasta grubunu tanımlamak için kullanılan hesaplama yöntemlerindendir. NSLN metastazını hesaplamada MSKCM ve Stanford nomogramlarının ne kadar etkin olduğunu ve bu risk üzerinde hangi faktörlerin etkili olduğunu araştırmaktır. Mayıs 2003 ve Haziran 2008 tarihleri arasında meme kanseri tanısı alan ve SLN biyopsisi yapılan hastalar çalışmaya retrospektif olarak dahil edildi. Hastaların klinikopatolojik özellikleri ve NSLN'de metastaz olup olmadığı kaydedildi. Her bir hastanın NSLN metastaz riski hem MSKKM hem de Stanford nomogramı ile hesaplandı. NSLN'nin metastaz durumu ile elde edilen risk skorları ve klinikopatolojik veriler istatistiksel yöntemler ile kıyaslandı. MSKKM ve Stanford nomogramları için hesaplanan eğri altı alan (EAA) sırasıyla 0.651 (p=0.004) ve 0.631 (p=0.001) olarak saptandı. Hastaların ortalama yaşı 51.4 (30-85); ortalama tümör çapı 2.70 cm (0.7-8.5) idi. Mikrometastaz, makrometastaz ve SLN tutulum oranı NSLN metastazı üzerine etkisi istatistiksel olarak anlamlıydı. Yaş, tümör çapı, histolojik tip, grade, lemfatik invazyon, multifokalite ve östrojen reseptör durumu istatistiksel açıdan anlamlı değildi. MSKKM ve Stanford nomogramları NSLN metastaz riskini çalışmamızda zayıf olarak tahmin edebilmiştir. Z011 çalışması ile her ne kadar nomogramların değeri azalmış gibi görünse de, etkinlikleri arttırılabilirse, aksiller diseksiyonun lokorejiyonel ya da sistemik hastalık rekürrensinin önlenmesine ne kadar fayda sağlayacağı hakkında hastalara ve hekimlere fikir verebilecektir.
**Anahtar kelimeler:** Aksiller metastaz, meme kanseri, meme kanseri nomogramı, sentinel lenf nodu, SLN biyopsisi

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## Introduction

Sentinel lymph node (SLN) biopsy became the standard method to determine the nodal status of breast cancer, and has been accepted and implemented by worldwide institutions to decide further treatment options. Patients who have SLN metastasis are offered to have axillary lymph node dissection (ALND). However, many researchers found that 50-70% of patients with positive SLN biopsy have no further non-sentinel lymph node (NSLN) metastasis and believe that some patients have unnecessary ALND (1-5). To identify which breast cancer patients are in a high risk for NSLN metastasis some researchers developed nomograms with using patients' pathologic features. Memorial Sloan Kettering (MSKCC) and Stanford nomograms are the two nomograms which have been used by physicians to identify patients who have low risk for NSLN metastasis and to save

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them from unnecessary axillary lymph node dissection. These nomograms have been validated by some researchers, however, the accuracy of these nomogram may be different in distinct populations. Our aim in this study is to investigate how MSKCC and Stanford nomograms are accurate in a subset of Turkish breast cancer patients and which patient clinicopathologic factors are effective on NSLN metastasis.

## Material and Methods

We reviewed the University of Istanbul Cerrahpasa Medical School breast cancer patient database between May 2003 and June 2008. Patients who underwent SLN biopsy due to the breast cancer were selected and enrolled to the study. Age, tumor size, histology, grade, lymphatic invasion, multifocality, number of SLN excised, number of positive SLN, number of negative SLN, size of nodal metastasis, SLN method of detection, estrogen reseptor status and ALND pathology reports were recorded to the Excel database program. Patients were cathegorized into NSLN negative (no metastasis in NSLN) and NSLN positive (metastasis present in NSLN) groups.

*SLN Biopsy Technique*

Patients underwent SLN biopsy with either methylene blue (Neopharma GmbH & Co. KG, Aschau, Germany) or methylene blue with 99Technetium tincolloid injection, defined as combination technique, to assess the axillary lymph node status. All procedures were performed under general anesthesia. Regarding combination technique, 0.5-1 mCi (17.5-37 MBq) 99mTc tincolloid or nanocolloid was injected into four sites of the periareolar region. The dose was 37 MBq if the procedure was done the day before surgery or 17.5 MBq if the injection was on the day of the surgery. In the operating room, 3-5 cc of methylene blue dye was injected to the peritumoral or subareolar area after the induction of general anesthesia. Then, the breast was massaged for 5-10 min. to help the migration of the blue dye to the lymph nodes. The SLNs were identified by both tracing them with the gamma probe and following the blue colored lymph channels or nodes. A sentinel node was defined as any blue or hot, or both blue and hot nodule. All removed sentinel lymph nodes were evaluated by a pathologist intraoperatively.

*Pathology*

SLNs were sent to the pathology department after the excision was completed. Multiple sections were prepared for imprint cytology. If the frozen analysis was negative, the patient did not undergo ALND and the SLNs were taken to routine analysis. The multiple sections were analyzed by Hematoxilen&Eosine dye, and in case of a negative result immunohistochemistry procedure was done to detect size of nodal metastasis. The nodal metastasis is defined as macrometastasis if the size is >2mm; micrometastasis if the size is between 0.2 – 2mm; and isolated tumor cells (ITC) if the size is <0.2mm. Patients, whose SLNs were found positive for malignancy, underwent complete axillary dissection. Otherwise, no further surgical treatments were performed for negative sentinel nodes. In addition, all patients had mastectomy after SLN biopsy.

*Calculating NSLN Metastasis Risk*

For each patient, NSLN metastasis risks were calculated from MSKCC`s and Stanford`s online website calculator which are available on the internet.
(http://www.mskcc.org/mskcc/html/15938.cfm and www.stat.stanford.edu/~olshen/ SDLNcalculator)

*Statistical Analysis*

To measure nomogram discrimination, ROC (receiver operating characteristic) curve was constructed and AUC values were calculated (Figure 1). Statistical analysis of risk scores and NSLN involvement was investigated. The relations between NSLN metastasis and age, tumor size, and rate of SLN involvement were analyzed by t-test; histology, lymphatic invasion, multifocality, estrogen receptor status, micrometastasis, and macrometastasis were analyzed by chi-square; grade was analyzed by Mann Withney U test (Table 1).

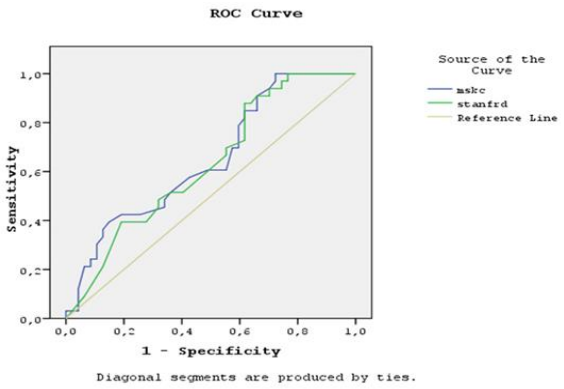


**Figure 1.** Receiver-operator characteristic (ROC) curve for MSKCC and Stanford nomogram calculated from Cerrahpasa Medical School's data.

## Results

For NSLN negative and positive groups, mean age of the patients were 52.96 (32-77) and 49.18 (30-85); mean tumor sizes were 2.69 (0.8-8.5) and 2.71 (0.7-6.0) cm respectively. The AUC values for MSKCC and Stanford nomograms were 0.651 (p=0.004) and 0.631 (p=0.001) respectively and they were found statistically significant. Clinicopathologic features of NSLN positive and

negative patients were summarized in Table 2. Regarding the relation between the NLSN metastasis and the patient features micrometastasis, macrometastasis and SLN involvement proportions were found statistically significant. No statistical significance was found regarding age, tumor size, histology, grade, lymphatic invasion, multifocality and estrogen receptor status.

**Table 1.** Relation of patient characteristics and NSLN metastasis.

| Patient Characteristics | Statistical Test | P |
|---|---|---|
| Age | t-test | 0.150 |
| Tumor Size | t-test | 0.953 |
| Histology | Chi-Square | 0.350 |
| Grade | Mann-Whitney | 0.953 |
| Lymphatic Invasion | Chi-Square | 0.140 |
| Multifocality | Chi-Square | 0.60 |
| Estrogen Receptor Status | Chi-Square | 1.00 |
| Ratio of involved SLN | t-test | 0.0497 |
| Micrometastasis | Chi-Square | 0.009 |
| Macrometastasis | Chi-Square | 0.009 |

**Discussion**

In this study, the efficacy of MSKCC and Stanford nomograms to predict NSLN metastasis risk in SLN positive breast cancer patients and the patients' clinicopathologic features that were effective on NSLN metastasis were evaluated. Both MSKCC and Stanford nomograms weakly predicted NSLN metastasis risk in our patient group. The AUC values were 0.651 and 0.631 respectively, and they were found statistically significant. SLN involvement ratio and SLN metastasis size (micro or macrometastasis) were the significant factors to be responsible for the NSLN metastasis. Tumor size was expected to be a significant factor, however, it was not. The reason may be due to the fact that there was more number of T1 (n=36) and T2 (n=38) tumors than the number of T3 (n=6) tumors in our patient distribution.

The first breast cancer nomogram was developed by Van Zee with using the retrospective data of breast cancer patients, which were validated on prospective patients, in MSKCC (6). AUC values for retrospective and prospective patients in MSKCC were 0.76 and 0.77 respectively. Stanford nomogram is another nomogram developed from the data of two centers (Bay Area SLN Study for Detection of Axillary Metastasis in Breast Cancer Data and Northwestern Memorial Hospital records). The AUC values calculated from these centers were reported as 0.77 and 0.62 respectively (7). However, the AUC value calculated from our patients' data by both MSKCC and Stanford breast cancer nomograms were less than the original AUC values. The reason for the weak positivity of these nomograms can be due to the clinicopathologic discrepancies between the population groups.

**Table 2.** Patient features for the NSLN positive and negative patients.

| Patient Features | NSLN + | NSLN - |
|---|---|---|
| Mean Age | 49.18 (30-85) | 52.96 (32-77) |
| Mean Tm Size | 2.71 (0.7-6.0) | 2.69 (0.8-8.5) |
| Number of T1 tm | 14 (42.4%) | 22 (46.8%) |
| Number of T2 tm | 16 (48.4%) | 22 (46.8%) |
| Number of T3 tm | 3 (9.2%) | 3 (6.4%) |
| Tm Histology | | |
| Ductal | 23 (69.7%) | 37 (78.7%) |
| Lobular | 10 (30.3%) | 10 (21.3%) |
| Grade | | |
| I | 0 (0%) | 4 (8.5%) |
| II | 28 (84.8%) | 32 (68.1%) |
| III | 5 (15.2%) | 11 (23.4%) |
| LVI | | |
| Present | 29 (87.9%) | 35 (74.5%) |
| Absent | 4 (12.1% | 12 (25.5%) |
| Unifocal Tm | 27 (81.8%) | 45(%95.7) |
| Multifocal Tm | 6 (18.2%) | 2 (4.3%) |
| N. metastatic SLN | | |
| 1 | 21 (63.6%) | 37 (78.7%) |
| 2 | 8 (24.2%) | 9 (19.1%) |
| 3 | 3 (9.1%) | 1 (2.1%) |
| 7 | 1 (3%) | 0 (0%) |
| N. non-metastatic SLN | | |
| 0 | 25 (75.8%) | 25 (53.2%) |
| 1 | 3 (9.1%) | 10 (21.3%) |
| 2 | 2 (6.1%) | 7 (14.9%) |
| 3 | 2 (6.1%) | 3 (6.4%) |
| 4 | 0 (0%) | 1 (2.1%) |
| 6 | 1(3%) | 1 (2.1%) |
| Micrometastasis | 0 (0%) | 9 (19.1%) |
| Macrometastasis | 33 (100%) | 38 (80.9%) |
| ER + | 31 (93.9%) | 43 (91.5%) |
| ER - | 2 (6.1%) | 4 (8.5%) |

N: Number; Tm: Tumor; ER :estrogen receptor.

The performance of MSKCC and Stanford nomograms were evaluated in the literature and the results are summarized in Table 3. Gur et al. (8) and Pinero et al. (9) designed their studies from multicenters and have the highest number of patients. It can be seen from Table 3 that the studies which have poor AUC values usually have small number of patients. Therefore, the number of study patients may play an important role in the nomogram validation. Tanaka et al. (28) applied

these nomograms for micrometastatic\ITC and macrometastatic patients separately and reported that AUC values were 0.469 and 0.680 for MSKCC respectively, 0.574 and 0.676 for Stanford nomogram respectively, and concluded that nomograms were not effective on micrometastatic\ITC group. Ozbas et al. (29) evaluated the nomograms in $ER^+$ and triple negative breast cancer patients separately and concluded that the nomograms predict the metastasis risk better in $ER^+$ patients than triple negative patients.

**Table 3.** The validation studies for MSKCC and Stanford nomogram.

| Author | Year | N | Mean Age | MSKCC | Stanford |
|---|---|---|---|---|---|
| Smidt[10] | 2005 | 222 | NA | 0.78 | - |
| Degnim[11] | 2005 | 462 | 57&53 | 0.72 | - |
| Lambert[12] | 2006 | 200 | NA | 0.71 | - |
| Cripe[13] | 2006 | 92 | 56 | 0.82 | - |
| Dauphine[14] | 2007 | 39 | 53 | 0.063 | - |
| Zgajnar[15] | 2007 | 276 | NA | 0.72 | - |
| Alran[16] | 2007 | 588 | 57 | 0.72 | - |
| Klar[17] | 2007 | 98 | NA | 0.58 | - |
| Ponzone[18] | 2007 | 186 | NA | 0.71 | - |
| Pal[19] | 2008 | 118 | NA | 0.68 | - |
| Kohrt[7] | 2008 | 77 | 55.8 | 0.62 | 0.74 |
| Scow[20] | 2009 | 464 | NA | 0.74 | 0.72 |
| Gur[21] | 2009 | 319 | 54.2 | 0.70 | 0.64 |
| Coufal[22] | 2009 | 330 | NA | 0.68 | 0.66 |
| Coutant[23] | 2009 | 561 | NA | 0.78 | - |
| Gur[8] | 2010 | 607 | 50.4 | 0.70 | 0.58 |
| Moghaddam[24] | 2010 | 108 | NA | 0.63 | 0.67 |
| Sanjuan[25] | 2010 | 114 | 57.05 | 0.67 | - |
| Hidar[26] | 2011 | 87 | 51.3 | 0.73 | 0.76 |
| Lombardi[27] | 2011 | 139 | NA | 0.76 | 0.70 |
| Tanaka[28] | 2011 | 89 | NA | 0.70 | 0.75 |
| Pinero[9] | 2012 | 501 | 55.4 | 0.68 | 0.65 |
| Ozbas[29] | 2012 | 649 | 51 | | |
| ER + | | 441 | | - | 0.70 |
| Trip.neg. | | 128 | | - | 0.61 |

NA: Not available; ER: Estrogen receptor; Trip.neg: Triple negative.

Breast cancer nomograms were developed to help physicians and patients whether ALND is helpful in preventing and controlling loco-regional or systemic disease recurrence. Proponents of ALND argue that extra-information may help patients to decide taking chemotherapy and ALND can decrease loco-regional disease recurrence and distant metastasis (30-32). Opponents of ALND express that the benefits of ALND is minimal because majority of patients take adjuvant systemic therapy and no further metastasis can be detected in 50% of patients who have positive SLNB (1-5). Although breast cancer nomograms were seen as a solution for this debate, weak positive results suggested us that they were not perfect by now.

Recently, ACOSOG Z0011 study reported that there was no local or regional recurrence difference between the SLN positive patients who had or had not ALND in early stage breast cancer (33). Even though this result brings to mind that the value of the nomograms have been diminished, Z0011 study has the following limitations. Firstly, the concept has not been prevailed worldwide; secondly, patients were limited to T1 and T2 tumors; thirdly, the study was achieved on the patients who had breast conserving surgery; and lastly, there were small number of patients to make a generalization.

To understand how Z011 study effected surgeons, Caudle et al. (34) studied the surgeon practice in SLN positive patients before and after Z0011 study. They found the ALND rates as 85% and 24% respectively. They also reported that surgeons perform ALND for lager tumors and clinicopathologic factors influence ALND decision after Z011 study. Thus, nomograms may be helpful for surgeons while discussing ALND with patients. As a conclusion, both MSKCC and Stanford nomograms weakly predicted NSLN metastasis in our patient group. Although the value of the nomograms seems to be diminished after Z011 study, if improved, they can help physicians and patients to decide whether ALND is beneficial in preventing and controlling loco-regional or systemic disease recurrence.

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ethics committee of University of Istanbul Cerrahpasa Medical School (15.04.2008/10232).

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