Original Study

Predicting the Likelihood of Nonsentinel Lymph Node Metastases in Triple Negative Breast Cancer Patients With a Positive Sentinel Lymph Node: Turkish Federation of Breast Disease Associations Protocol MF09-01

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Abstract

Our aim was to determine the frequency of nonsentinel lymph node involvement of patients with operable triple negative breast cancer and with a positive sentinel lymph node, and to predict the likelihood of nonsentinel lymph node metastases in this cohort of patients by using 4 different nomograms. The accuracy of nomograms in patients for triple negative is yet to be determined.

Background: Triple negative (TN) tumor has a relatively high rate of recurrence and distant metastasis, but results of studies revealed that triple positive tumor is an independent predictor of axillary lymph node involvement. Our aim was to evaluate the frequency of nonsentinel lymph node metastasis (NSLNM) involvement in operable TN breast cancer with positive sentinel lymph node (SLN) and predicting the likelihood of NSLNM in this cohort of patients by using 4 different nomograms. **Methods:** A total of 128 patients with TN and SLN^+ underwent complete axillary lymph node dissection in 14 different centers in Turkey. For comparison, we used our previous multicenter MF08-01 Protocol, which identified 441 patients with estrogen receptor (ER^+) who had a positive SLN biopsy and underwent subsequent complete axillary lymph node dissection. Turkish, Cambridge, and Stanford nomograms and the Tenon Score system were used to calculate the probability of NSLNM. **Results:** Patients with TN tumor had a larger tumor size. The actual percentage of NSLN positivity was 41% in the TN group and 47.1% in patient with ER^+. The Tenon

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Nonsentinel Lymph Node Metastases in Triple Negative Breast Cancer

Score was ≤3.5 in 12% of patients with TN and ER$^+$; the area under the curve in the receiver operating characteristics curve were 0.53 and 0.59, respectively. Based on the Turkish, Cambridge, and Stanford nomograms, areas under the curve were 0.54, 0.53, and 0.61, respectively in patients with TN, and were 0.79, 0.72, and 0.70, respectively, in patients with ER$^+$. **Conclusion:** Using the Tenon Score system underestimates NSLN positivity, and tested nomograms are not good discriminators of NSLNM in patients with TN and positive SLN.

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Key words: Breast carcinoma, Nomogram, Nonsentinel lymph node, Sentinel lymph node, Triple negative

Introduction

The 3 predictive markers, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), have an independent prognostic value in breast cancer (BC) patients.[1] ER is expressed in 80%-90%, and PR is expressed in 70%-80% of all BCs.[2] HER2 is overexpressed in about 15%-20% of cases.[3-5] Steroid and HER2 receptors are strongly associated with survival,[6-11] and results of recent studies have revealed survival rates in great variations among BC patients based on different combinations of ER and PR status.[12-18] BC, therefore, is better presented by the combined receptor expression rather than by each receptor status alone.

The axillary lymph node (ALN) status is one of the strongest independent prognostic factors for disease-free and overall survival of BC, but some tumors are already systemic, even if ALNs are not involved.[1,19] Women with an ER$^-$, ER$^+$/PR$^-$ or HER2$^+$ BC experience a shorter disease-free period than women with an ER$^+$/PR$^+$/HER2$^-$ BC despite no significant difference in ALN involvement among these groups.[20] Rates of ALN involvement in the different prognostic BC subgroups based on the combined immunohistochemistry expression of steroid receptors and HER2 status have not been described in detail in the literature. Here, in this study, our aim is to examine the frequency of nonsentinel lymph node metastases (NSLNM) in operable triple negative (TN) BC cancers with a positive sentinel lymph node (SLN) and secondly to predict the likelihood of NSLNM in this cohort of patients by using 4 different nomograms.

Patients and Methods

We retrospectively reviewed 128 BC patients with TN who underwent SLN biopsy and subsequent completion ALN dissection (CALND) at 14 different breast centers in Turkey. Receptor status was determined by immunohistochemistry staining of ER/PR/HER2, and equivocal HER2 status was validated by fluorescence in situ hybridization. For comparison, we used the patient cohort from our previous multicenter MF08-01 Protocol (where we identified 441 patients who were ER$^+$ and who had a positive SLN biopsy specimen and underwent subsequent CALND).[21] The patients who received neoadjuvant chemotherapy were excluded from the analysis. All the patients underwent SLN biopsy by using isosulfan blue dye alone or in combination with technetium Tc99m sulfur colloid. The technique was performed as previously described in the literature.[22]

Nomogram Analysis

Turkish and Cambridge formulas, Stanford nomograms, and the Tenon Score system were used to calculate the probability of NSLNM because ER status is not a variable in these formulas.[21,23-25] The area under the curve in the receiver operating characteristics (ROC) curve was calculated for each nomograms, and a value >0.70 was accepted as good discrimination. According to Tenon Score system, patients whose scores were ≤3.5 (which constituted the median score) have a 97.3% chance of negative NSLNM.

The Tenon Score system, developed by Barranger et al[23] at the Tenon Hospital was applied to our data set. Three parameters are used for this scoring system (0-7 points): histologic tumor size, macro- or micrometastasis in SLN, and the proportion of involved SLNs among all removed SLNs. Patients with a score ≤3.5 (which constituted 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 the original article by Barranger et al.[23] The formula developed by Pal et al[24] at Cambridge University uses grade, overall metastasis size (OMS), and the proportion of involved SLNs among all removed SLNs. In our study, to standardize OMS, we accepted OMS as 2 mm if the largest metastatic tumor size was smaller than 2 mm. The third nomogram, developed by Stanford University,[25] uses tumor size, status of lymphovascular invasion (LVI), and the largest size of SLN metastasis. Stanford nomogram calculations were done by using the online version of this method (https://www3-hrpdcc.stanford.edu/nsln-calculator/). The final nomogram recently developed by the Turkish Federation of Breast Disease Associations,[21] uses LVI, proportion of positive SLNs to all removed SLNs, and OMS.

Statistical Analysis

The areas under the ROC curve 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, which represents 100% sensitivity and 100% specificity. For perfect validation of a model, the ROC value has to be one that requires a perfect match between the 2 data sets, 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 an ROC of 0.81-0.9 has excellent discrimination.[26,27] The χ^2 and Fisher exact tests were used for comparisons between the nominal (categorical) variables. One-way analysis of variance and Student *t* tests were used for nonparametric (continuous) analysis. *P* values ≤.05 were considered as statistically significant. All analyses were performed by using IBM SPSS Statistics version 18 software (IBM Corporation, Somers, NY).

Table 1 Tumor and Characteristics of Patients Triple Negative (TN) Breast Cancer and Estrogen Receptor Positive (ER^+)

Parameters	TN (n = 128)	ER^+ (n = 441)
Age (y, Median)	51 (29-88)	51 (24-87)
Tumor Size (cm, Median)	3.0 (0.3-10)	2.4 (0.2-10)
Pathologic Tumor Size >2 cm	70%	53%
Nuclear Grade >1	91%	94%
Tumor Grade 3	68%	33%
Multifocal/Multicentric	16%	19%
Lymphovascular Invasion	55%	57%
Macrometastasis (Overall)	93%	93%
Proportion of Positive SLN Numbers to the Number of all Removed SLN	62.5%	52%
Non-SLN Positivity Rate	41%	47%

Abbreviation: SLN = sentinel lymph node.

Results

The mean patient age was 51 years (range, 29-88 years). The mean tumor size was 30 mm (range, 3-100 mm) and multifocality/centricity was present in 16.4% of the cases (n = 21). The mean number of dissected SLNs was 2 (range, 1-13), and the mean number of positive SLNs was 1 (range, 1-6). The mean OMS was 11.5 mm (range, 0.2-33 mm). The actual percentage of NSLN positivity is 41% in TN group and it was 47.1% in patients who were ER^+. The mean number of dissected ALNs was 15 (range, 3-44), and the mean number of involved NSLNM was 2 (range, 0-21). Pathologic tumor size was >2 cm in 70% of patients with TN, and it was 53% in patients with ER^+; pathologic characteristics of both patients with TN and with ER^+ are presented in Table 1.

The variables that we compared among the patients with NSLNM and who only had SLN metastasis were as follows: multifocality/centricity, tumor grade, tumor type, LVI, number of SLN dissected, number of positive SLNs, the proportion of involved SLNs among all removed SLNs, micrometastasis, age, tumor size, and OMS. None of these were statistically significant ($P > .05$). The Tenon Score was ≤3.5 in 12% of patients with TN and those with ER^+ in this analysis. In the literature, it was stated that patients with Tenon scores of <3.5 (which constitutes the median score) have a 97.3% chance of having negative NSLNM in the original article.[23] Compared with the literature having a positive NSLNM was almost 6 times higher in TN patients with a Tenon score of <3.5. All 4 nomograms were applied to 128 patients with TN and 441 patients with ER^+. Based on the Turkish and Cambridge formulas, Tenon Score, and Stanford nomograms, areas under the curve were 0.54, 0.53, 0.53, and 0.61, respectively, in patients with TN (Figure 1) and were 0.79, 0.72, 0.59, and 0.70, respectively, in patients with ER^+ (Table 2).

Figure 1 Receiver Operating Characteristic Curves for Turkish, Tenon, Stanford and Cambridge Formulas for the Data Set With 128 Subjects (Triple Negative Group)

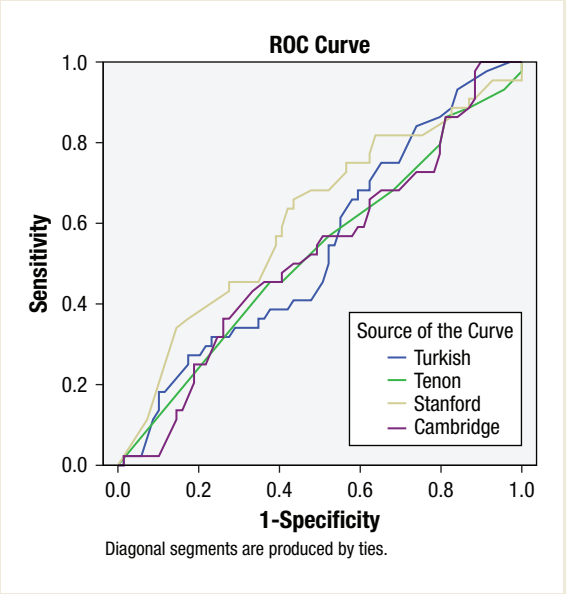

Table 2 Comparison of Area Under the Curve of 4 Different Models in Predicting the Likelihood of Nonsentinel Lymph Node Metastases in Patients With Triple Negative Breast Cancer and Estrogen Receptor Positive (ER^+) And With a Positive Sentinel Lymph Node

	Triple Negative	ER^+
Tenon Score	0.527	0.591
Turkish Formula	0.541	0.79
Cambridge Nomogram	0.525	0.72
Stanford Nomogram	0.614	0.70

Discussion

BC is a heterogenous disease that consists of multiple molecular subtypes. Despite the existence of many readily available prognostic factors, only a few predictive factors are used routinely and widely in the clinics. The presence of ER, PR, and HER2 is of paramount importance in the decision-making process for patients with BC.

The TN group is a biologically diverse group of BC patients with both steroid receptors and HER2 negativity. TN tumors have an overall poorer prognosis than non-TN tumors, showing significantly higher vascular invasion rates.[28] They tend to spread hematogenously, which causes a higher incidence of distant organ metastasis. They are more likely to affect younger and/or premenopausal women; in addition, there is a lack of response to a therapeutic target (nonresponsive to hormonal therapy or trastuzumab). Despite being responsive to traditional chemotherapy, mortality rates remain higher.[29,30]

The strength of this study is that all cases were SLN positive and underwent CALND, which allowed evaluation of the exact NSLNM rate. A potential weakness of the study is that the patients were

enrolled from different breast centers in Turkey. Patients were treated at different centers, and analyses for ER, PR, HER2 were confirmed by different pathologists. One may claim that having basal-like tumors not distinguished from TN tumors is a potential weakness as well.

Results of previous studies have shown that TN tumors do not differ significantly from other types of BC in terms of stage at diagnosis.[18] However, it has been shown that the TN subgroup is more frequently diagnosed between screening periods as an interval cancer. The locoregional relapse rate for TN cancer appears to be identical to that of other molecular subgroups after conservative surgical management; however, the TN phenotype is associated with a higher rate of distant metastasis.[31] TN BCs also exhibit differences in the timing of relapse. Dent et al,[32] showed that patients who were treated with mastectomy or breast-conserving therapy, TN cancers had similar overall local recurrence rates to those of the non-TN group (13% vs. 12%; $P = .77$), but the mean time to local recurrence was significantly shorter for patients with TN (2.8 vs. 4.2 years; $P = .02$). Nguyen et al[33] detected that the 5-year cumulative incidence of local recurrence was 0.8% for luminal A, 1.5% for luminal B, 8.4% for $HER2^+$, and 7.1% for TN. The risk of recurrence appears to be highest in the first 5 year after diagnosis, with relatively few systemic recurrences after this period.

By using the most common subtype of BC as a reference $ER^+/PR^+/HER2^-$, the patients with TN BC has a significantly increased probability of ALN metastasis.[34] Generally, the ALN metastasis rate increases with increased tumor size but Dent et al,[32] revealed that, among the TN group, there was no correlation between tumor size and node status in women with tumors <5 cm. Even the small tumors in the TN group had a high rate of node positivity; 55% of women with tumors of ≤1 cm had at least one positive lymph node.[32] In this study, we found that there was no relationship between the size of the tumor and ALN positivity. Involvement of NSLNM also is associated with increased rate of systemic metastasis over time. The NSLNM rate of patients with TN was 41% in this study and 47.1% in ER^+ tumors.

With a short-term follow-up, it has become clear that HER2 is a prognostic factor for disease-free and overall survival in node positive disease. With a longer follow-up, it is a prognostic factor as well in BC patients who are node negative.[35] The joint expression of steroid receptors and HER2 has a greater predictive value than the expression of each receptor alone. Women with an ER^-, ER^+/PR^-, or $HER2^+$ BC experience a shorter disease-free period than ER^+/PR^+ and $HER2^-$ BC despite no significant difference in ALN involvement between these groups. HER2 overexpression in operable BC has been associated with a positive ALN.[36,37] Because the predictive role of HER2 for ALN involvement has not been reported in the literature well, one may initiate a larger multicenter study to analyze the probability of non-SLN metastasis in patients who are SLN positive by considering all molecular subtypes.

In a published study, triple positive tumors have more frequent involvement of ALN, thus triple positivity is an independent predictor of ALN involvement similar to age, size, and grade of the tumor.[38] They found that triple positive BC has a 1.3-fold increase in axillary involvement higher than BCs of any other ER/PR/HER2 phenotype.[39] The main reason for this higher probability of ALN involvement could be young age and tumor characteristics, such as tumor size and grade in this cohort of patients. In our study, we found that patients with TN who had a larger tumor size (3.0 cm vs. 2.4 cm) than patients with ER^+, and 70% of patients TN had a tumor size >2 cm compared with 53% of women who had a 2 cm or larger tumor in patients with ER^+. Grade 3 tumor was 2 times higher in patients with TN compared with patients who were ER^+. Sixty-three percent of patients with TN had only one SLN dissected. Other parameters, such as age, LVI, micrometastases, multifocality/centricity, and NSLNM rate, were similar in patient with TN and those who were ER^+ (Table 1).

Generally, NSLNM is detected in 35%-50% of patients who were SLN positive. CALND is recommended when the SLN is positive. Nomograms do not predict the probability of NSLNM perfectly in patients with SLN positive BC, but it is more valuable than clinical judgment only.[38,40] Several institutions developed nomograms to identify patients with low risk of NSLNM to avoid unnecessary CALND. The Memorial Sloan-Kettering Cancer Center nomogram was developed and published in 2003, and 3 additional nomograms from England, France, and the United States (Stanford) have been developed and validated. We considered only 4 of these nomograms because ER is one of the parameters in the Memorial Sloan-Kettering Cancer Center nomogram. In 2010, Turkish Federation of Breast Disease Associations evaluated the available BC nomograms to predict NSLNM and to determine the predictors of ALN involvement that yield a nomogram; Turkish Formula that has been validated by other institutions.[41]

The Turkish formula includes 3 variables as follows: LVI, OMS, and proportion of positive SLNs to total SLNs, which were determined as a predictor of NSLNM in the multivariate analysis. We validated the Cambridge formula, and Stanford nomogram as good discriminators of NSLNM in patients with SLN and positive BC for a Turkish population.[21] In this current study, we evaluated patients with TN and ER^+ with SLN positivity. In the patients with TN, all ROC formulas were <0.7, which should be considered as a poor discrimination. In patients who were ER^+, Turkish formula, Cambridge formula, and Stanford nomogram were good predictors of NSLNM, but the Tenon Score did not reach the threshold of 0.7.

Conclusion

Our results showed that the Tenon Score system underestimates NSLN positivity and the Turkish formula, Cambridge formula, and Stanford nomogram are not good discriminators of NSLNM in patients SLN positive and with TN BC. Until a new formula is developed to predict the NSLNM in patients SLN positive and with TN BC, and validated in prospective studies on different patient populations, clinicians should be cautious to use a nomogram on a patient with TN BC.

Clinical Practice Points

- Patients with TN BC are biologically diverse group with disease of both steroid receptors and HER2 negativity, and comprise 15% of all BCs. Although, it has a relatively high rate of recurrence and distant metastasis, it is not clear whether TN tumor is an independent predictor of ALN involvement. In this study, our aim is to examine the frequency of ALN involvement of operable TN BCs

with a positive SLN and to predict the likelihood of NSLNM in this cohort of patients by using 4 different nomograms.

- Patients with TN BC had a larger tumor size, and 50% of the patients had only one SLN dissected. The median age of patients was 51 years. The actual percentage of NSLN positivity was 41% in the TN BC group and 47.1% in patients with ER^+. In the patients with TN BC, all ROC formulas were <0.7, which should be considered as poor discrimination. In the patients with ER^+, the Turkish, Cambridge, and Stanford nomograms were good predictors of NSLNM but the Tenon Score did not reach the threshold of 0.7.
- Until more data are available, physicians should be very cautious when using a nomogram for TN BC patients.

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Disclosure

All the authors have no conflicts of interest.

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