Ann Med Res 2021;28(11):2071-9

Annals of Medical Research

DOI: 10.5455/annalsmedres.2021.03.295

Original Article

Factors effecting the development of sentinel lymph node metastasis in clinical early-stage breast cancers (cT1-2N0): Clinical significance of primary tumor – skin distance

Levent Zirek[1], Azmi Lale[2], Merve Zirek[3], Hatice Nur Lale[4], Ali Cihan Yildirir[1], Erhan Aygen[5]

[1]Department of General Surgery, Cumhuriyet University Medical Faculty Hospital, Sivas, Turkey
[2]Department of Surgical Oncology, Aydin State Hospital, Aydin, Turkey
[3]Department of Biochemistry, Faculty of Medicine, Cumhuriyet University Hospital, Sivas, Turkey
[4]Department of Public Health, Elazig Provincial Health Directorate, Elazig, Turkey
[5]Department of General Surgery, Firat University Medical Faculty Hospital, Elazig, Turkey

Abstract

Aim: It was aimed to determine the demographic, clinicopathological and radiological predictors that may be effective in the development of sentinel lymph node (SLN) metastasis in patients with clinical early-stage breast cancer (cT1-2N0).

Materials and Methods: 178 patients were included in the study. Demographic, clinicopathological and radiological characteristics of the patients were recorded. Among these, there were age, neutrophil / lymphocyte ratio (NLR), HER2, estrogen receptor (ER) and progesterone receptor (PR), proliferation index (Ki- 67), morphological grade, molecular subtype, histopathological subtype, tumor size and localization, multifocality and multicentricity, nipple-areola complex (NAC) infiltration, perineural invasion (PNI), lymphatic invasion (LI), vascular invasion (VI), primary tumor -breast skin distance (DFS).

Results: Larger tumor size, HER-2 positivity, grade 3 histopathology, LI, VI, PNI, and closer DFS were found to be significant in univariate regression analyzes. In ROC analysis, the optimum cut-off value for DFS was found to be 13.5mm. In multivariant regression analyzes, HER-2 positivity, LI, PNI and ≤13.5mm DFS were found as independent SLN metastasis predictors.

Conclusion: Closer DFS, HER-2 positivity, LI and PNI are very strong predictors in patients with clinical early-stage breast cancer that must be taken into account in the development of SLN metastasis in cT1-2N0 breast cancers. These factors can guide clinicians to take accurate decisions in the treatment process.

Keywords: Axillary node metastasis; c-erbB2/HER2-neu; distance from skin; lymphovascular invasion; sentinel lymph node metastasis predictors

INTRODUCTION

The infiltration of the axillary lymph nodes by tumor cells, which is related to the nature of the breast cancer, is the most important clinical entity that determines the prognosis of the disease. In addition, it is the most valuable parameter that the clinician should consider when deciding which treatment modality to perform while treating the disease. Today, we know that axillary lymph node dissection (ALND) provides both the locoregional control of the disease and the determination of the treatment protocol by presenting the nodal stage of the disease (1,2). On the other hand, the morbidities like lymphedema, persistent seroma, and iatrogenic nerve injuries due to ALND should not be underestimated (2-4). Additionally, the fact that the patient has to restrict the upper extremity from some daily activities also disrupts the comfort of life. In contrary with the medical and surgical treatment advantages of ALND, the destructive morbidities forced the clinician to make modifications in axillary nodal grading methods.

In recent studies, it was shown that Sentinel Lymph Node Biopsy (SLNBx) is quite successful in representing the axillary nodal metastasis situation. This method, which provides the advantage of preventing unnecessary ALND and its negative effects by applying ALND only to cases with metastatic Sentinel Lymph Node (SLN), has become a widely preferred surgical procedure today (1,5,6). At this point, the surgeon's prediction about the SLN tumoral

Received: 03.04.2021 **Accepted:** 15.05.2021 **Available online:** 23.11.2021
Corresponding Author: Azmi Lale, Department of Surgical Oncology, Aydin State Hospital, Aydin, Turkey
E-mail: dr.azmilale@hotmail.com

infiltration status would be provide to making more accurate decisions while planning the surgical procedure for breast cancer.

Several parameters as higher T-stage, HER-2 positivity, tumoral poor differentiation, lympho-vascular invasion and tumor location, have been described in relation with the development of nodal metastasis (7-15). In the literature data, there are few studies that evaluating the effect of primary tumor distance-from-skin (DFS) on SLN metastasis (SLNM) (16-19). In addition, the results of these studies are still controversial.

Therefore, in this study, it was aimed to determine the demographic, clinicopathological and radiological predictors that may be effective in the development of sentinel lymph node (SLN) metastasis in patients with clinical early-stage breast cancer (cT1-2N0) and to present evidence-based data to the literature by evaluating the clinical effect of DFS on SLNM.

MATERIALS and METHODS

Patient Characteristics

A total of 388 patients who were diagnosed breast cancer and who were breast-conversing surgery or total mastectomy and SLND followed by ALND between the dates of January 2014 and May 2019, were included in the study.

Female gender and clinical T1-2N0 were the inclusion criteria. Male gender, neoadjuvant treatment history, T3-4 tumor, SLNM >2, micrometastasis in SLNs, presence of ALNM and/or distant metastasis were the exclusion criteria. Finally, a total of 178 patients were included in the study. The patients included in the study were divided into two groups as SLNM and non-SLNM. Risk factors determined as predictive parameters for sentinel lymph node metastasis were compared in groups.

SLND and ALND

SLN mappings were performed intraoperatively by 5 ml isosulfan blue or methylene blue dye injection to periareolar subcutaneous field. All the patients received breast massage for 5-10 min after injection. The lymph nodes that were stained with blue dye were accepted as SLNs, and those that were not stained were accepted as nonSLNs. The patients, who were found to have SLNM and nonSLNM by intraoperative frozen section evaluation, were performed level 1 and 2 lymph node dissection. SLNM were defined as macrometastasis (pN1, metastasis size >2 mm), micrometastasis (pN1mi, metastasis size between >0.2 mm to ≤2 mm), or isolated tumor cells (ITCs) (pN0[i+], metastasis size ≤0.2 mm) (20). Hematoxylin and eosin staining was used to evaluate the involvement of lymph nodes.

Risk factors

The demographic parameters, clinicopathologic and radiologic findings were recorded retrospectively from a prospectively recorded database. Among these there were age, neutrophil / lymphocyte ratio (NLR), HER2, estrogen receptor (ER) and progesterone receptor (PR), proliferation index (Ki- 67), morphological grade, molecular subtype, histopathological subtype, tumor size and localization, multifocality and multicentricity, nipple-areola complex (NAC) infiltration, perineural invasion (PNI), lymphatic invasion (LI), vascular invasion (VI), DFS.

Definitions and measurements

The tumor diameter was accepted as the widest millimeters measured by histopathological evaluation. The TNM staging was carried out according to the American Joint Committee on Cancer (AJCC) staging system (20). MFBC was defined as multiple tumor foci in the same breast quadrant. MCBC was defined as multiple foci in the different quadrants of the same breast. By considering the St. Gallen 2015 Consensus results, the patients were divided into two groups according to Ki-67 index being below and over 20% (21). According to the ASCO guideline, the patients who had HER2 3+ by immunohistochemical (IHC) staining, were accepted as positive. Those who had 2+ (equivocal) were evaluated with in situ hybridization (ISH). Those who had 1+ and 1 – were accepted as negative (22). The ER and PR status were evaluated according to the Allred Score Guideline as 3 or more indicating ER or PR positivity (23). Tumor differentiation grades were scored according to the Elston/Nottingham Modification of Bloom-Richardson System as grades 1,2,3 (24). The molecular subtypes were determined according to 2015 St. Gallen Criteria as luminal A-like (ER-positive and/or PR-positive, HER2-negative, Ki-67 <%20), luminal B-like (ER-positive and/or PR-positive, HER2-negative, Ki-67 >%20-29), luminal HER2-like (ER-positive and/or PR-positive and HER2-positive), HER2-like (ER-negative and PR-negative, HER2-positive), triple negative (ER-negative, PR-negative and HER2-negative) (25). Histopathological subtypes were defined as invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), and mixed type (IDC + ILC). Nipple-areola infiltration by histopathological evaluation was recorded. DFS was defined as the distance between the breast skin and the tumoral closest surface. Measurements recorded in millimeters according to the ultrasonography (USG) findings. The patients who have multifocal and multicentric breast cancer were excluded in the DFS calculation. All USG examinations were performed by the same radiological team with more than 15 years of experience exclusively on breast diseases.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics Version 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) statistical software package. Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and minimum-maximum where appropriate. Chi-square test was used to compare categorical variables between the groups. The normality of distribution for continuous variables was confirmed with the Kolmogorov-Smirnov test. Mann Whitney U-test was used for comparison of continuous variables. Logistic regression analyzes were performed to determine the independent

predictors of nonSLNs metastasis. Significant variables in the univariate analysis were entered in multiple logistic regression analysis. A receiver operator characteristic (ROC) curve analysis was performed in order to identify the optimal cut-off point of the DFS. The most suitable cut-off point was determined according to the highest sensitivity and specificity rates using the ROC curve analysis. The statistical level of significance for all tests was considered to be <0.05.

Ethics
The study was approved by the institutional review board, and the data were collected following the principles of the Declaration of Helsinki.

RESULTS

The clinicopathological and demographic findings of the patients are shown in Table 1. The mean age of the patients was 54.5. The number of patients with SLN metastasis was 109 and the number of patients without SLN metastasis was 69.

Table 1. Demographic and clinicopathological data of the patients

Variables	n(%)*
Age (year)	
Mean ± SD	54.5±11.7
Median (min-max)	54(28–86)
Surgery	
BCS	60(33.7)
Total Mastectomy	118(66.3)
NLR	
Mean ± SD	2.50± 1.47
Median (min-max)	2.16 (0.37 – 12.81)
Tumor Localization	
Right breast	91(51.1)
Leftbreast	87(48.9)
LIQ	8(4.5)
UIQ	24(13.5)
LOQ	9(5.1)
UOQ	98(55.1)
Central	4(2.2)
Multicentric	35(19.7)
Multifocal	19(10.7)
Tumor Size (cm)	
Mean ± SD	2.79± 1.37
Median (min-max)	2.50 (0.7 – 9.0)
T stage	
T1	62(34.8)
T2	116(65.2)
DFS (mm)	
Mean ± SD	14.9±12.2
Median (min-max)	13(0-71)
≤13,5	90(50.6)
>13,5	88(49.4)
Histopathological Subtypes	
IDC	130(73.0)
ILC	27(15.2)
Mixt (IDC + ILC)	21(11.8)
ER	
-	18(10.1)
+	160(89.9)
PR	
-	27(15.2)
+	151(84.8)
HER2	
-	100(56.2)
+	78(43.8)
Ki67	
Mean± SD	31.7± 20.9
<%20	44(24.7)
≥%20	134(75.3)
Molecular Subtypes	
Luminal A-like	22(12.4)
Luminal B-like	45(25.3)
Luminal Her2like	95(53.4)
Her2 like nonluminal	10(5.6)
Tripple negative	6(3.4)
Tumor Grade	
Grade 1	43(24.2)
Grade 2	109(61.2)
Grade 3	26(14.6)
LI	
-	69(38.8)
+	109(61.2)
VI	
-	90(50.6)
+	88(49.4)
PNI	
-	88(49.4)
+	90(50.6)
Number of SLN	
1	125
2	53
SLN metastasis	
-	69(38.8)
+	109(61.2)
pN Stage	
N0	69(38.8)
N1	56(31.5)
N2	33(18.5)
N3	20(11.2)
NAC infiltration	
-	169(94.9)
+	9(5.1)

*: Categorical data except Mean ± SD and Median (min-max) were expressed as n (%).
SD: Standart derivation, BCS: Breast Conservative Surgery, NLR: Neutrophil / Lymphocyte Rate, LIQ: Lower inner quadrant, UIQ: Upper iner quadrant, LOQ: Lower outer quadrant, UOQ: Upper outer quadrant, DFS: Distance from skin, IDC: Invazive ductal carsinom, ILC: Invazive lobuler carcinom, ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human Epidermal Growth Factor -2, LI: Lymphatic Invasion, VI: Vascular Invasion, PNI: Perineural Invasion SLN: Sentinel Lymph Node, pN: Histopathological N stage, NAC: nipple/areola complex

The cross-comparative analysis of the variables that were determined as predictive factors for the development of SLN metastasis is shown in Table 2. According to cross-comparative analysis HER-2, histopathological subtype, LI, VI, PNI, primary tumor diameter, DFS were significant factors.

Table 2. Cross analysis of multiple predictors for metastasis to SLNs

Variables	Metastatic SLNs		P value
	Negative n(%)	Positive n(%)	
Age*	54.6 (32-78)	54.4(34-78)	0.107
Tumor Localization			
Right breast	42(46.2)	49(53.8)	0.154
Left breast	31(35.6)	56(64.4)	
LIQ	3(37.5)	5(62.5)	
UIQ	12(50.0)	12(50.0)	
LOQ	4(44.4)	5(55.6)	0.734
UOQ	42(42.9)	56(57.1)	
Central	1(25.0)	3(75.0)	
Multicentric	11(31.4)	24(68.6)	
Multifocality			
No	68(42.8)	91(57.2)	0.168
Yes	5(26.3)	14(73.7)	
T stage			
T1	30(48.4)	32(51.6)	0.144
T2	43(37.1)	73(62.9)	
HER2			
-	49(49.0)	51(51.0)	**0.014**
+	24(30.8)	54(69.2)	
ER			
-	66(41.3)	94(58.8)	0.847
+	7(38.9)	11(61.1)	
PR			
-	65(43.0)	86(57.0)	0.192
+	8(29.6)	19(70.4)	
Ki-67			
<%20	21(47.7)	23(52.3)	0.297
≥%20	52(38.8)	82(61.2)	
Molecular Subtypes			
Luminal A-like	11(50.0)	11(50.0)	
Luminal B-like	18(40.0)	27(60.0)	0.890
Luminal Her2 like	37(38.9)	58(61.1)	
Her2 like nonluminal	4(40.0)	6(60.0)	
Triple negative	3(50.0	3(50.0)	
Histopathological Subtypes			
IDC	58(44.6)	72(55.4)	**0.024**
ILC	9(33.3)	18(66.7)	
Mixt (IDC + ILC)	6(28.6)	15(71.4)	
Tumor Grade			
Grade 1	24(55.8)	19(44.2)	0.230
Grade 2	43(39.4)	66(60.6)	
Grade 3	6(23.1)	20(76.9)	
LI			
No	50(72.5)	19(27.5)	**<0.001**
Yes	23(21.1)	86(78.9)	
VI			
No	55(61.1)	35(38.9)	**<0.001**
Yes	18(20.5)	70(79.5)	
PNI			
No	53(60.2)	35(39.8)	**<0.001**
Yes	20(22.2)	70(77.8)	
NAC Infiltration			
No	72(42.6)	97(57.4)	0.084
Yes	1(11.1)	8(88.9)	
DFS (mm)**	19(0-71)	10(0-53)	**<0.001**
NLR**	2.12 (0.50-6.63)	2.16 (0.37-12.81)	0.889
Ki-67%**	23(1-80)	30(1-95)	0.101
Tumor Size (mm)**	23(10-50)	26(7-90)	**0.022**

***:mean(min-max), **: median(min-max), LIQ: Lower Inner Quadrant, UIQ: Upper Inner Quadrant, LOQ: Lower Outer Quadrant, UOQ: Upper Outer Quadrant, HER-2: Human Epidermal Growth Factor -2, ER: Estrogen Receptor, PR: Progesteron Receptor, IDC: Invasive Ductal Carcinoma, ILC: Invasive Lobular Carcinoma, LI: Lymphatic Invasion, VI: Vascular Invasion, PNI: Perineural Invasion, NAC: nipple/areola complex, DFS: Distance from skin, NLR: Neutrophil / Lymphocyte Rate**

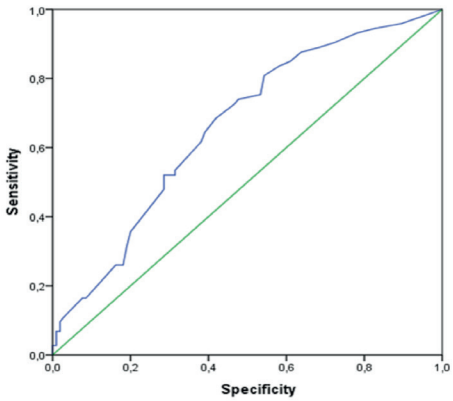

Figure 1. Areas under the ROC curve for distance from skin. (AUC: 0.66 (0.58 – 0.74) CI: %95)

ROC analysis was performed to determine the optimum threshold value for DFS with maximum sensitivity and specificity. Accordingly, the cut-off value in the development of SLN metastasis was found to be 13.5 mm (AUC-ROC: 0.66 (0.58 - 0.74 CI: 95%) p <0.001) (Figure1).

Univariate and multivariate regression analysis results are shown in Table 3. In univariate analyzes, large tumor diameter (OR: 1.03 CI: 95% p = 0.015), HER-2 positivity (OR: 2.16 CI: 95% p = 0.015), grade 3 histopathology (OR: 4.21 CI: 95% p = 0.01), LI (OR: 9.84 CI: 95% p <0.001), VI (OR: 6.11 CI: 95% p <0.001), PNI (OR: 5.30 CI: 95% p <0.001), DFS ≤13.5mm (OR: 2.82 CI 95% p = 0.001) were found to be significant.

In multivariate regression analysis HER-2 positivity (OR: 3.37 CI: 95% p = 0.003), LI (OR: 9.49 CI: 95% p <0.001), PNI (OR: 2.53 CI: 95% p = 0.02) and DFS ≤13.5mm (OR: 3.94 CI 95% p = 0.001) were found to be significant on SLN metastasis.

Table 3. Univariate and Multivariate Analysis for Clinicopathological Risk Factors of Sentinel Lymph Node Metastasis

Variables	Univariate Analysis		Multivariate Analysis	
	OR(CI)	p	OR(CI)	p
Age*				
SLN –	1.00	0.914		
SLN +	1.0(0.97-1.03)			
Tumor size				
SLN –	1.00	0.015		
SLN +	1.03(1.01-1.06)			
T stage				
T1	1.00	0.145		
T2	1.59(0.85-2.97)			
HER-2				
-	1.00	**0.015**	1.00	**0.003**
+	2.16(1.16-4.02)		3.37(1.50-7.62)	
ER				
-	1.00	0.847		
+	1.10(0.41-3.00)			
PR				
-	1.00	0.196		
+	1.80(0.74-4.36)			
Ki-67 (% mean)				
nonSLN –	1.00	0.093		
nonSLN +	1.01(1.00-1.03)			
Ki-67				
<%20	1.00	0.298		
≥%20	1.44(0.73-2.86)			
Molecular Subtypes				
Luminal A-like	1.00	-		
Luminal B-like	1.50(0.54-4.19)	0.439		
Luminal Her2 like	1.57(0.62-3.98)	0.344		
Her2 likenonlum.	1.50(0.33-6.83)	0.600		
Triplenegative	1.00(0.16-6.08)	1.000		
Histopathological Subtypes				
IDC	1.00	-		
ILC	1.61(0.67-3.85)	0.284		
Mixt (IDC + ILC)	2.01(0.73-5.51)	0.173		
Tumor Grade				
Grade 1	1.00	-		
Grade 2	1.94(0.95-3.96)	0.069		
Grade 3	4.21(1.41-12.56)	**0.010**		
LI				
-	1.00	**<0.001**	1.00	**<0.001**
+	9.84(4.88-19.82)		9.49(4.10-21.96)	
VI				
-	1.00	**<0.001**		
+	6.11(3.13-11.93)			
PNI				
-	1.00	**<0.001**	1.00	**0.020**
+	5.30(2.75-10.21)		2.53(1.56-5.55)	
Tumor localization				
Right breast	1.00	0.155		
Leftbreast	1.55(0.85-2.83)			
LIQ	1.00	-		
UIQ	0.60(0.17-3.09)	0.541		
LOQ	0.75(0.11-5.24)	0.772		
UOQ	0.80(0.18-3.54)	0.769		
Central	1.8 (0.12-26.20)	0.667		
Multicentiricity				
-	1.00	0.741		
+	1.31(0.26-6.48)			

Multifocality				
-	1.00	0.176		
+	2.09(0.72-6.09)			
NAC infiltration				
-	1.00	0.097		
+	5.94(0.73-48.55)			
DFS				
≤13.5mm	1.00	**0.001**	1.00	**0.001**
>13.5mm	2.82(1.52-5.24)		3.94(1.78-8.72)	
NLR				
SLN –	1.00	0.744		
SLN +	1.04(0.84-1.27)			

***: Adjustment factor, SLN: Sentinel lymph node, HER2: Human Epidermal Growth Factor -2, ER: Estrogen receptor, PR: Progesterone receptor, IDC: Invazive ductal carsinom, ILC: Invazive lobuler carcinom, LI: Lymphatic Invasion, VI: Vascular Invasion, PNI: Perineural Invasion, LIQ: Lower inner quadrant, UIQ: Upper iner quadrant, LOQ: Lower outer quadrant, UOQ: Upper outer quadrant, NAC: nipple/areola complex, DFS: Distance from skin, NLR: Neutrophil / Lymphocyte Rate**

DISCUSSION

In this study, in multivariate regression analysis HER-2 positivity, LI, PNI and DFS ≤13.5mm were found to be independent predictors of SLN metastasis. Large tumor size, grade 3 histopathology and VI were significantly increased the frequency of SLN metastasis in univariate regression analyzes, but they were not significant in multivariate regression analyzes.

It is known that breast cancer in young patients exhibited a more aggressive biological behavior and a worse prognosis (26). In a large series study by Caywood J., et al., nodal metastasis was found to be riskier in patients <66 years of age (7). In the study conducted by Ding J., et al., SLN metastasis risk was found to be 2.18 times higher in patients <40 years of age (8). In our study, it was shown that it was not effective in SLN metastasis because the mean age and median values of the groups were very close to each other.

Recent studies have shown that the possibility of SLN metastasis is higher in breast cancers with high tumor burden. Patients with larger tumor diameter and higher T-stage can be considered risky (7-11). However, these factors were not found significant in our study. We attribute this to the heterogeneity of the groups in patient distribution and the limitation of the number of cases included in the study.

The Ki-67 index is the most popular biomarker used in predicting prognosis and response to chemotherapy in breast cancer. It has been shown that the higher the level, the more aggressive the tumor progresses (8,27,28). In our study, in accordance with the literature data, the SLN metastasis risk was 1.44 times higher in patients with a Ki-67 level of ≥20%, but it was not significant.

In the literature data, there are many studies have shown that the frequency of SLN metastasis increases in HER2 +, ER and PR negative patients (11-13). In our study, it was found that HER-2 positive patients were significantly 3.37 times riskier in developing SLN metastasis, similar to the literature data. ER and PR conditions were insignificant in our study, but when they are negative, it can be mentioned a minimal increase in the risk of nodal metastasis. When breast cancers are classified according to their molecular subtypes, HER2 positive subgroups and luminal B have been shown to be riskier in SLN metastasis in recent studies (14,15). Similarly, in our study, the risk increased approximately 1.5 times in these groups, but they were not significant.

The general view in current studies is that IDK and ILKs have similar SLN metastasis frequencies. In a large-series study by Adachi Y et al., ILCs were shown to be riskier for axillary metastasis (29). However, in contrast to these results in Vandorpe T., et al. study, similar to our findings, ILKs were found to be relatively riskier (30). Additionally, in our study mixt IDC and ILC tumors were 2 times riskier than pure IDCs, but it was not significant.

The grade of histopathological differentiation of the tumor tissue is directly proportional to the tumor behavior. There are many studies have shown that the frequency of axillary metastasis is higher in poorly differentiated breast cancers (8,10,11,31). In our study, grade 3 tumors were clearly found to be riskier in the development of SLN metastasis, but this was insignificant in multivariate analyzes.

The presence of LVI has been shown as one of the strongest predictors of axillary metastasis development in current literature (7,9-11,15). Preoperative histopathological evaluation of primary tumor tissue biopsy may not have sufficient reliability to detect LVI status (32). Therefore, in the prediction of SLN metastasis via LVI to be found can turn into a very difficult situation in the preoperative period. However, in cases where LVI is detected as a result of biopsy, the surgeon should strongly consider the presence of SLN metastasis and make the surgical plan accordingly. In our study, LI was found to be the strongest factor among independent predictors. While VI increased the risk significantly in univariate analyzes, but it was not significant in multivariate analyzes.

PNI positivity in breast cancers can be considered as an indicator of the aggressive behavior of the tumor. In the study of Karak SG et al., PNI was shown to be associated with advanced T stage, poor tumor differentiation, LVI, and poor prognosis (33). In addition, similar to our findings, in the study of Duraker N. et al. PNI positivity has been shown to be associated with an increase in the frequency of nodal metastasis (34).

Inflammatory reactions caused by the immune system play an important role in the development and progression of breast cancer. The inflammatory response caused by cancer cells is effective in neoangiogenesis and metastasis. Due to the immune response, there is a decrease in the lymphocytes in the circular system (35). Therefore, it is expected that the preoperative measured NLR in patients with aggressive breast cancer will be high. However, in our study, the NLR results between the groups were similar.

In several studies evaluating the effects of tumor localization on the development of axillary metastasis, it has been shown that central or axillary tail-located tumors increase the risk of SLN metastasis (36). In our study, centrally located tumors were considered to be more risky, while tumors located in the UIC were found to be the least risky, but these results were not significant. In the study conducted by Capdet J. et al, it was shown that SLN metastasis was significantly less in tumors located in the inner quadrant in accordance with our study (37). In addition, tumors located in the left breast were found 1.55 times riskier than the right breast location in our study, but it was insignificant.

Multicentric and multifocal breast cancers can be considered to have a more aggressive course due to the presence of multiple tumor foci in different localizations (10,11). In this study, there was an increased risk for nodal metastasis in multiple tumors, but the results were not significant, probably due to the insufficient number of patients.

Some clinicopathological factors such as younger age, tumors located near the nipple, larger than 5 cm in diameter and advanced T stage have been associated with NAC infiltration (38). Tumors located closer to NAC increase the frequency of axillary metastasis (16,17). Similarly, in our study, SLN metastasis risk was found 5.94 times higher in univariate analyzes with NAC infiltration, but it was not significant.

In breast anatomy, the lymphatic network system in the dermal layer is richer than in the parenchyma and it was suggested in recent studies that the dermal lymphatic plexus is responsible for nodal involvement in cancer metastasis pathway (18). In relation with this, only a few studies have investigated the relation between the proximity of the tumor to the skin and the axillary nodal involvement (18,19,39,40). In a large series study by Chao C, et al., palpable breast tumors have been shown to be riskier in nodal metastasis than in non-palpable breast tumors (40). Ansari B., et al, found that shorter DFS is an independent risk factor for the development of nodal metastasis (17).

In the study conducted by Cunningham JE et al., they evaluated the tumor - skin distance in patients with T1 and T2 stage breast cancer, just like our study. Accordingly, they found the cut-off value of 14mm to be significant in the development of nodal metastasis (18). In this study, the cut-off value was measured similarly 13.5mm. It has shown that SLN metastasis frequency was 3.94 times higher in DFS ≤13.5mm in multivariate analysis. In a study by Eom YH, et al., the cut-off value was found to be 3 mm (19).

In the study of Tostenson T., et al., DFS ≤ 10mm was shown to increase the risk of nodal metastasis 1.7-2.0 times. In the same study, they showed that when DFS and tumor-nipple distance variables adapted the Memorial Sloan Kettering Cancer Center (MSKCC) and MD Anderson Cancer Center (MDACC) nomograms, which are currently used in SLN metastasis risk prediction, the predictive performance of these models increased (16).

LIMITATIONS

The retrospective nature of the study and the limited number of patients in a similar ethnic population in a single center limit the results and potency of this study.

Objective results may not be obtained in the measurement of primary tumor - breast skin distance due to the speculations of the tumor margins, the variations in breast size in different patients and the experience of the radiologist who performed the sonography before surgery and the pressure changes applied to the breast with USG probe.

The exclusion of some other factors such as the history of hormone replacement therapy, menopause, pregnancy history, breastfeeding, family history, which may have an effect on the development of SLN metastasis, may have caused the independent predictors of this study to be exaggerated.

CONCLUSION

In patients with clinical early-stage breast cancer, the closer of the primary tumor to the skin distance, HER-2 positivity, LI and PNI are very strong predictors that should be considered in the development of SLN metastasis. By including these factors in nomograms that used to predict the axillary nodal state, more reliable results can be obtained and can guide clinicians to make more accurate decisions in the treatment process.

Acknowledgments: This manuscript was produced from specialist Levent Zirek's thesis project.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: This study was approved by the Firat University Medical Faculty review board and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (2019-11-08).

REFERENCES

1. Giuliano AE, Ballman KV, McCall L, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA 2017;318:918-26.
2. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 2010;11:927-33.
3. Nguyen TT, Hoskin TL, Habermann EB, et al. Breast Cancer-Related Lymphedema Risk is Related to Multidisciplinary Treatment and Not Surgery Alone: Results from a Large Cohort Study. Ann Surg Oncol 2017;24:2972-80.
4. Zou L, Liu FH, Shen PP, et al. The incidence and risk factors of related lymphedema for breast cancer survivors post-operation: a 2-year follow-up prospective cohort study. Breast Cancer 2018;25:309-14.
5. Nayyar A, Strassle PD, Shen MR, et al. Survival analysis of early-stage breast cancer patients undergoing axillary lymph node dissection and sentinel lymph node dissection. Am J Surg 2018;216:706-12.
6. Lyman GH, Somerfield MR, Bosserman LD, et al. Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J. Clin Oncol 2017;35:561-4.
7. Caywood J, Gray RJ, Hentz J, Pockaj BA. Older age independently predicts a lower risk of sentinel lymph node metastasis in breast cancer. Ann Surg Oncol 2005;12:1061-5.
8. Ding J, Jiang L, Wu W. Predictive Value of Clinicopathological Characteristics for Sentinel Lymph Node Metastasis in Early Breast Cancer. Med Sci Monit 2017;23:4102-8.
9. Fujii T, Yajima R, Tatsuki H, et al. Significance of lymphatic invasion combined with size of primary tumor for predicting sentinel lymph node metastasis in patients with breast cancer. Anticancer Res 2015;35:3581-4.
10. Malter W, Hellmich M, Badian M, et al. Factors Predictive of Sentinel Lymph Node Involvement in Primary Breast Cancer. Anticancer Res 2018;38:3657-62.
11. Yoo SH, Park IA, Chung YR, et al. A histomorphologic predictive model for axillary lymph node metastasis in preoperative breast cancer core needle biopsy according to intrinsic subtypes. Hum Pathol 2015;46:246-54.
12. Jaime Jans B, Nicolás Escudero M, Dahiana Pulgar B, et al. Clinicopathologic subtypes and compromise of lymph nodes in patients with breast cancer. Ecancermedicalscience 2014;8:448.
13. Reyal F, Rouzier R, Depont-Hazelzet B, et al. The molecular subtype classification is a determinant of sentinel node positivity in early breast carcinoma. PLoS One 2011;6:e20297
14. Mazouni C, Rimareix F, Mathieu MC, et al. Outcome in breast molecular subtypes according to nodal status and surgical procedures. Am J Surg 2013;205:662-7.
15. Houvenaeghel G, Lambaudie E, Classe JM, et al. Lymph node positivity in different early breast carcinoma phenotypes: a predictive model. BMC Cancer 2019;19:45.
16. Torstenson T, Shah-Khan MG, Hoskin TL, et al. Novel factors to improve prediction of nodal positivity in patients with clinical T1/T2 breast cancers. Ann Surg Oncol 2013;20:3286-93.
17. Ansari, B, Morton, MJ, Adamczyk, DL. Distance of breast cancer from the skin and nipple impacts axillary nodal metastases. Ann Surg Oncol 2011;18: 3174-80.
18. Cunningham JE, Jurj AL, Oman L, et al. Is risk of axillary lymph node metastasis associated with proximity of breast cancer to the skin? Breast Cancer Res Treat 2006;100:319-28.
19. Eom YH, Kim EJ, Chae BJ, et al. The distance between breast cancer and the skin is associated with axillary nodal metastasis. J Surg Oncol 2015;111:824-8
20. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017;67:93-9.
21. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol 2015;26:1533-46.
22. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 2013;31:3997-4013.
23. Allred DC, Harvey JM, Berardo M, Clark GM. Prognostic and predictive factors in breast cancer by immunohistochemical analysis. Mod Pathol 1998;11:155-68
24. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology 1991;19:403-10.
25. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol 2015;26:1533-46.
26. Anderson WF, Rosenberg PS, Prat A, et al. How many etiological subtypes of breast cancer: two, three, four, or more? J Natl Cancer Inst 2014;106.
27. Denkert C, Budczies J, von Minckwitz G, et al. Strategies for developing Ki67 as a useful biomarker in breast cancer. Breast 2015;24:67-72.

28. Shigematsu H, Nishina M, Yasui D, Hirata T, et al. Minimal prognostic significance of sentinel lymph node metastasis in patients with cT1-2 and cN0 breast cancer. World J Surg Oncol 2019;17:41.
29. Adachi Y, Sawaki M, Hattori M, et al. Comparison of sentinel lymph node biopsy between invasive lobular carcinoma and invasive ductal carcinoma. Breast Cancer 2018;25:560-5.
30. Vandorpe T, Smeets A, Van Calster B, et al. Lobular and non-lobular breast cancers differ regarding axillary lymph node metastasis: a cross-sectional study on 4,292 consecutive patients. Breast Cancer Res Treat 2011;128:429-35.
31. Černá M, Zedníková I, Ňaršanská A, et al. [Avoidance of axillary lymph node dissection in breast cancer patients with metastatic sentinel node - a pilot study]. Rozhl Chir 2015;94:117-25.
32. Harris GC, Denley HE, Pinder SE, et al. Correlation of histologic prognostic factors in core biopsies and therapeutic excisions of invasive breast carcinoma. Am J Surg Pathol 2003;27:11-5.
33. Karak SG, Quatrano N, Buckley J, Ricci A Jr. Prevalence and significance of perineural invasion in invasive breast carcinoma. Conn Med 2010;74:17-21.
34. Duraker N, Caynak ZC, Turkoz K. Perineural invasion has no prognostic value in patients with invasive breast carcinoma. Breast 2006;15:629-34.
35. Colotta F, Allavena P, Sica A, et al. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis 2009;30:1073-81.
36. Desai AA, Hoskin TL, Day CN, et al. Effect of Primary Breast Tumor Location on Axillary Nodal Positivity. Ann Surg Oncol 2018;25:3011-8.
37. Capdet J, Martel P, Charitansky H, et al. Factors predicting the sentinel node metastases in T1 breast cancer tumor: an analysis of 1416 cases. Eur J Surg Oncol 2009;35:1245-9.
38. D'Alonzo M, Martincich L, Biglia N, et al. Clinical and radiological predictors of nipple-areola complex involvement in breast cancer patients. Eur J Cancer 2012;48:2311-8.
39. Bae MS, Shin SU, Song SE, et al. Association between US features of primary tumor and axillary lymph node metastasis in patients with clinical T1-T2N0 breast cancer. Acta Radiol 2018;59:402-8.
40. Chao C, Edwards MJ, Abell T, et al. Palpable breast carcinomas: a hypothesis for clinically relevant lymphatic drainage in sentinel lymph node biopsy. Breast J 2003;9:26-32.