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The effect of the tumor-to-skin distance on axillary lymph node metastasis in breast cancer

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SUMMARY

OBJECTIVE: Tumor-to-skin distance is known to have an effect on axillary lymph node metastasis but has no clinical use with nomograms. This study aimed to investigate the effect of tumor-to-skin distance on axillary lymph node metastasis alone and in combination with nomogram for clinical use.

METHODS: A total of 145 patients who underwent surgery for breast cancer (T1–T2 stage) and whose axillary lymph nodes were evaluated (axillary dissection or sentinel lymph node biopsy) between January 2010 and December 2020 were included in the study. Tumor-to-skin distance and other pathological data of the patients were evaluated.

RESULTS: Of the 145 patients, 83 (57.2%) had metastatic lymph nodes in the axilla. Tumor-to-skin distance was different in terms of lymph node metastasis (p=0.045). In the receiver operating characteristic curve for tumor-to-skin distance, area under curve was 0.597 (95%CI 0.513–0.678, p=0.046), area under curve of the nomogram was 0.740 (95%CI 0.660–0.809), p<0.001) and nomogram+tumor-to-skin distance was 0.753 (95%CI 0.674–0.820), p<0.001). No statistical difference was found for axillary lymph node metastasis between the nomogram+tumor-to-skin distance and the nomogram alone (p=0.433).

CONCLUSION: Although tumor-to-skin distance demonstrated a significant difference in axillary lymph node metastasis, it had a poor association with an area under curve value of 0.597 and did not produce a significant improvement in predicting lymph node metastasis when combined with the nomogram. The tumor-to-skin distance may be unlikely to enter clinical practice.

KEYWORDS: Axilla. Breast. Lymph nodes. Lymphatic metastasis. Neoplasms.

INTRODUCTION

Breast cancer is the most common type of cancer among women worldwide. According to the World Health Organization, there were 2.3 million new diagnoses and 685,000 deaths in 2020[1]. Regional metastases to lymph nodes and surrounding tissues and distant metastases to organs such as bone, liver, and brain are considered to be among the factors that adversely affect the prognosis in breast cancer[2,3]. Evaluation of axillary lymph node metastases in breast cancer is important in planning the patient's treatment[4].

The most commonly used methods to evaluate axillary lymph nodes are preoperative Tru-Cut biopsy or intraoperative sentinel lymph node biopsy (SLNB)[5]. Both of these techniques are invasive and require a pathologist. Therefore, noninvasive efforts have been tried to be developed to detect metastatic lymph nodes. As part of these efforts, studies have been conducted to examine the relationship between tumor-to-skin distance (TSD) and metastatic axillary lymph nodes in breast cancer. The rate of lymph node metastasis was found to be high in tumors close to skin[4,6-10]. Although the results of these studies presented similar characteristics, there has been no use of TSD in clinics or nomograms[11,12]. This has led us also to investigate the diagnostic value of TSD.

The present study aimed to examine the area under curve value of TSD alone and in combination with nomogram and evaluate their potential use in clinical practice for axillary lymph node metastasis in breast cancer.

METHODS

Ethical approval

This study was conducted with the approval of Ethics Committee for Non-Interventional Research (No. 2021/02-18, Date: 04.02.2021) of the Fırat University.

Patient selection

Between January 2010 and December 2020, 177 female patients who underwent surgery for T1–T2 stage breast cancer were selected using the hospital data system. The exclusion criteria were as follows:

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- Having neoadjuvant chemoradiotherapy,
- T3–T4 stage tumor,
- Paget's disease,
- Recurrence of disease,
- Skin invasion,
- Multicentric cancer,
- Previous breast surgery in the studied breast,
- Skin-sparing mastectomy or excisions,
- Failure to investigate axillary lymph node status,
- Diseases that may cause alterations in the breast tissue (chronic heart/kidney disease).

This study included 145 female patients aged between 18 and 90 years who did not meet any of the exclusion criteria. The patients were classified into two groups based on having axillary lymph node metastasis. Group 1 comprised axillary nonmetastatic (N0) patients, and group 2 comprised metastatic (N+) patients. Memorial Sloan Kettering Cancer Center nomogram was used for prediction of axillary lymph node metastasis[12]. Demographic and histopathological data were recorded for evaluation.

Pathological and immunohistochemical examination

All resection samples were examined by the pathology department of our institution based on standard clinical protocols. Immunohistochemistry was performed using 4-µm-thick histological tissue slides obtained from the paraffin blocks. The Olympus Microscope Digital Camera model DP71 (Olympus Co., Shinjuku, Tokyo, Japan) software imaging system was used for histological analysis of estrogen, and progesterone status was defined as positive when 10% or more of nuclei showed positive staining. For HER2 status, tumors with IHC staining of 3+ (uniform, intense membrane staining of 30% of invasive tumor cells) were considered HER2-positive. Cases with an IHC staining of 2+ were considered positive if they turned out to be positive in subsequent HER2/neu gene amplification (fluorescence in situ hybridization). HER2 1+ status and the absence of staining were considered negative. Breast cancer is divided into five molecular subtypes[13]. Histological grades were determined using the Modified Bloom-Richardson Nottingham Score index. TSD was measured macroscopically or under a light microscope.

Statistical analyses

Data analysis was performed using the SPSS 21.0 software (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov/Shapiro-Wilk test was applied to assess the distribution normality of the data. Nonparametric data were presented as median (minimum-maximum) and parametric data as mean±standard deviation. The independent sample t-test was applied for normally distributed data, the Mann–Whitney U test was used for non-normally distributed data, and the chi-square or Fisher's exact test was used for nominal/ordinal data. Logistic regression analysis was performed to determine significant predictors of the axillary lymph node metastasis with univariate and multivariate analyses. Odds ratios (OR) with 95% confidence intervals were used. The optimal cutoff point of the TSD was evaluated by receiver operating characteristic (ROC) curve analysis. The comparison of nomogram with TSD+nomogram area under curves (AUCs) and the examination of the statistical significance of the AUCs were performed via the DeLong method[14]. An AUC-ROC >0.7 indicates a good discrimination model[15]. Binary logistic regression formula for TSD+nomogram was "Y=[(100–Nomogram)*(-0.04539)]+[TSD*(-0.03779)]+3.12636." The statistical level of significance for all tests was considered to be <0.05.

RESULTS

A total of 145 female patients [62 (42.8%) in group 1 and 83 (57.2%) in group 2] were included in the study. The demographic characteristics of the patients are presented in Table 1. There was a significant difference between the groups for TSD [20 mm in group 1 (1–55) and 15 mm in group 2 (2–45), p=0.045). A significant difference was observed between the groups for LVI and tumor grade (p<0.001 and p=0.008, respectively). No significant difference was observed between groups in terms of other data (p>0.05).

Univariate analysis showed that the TSD, LVI, nomogram, and grade were significantly associated with a higher risk of metastasis (p<0.05). In multivariate analysis, TSD (p=0.015) and LVI (p<0.001) were the independent risk factors of axillary lymph node metastasis. Nomogram was not entered into multivariate analysis owing to multicollinearity.

In the ROC curve analysis, the cutoff value of TSD for lymph node metastasis was calculated to be 21 mm (sensitivity 77.1%, specificity 38.7%, p=0.046). The cutoff value of the nomogram for lymph node metastasis was calculated to be 52.5 (sensitivity 69.9%, specificity 72.6%, p<0.001), and nomogram+TSD was 0.404 (sensitivity 89.1%, specificity 48.4%, p<0.001) (Figure 1). The comparison of the nomogram and TSD+nomogram curves indicated that the difference was not significant (p=0.433) (Table 2).

Table 1. Distribution of data within groups.

Variables		Group 1 (n=62) mean±std/median (min–max)	Group 2 (n=83) mean±std/median (min–max)	Total (n=145)	OR	p-value
Age		60.29±1.586	60.78±1.257	60.57±0.986		0.806[a]
Tumor-to-skin distance (mm)		20 (1–55)	15 (2–45)	17 (1–55)		**0.045***
Tumor diameter (mm)		26 (7–50)	27 (9–47)	26 (7–50)		0.307*
Tumor site	Right	32	45	77	1.05	0.756**
	Left	30	38	68	0.95	
Quadrant	UOQ	27	39	66		0.970***
	LOQ	8	11	19		
	LIQ	8	12	20		
	UIQ	17	19	36		
	Central	2	2	4		
ER	Negative	10	14	24	0.95	0.906**
	Positive	52	69	121	1	
PR	Negative	9	18	27	0.67	0.272**
	Positive	53	65	118	1.09	
HER2	Negative	39	48	87	1.09	0.537**
	Positive	23	35	58	0.88	
Luminal types	Type A	5	11	16		0.698***
	Type B HER2-negative	29	30	59		
	Type B HER2-positive	19	30	49		
	HER2-positive	4	5	9		
	Triple negative	5	7	12		
Menopausal status	Premenopausal	17	18	35	1.26	0.425**
	Postmenopausal	45	65	110	0.927	
Grade	1	27	19	46	1.90	**0.008****
	2/3	35	64	99	2.598	
Lymphovascular invasion	Negative	43	11	54	0.36	**<0.001****
	Positive	19	72	91	4.43	
Histological type of cancer	IDC	47	65	112		0.646***
	ILC	6	10	16		
	Mix type and others	9	8	17		

[a]Independent sample t-test; *Mann-Whitney U test; **Chi-square test; ***Fisher's exact test. UOQ: upper outer quadrant; LOQ: lower outer quadrant; LIQ: lower inner quadrant; UIQ: upper inner quadrant; IDC: invasive ductal cancer; ILC: invasive lobular cancer. Bold values indicate statistical significance at the p<0.05 level.

DISCUSSION

This study aimed to examine the effect of TSD on axillary lymph node metastasis in breast cancer and its feasibility in clinical practice. According to the results of the study, although the TSD differed significantly between the groups, it was not superior to the nomogram, and it was not effective when used together with the nomogram. Low AUC-ROC curve value of TSD and lack of a significant difference for its combined use with nomogram compared to nomogram alone indicated that it was an inefficient parameter for clinical use in breast cancer.

Axillary lymph node metastasis plays an important role in the prognosis of breast cancer, such as the surgical margin[16,17]. Therefore, the most reliable method for axillary lymph node involvement today is the SLNB examination[18]. There have been

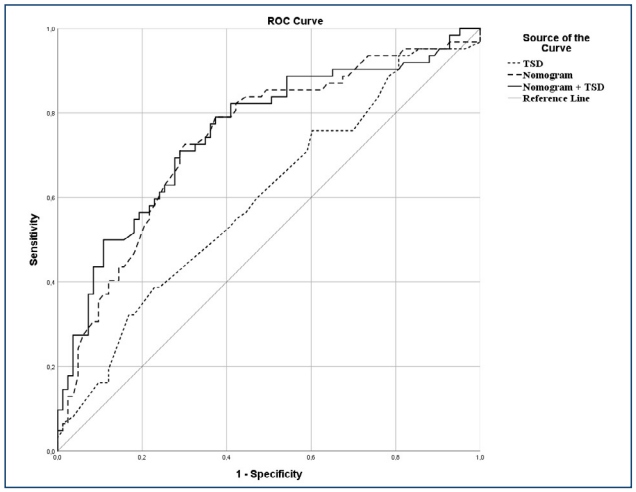

Figure 1. Areas under the receiver operating characteristic curve for comparisons of tumor-to-skin distance, nomogram, and tumor-to-skin distance+nomogram. The area under curve of the tumor-to-skin distance, nomogram, and nomogram+tumor-to-skin distance were 0.597 (95%CI 0.513–0.678), 0.740 (95%CI 0.660–0.809), and 0.753 (95%CI 0.674–0.820), respectively.

Table 2. Comparison of groups' discriminative abilities for axillary lymph node metastasis.

Comparison of groups	Difference between AUCs	Significance level (p)
Nomogram vs. TSD	0.143	**0.024**
Nomogram vs. nomogram+TSD	0.0128	0.433
TSD vs. nomogram+TSD	0.155	**0.003**

TSD: tumor-to-skin distance; AUC: area under curve. Bold values indicate statistical significance at the p<0.05 level.

efforts to predict the status of breast regional lymph nodes using other methods without resorting to SLNB[11,12,19-22]. TSD is one of them. This method was reported to be associated with the tumor's proximity to dermal lymphatics[23].

Studies reported a significant relationship between TSD and axillary lymph node metastasis[4,6-10]. Only a study by Lee et al., reported no significant difference for TSD[20]. The studies indicated different cutoff values in the range of 3–14 mm[4,6-10]. The lack of a clear cutoff value complicates the clinical use of TSD. In the present study, cutoff value was found at 21 mm. In tumors close to the skin, the rate of lymph node metastasis was higher than that in tumors far from the skin.

In the present study, the AUC-ROC value of TSD was <0.7. Therefore, the discrimination ability was categorized as weak[15]. In addition, the low sensitivity and specificity of the cutoff value is a reflection of this weak effect. In our study, although there was a small increase in AUCs in nomogram+TSD compared to nomogram, no significant difference was observed between the groups in the DeLong method. Nomogram alone indicated a significant statistical superiority to the TSD. Therefore, TSD may only be a statistical parameter for predicting axillary lymph node metastasis and it may not be clinically useful. Torstenson et al., reported that TSD measurement increased the AUC-ROC from 0.71 to 0.75 on the nomogram[10]. However, this study made no mentioning of the pairwise comparison of ROC curves analysis that was performed for the AUC-ROC values. Therefore, it may not be possible to make a statistical comment about the AUC-ROC values. The present study is the first to compare the AUC-ROC values of nomogram with nomogram+TSD combination in the literature.

Different measurement methods can affect the results of studies. While USG was used in many studies, Ojha et al., used pathology specimens[4,6-10]. The inability of radiologists to stabilize probe pressure while measuring with USG may have led to varying results. In our study, pathological specimens were used for the measurement.

Hormonal status and T stage are important factors that affect the treatment of breast cancer. In the present study, hormonal status of the tumor did not indicate any difference in groups. There are opposing views on hormonal status and tumor diameter[4,6-10]. Song et al., reported no difference between groups for the luminal types, while a study reported difference between luminal A and triple negative[13,24]. In our study, no difference was observed among the luminal types for groups. Eom et al.,[10] did not report any difference among patient groups with different tumor sizes for lymph node metastases, while other studies found varying rates of difference[4,6-8]. In the present study, no relationship was found between lymph node metastasis and tumor diameter.

Lymphovascular invasion affects tumor aggressiveness and lymph node metastasis. Eom et al., found no association between lymph node metastasis and LVI[8]. However, several other studies and the present study found a significant correlation between LVI and axillary lymph node metastasis[4,7,10]. In the present study, LVI was the independent risk factor for axillary lymph node metastasis. Moreover, there was a significant difference in grade between groups. The grade was high in the axillary metastatic group. Similar to our findings, Cunningham et al.[7] reported higher lymph node metastasis in higher grades while other studies reported no difference[10,24,25].

Among the study limitations are the retrospective and single-center nature of the study. Besides, the TSD measurements

were conducted by multiple pathologists, and on a limited number of patients, which may have affected the study results.

CONCLUSION

The effect of TSD in predicting axillary lymph node metastasis is poor due to the low AUC value. Moreover, TSD was not superior to the nomogram. Due to the low AUC value of TSD and lack of a significant difference between nomogram+TSD and nomogram AUC-ROC curves, the TSD may not constitute a useful parameter for clinical use in breast cancer.

AUTHORS' CONTRIBUTIONS

MY: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **EA**: Conceptualization, Data curation, Formal Analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **YSİ**: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Supervision, Validation, Visualization. **AL**: Data curation, Investigation, Visualization. **MFE**: Data curation, Methodology, Software, Supervision, Visualization.

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