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The Relationship between the Distance of Breast Mass from the Skin and the Incidence of Axillary Nodal Metastasis in Early Breast Cancer

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ABSTRACT

Background: Axillary lymph node metastasis (ALNM) is an important part of the course of breast cancer (BC), the most frequent cancer in women globally. Some studies suggest that tumor proximity to the skin may influence lymphatic spread, yet definitive correlations remain unclear. **Objective:** This study examines the relationship between tumor-to-skin distance and ALNM incidence in early-stage breast cancer.

Patients and methods: This prospective cross-sectional research included 85 female patients who had early-stage breast cancer (T1 and T2) at Suez Canal University Hospital. Preoperative imaging, including ultrasound (US) and mammography, measured tumor-to-skin distance, which was later compared with histopathological findings. Statistical analysis evaluated correlations between tumor characteristics and ALNM.

Results: The mean patient age was 53.04 ± 8.84 years, with invasive ductal carcinoma being the most common histological type (86%). The upper outer quadrant was the predominant tumor location (63.5%). ALNM was present in 55.5% of patients, with 47 cases classified as N1 and seven as N2. US measurements of tumor-to-skin distance showed no significant difference from histopathological findings ($p = 0.8283$), confirming its accuracy. A strong correlation was found between tumor proximity to the skin and ALNM ($p = 0.0001$), with closer tumors exhibiting higher nodal involvement. Additionally, tumors in the upper outer quadrant had a significantly higher risk of ALNM ($p = <0.0001$).

Conclusion: These findings highlight the prognostic value of tumor-to-skin distance in ALNM risk assessment. Incorporating this parameter into preoperative evaluations may improve staging accuracy.

Keywords: BC, ALNM, Tumor-to-skin distance, Early-stage breast cancer, Tumor location, histopathology.

INTRODUCTION

In 2020, female BC was found to be more prevalent than lung cancer, with a projected 2.3 million new cases. This accounted for 11.7% of all cancer diagnoses. It ranks as the seventh leading cause of cancer-related deaths globally, accounting for an estimated 685,000 lives lost. When it comes to female cancers, breast cancer accounts for one in four occurrences and one in six fatalities. In 110 countries, it is the leading cause of death, and among 185 countries, it is the leading cause of occurrence [(1)].

More than 22,000 new cases of BC are identified every year in Egypt, making it the most common malignancy in women. Egypt still reports 5-year survival rates between 28% and 68%, even though richer nations' rates have significantly improved. This discrepancy is mostly caused by socio-medical factors and late-stage diagnoses [(2)].

As a first clinical sign of distant metastasis, ALNM is often the first thing doctors look for when diagnosing early-stage metastatic BC [(3)]. The pathologic staging of BC is determined by the existence, number, and anatomical distribution of metastatic lymph nodes. Nodal involvement is the most important prognostic marker for recurrence risk and overall survival. Disease staging, therapeutic decision-making, and the guidance of systemic therapy, surgical extent, and post-mastectomy radiation therapy are all dependent on accurate axillary lymph node (ALN) assessment. [(4)].

Over time, axillary surgical management has transitioned from extensive dissection to more conservative techniques, aiming to minimize postoperative morbidity such as seroma, pain, neuropathy, restricted arm mobility, lymphedema, and cellulitis. Consequently, axillary lymph node dissection (ALND) is no longer the main staging method for patients who test negative for lymph nodes; sentinel lymph node biopsy (SLNB) has replaced it [(5)]. The evolving treatment paradigm increasingly favors reducing axillary surgical intervention, even when sentinel lymph nodes (SLNs) are involved [(6)].

The axillary care options must be tailored based on the nodal status at the time of initial diagnosis. It is routine practice to administer SLNB before or after primary systemic treatment (PST) for patients who present with clinically node-negative illness. The National Comprehensive Cancer Network (NCCN) recommends reevaluating patients after PST if they had ALNs affected at diagnosis. If the axilla continues to show clinical negativity, SLNB or ALND might be explored instead of ALND, but ALND is always the best option when clinical positivity persists [(7)].

Breast ultrasound (US) is a fundamental imaging modality, complementing mammography, magnetic resonance imaging (MRI), and image-guided biopsy for BC diagnosis [(8)]. Preoperative imaging plays a crucial role in evaluating axillary nodal involvement due to its noninvasive, convenient, and comprehensive nature. US enhances the detection of breast malignancies and assists in predicting nodal metastases [(9)].

The gold standard for detecting involvement of the ALNs is a combination of axillary ultrasound (AUS) and U-guided core biopsy or FNAC [(10)]. The diagnostic accuracy is enhanced when AUS is used with needle biopsy, even though the sensitivity and specificity are moderate [(11)]. U/S also allows for more accurate and

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reliable tumor size and skin proximity measurements than manual palpation [12].

Several studies suggest that lymphatic drainage pathways in the dermis may play a crucial role in BC metastasis, with superficial lymphatic plexuses facilitating axillary spread. Anatomically, the breast lymphatic network is a dense meshwork of dermal lymphatics, potentially predisposing superficial tumors to a higher metastatic risk. Moreover, research has correlated tumor proximity to the skin with increased axillary metastases, emphasizing the need for precise imaging assessment [12].

In order to determine if axillary nodal involvement is likely, several studies have looked at factors such as tumor size, location, histologic grade, palpability, and lymphovascular invasion. However, the correlation between tumor closeness to the skin and nodal metastasis has only been studied in a small number of studies. Existing studies assessing tumor-to-nipple and tumor-to-skin distances have faced methodological limitations, including small sample sizes and indirect imaging-based distance measurements, which may be affected by probe-induced compression during ultrasound examinations [12]. Examining the correlation between breast mass to skin surface distance and ALNM was the primary objective of this research.

PATIENTS AND METHOD

The purpose of this prospective cross-sectional study was to examine the characteristics of 85 female patients diagnosed with early-stage breast cancer (T1 or T2) at the Surgical Oncology Unit of Suez Canal University Hospital. The patients were included in the study if they were diagnosed between August 2023 and August 2024 and if they underwent imaging and a Tru-Cut biopsy to confirm their diagnosis.

Inclusion criteria: Female patients of any age diagnosed with early-stage BC (T1 or T2) were eligible for inclusion. Additionally, only patients deemed fit for surgery were selected for the study.

Exclusion criteria: Patients with metastatic or multicentric BC were excluded from the study. Likewise, those undergoing neoadjuvant chemotherapy were not included.

Preoperative Assessment

All patients underwent a thorough clinical evaluation, including complete history-taking and physical examination. Standard preoperative investigations included an electrocardiogram (ECG), complete blood picture, coagulation profile (PT, INR), blood glucose levels, renal function tests (creatinine, urea), and liver function tests (SGOT, SGPT).

Imaging modalities included sono-mammography to assess tumor size, location, and proximity to the skin, along with preoperative ultrasound evaluation of ALNs. Tissue diagnosis was confirmed via Tru-Cut or core biopsy. In cases where a metastatic workup was required, a CT scan of the chest and abdomen was performed, and a bone scan was conducted when clinically indicated.

Surgical Procedures

Patients underwent either breast-conserving surgery (BCS) or modified radical mastectomy (MRM) under general anesthesia with endotracheal intubation in the supine position. The surgical approach was determined based on tumor histopathology, mass size, breast size, and tumor location. Patients were counseled on surgical options preoperatively, and informed consent was obtained.

BCS aimed to preserve the breast while achieving cosmetically acceptable results. Surgical factors such as incision placement, lumpectomy cavity management, and the extent of axillary dissection influenced the final outcome. In contrast, MRM spared the pectoralis major muscle but removed the skin, areola, nipple, and ALNs from the breasts.

Pathological Assessment and Follow-Up

Final histopathological reports included details on safety margins, tumor histology, tumor distance from the skin and nipple, the number of involved ALNs, and immunohistochemical expression of ER, PR, and Her2/neu.

Postoperatively, patients were scheduled for follow-up and referred to the oncology outpatient clinic for further treatment planning. Additional treatments, including radiotherapy, chemotherapy, and hormonal therapy, were determined based on pathology results.

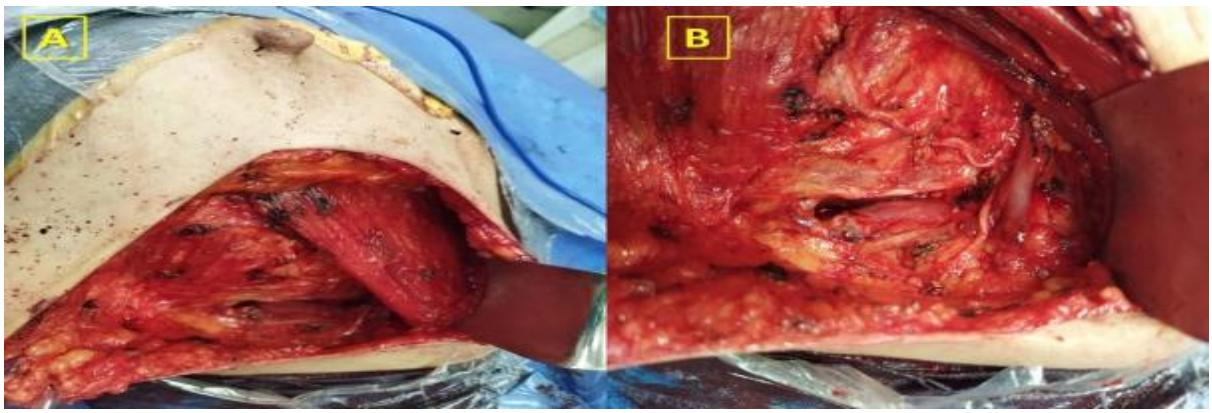

Figure (1): Breast conservative surgery with appearance of axilla after axillary clearance with preservation of long thoracic nerve and thoracodorsal bundle.

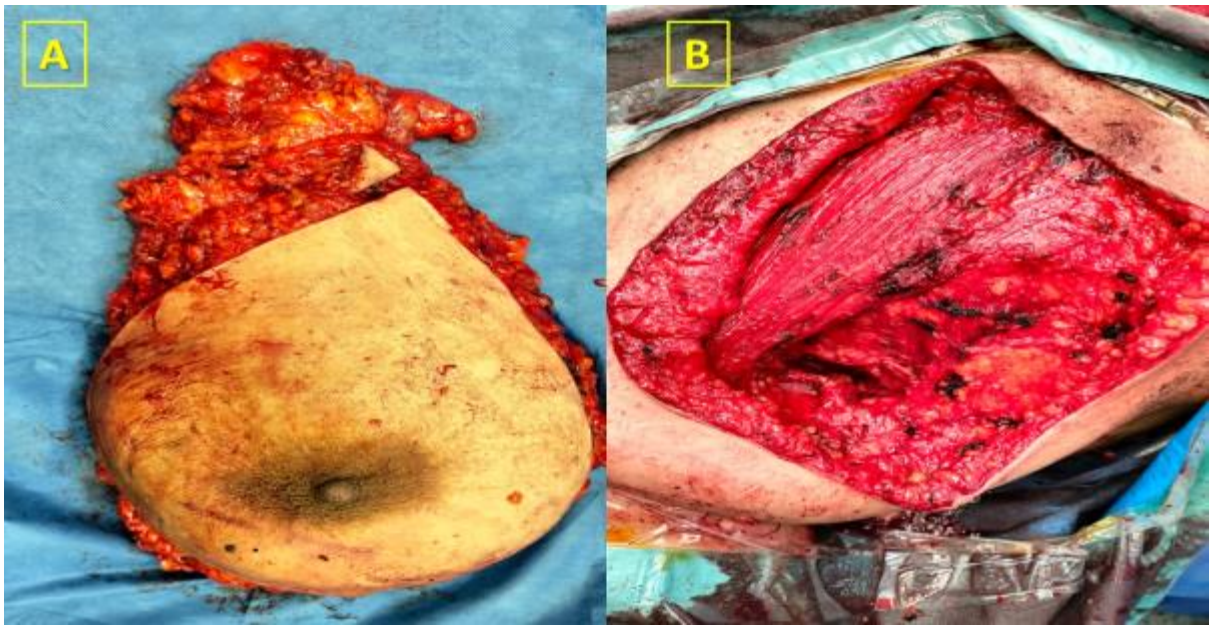

Figure (2): Modified radical mastectomy with appearance of axilla after axillary clearance.

Ethical approval:

Suez Canal Faculty of Medicine's Ethics Committee accepted this work. After receiving all of the information, each participant signed her permission. The Helsinki Declaration was followed throughout the course of the investigation.

Statistical analysis:

SPSS Statistics Version 25.0 was utilized for the analysis of the data. Mean ± SD, median, and range summarized numerical data, which were compared by Student's t-test. Frequencies and percentages described categorical variables, which were compared by Fisher's exact test. A p-value <0.05 was considered significant.

RESULTS

The result showed that the overall mean age of 53.04 years (SD = 8.84). Also, showed that 34 out of 85 patients (40%) have a positive family history of BC, and out of the total patients, 64 patients (75%) were multiparous, as shown in table 1.

Table (1): Distribution of the studied group according to age, family history, and parity

Feature		All (N = 85)
Age (years)	Mean ± SD. (Median; range)	53.04 ± 8.84 (53; 35-70)
Family history	Positive	34
	Negative	51
Parity	Nullipara	21
	Multipara	64

The most common type of BC was invasive ductal carcinoma 73 patients (86%), while 12 patients (14%) had invasive lobular carcinoma.

The upper outer quadrant was the predominant tumor location (63.5%). We found that 36.5% of patients (31 patients) had negative ALNs, 55.5% (47 patients) had one to three positive axillary nodes, and 8.0% (seven patients) had four to nine positive nodes, as shown in table 2.

Table (2): Location of tumor and ALN status determine distribution.

Feature		All (N = 85)
Location	Upper outer quadrant	54
	Lower outer quadrant	10
	Upper inner quadrant	13
	Lower inner quadrant	8
Nodal staging		
N0	**N1**	**N2**
31	47	7

Our results showed that 28 patients (33%) had T1 tumor size (≤20 mm), while 57 patients (67%) had T2 tumor size (>20 mm but ≤50 mm). Our results showed that 72 patients (85%) had (histologically detected of lymph node), as illustrated in table 3.

Our results showed that 55 out of 85 patients (64.7%) underwent simple mastectomy, and 30 out of 85 patients (35.3%) underwent MRM.

Table (3): Tumor size and staging of the studied patients

Tumor size		
T1		**T2**
28		57
Staging		
I	**II**	**III A**
8	71	7
T1: ≤20 mm, T2:	>20 mm, but ≤50 mm	

The mean distance of tumor from skin preoperatively by US was insignificantly different from postoperatively by histopathology, as showed in table 4.

Table (4): Distance of tumor from skin (mm) by US and histopathology

	Preoperative by US (N = 85)	Postoperative by histopathology (N = 85)	Independent t-test	P value
Distance of tumor from skin Mean ± SD (Median; range)	11.31± 6.5 (12; 2-23)	11.52±6.1 (11; 2.2-25)	0.2172	0.8283

By contrast, the difference of average age of patients whose lymph nodes were positive and those whose lymph nodes were negative was insignificantly different as shown in table 5.

Table (5): Correlation of age with nodal status of the studied patients

Feature	LN		Independent t-test	P value
	Negative (N = 31)	Positive (N = 54)		
Age (years) Mean ± SD (Median; range)	54.85 ± 8.131 (56;39-70)	52.14 ± 9.18 (52;35-70)	1.3643	0.1762

In our study, tumor size was correlated with nodal status. 20 patients of T1 tumor size had positive nodes. 34 patients of T2 tumor size had positive nodes (Table 6).

Table (6): Correlation of tumor size with nodal status of the studied patients

Tumor size	Total nodes positive (%)	Total nodes negative (%)	P value
T1	20 (71.4%)	8 (28.6%)	0.3434
T2	34 (59.5%)	23 (40.5%)	
Fisher's exact test			

Tumors in the upper outer quadrant had a significantly higher risk of ALNM than the other quadrants (Table 7).

Table (7): Distribution of lymph nodes according to location of the tumor

Feature		Lymph nodes		
		Negative (N = 31)	Positive (N = 54)	P value
Location	**Upper outer quadrant**	9	45	0. 0296
	Lower outer quadrant	7	3	
	Upper inner quadrant	9	4	
	Lower inner quadrant	6	2	
Fisher's exact test				

46 out of the 73 patients diagnosed with invasive ductal carcinoma had positive lymph node (LN) results. Eight individuals with invasive lobular carcinoma tested positive for LN. Table 8 shows that there was no statistically significant result.

Table (8): Types of breast cancer in our study

Feature		Total nodes positive (%)	Total nodes negative (%)	P value
Histological type of cancer	**Invasive ductal carcinoma**	**46 (63%)**	**27 (37%)**	**1**
	Invasive lobular carcinoma	**8 (66%)**	**4 (34%)**	
Fisher's exact test				

Patients with negative lymph nodes had a significantly longer mean distance of tumor from skin was than those with positive lymph nodes (Table 9).

Table (9): Distance of tumor from skin (mm) by US and histopathology

Feature	Lymph nodes		Independent t-test	P value
	Negative (N = 31)	Positive (N = 54)		
Distance of tumor from skin by US Mean ± SD (Median; range)	15.4 ± 5.1 (16; 3-23)	8.5 ± 3.5 (9; 0.2-1.3)	7.4852	0.0001

A correlation was found between the nodal status and the measured distance between the tumor and the skin. Almost all the patients had tumors that were more than 0.3 cm distant from the skin (Table 10).

Table (10): The relationship between the tumor's distance from the skin and its nodal status

Measurement in centimeters of the tumor's distance from the skin	The percentage of positive nodes	The percentage of negative nodes (%)	P value
<0.3	2(66.7%)	1 (33.3%)	1
>0.3	52 (63%)	30 (37%)	
Fisher's exact test			

DISCUSSION

The status of ALNs has been recognized as one of the most significant and reliable prognostic markers in BC. It plays a crucial role in staging and guiding treatment decisions [13]. Preoperative prediction of axillary nodal status is essential, as it allows for psychological preparedness among patients who may require ALND. Additionally, it facilitates surgical contingency planning, particularly for those opting for immediate breast reconstruction [14].

Preoperative imaging assessments provide valuable insights due to their non-invasive, comprehensive, and efficient nature. Among imaging modalities, ultrasound (U/S) remains a fundamental tool in detecting breast malignancies and predicting ALNM [9]. Breast cancer's biological behavior is affected by various elements, such as demographic and clinical data, pathological features, lymph node involvement, and molecular tumor markers [15].

Included in this study were 85 patients diagnosed with BC, specifically T1 or T2. Only 30 underwent a modified radical mastectomy (MRM), while 55 underwent breast-conserving surgery (BCS). Radiological and pathological distances were measured for all patients. The patients' average age of 53.04 ± 8.84 years differs from the data reported by **Ansari *et al.*** [16] **and Eom *et al.*** [17] who found an average age of 50.3 and 66.2 years, respectively.

In this study, 40% (34 out of 85 patients) had a positive family history of BC, and 25% (21 patients) were nulliparous. These findings align with **Cunningham *et al.*** [12] who reported similar results regarding parity and family history, without statistically significant differences between the nodal-positive and nodal-negative groups.

The most common histological type was invasive ductal carcinoma (IDC), affecting 73 patients (86%), while 12 patients (14%) had invasive lobular carcinoma (ILC). Similar findings were reported by **Ansari *et al.*** [16], with 76% IDC and 12% ILC, and **Bae *et al.*** [18] who found 92% IDC among their study population.

The distribution of cases with respect to tumor site was as follows: On average, malignancies were found in the following four quadrants: upper outer (53.5%), lower outer (12.5%), upper inner (15%), and lower inner (9.5%). Our present results are consistent with those of **Cunningham *et al.*** [12] **and Ansari *et al.*** [16], who demonstrated that tumors are more prevalent in the outer quadrants of the brain.

ALN status was as follows: 31 patients (36.5%) had negative axillary LNs, 47 patients (55.5%) had one to three positive LNs, and seven patients (14%) had four to nine positive LNs. These findings differ from **Eom *et al.*** [17], who reported 64.4% node-negative cases, with 24.2% having one to three positive nodes and 6% having four to nine positive nodes.

Tumor size analysis revealed that 67% of patients (57 cases) had T2 tumors, while 33% (28 cases) had T1 tumors. No statistically significant correlation was observed between tumor size and axillary nodal metastasis (P = 0.3434), in agreement with **Essa *et al.*** [19]. However, these findings contrast with **Bae *et al.*** [18] who found that 76.8% of patients had T1 tumors, while only 23.2% had T2 tumors.

No statistically significant difference was seen between the groups in terms of age; patients with negative lymph nodes had an average age of 54.85 ± 8.13 years, while those with positive lymph nodes had an average age of 52.14 ± 9.18 years (P = 0.1762). Consistent with previous research, our data show that there was no significant age-related difference in ALNM (P = 0.1762). This conclusion is in line with those of **Ansari *et al.*** [16] and **Eom *et al.*** [17] who also observed comparable results.

A significant correlation was observed between tumor location and axillary LN involvement (P = <0.0001). Specifically, 45 out of 54 patients with upper outer quadrant tumors had positive LNs, compared to three out of ten in the lower outer quadrant, four out of 13 in the upper inner quadrant, and two out of eight in the lower inner quadrant. These findings support **Ansari *et al.*** [16] who reported a statistically significant association between tumor location and nodal involvement (P = 0.001), although they differ from **Cunningham *et al.*** [12] who found no significant correlation (P = 0.138).

With no statistically significant change (P = 0.8283), the mean tumor-to-skin distance was 11.31 mm before surgery on U/S and 11.52 mm after surgery on histology. This provides more evidence that ultrasonography is a valid and trustworthy way to measure the distance from the skin to BC. In addition, the mean tumor-to-skin distance for patients with negative lymph nodes was 15.4 mm (median 16 mm), while for those with positive lymph nodes, it was 8.5 mm (median 9 mm). A lower tumor-to-skin distance is associated with a higher chance of nodal metastasis, according to the statistically significant correlation (P = 0.0001). There is agreement between these results and those of **Sivakanthan *et al.*** [20] who found that node-positive patients had a median tumor-to-skin distance of 10 mm and node-negative patients 12.5 mm (P = 0.004).

Histopathological analysis revealed that among patients diagnosed with IDC, 46 had positive LNs, while 27 had negative LNs. In contrast, among those diagnosed with ILC, eight had positive LNs, while four had negative LNs, with no statistically significant difference (P = 1).

These findings align with **Cunningham *et al.*** [12] who reported similar distributions across histological subtypes with no statistically significant association (P = 0.207).

On average, the tumor-to-skin distance was 4.3 mm in the nodal-negative group and 4.67 mm in the nodal-positive group, according to research by **Eom *et al.*** [17]. There was a statistically significant difference (P = 0.047) in this regard.

According to **Ansari *et al.*** [16] axillary node metastasis at diagnosis was related with more superficial cancers. Reducing tumor-to-skin distance was associated with positive ALNs in a multivariate analysis of 233 breast tumors (T2 and T3). The incidence of positive lymph nodes increased by 15% for every 1 mm decrease in tumor-to-skin distance (odds ratio 1.15, P = 0.003). In a similar vein, **Bae *et al.*** [18] discovered that ALNM was substantially linked with a shorter tumor-to-skin distance in univariate analysis (P = 0.019). Independent predictors for ALNM, as verified by multivariate analysis, included a closer distance between the tumor and the skin (P = 0.040) and any related architectural distortion.

In the current study, positive axillary nodes were observed in 2 of 3 patients (66.7%) whose tumors were located less than 3 mm from the skin. Among patients with tumors greater than 3 mm from the skin, 52 out of 82 patients (63%) exhibited positive axillary nodes. Although there was no statistically significant variation (P = 1), this lack of significance could be attributed to the limited sample size, as only three tumors measured less than 3 mm from the skin.

In line with these findings, **Sivakanthan *et al.*** [20] also discovered that tumors closer to the skin, less than 3 mm away, had a higher likelihood of being node-positive (66.67%) than tumors farther away from the skin, more than 3 mm away (46.25%), however no statistical significance was achieved.

On the other hand, **Ojha *et al.*** [21] found that although 47% of nodal-positive patients (48 instances) had tumors that were more than 3 mm from the skin, 88.7% of nodal-positive patients (87 cases) had cancers that were less than 3 mm from the skin. The study found that there was a statistically significant increase in the frequencies of axillary node metastasis when the tumor-to-skin distance was less than 3 mm (P < 0.001).

Eom *et al.* [17] further confirmed that a tumor-to-skin distance of less than 3 mm correlated with increased axillary nodal metastasis (P = 0.039), reinforcing the role of tumor location as a key factor in predicting lymphatic dissemination in breast cancer.

CONCLUSION

Before undergoing surgery for breast cancer, patients should have an ultrasound to determine the likelihood of axillary nodal metastasis, which takes into account the cancer's distance from the skin. It is more common for tumors to affect nodes if they are situated near the skin or in the upper outer quadrant. Validation of these findings requires additional prospective studies with bigger samples and a consistent ultrasonography procedure.

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