The relationship between distance of breast cancer from the skin and incidence of axillary nodal metastasis in female patients with early cancer breast: correlation between radiological and pathological distance

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Background
The aim of this study was to evaluate the relation between proximity of breast cancer to the skin and incidence of axillary nodal metastasis in order to clarify a new guideline in the treatment of early cancer breast.
Patients and methods
This study included 50 female patients with early cancer breast (T1 and T2). All patients underwent breast ultrasonography, with special confirmation on the breast cancer distance from skin surface (radiological distance) in addition to pathological assessment of the distance (pathological distance) after surgical excision and its correlation with radiological distance. Breast conservative surgery with axillary clearance was done for 46 patients, whereas four patients underwent modified radical mastectomy.
Results
This study showed that the more proximal the cancer from the skin, the higher the incidence of axillary lymph node metastasis, and the cut-off radiological distance was 1.55 cm, whereas cutoff pathological distance was 1.5 cm. It also proved that ultrasonography is an accurate and reliable method in assessing the breast cancer distance.
Conclusion
Results revealed that breast cancers located closer to the skin surface have a higher incidence of axillary lymph node metastasis.

Keywords:
axillary lymph node metastasis, distance from the skin surface, early breast cancer, ultrasonography in cancer breast

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Background

In spite of pathological features and molecular biology of breast cancer, the status of axillary lymph nodes (LNs) is one of the most reliable and important prognostic factors in addition to its role in guidance of adjuvant cancer breast treatment [1].

Axillary LN dissection (ALND) has been a routine part of cancer breast treatment for long time because it provides data about the status of axillary LN (prognostic role) in addition to removal of axillary tumors in patients presented with positive LNs (therapeutic role). Incidences of postoperative complications of ALND are 15–30% and include postoperative bleeding, local swelling, numbness, decrease range of motion, wound infection, neuropathy, and chronic lymphedema [2]. So, predication of axillary nodal status before surgery is essential to prepare a patient psychologically for axillary lymph node dissection (ANLD) and in planning for immediate breast reconstruction in addition to avoidance of ANLD if axilla is negative for metastasis [3].

Several studies have reported that the lymphatic pathway present in the dermis is responsible for cancer breast metastatic pathway and suggest that the parenchyma of the breast is not rich in lymphatic plexus than that in the superficial dermal and subdermal layers [4].

Only few studies have investigated the relation between the breast cancer distance from skin surface and axillary nodal deposits. Ultrasonography (U/S) is a more accurate tool for detection of the distances from the skin. Distances of cancer breast from the skin on mammography are subject to variability because of

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patient positioning [5,6]. The aim of our study was to evaluate the relation between breast cancer distance from the skin and axillary LN metastasis.

Patients and methods

Study design

This prospective study included 50 female patients with early cancer breast who were diagnosed and managed at General Surgery Department, Benha University Hospital, from April 2017 to October 2019.

Inclusion criteria

The following were the inclusion criteria:

(1) Female patients with T1 or T2 cancer breast.
(2) Patients who have tumors visible on breast U/S or mammography.

Exclusion criteria

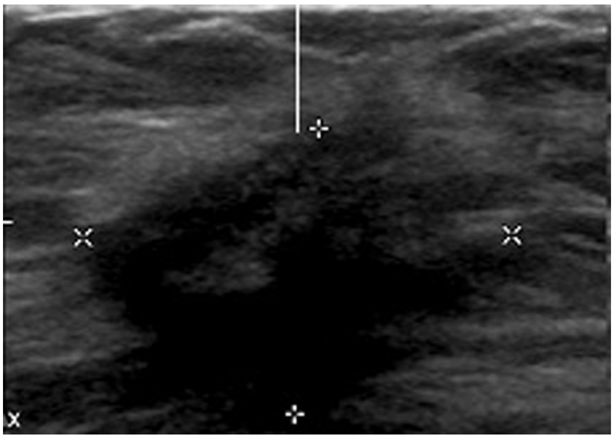
The following were the inclusion criteria:

(1) Locally advanced breast cancer (T3 and T4).
(2) Metastatic cancer breast.
(3) Multicentric breast cancer.
(4) Benign breast lumps.
(5) Women who received neoadjuvant chemotherapy.

The study was initiated after approval of the study by Benha Faculty of Medicine Ethical Committee and obtaining written informed consent from the patients for the participation in the study. Patients were fully informed about the hazards and benefits of the surgery. The patients were assessed by a multidisciplinary team (includes one or more specialized representatives from general surgery, pathology, radiology, radiotherapy, and medical oncology), and patients were enrolled in the study if they fulfilled our inclusion criteria. All patients underwent the following:

(1) Full detailed history.
(2) Clinical examination.
(3) Laboratory investigations: complete blood picture, fasting and postprandial blood glucose, liver function tests, and renal function tests.
(4) Radiological investigations (measurement of cancer distance from the skin): both breasts were examined by a radiologist using US device equipped with linear transducer for three-dimensional image (5–12 MHz). In all patients, the distance was measured perpendicularly from the skin surface to the anterior hyopechoic edge of the tumor before the biopsy. All US images are recorded and subsequently taken for retrospective measurements of breast cancer proximity from surface of the skin (Fig. 1). Bilateral mammography was also done.

Figure 1



Distance of cancer breast from the skin by ultrasonography (white line).

(5) Metastatic workup: computed tomography of chest and abdomen was done in addition to bone scan if indicated.
(6) Pathological evaluation (measurement of cancer distance from the skin): wide local excision of the breast lump is done with an elliptical incision of the overlying skin and then it is sent for histopathological assessment with measurement of pathological distance (Fig. 2). The specimen is oriented by stitches to detect the margins for further management.

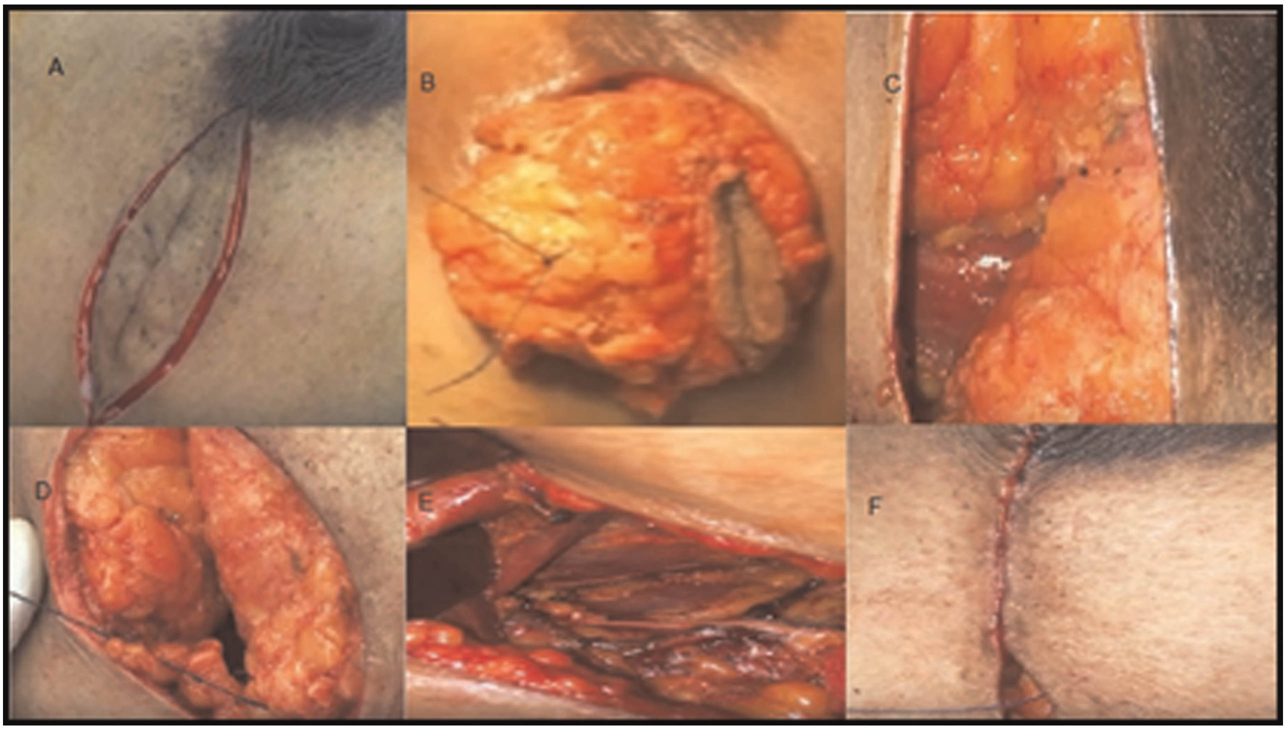
Operative plan

Breast conservative surgery (BCS) or modified radical mastectomy (MRM) was explained to the patient preoperatively, and an informed consent was taken. Type of surgery done for our patients was conducted based on the type of histopathology, size of the mass, breast size, site of the mass, and socioeconomic status. Patients in our study underwent either BCS with axillary clearance or MRM (Fig. 2).

A final pathology report is included with special emphasis on the safety margins, histopathological type, distance from the skin, and number of involved axillary LNs in addition to the immunohistochemical assay for estrogen, progesterone receptors status [estrogen receptor (ER) and progesterone receptor (PR)], and Her2/neu expression in the specimen. In case of BCS, if the safety margin is inadequate (< 1 cm), redo excision is done.

After fulfillment of the patients' data, they are informed regarding the dates of the regular follow-up, and they

Figure 2



Breast conservative surgery (a) elliptical incision, (b) orientation of specimen, (c) mobilization of breast pillar, (d) suturing of pillars, (e) axillary clearance, and (d) Suturing of the skin.

were referred to the outpatient oncology clinic for further management plan regarding radiotherapy, chemotherapy, in addition to hormonal therapy according to the final pathology report.

Primary end point

Evaluation of the prognostic importance of assessing the proximity of cancer breast to the skin and incidence of axillary LN metastasis was the primary end point.

Secondary outcomes

Evaluating the sensitivity of breast U/S and pathological assessment in detecting the distance between the cancer breast and the skin was the secondary end point.

Statistical analysis

Data were statistically described in terms of mean±SD, median and range, or frequencies (number of cases), and percentages when appropriate. Comparison of numerical variables between the study groups was done using Kruskal–Wallis test. Within-group comparison of distance was done using paired t test. For comparing categorical data, χ^2 test was performed. Exact test was used instead when the expected frequency is less than 5. Accuracy was represented using the terms sensitivity and specificity. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut-off value for the studied diagnostic markers. P values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Sciences; IBM Corp., Armonk, New York, USA) release 22 for Microsoft Windows.

Results

This prospective study included 50 female patients presented with early cancer breast (T1 and T2). BCS was done for 46 patients, whereas four patients underwent MRM owing to centrally located tumors, tumors that are large in relation to small breast size, or sometimes patient wishes. There was no statistically significant difference between the age of the patient (mean±SD, 46.78±8.57) and incidence of axillary LN metastasis (P=0.165) (Table 1). There was no significant statistical variation between the location of tumor and the incidence of axillary nodal metastasis (P=0.175) (Table 2). The relation between US BIRAD classification of breast mass and incidence of axillary LN metastasis showed no statistically significant difference (P=0.486) (Table 3). There was no significant variation between tumor size (T stage) and incidence of nodal metastasis (P=0.758) (Table 4). Mean size of the tumor was 2.65 cm. There was no statistically significant variation noted for ER, PR, or HER2 statuses and incidence of axillary nodal deposits (P=0.267, 0.124, 0.542, respectively) (Tables 5 and 6).

Primary outcome

There was statistically significant variation between the incidence of axillary nodal metastasis and the radiological distance (*P*= 0.001). ROC analysis revealed that the most accurate cutoff radiological distance was at 1.55 cm, which achieved sensitivity and specificity of 100 and 72.7%, respectively. This means that early breast cancers with distance less than or equal to 1.5 cm from the skin are more likely to develop axillary LN metastasis, and those with tumors that are deep to this cut-off level are less likely to have axillary nodal metastasis. There was a statistically significant difference between the incidence of axillary nodal deposits and the pathological distance (*P*= 0.001). ROC analysis revealed that the most accurate cutoff pathological distance was at 1.5 cm, which achieved 100% sensitivity and 78.6% specificity (Fig. 3).

Of 50 patients, 17 patients had positive axillary LNs; eight of them were staged as N1 and the other nine patients were staged as N2. There was a significant statistical difference between the radiological distance and progression of axillary nodal metastasis from N1 to N2 stage (*P*= 0.014). ROC analysis showed that 1.35 cm radiological distance was the most accurate cutoff distance that achieved 100% sensitivity and 60% specificity. There was a significant statistical variation between pathological distance and N1 to N2 progression of axillary LN metastasis (*P*= 0.001), ROC analysis revealed that 1.25 cm pathological distance achieved 83.3% sensitivity and 100% specificity, and 1.4 cm achieved 86.3% sensitivity and 66.7% specificity (Fig. 4).

Table 1 Relation between patients' age and axillary nodal metastasis

N	Age
0	
Number	33
Mean	51.87
SD	6.483
Median	51.00
1	
Number	8
Mean	46.78
SD	4.734
Median	46.50
2	
Number	9
Mean	52.67
SD	8.570
Median	52.00
Total	
Number	50

Table 2 Relation between breast tumor location and axillary nodal metastasis

	N			
	0	1	2	Total
Tumor location				
Central				
Count	4	0	0	4
% within tumor quadrant	100.0	0.0	0.0	100.0
% within N	12.1	0.0	0.0	8.0
Lower inner quadrant				
Count	2	4	1	7
% within tumor quadrant	28.5	57.1	14.2	100.0
within N	6.06	50.0	11.1	14.0
lower outer quadrant				
Count	4	2	2	8
% within tumor quadrant	50.0	25.0	25.0	100.0
% within N	12.1	25.0	22.2	16.0
upper inner quadrant				
Count	3	2	1	6
% within tumor quadrant	50.0	33.3	16.6	100.0
% within N	9.09	25.0	11.1	12.0
upper outer quadrant				
Count	20	0	5	25
% within tumor quadrant	80.0	0.0	20.0	100.0
% within N	60.6	0.0	55.5	50.0
Total				
Count	33	8	9	50
% within tumor quadrant	66.0	16.0	18.0	100.0
% within N	100.0	100.0	100.0	100.0

Table 3 Relation between tumor BIRAD and axillary nodal metastasis

	N			
	0	1	2	Total
BIRAD				
4A				
Count	2	0	0	2
% within BIRAD	100.0	0.0	0.0	100.0
% within N	6.3	0.0	0.0	4.0
4B				
Count	6	2	0	8
% within BIRAD	75.0	25.0	0.0	100.0
% within N	18.8	22.2	0.0	16.0
4c				
Count	11	1	4	16
% within BIRAD	68.8	6.3	25.0	100.0
% within N	34.4	11.1	44.4	32.0
5				
Count	13	6	5	24
% within BIRAD	54.2	25.0	20.8	100.0
% within N	40.6	66.7	55.6	48.0
Total				
Count	32	9	9	50
% within BIRAD	64.0	18.0	18	100.0
% within N	100.0	100.0	100.0	100.0

Relation between tumor Breast Imaging Reporting and Data System and axillary nodal metastasis BIRAD, Breast Imaging Reporting and Data System.

Table 4 Relation between breast tumor size (T) and axillary nodal metastasis

	N			
	0	1	2	Total
T stage				
1				
Count	8	3	4	15
% within T	53.3	20.0	26.7	100.0
% within N	26.7	30.0	40.0	30.0
2				
Count	22	7	6	35
% within T	62.9	20.0	17.1	100.0
% within N	73.3	70.0	60.0	70.0
Total				
Count	30	10	10	50
% within T	60	20.0	20.0	100.0
% within N	100.0	100.0	100.0	100.0

By using the *t* test, the mean radiological distance was 1.46 cm, whereas the mean pathological distance was 1.59 cm. The mean difference between both measurements was only 0.13 cm. There was no significant statistical difference between the radiological and pathological distance (P=0.647).

Secondary outcome

U/S is an accurate and reliable method in assessing the breast cancer distance. ROC analysis also showed that the overall accuracy of U/S in this test is 88.6%.

Discussion

Status of axillary LN is one of the most important and reliable prognostic indicators and is an essential factor to detect staging and treatment of cancer breast cancer [1]. Prediction of axillary nodal status before surgery is important for many reasons. It can prepare patients psychologically for ANLD if required, in addition to it can assist with contingency planning for patients who desire immediate breast reconstruction. Accurate prediction of axillary LN status can avoid ANLD and its associated complications [7–9].

Table 5 Relation between breast tumor ER and PR status and axillary nodal metastasis

	N			
	0	1	2	Total
Estrogen receptor (ER)				
Negative				
Count	3	0	2	5
% within ER	60.0	0.0	40.0	100.0
% within N	9.1	0.0	22.2	10.0
Positive				
Count	30	8	7	45
% within ER	66.7	17.8	15.6	100.0
% within N	90.9	100.0	77.8	90.0
Total				
Count	33	8	9	50
% within ER	66.0	16.0	18	100.0
% within N	100.0	100.0	100.0	100.0
Progesterone receptor (PR)				
Negative				
Count	5	1	5	11
% within PR	45.5	9.1	45.5	100.0
% within N	15.6	11.1	55.6	22.0
Positive				
Count	27	8	4	39
% within PR	69.2	20.5	10.3	100.0
% within N	84.4	88.9	44.4	87.0
Total				
Count	32	9	9	50
% within PR	64.0	18.0	18.0	100.0
% within N	100.0	100.0	100.0	100.0

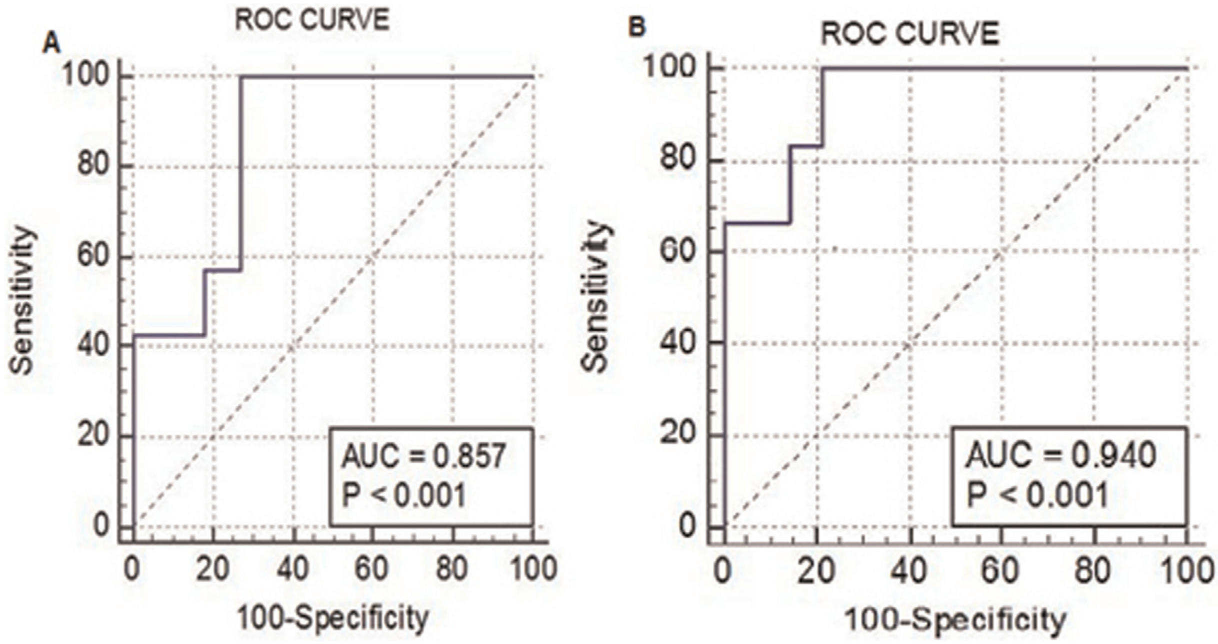
Relation between breast tumor estrogen and progesterone receptor (ER and PR) status and axillary nodal metastasis.

Table 6 Relation between breast tumor Her2/neu status and axillary nodal metastasis

	N			
	0	1	2	Total
HER2				
Negative				
Count	33	8	5	46
% within HER2	71.7	17.4	10.9	100.0
% within N	91.7	88.9	100.0	92.0
Positive				
Count	3	1	0	4
% within HER2	75.0	25.0	0.0	100.0
% within N	8.3	11.1	0.0	8.0
Total				
Count	36	9	5	50
% within HER2	72	18.0	10.0	100.0
% within N	100.0	100.0	100.0	100.0

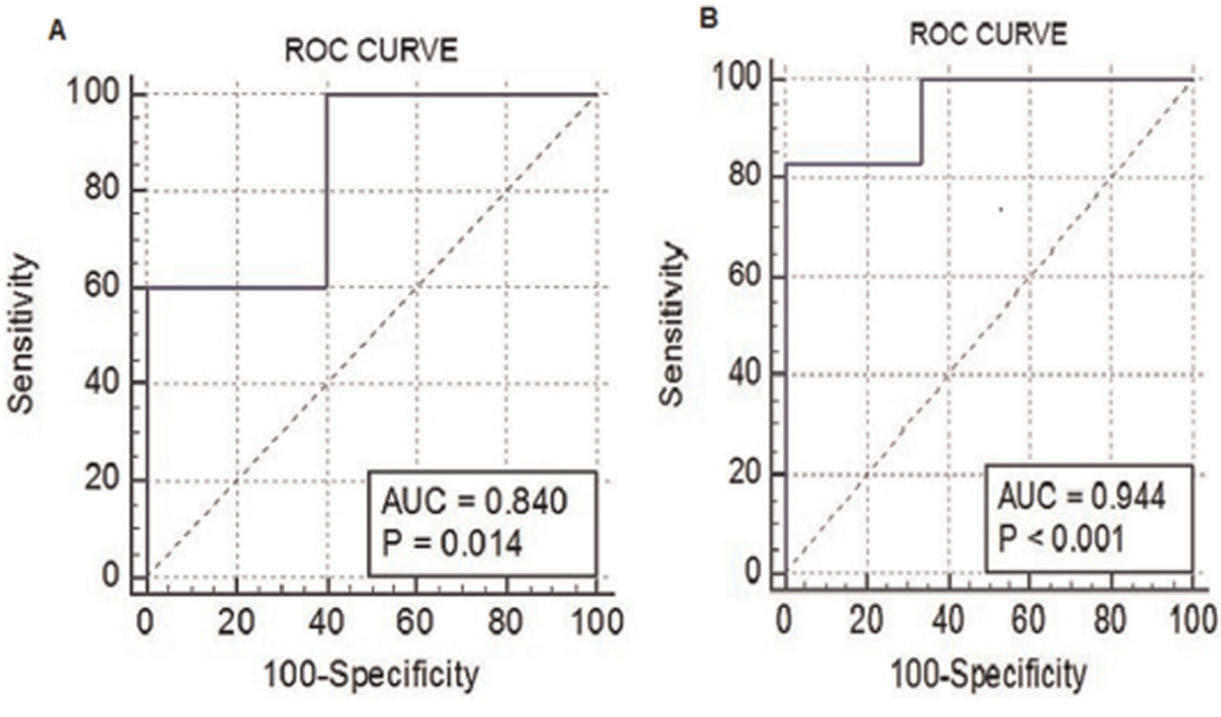
Many clinical, histopathological, and molecular features have been related to the likelihood of axillary nodal metastases in patients with cancer breast [10–14]. Several nomograms have been initiated for the prediction of axillary LN metastasis, such as those developed at Memorial Sloan Kettering Cancer Center and MD Anderson Cancer Center. These nomograms have specified several predictors of axillary nodal deposits such as: size of the tumor, age of the patient, anatomical location, lymphovascular invasion, histological type of the tumor, tumor grading, hormonal status of the tumor (ER and PR), in addition to focality and centricity of the tumor. These developed nomograms did not involve breast cancer distance from the skin and nipple–areola complex in their validation [5,6,15].

Figure 3



Receiver operator characteristic curve analysis: (a) radiological distance and (b) pathological distance.

Figure 4



Receiver operator characteristic curve analysis of axillary nodal metastasis progression from N1 to N2: (a) radiological distance and (b) pathological distance.

In our study, 50 patients of early breast cancer (T1 and T2) were involved, where they underwent BCS (46 patients) or MRM (four patients); for all patients, the radiological and pathological distances were measured. A total of 33 (66%) patients were node negative and 17 (34%) patients were node positive, and eight (16%) and nine (18%) patients were staged as N1 and N2, respectively. ANLD was done for all patients, and the mean number of excised LNs was 21.78. This compares well with the previous studies, like Cunningham *et al.* [4], which included 209 patients, where 61 (29%) had axillary nodal metastasis and 148 (71%) had no known metastases, and the study of Ansari *et al.* [5], in which data were collected on 233 patients with early breast cancer, where 177 (76%) were node negative and 56 (24%) were node positive.

The mean age of the patients in our study was 51.87±6.48 years for node-negative patients, 46.78±4.73 for N1 patient group, and 52.67±8.57 for N2 patient group. Eom *et al.* [5], reported that the mean age for node-negative patients was 51.07 years, and for node-positive patients was 48.69 years. However, Ansari *et al.* [5] reported that the mean age of all patients was 66.2 years, whereas the mean age for node-negative and positive-patients was 66.9 and 63.9, respectively. In our study, there was no statistically significant difference between the age of the patient and the incidence of axillary nodal metastasis (P=0.165). Cunningham *et al.* [4] reported similar results and declared there was no statistical significant variation between the age of the patient and the incidence of axillary LN metastasis (P=0.399).

In this study, there was no significant statistical variation between the location of the tumor and incidence of axillary LN deposits (P=0.185). This compares well with the study of Cunningham *et al.* [4], which revealed there was no significant statistical variation between the tumor location and incidence of axillary nodal metastasis (P=0.138). However, some studies like Ansari *et al.* [5] showed that there was a significant statistical variation between the tumor location and incidence of axillary LN metastasis (P=0.001). This may be explained by sample size difference.

In our study, there was no statistically significant variation between the tumor size and the incidence of axillary nodal metastasis (P=0.758). Mean tumor size in our study was 2.65 cm. Eom *et al.* [16] reported that the mean tumor size for node-negative and node-positive patients was 1.92 and 2.76 cm, respectively, and this matches with our result, which showed there was no statistically significant relation between the tumor size (T) and incidence of axillary LN metastasis (P=0.709). Other studies reported different data, like Ansari *et al.* [5], in which the mean tumor size for all patients was 1.34 cm, and it was 1.24 cm and 1.68 for node-negative and positive-patients, respectively; they showed significant statistical difference between the size of tumor and incidence of axillary nodal metastasis. Patients T1c and T2 stages were 7.7 and 8.6 times more likely to have positive nodes, respectively, than patients with T1a and T1b stages (P=0.001). Cunningham *et al.* [4] reported that tumors in the node-positive patients tended to be larger (P=0.002).

In the present study, no significant statistical difference was observed for ER, PR, or HER2 status and axillary LN positivity (P=0.267, 0.124, and 0.542, respectively). This is similar to the study reported by Eom *et al.* [16], in which there were no significant variations observed for ER, PR, or HER2 statuses between patients with positive and negative axillary LN (P=0.478, 0.534, and 0.422, respectively). Ansari *et al.* [5] showed also that there was no significant variation noted for ER, PR, or HER2 statuses between patients with positive and negative axillary nodes (P=1.0, 0.14, and 1.0, respectively).

In this study, it was found that there was a statistically significant correlation between the incidence of axillary LN metastasis and the radiological distance (P= 0.001); the most accurate cutoff level at 1.55 cm achieved 100% sensitivity and 72.7% specificity. Moreover, it was noted that there was a statistically significant correlation between the incidence of axillary LN metastasis and the pathological distance (P= 0.001); the most accurate cutoff at 1.5 cm achieved 100% sensitivity and 78.6% specificity. It was obvious in our study that no patient with cancer deep to 1.55 cm from the skin had any positive axillary LNs. This means that 1.55 cm is the most likely cutoff distance at which positive axillary LN is to be predicted. Eom *et al.* [16] reported that patients with cancer breast closer to the skin are more likely to develop positive axillary LNs than those with tumor far from the skin (P=0.047). This also compared well with Ansari *et al.* [5], who reported that closer proximity of the cancer to the skin was associated with positive axillary LNs, and each 1-mm decrease in the cancer distance from the skin was associated with a 15% increased likelihood of LN metastasis. Ansari *et al.* [5] studied also the relationship between the size of the largest metastatic axillary LN and the breast cancer distance from the skin and reported that there was no statistically significant association between the size of the largest LN metastasis and distance from the skin (P=0.72), and also there was no significant statistical correlation between the number of positive axillary LNs and the distance of the tumor from the skin (P=0.29). Cunningham *et al.* [4] reported that of none of the 26 cancers with distance greater than 14 mm measured by U/S had metastasized to axillary LNs. In logistic regression analysis, size of the tumor, histologic grade, and proximity of the tumor to the skin were significantly associated with odds of axillary nodal metastasis. Among cancers within 14 mm distance, proximity was not an independent predictor.

Our study revealed that there was a statistically significant relation between the radiological distance and progression of axillary LN metastasis from N1 to N2 stage (P= 0.014), and the most accurate cutoff radiological distance at which progression from N1 to N2 stage was most likely to occur was at 1.35 cm, which achieved 100% sensitivity and 60% specificity. There was a significant statistical correlation between the pathological distance and axillary LN metastasis progression from N1 to N2 stage (P= 0.001), and the most accurate cutoff pathological distance was between 1.25 cm, which achieved 83.3% sensitivity and 100% specificity, and 1.4 cm, which achieved 86.3% sensitivity and 66.7% specificity.

We also compared radiological distance with the pathological distance in order to clarify the accuracy of U/S in detecting breast cancer distance. We found that the mean radiological distance was 1.46 cm, whereas the mean pathological distance was 1.59 cm. The mean difference between both distances was only 0.17 mm. There was no significant statistical variation between the two methods of measurement (P=0.647). The overall accuracy of the U/S was 88.6%. This means that U/S is considered to be a reliable investigating method in the detection of the distance between the breast cancer and the surface of the skin.

There are some limitations of this study that have to be addressed, including technical factors that could have affected the distance from the skin, that is, the scan technique and ability of the U/S physician to obtain the proper image through the image plane that most accurately evaluates the proximity of the tumor to the skin surface, which may result in induced U/S measurement error. Some tumors had poorly defined edges, and others had hyperechoic halos surrounding the tumor. U/S characteristics that make accurate measurements are more difficult to obtain. The size of breast was not involved in this study, and the relation between tumor size and breast size may influence proximity to the skin, especially in smaller breasts, and it is well known that distance from the skin is shorter in smaller breasts than in larger breasts; therefore, effect of breast size on nodal metastases cannot be excluded. Sample size of the patients was small, which was also a limiting factor, so further prospective studies with larger patient numbers and a standardized US protocol would be required.

Ultimately, in the future, we may be looking to detect which patients are able to avoid any axillary surgery including sentinel lymph node biopsy.

Conclusion

Cancer distance from the skin should be taken into consideration when preoperatively evaluating a patient with breast cancer before surgery and assessing the risk of axillary nodal deposits.

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The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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