Evaluation of the diagnostic accuracy of preoperative ultrasound for axillary lymph nodes in breast cancer patients

Mahmoud Ali, Suzan S. Abusahmen, Emad Khallaf, Mohamed Attia

Department of General Surgery, Faculty of Medicine, Cairo University, Cairo, Egypt

Correspondence to Mohamed A. S. Attia, MD, Mobile: +0122 992 3636; Tel: 01019059780; e-mail: massabry@kasralainy.edu.egy

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Background
Breast cancer is the most prevalent cancer and the second leading cause of death among women is breast cancer. The likelihood of survival rises with early breast cancer diagnosis, which lowers death rates. For the treatment of breast cancer, axillary lymph nodes (ALNs) must be correctly staged and managed. The main goals of ALNs staging are to gather prognostic data and information that might influence management decisions.
Objective
To evaluate the accuracy of the preoperative ultrasound in detection of malignant ALNs in breast cancer patients.
Methods
The records of breast cancer patients at the breast surgery unit of Kasr Alainy Hospital, between 2017 and 2020, were reviewed. Patients with an axillary ultrasound report who underwent a sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND) were enrolled in the present study. Demographic and clinicopathologic characteristics including age, family history, body mass index (BMI), primary tumor size, histological and biological grade, Lymphovascular invasion (LVI), extracapsular invasion (ECE), were evaluated.
Results
Out of the 348 Breast Cancer patients who were managed in our department, the age range was 28–89 years (median age 52 years). The histopathology results of the tumor were 96% with invasive duct carcinoma (IDC) 2.3% invasive lobular carcinoma (ILC) and 1.7% were mixed ductal/lobular. Cortical thickness greater than 3 mm had a significant difference for positive nodal status, effacement of hilum had a sensitivity 56.2% in detecting positive lymph nodes (LNs), round LNs shape had a sensitivity of 82.3% in detecting true positive LNs. Pathological LNs by ultrasound had a sensitivity of 93% and specificity of 77% in detecting true positive LN_S, BMI was not significant in ultrasound detection of pathological LNs.
Conclusion
The data shows that axillary ultrasound by its assessment has revealed to be useful in detection of malignant LNs with a sensitivity of 93.1% and specificity 77% in detecting true malignant LNs.

Keywords:
axillary ultrasound, breast cancer, evaluation, lymph nodes, pathological

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Introduction

One in three cases of cancer in women are breast cancer cases, making it the most prevalent malignancy. Breast cancer accounts for 18.9% of all instances of cancer among women, with a preponderance among young age, according to data from the Egyptian National Cancer Institute (NCI) [1]

The diagnosis of axillary lymph node (ALN) staging has two main objectives: first, to gather data that may influence treatment choices, and second, to gather prognostic data. The strongest predictors of prognosis in Breast Cancer [2] are ALN status, including whether lymph node metastases are present or absent, as well as the number and extent of LNS involved. From the subareolar plexus, lymphatic channels in the breast go centrifugally by main lactiferous ducts and efferent veins to draining nodes [3].

No further axillary surgery is advised for individuals who have a benign SLNB or a modest tumor load in the form of isolated tumor cells (ITCs) or micro-metastases. The value of ALND in these patients has been questioned as a result of the American College of Surgeons Oncology Group (ACOSOG Z0011) randomized trial's recommendation to forgo

ALND in patients with two or fewer positive LNS, which did not adversely affect survival when compared with patients in whom axillary clearance was performed. The ALND is still advised for patients who have three or more positive SLNB, along with neoadjuvant therapy [4].

For the therapy of breast cancer, axillary lymph nodes (ALNs) must be managed correctly and staged precisely. Preoperative axillary ultrasound's function as a staging technique has been discussed. Without a doubt, a competent examiner's axillary ultrasound gives important information for the identification of axillary metastatic involvement [5]. Axillary ultrasound staging of the axilla, which takes into account the size, shape, cortical thickness, and echogenicity of the axilla, is increasingly employed to identify worrisome axillary nodes. (Nowadays, it serves as a guide for SNLB or ALND).

Staging of breast cancer

Breast cancer patients are staged with the goal of grouping patients who will have similar outcomes. Patients must be staged in order to develop a treatment plan, however in the case of breast cancer treatment, considerations go beyond conventional TNM staging. Therefore, it is important to consider facts that will affect the patient's treatment rather than only gathering data to offer the TNM staging. The clinical stage of breast cancer is determined by the findings of the physical examination and imaging tests (except PET scans), whereas the pathologic stage is determined by the combined results of these tests and the surgical procedures.

Since it gives a direct sense of the cancer's extent, pathologic staging is likely to be more accurate than clinical staging. When addressing a specific patient, it is crucial to be clear about whether one is referring to clinical or pathologic staging. It is also crucial to understand when further clinical staging information may be required to make therapeutic recommendations [6]. The key goal for radiologists is to detect the metastasis in non-palpable ALN and to reduce the selected patients for upfront ALND [7]. The diagnosis of lymph node metastasis impacts the prognostic relevance in breast cancer patients. Another indicator of tumor biology is nodal status, with node-positive tumors having a poorer prognosis than node-negative tumors [8].

It was thought that the identification of enlarged axillary lymph nodes indicated enlargement and, hence, metastatic illness. All patients' lymph nodes can be found using contemporary high-resolution ultrasonography. Axillary lymph nodes in women with and without breast cancer could be detected even if healthy. As a result, the simple existence of axillary lymph nodes may not signify cancer [9].

In this patient population, axillary ultrasound imaging has the potential to yield important data. since previously mentioned, axillary ultrasonography with percutaneous biopsy is recommended at the time of first diagnosis (before treatment), since it improves clinical staging and enables the detection of node positive illness. Axillary ultrasonography can be used to analyses the morphology of the axillary lymph nodes after chemotherapy and before surgery. This can help determine if the nodes have now returned to normal or whether morphological abnormalities still exist.

The objective of this study is to investigate the precision of preoperative axillary ultrasonography in determining the state of the axillary LNS in relation to the post-operative histological analysis.

Methodology

This is a retrospective cohort study conducted in Kasr Alainy University Hospitals, Cairo University.

The study protocol was reviewed and permitted by the institutional research and ethics committee. The study involved 384 breast cancer patients.

All patients diagnosed with both invasive and noninvasive breast cancer operated in the breast surgery unit- Kasr Alainy Hospital from January 2017 to December 2020.

Metastatic breast cancer patients were excluded from the study.

Methods and patients

Data were collected from medical records, including operative notes, radiology reports, and pathology reports from the data base system of the oncology department a total of 3000 breast cancer patients files our criteria matches with 348 patients.

Filling the patient's data in a spreadsheet, that includes: patients' BMI, biological subtype of the tumor, clinical examination of both breast and axilla, Lymphovascular invasion, Extra Capsular Extension, size and number of nodal metastasis and histopathology reports of sentinel lymph node or axillary node dissection.

Comparing the preoperative axillary sonographic appearance with the post-operative pathology reports in patients with clinically negative/positive axilla. Patients were admitted to our department after they had a preoperative axillary ultrasound then underwent either Sentinel Lymph Node Biopsy (SLNB) or Axillary Lymph Node Dissection (ALND).

Regarding the axillary ultrasound finding effaced hilum and muffled hilum collected as a different criterion but both considered suspicious for pathological ALN.

All breast cancer patients who met our inclusion criteria, during the period from 2017 to 2020, were enrolled in our study. Patients with preoperative pathological lymph nodes by U/S underwent ALND whether they received neoadjuvant treatment or not. On the other hand, patients with clinically node negative axilla underwent SLNB using Methylene Blue 1%.

All patients had their axillary lymph nodes evaluated by ultrasound done by an experienced radiologist by the ultrasound of (Simens GA logic S8). Regarding histopathology, each node is multisector, and one representative section is then processed. Each section is 4 mm cut, then processed by automated processor using different alcohol concentrations followed by xylene and paraffin wax. The paraffin blocks are serially cut at a 4-micron thickness, then stained by hematoxylin and eosin stains for pathological evaluation. All slides were also evaluated by an experienced pathologist.

Statistical analysis

Statistical analysis was conducted using SPSS 27 version, numeric variables were presented in mean ±Standard deviation and compared using Mann–Whitney *U* test. Categorical variables were presented in frequency and percentages. Paired comparison was conducted using McNamara test to evaluate the compatibility of radiological and histopathology findings. Logistic regression model was conducted to evaluate the correlation between ultrasound findings and BMI. Any *P* value less than 0.05 was considered significant.

Results

A total of 348 breast cancer female patients were included in our final analysis, they had a mean age 52.6±SD 11.4 years old, and mean BMI 34±SD [8]. 20.4% had a positive family history of breast or ovarian cancers. Postmenopausal Axillary ultrasound represented 203 (58.3%) of the include patients versus 145 (41.7%) premenopausal Axillary ultrasound 177 (51.5%) received neo adjuvant treatment and 48.5% had an upfront surgery Table 1.

ALND was performed in 242 (69.5%) of the cases while SLND was done in 106 (30.5%) only. Regarding clinical T stage, 195 (56%) of cases were presented in T2, followed by T3 121 (34.8%), T4 in 25 (7.2%) and finally 7 (2%) with T1 Table 1.

Regarding histopathology examinations, 336 (96.6%) of the samples demonstrated features consistent with IDC, 8 (2.3%) ILC, and 4 (1.1%) were mixed. 222 (63.8%) were grade II, 120 (34.5%) were grade III, and

Table 1 Demographics and clinic-pathological data of the included patients

	N (%)
AGE	52.6 (11.4)
BMI	34 (19)
Family history	
Negative	273 (78.4%)
Positive	71 (20.4%)
Unknown	4 (1.1%)
Menopausal Axillary ultrasound status	
Premenopausal axillary ultrasound	145 (41.7%)
Postmenopausal Axillary ultrasound	203 (58.3%)
T stage	
T1	7 (2.0%)
T2	195 (56.0%)
T3	121 (34.8%)
T4	25 (7.2%)
Neo adjuvant chemotherapy	
No	167 (48.5%)
Yes	177 (51.5%)
Axillary dissection	
SLND	106 (30.5%)
ALND	242 (69.5%)
Histological grade	
I	6 (1.7%)
II	222 (63.8%)
III	120 (34.5%)
Histopathology	
IDC	336 (96.6%)
ILC	8 (2.3%)
Mixed	4 (1.1%)
Extra nodal extension (ENE)	
No	278 (79.9%)
Yes	70 (20.1%)
Lymph vascular invasion (LVI)	
No	294 (84.5%)
Yes	54 (15.5%)
Nodal status	
Negative	146 (42.0%)
Positive	202 (58.0%)
Number positive nodes (mean±SD)	2.8 (4.2)
Number of dissected nodes (mean±SD)	11.2 (6.6)

5 (1.7%) were grade I. 165 (47.4%) of the included patients were Luminal A, 159 (45.7%) were luminal B, 16 (4.6%) were triple negative breast cancer, and 8 (2.3%) were Her2 enriched subtypes Table 1.

Extra nodal extension was reported in 70 (20.1%), while 54 (15.5%) had lymph vascular invasion. Nodal status was positive in 202 (58%) and negative in 136 (42%) of the included cases. Mean number of dissected LN during axillary nodal management was 11.2±SD 6.6 LN, while the mean number of positive LN was 2.8±SD 4.3 LN. LN size had a mean of 1.5 ±SD 0.8 cm. BIRADs of the breast masses was 4 in 182 (52.3%) of cases followed by 5 in 157 (45.1%) and 6 in 3 (0.9%) of cases Table 1.

319 (91.9%) of the included patients had a cortical thickening greater than 3 mm, LN was round in 203 (62.8%), the LN hilum was effaced in 105 (30.7%), axillary US detected pathological LN in 174 (29.9%) of the cases Table 2.

Using McNamara test cortical thickness greater than 3 mm had a significant difference from positive nodal status in pathology with *P* value 0.0001 with sensitivity 61.1% and specificity 78.6% Table 3.

Effacement of LN hilum had a sensitivity 56.2%, specificity 41.4% positive predictive value 29.6%, negative predictive value 68.3%, and diagnostic accuracy 45.9%in detecting positive axillary LN, however effacement had a significant difference from nodal status by pathology with *P* value 0.0001 Table 3.

Size of LN greater than or equal to 1 cm had a sensitivity 67.8%, and specificity 75.6% positive predictive value 90.6%, negative predictive value 40.4%, size showed significant difference in mimicking results of nodal status by histopathology with *P* value 0.0001 Table 3.

Round LN shape had a sensitivity of 82.3% and specificity 84.2%, positive predictive value 89.8%, negative predictive value 73.7%, in detecting true positive LN, moreover there is a significant difference between shape of LN and results of histopathology with *P* value 0.031 Table 3.

Table 2 Ultrasound findings

	N (%)
Cortical thickening	
Normal	28 (8.1%)
>3 mm	319 (91.9%)
LN helium	
Preserved	98 (28.7%)
Effaced	105 (30.7%)
Muffled	139 (40.6%)
LN shape	
Normal	120 (37.2%)
Round	203 (62.8%)
Axillary ultrasound	
Nonspecific	70 (20.1%)
Undetermined	104 (29.9%)
Pathological	174 (50.0%)
Size of LN (mean±SD)	1.5 (0.8
BIRADs	
Unknown	3 (0.9%)
3	3 (0.9%)
4	182 (52.3%)
5	157 (45.1%)
6	3 (0.9%)

Table 3 Paired comparison between nodal status in histopathology examination and ultrasound findings

	Nodal status			
Axillary ultrasound finding	Negative *N* (%)	Positive *N* (%)	McNamara test	*P* value
Cortical thickness				
Normal	22 (78.6%)	6 (21.4%)	105.3	0.0001
>3 mm	124 (38.9%)	195 (61.1%)		
LN hilum				
Preserved	99 (41.4%)	140 (58.6%)	46.5	0.0001
Effaced	46 (43.8%)	59 (56.2%)		
Size of LN				
<1 cm	59 (75.6%)	19 (24.4%)	42.3	0.0001
>=1 cm	87 (32.2%)	183 (67.8%)		
Shape of LN				
Normal	101 (84.2%)	19 (15.8%)	4.65	0.031
Round	36 (17.7%)	167 (82.3%)		
Axillary US				
Non specific	134 (77.0%)	40 (23.0%)	14.01	0.0001
Pathological	12 (6.9%)	162 (93.1%)		

Pathological LN by US had a sensitivity 93.1% and specificity 77% positive predictive value 80.2%, negative predictive value 91.8%, in detecting true positive LN Table 3. (Fig. 1).

Binary logistic regression model showed that effacement of hilum was an independent factor for detection of pathological LN by Ultrasound with odds ratio 0.1 (95% CI 0.04-0.22) *P* value 0.001. Rounded lymph node was an independent risk factor of detection of pathological lymph nodes by Ultrasound with *P* value 0.001. Extra nodal extension is an independent risk factor for diagnosis of pathological LN by ultrasound with *P* value 0.003.

Binary logistic regression model showed that biological subtype did not impact the accuracy of ultrasound as correlations showed that OR were 1.33, 1.27, and 1.28 for luminal A, luminal B and triple negative breast cancer respectively, and *P* values 0.58, 0.65, and 0.77, respectively.

Also, BMI was not a significant risk factor of detecting pathological LN by ultrasound with a *P* value = 0.426, OR = 0.991 and 95% CI.

Discussion

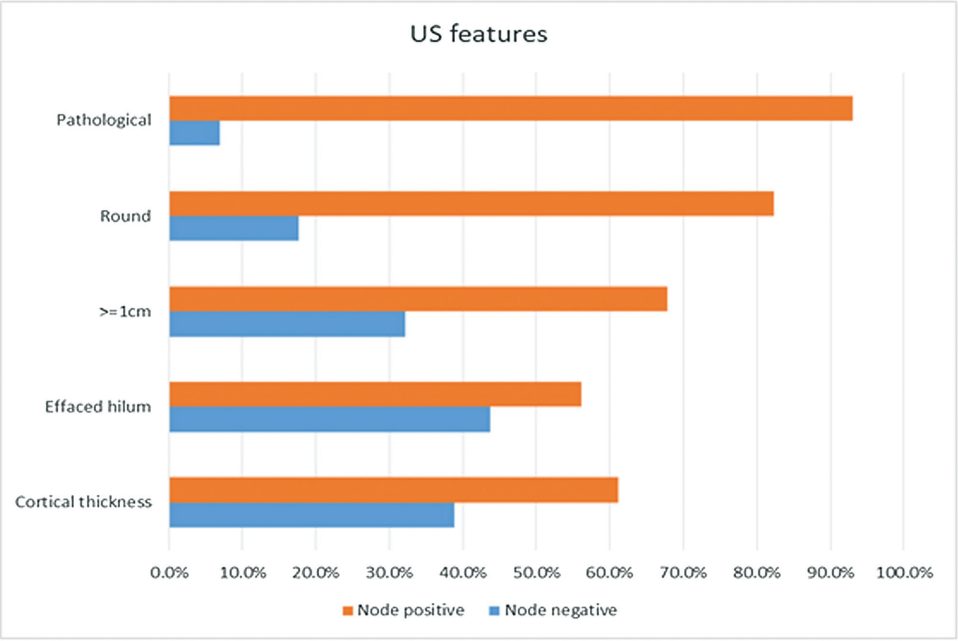
The condition of the axillary lymph nodes continues to rank among the most significant prognostic variables for breast cancer and is crucial for making therapy choices Wahab and colleagues [10]. Preoperative axillary staging and treatment planning benefit from the combination of physical examination and multimodal imaging. However, there are still not enough definite indicators of axillary lymph node involvement. However, axillary metastatic patients were able to learn about their lymph node involvement prior to surgery because axillary imaging Zaiton and colleagues [11].

In order to properly manage breast cancer, including staging, treatment options, and prognosis Mariam and colleagues [12], it is crucial that patients with recently diagnosed breast cancer have their axillary lymph node status evaluated before surgery. In instances when breast cancer is suspected, a conclusive histologic diagnosis is crucial [13].

Because of its accessibility, ease of use, and non-ionizing characteristics, axillary ultrasonography is one of the most often utilized preoperative assessment techniques Chang and colleagues [14]. However, because to its modest sensitivity and the likelihood of false-negative findings, SLNB is necessary De Coninck and colleagues [15].

Regarding the axillary ultrasound results in our study, LNs were (29.9%) identified as abnormal by US. In our investigation, our assessment of pathological ALN exhibited a sensitivity of 93.1% and a specificity of 77% in identifying genuine positive LN. These

Figure 1



Bar chart showing correlation between ultrasound features and nodal status.

findings are consistent with a 2015 study by Nowikiewicz and colleagues, who examined 353 potential breast cancer patients and had axillary ultrasounds performed on all of them. They discovered that the axillary ultrasound detects nodal metastasis with high specificity (89.3%) and an equal high predictive value of the negative test result (85.6%). Additionally, Stachs and colleagues found that the Axillary Ultrasound had a 78.7% accuracy rate, 47.6% sensitivity, 95.7% specificity, 85.9% positive predictive value, and 77% negative predictive value Chang and colleagues [14].

Dihge and colleagues discovered in 2016 that axillary ultrasound alone had a negative predictive value (NPV) of 68% and a positive predictive value (PPV) of 73%, with an overall sensitivity of 23% low. They came to the conclusion that in patients with low nodal metastatic load (axillary metastatic burden, defined by the nodal metastatic size in millimeters, and number of implicated ALNs), axillary ultrasound's sensitivity for the identification of metastatic ALNs in breast cancer was questionable Mariam and colleagues [12].

In our investigation, the pathologically confirmed malignant LNs displayed increased cortical thickness compared with the benign LNs, and the axillary ultrasonography criteria was sensitive (61.1% sensitivity) for identifying malignant lymph nodes. The widespread cortical thickening can be found with metastasis as well as benign nodes, however the specificity is only 78.6%. These findings are consistent with a research by Chang and colleagues from 2018, which examined 140 lymph nodes that were visible on axillary ultrasound imaging. In comparison to nonmetastatic axillary lymph nodes, they discovered that the metastatic nodes had a thicker cortex Fayanju and colleagues [16].

In addition, it was a sensitive conventional US criteria for diagnosing malignant lymph node 56.2% with specificity of 41.4% since the effaced hilum may be changed by NACT. The pathologically proved malignant LNs exhibited substantially greater numbers of effaced hilum compared with the benign LNs. This is consistent with a research by B. Lee *et al.* from 2021, [21] which discovered that the absence of a hyperechoic hilum in lymph nodes is a sign of metastatic illness. With a sensitivity of 40.8% and a specificity of 92.3%, the loss hyperechoic hilum with histologically proven nodal involvement was observed in 22.6% of instances as opposed to 37.4% of true-negative cases [17].

Riedel and colleagues research from 2020, on the other hand, revealed that the criteria of an effaced hilum had a (OR: 2.59, 95% CI: 1.09-6.15), $P = 0.03$, in detecting the existence of LN metastasis as determined by histological analysis [17].

Riedel and colleagues research from 2020, on the other hand, revealed that the criteria of an effaced hilum had a (OR: 2.59, 95% CI: 1.09-6.15), $P = 0.03$, in detecting the existence of LN metastasis as determined by histological analysis [17].

In our investigation, the round shape LNs had a sensitivity of 83.3% and a specificity of 84.2% in identifying metastatic ALNs because the round shape LN was not detected in the axillary ultrasound with benign inflamed ones, which may enlarge but maintain the typical oval form. The majority of pathologically confirmed LNs (82%) had a round form, while the majority of benign LNs (84.2%) had an oval shape. This finding is consistent with a research by Chang and colleagues that found 140 patients with visible axillary lymph nodes on axillary ultrasound imaging. Compared with nonmetastatic axillary lymph nodes, the form of the metastatic nodes tends to be round rather than oval Giuliano and colleagues [18]. The study by Chen and colleagues published in 2018, indicated, however, that the form of ALNS was not significant in identifying metastases in ALNS Harbeck and colleagues [19].

Additionally, we discovered that the biological subtype had no effect on the precision of axillary ultrasonography, with P values for luminal A, luminal B, and TN breast cancer of 0.58, 0.65, and 0.77, respectively, and ORs of 1.33, 1.27, and 1.28. According to a 2019 study by Helfgott *et al.*, the biological subtypes have no significant influence on the accuracy of axillary ultrasonography [20].

Conclusion

Axillary ultrasound can demonstrate axillary lymph nodes and differentiate benign from malignant nodes, and by its assessment has revealed to be useful in detection of malignant lymph nodes. Our data shows that Axillary ultrasound by its assessment has reveals to be useful in detection of malignant lymph nodes with a sensitivity of 93.1% and specificity 77% in detecting true malignant lymph nodes. The cortical thickening more than three millimeters was an independent factor for detection of pathological lymph nodes by axillary ultrasound with sensitivity 61.1% and specificity 78.6%. The effacement of

hilum also was an independent factor for detection of pathological LN by Ultrasound with sensitivity 56.2% and specificity 41.4%. Rounded lymph node was also an independent factor of detection of pathological lymph nodes by Ultrasound with sensitivity of 82.3% and specificity 84.2%. Extra nodal extension is an independent factor for diagnosis of pathological LN by ultrasound with *P* value 0.003. On the other hand, the biological subtype didn't impact the accuracy of ultrasound as well as the BMI was not a significant risk factor of detecting pathological LN by ultrasound.

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Conflicts of interest

There are no conflicts of interest.

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