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Diagnostic accuracy of axillary nodal ultrasound after neoadjuvant chemotherapy in node-positive breast cancer patients: A validation study

Syeda Sakina Abidi

Lubna Mushtaque Vohra

Asad Ali Kerawala

Imrana Masroor

Muhammad Umair Tahseen

RESEARCH ARTICLE

Diagnostic accuracy of axillary nodal ultrasound after neoadjuvant chemotherapy in node-positive breast cancer patients: A validation study

Syeda Sakina Abidi,[1] Lubna Mushtaque Vohra,[2] Asad Ali Kerawala,[3] Imrana Masroor,[4] Muhammad Umair Tahseen[5]

Abstract

Objective: To determine the accuracy and false negative rate of axillary ultrasound compared to sentinel node biopsy.

Method: The retrospective study was conducted at the Aga Khan University Hospital, Karachi, from February 1 to March 31, 2021, and comprised data of breast cancer patients who had undergone neo-adjuvant chemotherapy followed by axillary lymph node dissection or axillary disease diagnosed using lymph node biopsy or sentinel lymph node biopsy between January 1, 2016, and December 30, 2020. After receiving neoadjuvant chemotherapy, axillary ultrasound findings were compared with histopathology of lymph nodes. Data was analysed using SPSS 22.

Results: Of the 155 patients evaluated, 104(67.1%) were diagnosed with negative axillary lymph nodes and 51(32.9%) were diagnosed with positive axillary lymph nodes post-chemotherapy. The overall mean age was 51.13±1.3 years. When histopathology results were compared with those of axillary ultrasound, 36(23.2%) cases turned out to be true positive, while 23(14,8%) were false negative, yielding a positive predictive value of 75% and negative predictive value of 65%. Axillary ultrasound had 75% accuracy, false negative rate 30%, sensitivity 61% and specificity 84.4%.

Conclusion: Axillary ultrasound was found to be fairly useful, but not completely reliable, in identifying positive lymph nodes, .

Keywords: Neoadjuvant chemotherapy, Ultrasound axilla, Sensitivity, False negative rate.

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Introduction

For the past few decades, axillary nodal status has been the cornerstone in breast cancer staging, making axillary surgery part and parcel of breast cancer surgery.[1] Axillary lymph node dissection (ALND), however, comes with significant morbidity of swelling in the arms, numbness and restricted arm movements in up to 40% patients.[2] With increasing knowledge of tumour biology as a more important diagnostic factor and milestones achieved in the de-escalation of breast surgery to reduce morbidity, the need for ALND was questioned. This led to the concept of sentinel lymph node biopsy (SLNB) which now represents routine care in node-negative, early breast cancer patients.[3] Although neo-adjuvant chemotherapy (NACT) allowed breast conservation surgeries to be offered to patients who presented with advance disease, standard ALND remained in practice in post-neo-adjuvant settings. This was mostly because of concern that altered lymphatic drainage pertaining to post-systemic treatment fibrosis may lead to inaccurate SLNB results.[4] Nevertheless, enthusiasm to tailor breast and axillary surgery grew with the knowledge that a number of individuals who receive NACT achieve a pathologically complete response (pCR), defined as no residual infiltrating disease in the breast and the axillary lymph nodes. The rate of achieving pCR strongly correlated with subtypes of breast cancer.[5]

Two large multi-centre prospective clinical trials subsequently validated the feasibility of SLNB in individuals who had positive axillary nodal disease at presentation and achieved a clinically node-negative status after receiving NACT. Both the studies reported a false negative rate (FNR) of 12.6% to 14.2% for SLNB which was above the accepted threshold of 10%.[6-8] The FNR was optimised to <10% using dual tracer, removing three sentinel nodes and clipping biopsied nodes.[9]

Currently available imaging modalities for pre-operative evaluation of axilla in breast cancer patients include mammogram (MMG), axillary ultrasound (aUS), computed tomography (CT) and magnetic resonance imaging (MRI). MMG has diagnostic accuracy of 79.5%, but is unreliable as part of axilla may not be visualised on routine MMG. CT scan and MRI are not usually used for general evaluation of axilla as they are expensive, but are helpful when the extent of disease needs to be evaluated.[10] Thus, aUS is the imaging of choice for initial axillary assessment of patients, but there is significant difference of reported sensitivity (27-94%) and specificity (53-100%).[11] Despite

[1,2,4]Aga Khan University Hospital, Karachi, [3]Cancer Foundation Hospital, Karachi, [5]Dr. Ruth K.M Pfau, Civil Hospital Karachi, Pakistan.

Correspondence: Syeda Sakina Abidi. Email: sakina.abidi@aku.edu

being operator-dependent, it has outperformed other imaging techniques with the advantage of being less expensive and non-invasive, thereby becoming routine practice.[12] In an attempt to decrease FNR, studies have explored the use of US to identify nodes for SLNB and reported an FNR decrease to 9.8% when used with dual tracer techniques.[13] Sensitivity 71% and specificity 88% was reported using aUS with 83% negative predictive value (NPV) and 29% FNR.[14]

Formal re-staging of axilla post-NACT was adopted at the study site in 2015. The current study was planned to determine the accuracy and FNR of aUS compared to SLNB since the change.

Materials and Methods

The retrospective study was conducted at the Aga Khan University Hospital (AKUH), Karachi, from February 1 to March 31, 2021, and comprised data of breast cancer patients who had undergone NACT followed by ALND or SLNB between January 1, 2016, and December 30, 2020. After exemption from the institutional ethics review committee, hospital database was used to identify patients and data was collected on a self-designed questionnaire. Ultrasound axilla reports of patients who received primary NACT were matched with histopathology reports of axillary nodes after definitive surgery which is the gold standard, categorised as positive for lymph nodes with residual tumour, and negative on the absence of such findings. Data was also obtained on age, grade and biology of tumour, stage of breast cancer, and the chemotherapy regimen used. The sensitivity and specificity of aUS was identified through receiver operating characteristic (ROC) curve. Data was analysed using SPSS 22. Descriptive data was reported for quantitative and qualitative variables as mean and standard deviation, median and interquartile range (IQR), and frequencies and percentages, as appropriate. Chi-square test was used to test positive predictive value (PPV) and negative predictive value (NPV) of aUS in relation to post-ALND and immunohistochemistry. ROC curve was used to test the specificity and sensitivity of aUS. $P<0.05$ was considered statistically significant.

Results

Of the 155 patients evaluated, 104(67.1%) were diagnosed with negative axillary lymph nodes and 51(32.9%) were diagnosed with positive axillary lymph nodes post-chemotherapy. The overall mean age was 51.13±1.3 years. The median time for follow-up from the start of NACT to surgery was 6 months (IQR: 3-9 months). Demographic and baseline clinical data was noted (Table-1).

Table-1: Baseline characteristics of tumour and patient demographics.

Characterstics	No. (%)
Age (mean), years	51.13±1.13
Menopausal status	
Premenopausal	63 (40.6%)
Perimenopausal	71 (45.8%)
Postmenopausal	21 (13.5%)
Receptor Status	
ER-/PR-/Her2-	64 (41.5%)
ER/PR+/HEr2+	30 (19.5%)
ER/PR+/Her2-	45 (29.2%)
ER/PR-/HER2+	15 (9.7%)
Size of Invasive focus	
Complete Response	43 (27.7%)
<1 cm	41 (26.4%)
1-2 cm	35 (22.6%)
>2 cm	36 (23.2%)
Grade of cancer	
Grade I	1 (0.6%)
Grade II	90 (58%)
Grade III	64 (41.2%)
Clinical Stage	
T1N0	7 (4.5%)
T1N1	14 (9%)
T2N0	21 (13.5%)
T2N1	83 (53.5%)
T3N0	4 (2.5%)
T3N1	18 (11.6%)
T4N0	2 (1.3%)
T4N1	6 (3.8%)
Histopathology Findings	
IDC	5 (3.2%)
Others	150 (96.8%)
Lymph nodes status post NACT	
Negative axillary lymph nodes post NACT	101 (67.1%)
Positive axillary lymph nodes post NACT	54 (32.9%)
Total No Of Sentinel Nodes Retrieved	
No Sentinel lymph node retrieved	33 (42.2%)
1	5 (0.1%)
2	16 (0.6%)
3	33 (25.5%)
>3	22 (24.4%)
Axillary lymph nodes positive on histopathology after SLN Biopsy	
None	44 (75.9%)
1	11 (19%)
2	2 (3.4%)
3 or >3	1 (1.7%)
Axillary lymph node dissection given	112 (72.2%)
Nodes recovered in ALND	
None	3 (2.2%)
<3	1 (0.7%)
<10	7 (5.1%)
<20	63 (45.7%)
<30	34 (24.6%)
<40	5 (3.6%)
No. of positive lymph nodes after ALND	
None	55 (48.2%)
<3	30 (26.3%)
<5	8 (7.1%)
<10	15 (13.1%)
<20	6 (5.3%)

SD: Standard deviation, ER: Oestrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2, SLN: Sentinel lymph node, IDC: Invasive ductal carcinoma, NACT: Neo-adjuvant chemotherapy, ALND: Axillary lymph node dissection.

Table-2: Diagnostic characteristics of ultrasound (US) modality.

	Axillary US post NACT Residual Disease	Axillary US post NACT No Residual Disease	
Residual Disease on Histopathology	True Positive n=31	False Negative n=36	Sensitivity=61%
No Residual Disease on Histopathology	False Positive n=20	True Negative n=68	Specificity=84.4%
Accuracy= 75%	Positive Predictive Value = 75%	Negative Predictive Value = 65%	False Negative Rate =30%

NACT: Neo-adjuvant chemotherapy.

Table-3: Diagnostic PPV and NPV according to tumour phenotype.

Tumour histopathological subtype	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)
ER+ HER2-	100%	50%
ER+ HER2+	64%	57%
ER- HER2+	82%	71%
ER- HER2-	60%	75%

ER: Oestrogen receptor, HER2: Human epidermal growth factor receptor 2.

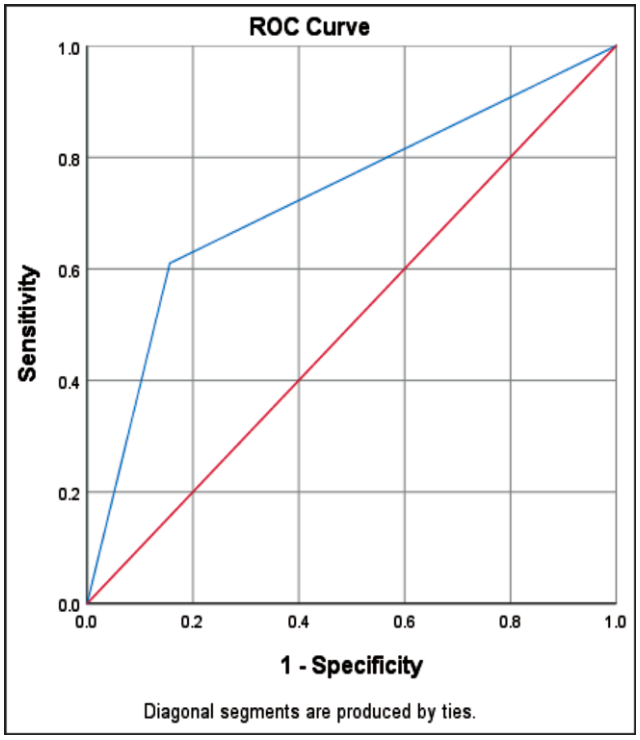
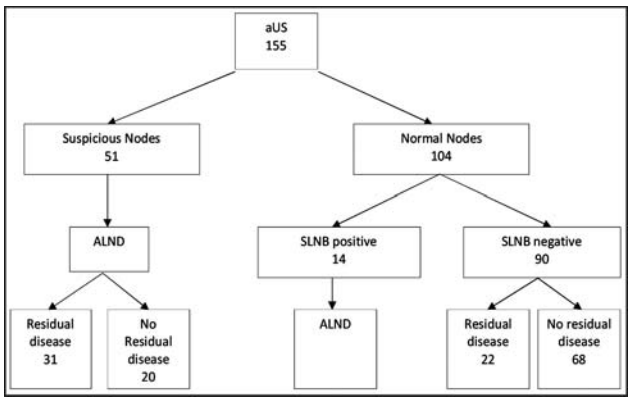


Figure-1: ROC: Receiver operating characteristic (ROC) curve illustrating the sensitivity and specificity of axillary ultrasound (aUS). Area under curve (AUC) = 0.73.

When histopathology results were compared with those of aUS, 36 cases turned out to be true positive (TP), while 23(%) were false negative (FN), yielding a PPV of 75% and NPV of 65%. The aUS had 75% accuracy, FNR 30%, sensitivity 61% and specificity 84.4% (Table-2).

ROC curve showed 61% aUS sensitivity and 84% aUS specificity (Figure-1). The area under curve (AUC) was 0.73



aUS: Axillary ultrasound, SLNB: Sentinel lymph node biopsy, ALND: Axillary lymph node dissection. SLNB is showing false negative rate (FNR) of 12.5% while aUS is showing FNR of 30%.

Figure-2: Boughey's algorithm.

(Standard error=0.04; p=0.001).

Diagnostic PPV and NPV according to tumour phenotype were noted separately (Table-3). SLNB had a FNR 12.5% compared to aUS FNR 30% (Figure-2).

Discussion

The aUS is a vital adjunct to breast imaging in the staging of breast cancers. The lymph nodal status not only guides the treatment, but also provides valuable prognostic information. The major lymphatic drainage from the breast is to the ipsilateral axillary nodes which are best assessed by US. They may be categorised as suspicious (thickened cortex, loss of fatty hilum) or normal (having an intact hilum, cortex <3mm). Concordance in US findings and histopathology may help avoid axillary surgery and its associated morbidity in certain patients.

In the current study, aUS FNR in post-NACT patients was 30%. FNR as low as 2% with targeted axillary dissection has been reported in studies.[15] Targeted axillary dissection, however, involves additional cost and procedures, like clip placement at the time of biopsy. Historically, FNR <10% has been considered significant to use the proposed method of nodal identification. FNR 9.8% can be achieved with a combination of aUS and

SLNB post-chemotherapy.[12]

The current study showed 61% sensitivity of aUS in diagnosing axillary metastasis post-NACT. Other studies have shown sensitivities ranging from 50% to 66% in different settings.[13,16,17] The specificity in the current study was 84%, which was comparable with other studies ranging from 37% to 92%.[18]

Studies[20,21] suggested that different subtypes of breast cancer affect the diagnostic aUS accuracy, and this should be kept in mind before making decisions. The studies reported an overall sensitivity of 60%,[19,20] which is in concordance with the current study. The specificity was 65%, which is lower than the current finding. The overall PPV and NPV were 82% and 38.5% compared to 75% and 65% in the current study. Higher PPV means that if there are suspicious US findings, there is high probability of the node being involved with cancer and the patient can proceed with an axillary dissection and prevent an unnecessary SLNB.

The studies[19,20] pointed towards non-luminal subtypes having a higher sensitivity compared to luminal subtypes, while the specificity was the same for both. The sensitivity was highest in triple-negative cancers. Similarly, the PPV was highest for luminal A subtype and the NPV was the highest for triple-negative cancer.[19,20] The current subset analysis of tumour phenotype showed similar results (Table-3). A study also presented the same results with almost 100% PPV for luminal A subtype.[21]

A newer approach to avoid unnecessary axillary dissection is called the Systemic Sonographic Axillary Staging. Any suspicious nodes after completion of NACT undergoes repeat needle biopsy, and axillary surgery is planned according to the status of biopsy results.[22]

The current study has limitations of having single-centre, retrospective data. Besides, the role of repeat biopsy of suspicious axillary nodes and effects of tumour phenotype on re-staging of axillary disease need further exploration.

Conclusion

The aUS was found to be a fairly useful, but not completely reliable, tool for identifying positive lymph nodes. Further intervention is necessary for diagnosis. Thus, histopathology remains the gold standard to identify axillary metastasis.

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Conflict of Interest: None.

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