Open Access

Original Article

Identification of Early Breast Cancer Patients with Limited Axillary Disease that Can Be Spared from Routine Axillary Nodal Clearance in Upfront Cases

Zenab Noorain, Ayesha Javed, Syeda Rifaat Qamar Naqvi, Saman Naz, Marrium Khurshid, Hira Ijaz

Department of Breast Surgery, Combined Military Hospital, Rawalpindi/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To compare clinically assessed limited axillary disease with final histopathological findings in breast cancer patients treated surgically as upfront cases and to determine the accuracy of clinical axillary assessment and its implications for contemporary axillary management.

Study Design: Diagnostic cross-sectional study.

Place and Duration of Study: Department of Breast Surgery, Combined Military Hospital, Rawalpindi, Pakistan from Feb to Nov 2025.

Methodology: A total of 420 patients were analyzed. Primary variable studied was the accuracy of preoperative clinical axillary assessment in identifying limited axillary disease, using final histopathological nodal status as the gold standard.

Results: The sensitivity of clinical axillary assessment was calculated as 58.0%, specificity was 90.9%, the positive predictive value was 83.8%, while the negative predictive value was 72.8%. The overall diagnostic accuracy of clinical axillary assessment was 76.2%. Agreement between clinically assessed limited axillary disease and final histopathological nodal status was evaluated using Cohen's kappa statistic. A κ value of 0.50 indicated moderate agreement beyond chance between the two methods ($p< 0.001$).

Conclusion: This study showed that preoperative clinical and imaging-based axillary assessment showed high specificity but only moderate sensitivity when compared with final histopathology in upfront surgery cases.

Keywords: Axillary, Breast Neoplasm, Biopsy, Lymph Node Dissection, Sentinel.

How to Cite This Article: *Noorain Z, Javed A, Naqvi SRQ, Naz S, Khurshid M, Ijaz H. Identification of Early Breast Cancer Patients with Limited Axillary Disease that Can Be Spared from Routine Axillary Nodal Clearance in Upfront Cases. Pak Armed Forces Med J 2026; 76(Suppl-8): S1301-S1306. DOI: https://doi.org/10.51253/pafmj.v76iSUPPL-8.14150*

INTRODUCTION

Breast cancer is the most diagnosed malignancy among women worldwide, accounting for approximately 2.3 million new cases annually, with a steadily rising incidence in low and middle-income countries including Pakistan. Axillary lymph node status remains a cornerstone for prognostication, staging, and decisions regarding adjuvant systemic and locoregional therapy. Historically, axillary lymph node dissection (ALND) was routinely performed for nodal staging and disease control; however, its well-documented morbidity, particularly lymphedema, shoulder dysfunction, sensory neuropathy, and impaired quality of life, has driven a global shift toward axillary de-escalation.[1]

Sentinel lymph node biopsy (SLNB) has now become the standard approach for clinically node-negative early breast cancer, offering reliable staging with minimal morbidity. Large, randomized trials have demonstrated that in selected patients with limited nodal metastasis, completion ALND does not improve overall survival or locoregional control when modern systemic therapy and radiotherapy are applied. The AMAROS trial was pivotal in this paradigm shift, showing that patients with one or two positive sentinel lymph nodes achieved equivalent axillary control and survival outcomes without ALND, provided appropriate axillary radiotherapy was delivered. These findings have been widely incorporated into international guidelines, supporting omission of routine ALND in patients with low nodal burden.[2]

Despite this progress, a critical challenge persists in upfront surgical cases, accurately identifying patients with truly limited axillary disease cN1 cases with 1-2 suspicious axillary lymph nodes on imaging before surgery. Consequently, patients deemed to have limited nodal disease preoperatively may either be overtreated with unnecessary ALND or undertreated due to underestimation of nodal involvement.[3]

Correspondence: Dr Zenab Noorain, Department of Breast Surgery, Combined Military Hospital, Rawalpindi Pakistan

Received: 04 Jan 2026; revision received: 25 Apr 2026; accepted: 26 Apr 2026

Histopathology remains the gold standard for axillary staging and provides the most accurate assessment of true nodal burden.[4] Correlating preoperative clinical and radiological assessment with final histopathological findings is therefore essential to refine patient selection for axillary de-escalation in upfront surgery by minimizing morbidity without compromising oncological outcomes.

METHODOLOGY

This diagnostic cross-sectional study was conducted at the Department of Breast Surgery, Combined Military Hospital Rawalpindi, Pakistan from February 2025 to November 2025 after ethical review board approval. (Vide Ser No. 805).

Sample size was calculated using a single-proportion formula, based on the expected rate of discordance between clinically assessed axillary nodal status and final histopathological findings. Contemporary literature reported anticipated discordance proportion of 57%, between clinically assessed axillary nodal status and final histopathological findings.[5] With a 95% confidence level and an absolute precision of 5%, the calculated sample size was 376 patients. To account for incomplete pathological data, protocol deviations, or loss of evaluable nodal specimens, a 10% attrition margin was added, yielding a final target sample size of approximately 420 patients. The study adhered to CONSORT guidelines and received approval from the institutional ethics committee. All participants provided informed consent.

Inclusion Criteria: Women (≥18 years) with newly diagnosed unilateral invasive breast cancer who underwent primary surgical treatment without neoadjuvant chemotherapy were included. All patients with clinically limited axillary disease on preoperative assessment, including only N1 biopsy-proven metastatic carcinoma cases with low-volume (1-2) suspicious imaging findings were included.

Exclusion Criteria: Patients who received neoadjuvant chemotherapy or endocrine therapy, presented with inflammatory or metastatic breast cancer, had prior ipsilateral axillary surgery or radiotherapy, recurrent breast cancer, or cN0 and cN2/cN3 disease were excluded from the study.

The study included 420 patients meeting inclusion criteria, with consecutive recruitment minimizing selection bias. Standardized clinical exams and structured ultrasound reporting reduced measurement bias, while tumor and molecular characteristics were recorded as potential confounders

All patients underwent detailed clinical axillary examination by a consultant breast surgeon. Lymph nodes were assessed for size, consistency, mobility, fixation, and the presence of matting. Based on physical examination, axilla was categorized as clinically impalpable or palpable, biopsy-proven metastatic carcinoma, cN1 disease provided there was no gross fixation or bulky disease.

All patients had axillary ultrasound by a consultant radiologist, assessing cortical thickness, hilum changes, morphology, and vascularity. Suspicious nodes were documented, and ultrasound-guided FNA or core biopsy was performed as per institutional protocol. All patients had upfront breast surgery with concurrent axillary staging, and level-II ALND was performed in all cN1+ cases.

Final axillary status was determined by histopathology as gold standard using standardized protocols. Total and involved lymph nodes were recorded for each patient. Pathological nodal staging was assigned using established criteria, with limited pathological axillary disease defined as pN1 (1–2 positive nodes) and pN2 defined as 3–9 positive nodes.

The primary variable was the accuracy of preoperative clinical axillary assessment in detecting limited disease, with histopathology as gold standard.

Biopsy proven metastatic carcinoma of most suspicious axillary lymph node with only 1-2 suspicious nodes on imaging was categorized as limited axillary disease and labelled cN1, while histopathological findings classified nodal involvement as limited (pN1, 1–3 positive nodes and pN2, 4–9 positive nodes) or extensive disease. The primary outcome focused on the degree of concordance and discordance between these two assessments, reflecting the reliability of clinical staging in upfront surgical cases.

Secondary variables included patient and tumor-related factors including tumor size, histological grade, lymphovascular invasion, molecular subtype, total number of lymph nodes retrieved, number of positive nodes, and presence of extra nodal extension. Additional secondary outcomes included the rate of axillary under staging and over staging on clinical assessment.

All analyses were performed using IBM Statistical Package for Social Sciences (SPSS) version 31. The primary variable, accuracy of preoperative clinical axillary assessment in identifying limited axillary disease, was evaluated by constructing a 2×2 contingency table comparing clinically assessed axillary status (limited vs non-limited) with final histopathological nodal status (gold standard). From this table, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy were calculated with corresponding 95% confidence intervals. Agreement between clinical and histopathological nodal classification was further assessed using Cohen's kappa (κ) statistic, interpreted according to standard benchmarks to quantify the strength of agreement beyond chance. The secondary variables included demographic, clinical, imaging, surgical, and pathological factors. Continuous variables such as age, tumor size, and total number of lymph nodes retrieved were first assessed for normality using the Shapiro–Wilk test. Normally distributed variables were summarized as Mean±SD and compared between limited and extensive pathological nodal groups using the independent-samples t-test, while non-normally distributed variables were expressed as median with interquartile range and compared using the Mann–Whitney U test. Categorical variables, including cN1 axillary disease, histological grade, presence of lymphovascular invasion, molecular subtype, extranodal extension, and number of suspicious nodes on ultrasound, were presented as frequencies and percentages and compared using the Chi-square test or Fisher's exact test where expected cell counts were small. A *p*-value of ≤0.05 was considered statistically significant.

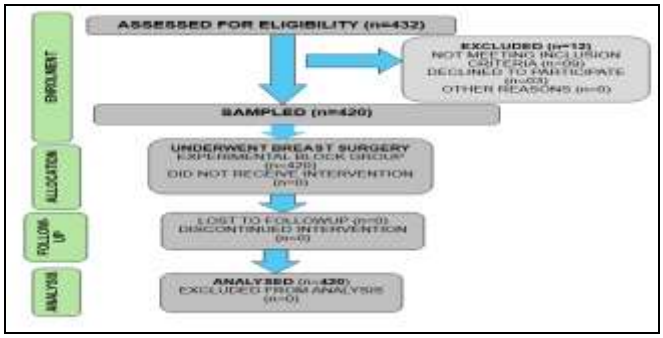

Figure : Patient Flow Diagram

RESULTS

A total of 420 patients were analyzed in the final study protocol. The mean age of the study population was 48.3±10.3 years, reflecting a relatively younger cohort typical of regional breast cancer demographics. The mean tumor size was 23.19±9.62 cm, indicating that most patients presented with early-stage disease suitable for upfront surgical management and potential axillary de-escalation. Level II Axillary Nodal Clearance performed in 100 patients (23.8%). With respect to tumor biology, lymphovascular invasion was present in 110 patients (26.2%). Estrogen receptor positivity was observed in 297 patients (70.7%), progesterone receptor positivity in 68 patients (16.2%), and triple-negative breast cancer in 55 patients (13.1%). Extra nodal extension on final histopathology was identified in 30 patients (7.1%), indicating a relatively low prevalence of advanced nodal pathology within the cohort (Table-I).

Table-I: Demographic and Clinical Variables of Study Participants(n=420)

Variable(s)	Values
Mean Age (Years)	48.37±10.29
Mean Tumor Size (Cm)	23.19±9.62
Mean Total Nodes Size (Cm)	2.07±3.57
3 Or More Suspicious Nodes on ultrasound	249(59.3%)
Needle Biopsy Done	420(100.0%)
Breast Conservation Surgery Done	192(45.7%)
Mastectomy Done	228(54.3%)
ALND DONE	100(23.8%)
LVI PRESENT	110(26.2%)
ER POSITIVE	297(70.7%)
PR POSITIVE	68(16.2%)
TNBC DISEASE	55(13.1%)
EXTRANODAL EXTENSION	30(7.1%)

**ALND: Axillary Lymph Node Dissection, LVI: Lymphovascular Invasion, ER: Estrogen Receptor, PR: Progesterone Receptor, TNBC: Triple Negative Breast Cancer*

Using histopathology as the gold standard, 109 patients (25.9%) were true positives, correctly identified as having nodal metastasis on clinical assessment, while 211 patients (50.2%) were true negatives. Clinical assessment failed to detect nodal involvement in 79 patients (18.8%), representing false negatives, and over staged nodal disease in 21 patients (5.0%), representing false positives. Based on these results, sensitivity of clinical axillary assessment was calculated as 58.0%, indicating that over half of patients with true nodal involvement were correctly identified preoperatively. Specificity was 90.9%, demonstrates high ability to correctly exclude nodal disease when nodes were histopathologically negative. The positive predictive value was 83.8%, while the

negative predictive value was 72.8%. The overall diagnostic accuracy of clinical axillary assessment was 76.2%, supporting moderate reliability of clinical staging while underscoring the continued importance of histopathology as the definitive standard for axillary nodal assessment in upfront breast cancer surgery (Table-II).

Table-II: Diagnostic Accuracy of Clinical Assessment vs Histopathological Findings (n=420)

	Histopathology Findings	
	Nodes Positive	**Nodes Negative**
Clinical Assessment Findings		
Nodes Positive	109 (25.9%)	21 (5.0%)
Nodes Negative	79 (18.9%)	211 (50.2%)
Sensitivity= True Positive/ (True Positive +False Negative) = 58.0%		
Specificity= True Negative / (True Negative +False Positive) = 90.9%		
Positive Predictive Value= True Positive/ (True Positive+ False Positive) = 83.8%		
Negative Predictive Value= True Negative/ (True Negative +False Negative) = 72.8%		
Diagnostic Accuracy= (True Positive +True Negative)/All Patients= 76.2%		

Agreement between clinically assessed limited axillary disease and final histopathological nodal status was evaluated using Cohen's kappa statistic. A κ value of 0.50 indicated moderate agreement beyond chance between the two methods (p<0.001).

DISCUSSION

In this study, a total of 420 upfront-operated breast cancer patients with clinically assessed limited axillary disease were analyzed to determine the accuracy of preoperative axillary assessment using final histopathology as the gold standard. Clinical assessment demonstrated a sensitivity of 58.0%, specificity of 90.9%, positive predictive value of 83.8%, negative predictive value of 72.8%, and an overall diagnostic accuracy of 76.2%. While clinical and imaging-based axillary evaluation showed high specificity and acceptable diagnostic accuracy. A substantial number of patients were clinically under-staged, showing limits of preoperative assessment alone. While axillary de-escalation is feasible in selected cases, biopsy results remain essential for omitting ALND.

Giuliano *et al*. showed omitting ALND in limited nodal disease doesn't compromise survival with appropriate systemic therapy and radiotherapy. Our findings align, with high specificity and PPV for low nodal burden, though moderate sensitivity highlights the risk of clinical understaging.[6] Donker *et al*. showed axillary radiotherapy matched ALND in regional control with lower morbidity. Our results highlight that clinical assessment alone misses limited nodal disease, underscoring the need for intraoperative and pathological evaluation to guide de-escalation.[2]

In another study, Bartels *et al*. advocate selective ALND omission for low nodal burden. In our cohort, SLNB was done in >96% and ALND in <25%, supporting guideline-based practice while cautioning against sole reliance on preoperative staging.[7] Galimberti *et al*. stressed axillary de-escalation should rely on pathological, not clinical, nodal assessment. Our study mirrored this, with nearly 20% clinically under staged, reinforcing histopathology as gold standard.

Abe *et al*. reported axillary US sensitivity of 50–65% and specificity >85%, closely mirrored in our study, highlighting its value but inherent limits for low-volume nodal disease.[1] In another study Alvarez et al. showed more suspicious nodes on ultrasound raise specificity but lower sensitivity, a pattern mirrored in our cohort with ≥3 nodes.[9] Contrasting to our study, Pilewskie *et al*. noted overestimation of axillary disease, but our study shows structured imaging and careful patient selection can minimize unnecessary ALND.[10]

Rezkallah et al. reported ultrasound diagnostic accuracy of 75–80%, closely matching the 76.2% observed in our study. This concordance supports the reliability of our diagnostic performance estimates.[11] Loibl et al. highlighted differences between upfront and post-neoadjuvant cohorts due to intact nodal architecture. Excluding neoadjuvant cases reduced confounding and clarified true clinicopathological discordance.[12] Another study reported operator-dependent variability in axillary USG due to assorted imaging criteria. Our modest agreement imitates these challenges while showing that standardized protocols can achieve performance equal to international benchmarks.[13] A previous study reported younger age at presentation and higher nodal positivity in South Asian patients. Despite similar demographics, our study showed lower extra nodal extension and ALND rates, signifying evolving disease patterns and improved early detection.[14]

Morrow et al. advocated shifting axillary surgery from staging toward therapeutic necessity. Our

findings provision this approach, showing that most patients with limited nodal burden can be managed without ALND.[15] In another study it was cautioned that clinical under staging could lead to undertreatment if axillary management decisions were based solely on preoperative assessment.[16] The false-negative rate observed in our study reinforced this concern highlighted continued importance of SLNB as an intermediary step.

Existing literature highlighted integrating systemic therapy and radiotherapy to offset reduced surgical intervention.[17] Our findings align with this approach, supporting safe axillary de-escalation within a multimodal treatment framework. Another study emphasized individualized axillary management based on tumor biology, nodal burden, and patient factors.[18] Our analysis supports this nuanced approach by incorporating lymphovascular invasion, receptor status, and extra nodal extension.

LIMITATIONS OF STUDY

Despite a robust sample size, the study was conducted in a limited number of centers, potentially limiting generalizability. Axillary clinical and ultrasound assessments are operator-dependent, and interobserver variability may have influenced diagnostic accuracy. Long-term oncologic outcomes, including axillary recurrence and survival, were not assessed, limiting decisions on long-term safety.

CONCLUSION

Preoperative clinical and imaging axillary assessment showed high specificity, but modest sensitivity compared to histopathology. Many patients were clinically under-estimated, highlighting histopathology as the gold standard. These results support selective axillary de-escalation while highlighting the need for SLNB for safe management.

Conflict of Interest: None.

Discolure:

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

ZN & AJ: Data acquisition, data analysis, critical review, approval of the final version to be published.

SRQN & SN: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MK & HI: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Pinheiro DJ, Elias S, Nazário AC. Axillary lymph nodes in breast cancer patients: sonographic evaluation. Radiol Bras 2014; 47(4): 240-244. https://doi.org/10.1590/0100-3984.2013.1689
2. Donker M, van Tienhoven G, Poncet C,. Sauvé N, Straver ME, van de Velde CJH, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (AMAROS): 10-year follow-up. J Clin Oncol 2023; 41(12): 2159–2168. https://doi.org/10.1016/s1470-2045(14)70460-7
3. Limberg JN, Jones T, Thomas SM, Ntowe KW, Dalton JC, van den Bruele AB, et al. Omission of axillary lymph node dissection in patients with residual nodal disease after neoadjuvant chemotherapy. Ann Surg Oncol 2024; 31(13): 8813–8820. https://doi.org/10.1245/s10434-024-16143-6
4. Tseng LJ, Matsuyama A, MacDonald-Dickinson V. Histology: the gold standard for diagnosis? Can Vet J 2023; 64(4): 389–390.
5. Goyal S, Jacob LA, Lokanatha D, Suresh Babu M, Lokesh K, Rudresha A, et al. Discordance in clinical versus pathological staging in breast cancer: are we undermining the significance of accurate preoperative staging in the present era? Breast Dis 2021; 41(1): 115–121. https://doi.org/10.3233/BD-201029
6. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of axillary dissection vs no axillary dissection on overall survival among women with invasive breast cancer and sentinel node metastasis. JAMA 2022; 327(8): 720–729. https://doi.org/10.1001/jama.2017.11470
7. Bartels SAL, Donker M, Poncet C, Meijnen P, van de Velde CJ, Mansel RE, et al. Axillary management in early breast cancer: long-term results of the AMAROS trial. Lancet Oncol 2020; 21(10): 1315–1324. https://doi.org/10.1016/s1470-2045(14)70460-7
8. Sharaf B, Seif A, Alawneh F, Bani Hani H, Sh Abrahim M, Jehad S, et al. De-escalating breast and axillary surgery in breast cancer: evidence, controversies, and future directions. Front Oncol 2026; 16: 1717340.https://doi.org/10.3389/fonc.2026.17173403
9. Alvarez S, Añorbe E, Alcorta P, López F, Alonso I, Cortés J. Role of axillary ultrasound in the diagnosis of lymph node metastases in breast cancer. Eur Radiol 2021; 31(3): 1620–1629. https://doi.org/10.2214/ajr.05.0936
10. Pilewskie M, Morrow M. Axillary nodal management following ultrasound staging in breast cancer. Ann Surg Oncol 2020; 27(6): 1890–1898. https://doi.org/10.1001/jamaoncol.2016.4163
11. Rezkallah EMN, Elsaify A, Tin SMM, Elsaify W. Diagnostic Accuracy of Ultrasonography in Axillary Staging in Breast Cancer Patients. J Med Ultrasound 2023; 31(4): 293-297. https://doi.org/10.4103/jmu.jmu_99_22
12. Loibl S, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast cancer. Lancet 2021; 397(10286): 1750–1769. https://doi.org/10.1016/s0140-6736(20)32381-3
13. Farooq HF, Aslam S, Gul A, Masud S, Zaidi B, Subzwari SAHW. Diagnostic Accuracy of Axillary Ultrasonography for Differentiating Benign and Malignant Lymph Nodes in Breast Cancer Patients: Diagnostic Accuracy of Axillary Ultrasound for Lymph Nodes. Dev med life sci 2025; 2(3): 4-8. https://doi.org/10.69750/dmls.02.03.099
14. Sultan N, Memon SA, Mooghal M, Wali S, Khan W, Tahseen H, et al. Ethnic predisposition, risk factors and breast cancer presentation; a 10-year data. Single centered prospective cohort study from Karachi. Ann Med Surg 2022; 82: 104612. https://doi.org/10.1016/j.amsu.2022.104612

15. Morrow M, Van Zee KJ, Patil S, Mamtani A, Barrio AV. Axillary dissection and nodal radiation: evolving concepts in early breast cancer. N Engl J Med 2022; 386(11): 1047–1056. https://doi.org/10.1056/NEJMra2108731
16. Damin AP, Zancan M, Melo MP, Biazus JV. Sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with node-positive breast cancer: guiding a more selective axillary approach. Breast Cancer Res Treat 2021; 186(2): 527-534. https://doi.org/10.1007/s10549-020-06011-8
17. Senkus E, Cardoso MJ, Kaidar-Person O, Łacko A, Meattini I, Poortmans P. De-escalation of axillary irradiation for early breast cancer - Has the time come? Cancer Treat Rev 2021; 101: 102297. https://doi.org/10.1016/j.ctrv.2021.102297
18. Brackstone M, Baldassarre FG, Perera FE, et al. Management of the axilla in early-stage breast cancer: ASCO guideline update. J Clin Oncol 2021; 39(27): 3056–3082. https://doi.org/10.1200/JCO.21.00934

.....