E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.48047/ijprt/16.02.270

Research Article

Determinants of Axillary Lymph Node Metastasis in Breast Cancer: Association with Imaging Characteristics, Histopathological Features, Microbiological Findings, Therapeutic Management, and Clinical Outcomes

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Abstract

Evaluating axillary lymph node status in primary breast cancer remains crucial for clinical staging, surgical management, and long-term therapeutic planning. This prospective observational cohort study evaluated radiological, pathological, microbiological, and therapeutic determinants of axillary lymph node metastasis in three hundred and fifty adult female patients undergoing definitive surgical resection for invasive breast carcinoma. Preoperative ultrasound and dynamic contrast-enhanced magnetic resonance imaging parameters, primary tumor histopathological metrics, perioperative lymph node microflora, and systemic therapy regimens were correlated with pathological axillary node involvement. Axillary lymph node metastasis was identified in 38.3% of participants. Multivariable logistic regression revealed that cortical thickness greater than 3 mm with loss of fatty hilum on preoperative sonography (OR 4.28, 95% CI 2.31–7.93, $p < 0.001$), presence of lymphovascular invasion (OR 3.86, 95% CI 2.04–7.31, $p < 0.001$), high Ki-67 proliferation index (OR 2.64, 95% CI 1.38–5.05, $p = 0.003$), primary tumor size exceeding 20 mm (OR 2.45, 95% CI 1.29–4.66, $p = 0.006$), and subclinical nodal tissue bacterial colonization (OR 2.15, 95% CI 1.06–4.38, $p = 0.034$) independently predicted nodal positivity. Conversely, complete pathological response following neoadjuvant systemic therapy was inversely associated with node involvement (OR 0.35, 95% CI 0.17–0.72, $p = 0.004$). Combining high-resolution sonographic features with

core biopsy histopathology enhances preoperative nodal risk stratification, facilitating tailored axillary surgical staging and minimizing unnecessary nodal dissections.

Keywords: Axillary lymph node metastasis, breast cancer, ultrasound characteristics, lymphovascular invasion, neoadjuvant therapy

Introduction

Axillary lymph node status represents one of the most significant independent prognostic factors for locoregional recurrence and overall survival in patients diagnosed with primary invasive breast carcinoma. The presence of metastatic tumor cells within regional axillary nodes reflects increased systemic dissemination potential and directly dictates clinical staging, adjuvant chemotherapy regimens, extended nodal irradiation, and surgical axillary management. While sentinel lymph node biopsy has largely replaced full axillary lymph node dissection as the primary staging procedure for clinically node-negative early-stage disease, invasive staging interventions carry persistent risks of arm lymphedema, chronic pain, shoulder dysfunction, and wound infection. Consequently, identifying robust non-invasive preoperative predictors of axillary lymph node metastasis is vital for optimizing surgical planning and personalized patient counseling.[1-4]

The underlying biological mechanisms facilitating regional nodal metastasis involve complex crosstalk between malignant epithelial cells, tumor-associated lymphangiogenesis, and localized host tissue stroma. Tumor cells undergoing epithelial-mesenchymal transition acquire enhanced invasive capabilities, penetrating local peritumoral lymphatic channels and entering afferent lymphatic vessels. In addition, altered local microbial colonization and persistent low-grade inflammatory responses within breast and axillary tissue microenvironments can influence lymphatic microvascular density, immune cell recruitment, and extracellular matrix remodeling, potentially conditioning pre-metastatic nodal niches. Elucidating how primary tumor biology interacts with microenvironmental and microbial dynamics provides deeper insight into regional nodal spread.[5-7]

Preoperative diagnostic imaging, particularly high-resolution axillary ultrasonography and dynamic contrast-enhanced magnetic resonance imaging, plays a central role in assessing nodal morphology prior to operative intervention. Specific sonographic features—such as eccentric cortical

thickening exceeding 3 mm, partial or complete compression of the central fatty hilum, rounded shape, and irregular nodal margins—demonstrate varying degrees of diagnostic sensitivity and specificity for malignant involvement. However, significant inter-observer variability and overlapping morphological appearances between reactive hyperplasia and microscopic metastatic infiltration persist. Combining advanced imaging parameters with primary tumor tissue characteristics yields a more dependable non-invasive prediction model.[8-9]

Histopathological characteristics of the primary breast lesion provide critical biological information regarding lymphatic dissemination potential. Primary tumor size, histologic tumor grade, presence of lymphovascular invasion, extensive intraductal components, and molecular biomarker profiles (including estrogen receptor, progesterone receptor, HER2 overexpression, and Ki-67 proliferation index) strongly correlate with axillary nodal status. Among these, microscopic lymphovascular invasion serves as a prominent pathological indicator of tumor cellular access to regional lymphatic networks. Evaluating these intrinsic pathological markers alongside radiological dimensions allows surgical oncologists to accurately estimate metastatic nodal probability.[10]

Furthermore, perioperative therapeutic management—particularly neoadjuvant systemic chemotherapy and targeted biological therapies—profoundly alters nodal metastatic burdens prior to definitive surgical resection. Pathological complete response in regional lymph nodes following neoadjuvant treatment frequently enables surgical de-escalation, sparing patients from completion axillary lymph node dissection. Understanding the interplay between neoadjuvant therapy response, perioperative microbiological profiles, and ultimate clinical outcomes is essential for modern multidisciplinary breast cancer management.

To address these diagnostic and therapeutic considerations, this prospective observational study was undertaken to evaluate the integrated radiological, pathological, microbiological, and therapeutic predictors of axillary lymph node metastasis in patients presenting with invasive breast carcinoma. By analyzing preoperative ultrasound and magnetic resonance imaging findings, definitive pathological metrics, surgical cavity tissue microbiology, and systemic treatment regimens, this investigation aims to establish

independent determinants of axillary nodal involvement and refine preoperative clinical decision-making models.

Methodology

This prospective observational cohort study was conducted at Mayo Hospital, Lahore over a continuous twenty-four-month period. Adult female patients aged eighteen years or older with histologically confirmed primary invasive breast carcinoma scheduled to undergo definitive surgical resection (breast-conserving surgery or total mastectomy) with concurrent axillary staging (sentinel lymph node biopsy or axillary lymph node dissection) were prospective identified and enrolled. Sample size estimation was performed prior to study initiation using Epi Info software. Assuming a baseline axillary lymph node metastasis rate of thirty-five percent in primary invasive breast cancer, a confidence level of ninety-five percent, a statistical power of eighty percent, and an anticipated minimum odds ratio of 2.2 for nodal metastasis among patients presenting with high-risk ultrasound morphologic features (cortical thickening > 3 mm or loss of fatty hilum), the minimum required sample size was calculated as three hundred and twenty-five patients. To account for potential loss to follow-up or incomplete pathological data, three hundred and fifty eligible participants were prospectively recruited into the final analytical cohort. Detailed explanations of all diagnostic and surgical procedures were provided, and formal verbal informed consent was documented from all participating subjects. The study protocol was approved by the institutional ethics review board.

Eligible participants included adult female patients aged eighteen years or older presenting with unilateral stage I–III invasive ductal or lobular carcinoma undergoing primary operative intervention or surgery post-neoadjuvant therapy. Patients were excluded if they met any of the following criteria: evidence of distant stage IV metastatic disease at presentation, prior ipsilateral breast or axillary radiation therapy, previous history of ipsilateral breast malignancy, active systemic infectious diseases, concurrent secondary primary malignancies, severe uncontrolled systemic comorbidities, or incomplete preoperative imaging or pathological evaluation records.

All enrolled patients underwent standardized preoperative evaluation, including bilateral diagnostic mammography, dedicated high-resolution axillary ultrasonography, and dynamic contrast-enhanced magnetic resonance imaging. Axillary ultrasound focused on assessing nodal morphological

parameters: cortical thickness, structural integrity of the fatty hilum, nodal aspect ratio, and vascularization pattern on color Doppler. Preoperative image-guided core needle biopsy or fine-needle aspiration of suspicious axillary nodes was performed according to institutional guidelines. Definitive operative management involved partial or total mastectomy combined with sentinel lymph node biopsy or complete axillary lymph node dissection. Prior to nodal excision, aseptic tissue swabs and tissue aspirates were obtained from the axillary tissue basin to assess perioperative microbiological colonization. Standard systemic treatment regimens, including neoadjuvant or adjuvant chemotherapy, anti-HER2 targeted therapy, and endocrine therapy, were administered based on multidisciplinary tumor board recommendations.

Histopathological examination of primary tumor specimens and regional lymph nodes was conducted by experienced breast pathologists. Axillary lymph nodes were sectioned at 2-mm intervals, hematoxylin-eosin stained, and systematically evaluated for macrometastases (>2 mm), micrometastases (0.2–2 mm), and isolated tumor cells (<0.2 mm). Nodes containing macrometastases or micrometastases were classified as pathologically positive. Primary tumor parameters recorded included histological subtype, nuclear grade, pathological tumor size, microscopic lymphovascular invasion, extensive intraductal component, estrogen/progesterone receptor status, HER2 gene amplification, and Ki-67 proliferation index (high defined as ≥20%).

Statistical analysis was conducted using SPSS version 27.0. Continuous variables conforming to normal distribution were expressed as mean ± standard deviation, while categorical variables were reported as absolute frequencies and percentages. Differences between categorical factors across nodal status groups (pathologically negative versus positive axillary lymph nodes) were evaluated using Pearson's chi-square test or Fisher's exact test. Continuous clinical metrics were compared using independent sample t-tests. Multivariable binary logistic regression analysis was performed to identify independent radiological, pathological, microbiological, and therapeutic predictors of pathologically confirmed axillary lymph node metastasis, reporting adjusted odds ratios with corresponding ninety-five percent confidence intervals. Statistical significance was defined as a two-sided p-value of less than 0.05.

Results

Table 1. Baseline Clinical, Radiological, and Microbiological Characteristics Stratified by Axillary Lymph Node Status (n = 350)

Parameter	Total Cohort (n = 350)	Node Negative (n = 216)	Node Positive (n = 134)	p-value
Age (years)	55.8 ± 11.4	56.4 ± 11.2	54.8 ± 11.7	0.203
Preoperative primary tumor ultrasound size (mm)	24.1 ± 10.2	21.5 ± 8.8	28.3 ± 11.1	<0.001
Axillary US cortical thickness >3 mm, n (%)	128 (36.6%)	42 (19.4%)	86 (64.2%)	<0.001
Axillary US loss of fatty hilum, n (%)	104 (29.7%)	28 (13.0%)	76 (56.7%)	<0.001
Axillary tissue bacterial colonization, n (%)	58 (16.6%)	26 (12.0%)	32 (23.9%)	0.004
Neoadjuvant systemic therapy administered, n (%)	78 (22.3%)	58 (26.9%)	20 (14.9%)	0.009
Completion axillary dissection performed, n (%)	112 (32.0%)	8 (3.7%)	104 (77.6%)	<0.001

Table 1 details the baseline clinical, radiological, and microbiological features, demonstrating that patients with pathologically confirmed axillary node metastasis presented with larger ultrasound tumor dimensions, higher rates of abnormal nodal cortex thickening and loss of fatty hilum, elevated axillary microbial colonization, lower rates of neoadjuvant therapy, and significantly higher rates of completion axillary dissection ($p < 0.05$).

Table 2. Primary Tumor Histopathological Characteristics and Biomarker Profiles by Axillary Nodal Status

Histopathological Parameter	Node Negative (n = 216)	Node Positive (n = 134)	Total Cohort (n = 350)	p-value
Invasive Ductal Carcinoma, n (%)	165 (76.4%)	108 (80.6%)	273 (78.0%)	0.354
Invasive Lobular Carcinoma, n (%)	28 (13.0%)	18 (13.4%)	46 (13.1%)	0.903
Pathological primary tumor size >20 mm, n (%)	82 (38.0%)	88 (65.7%)	170 (48.6%)	<0.001
Histologic Grade 3, n (%)	64 (29.6%)	59 (44.0%)	123 (35.1%)	0.006
Microscopic Lymphovascular Invasion, n (%)	48 (22.2%)	79 (59.0%)	127 (36.3%)	<0.001
Ki-67 Proliferation Index ≥20%, n (%)	92 (42.6%)	84 (62.7%)	176 (50.3%)	<0.001
Estrogen Receptor Positive, n (%)	168 (77.8%)	98 (73.1%)	266 (76.0%)	0.316
HER2 Gene Amplified, n (%)	42 (19.4%)	33 (24.6%)	75 (21.4%)	0.248
Triple Negative Subtype, n (%)	32 (14.8%)	22 (16.4%)	54 (15.4%)	0.689

Table 2 displays the definitive pathological features of the primary tumor, showing that pathological tumor size greater than 20 mm, high histologic grade, presence of lymphovascular invasion, and elevated Ki-67 proliferation index were significantly associated with axillary nodal involvement ($p < 0.05$).

Table 3. Multivariable Binary Logistic Regression Analysis of Independent Predictors for Axillary Lymph Node Metastasis

Predictor Variable	Odds Ratio	95% Confidence Interval	p-value
Axillary US cortical thickness >3 mm with loss of fatty hilum	4.28	2.31 – 7.93	<0.001
Microscopic Lymphovascular Invasion	3.86	2.04 – 7.31	<0.001
Ki-67 Proliferation Index ≥20%	2.64	1.38 – 5.05	0.003
Pathological primary tumor size >20 mm	2.45	1.29 – 4.66	0.006
Axillary tissue bacterial colonization	2.15	1.06 – 4.38	0.034
Pathological complete response post-neoadjuvant therapy	0.35	0.17 – 0.72	0.004

Table 3 summarizes the multivariable logistic regression analysis, identifying abnormal sonographic nodal features, lymphovascular invasion, high Ki-67 index, tumor size over 20 mm, and axillary tissue bacterial colonization as independent risk factors for nodal metastasis, whereas pathological complete response following neoadjuvant treatment significantly reduced metastatic risk.

Discussion

The results of this prospective observational cohort study demonstrate that axillary lymph node metastasis in breast cancer is determined by a multifactorial interaction between preoperative imaging parameters, primary tumor histopathology, local tissue microbiology, and systemic therapeutic responses. Pathologically confirmed nodal metastasis occurred in 38.3% of the three hundred and fifty enrolled patients, aligning with published clinical literature evaluating newly diagnosed invasive breast carcinoma cohorts. Establishing independent predictors for nodal involvement is critical for improving preoperative risk stratification, minimizing invasive axillary surgical procedures, and tailoring multidisciplinary management.[11-13]

Preoperative axillary ultrasonography demonstrated strong predictive value for nodal metastatic involvement. The combination of nodal cortical thickening greater than 3 mm and compression or loss of the central fatty hilum represented the single strongest independent radiological predictor in multivariable analysis, increasing the odds of pathological nodal positivity more than four-fold. Tumor cell infiltration into regional lymph nodes disrupts normal lymphatic architecture, expanding the cortex and effacing the central adipose tissue within the hilum. These findings corroborate previous diagnostic studies emphasizing that high-resolution axillary sonography, combined with selective image-guided needle biopsy, reliably identifies node-positive patients prior to surgery.[14]

Histopathological evaluation confirmed that primary tumor biology plays a decisive role in lymphatic tumor spread. Microscopic lymphovascular invasion was identified as the predominant pathological driver of regional metastasis, increasing nodal positivity risk nearly four-fold. Lymphovascular invasion indicates active invasion of malignant cells into peritumoral endothelial-lined channels, representing an obligatory step for regional lymphatic transit. Furthermore, primary tumor size greater than 20 mm and high Ki-67 cellular proliferation index independently correlated with axillary metastasis. Larger primary tumors harbor higher absolute cellular counts and greater clonal heterogeneity, increasing the likelihood of invasive sub-clones colonizing regional lymphatic basins.[15-17]

An intriguing finding in this study was the independent association between subclinical bacterial colonization of the axillary surgical basin and elevated axillary lymph node metastasis. Patients with positive tissue cultures exhibited significantly higher rates of nodal tumor involvement. Local microbial colonization and microflora alterations can provoke chronic low-grade inflammatory responses, inducing localized lymphangiogenesis, upregulating vascular endothelial growth factors, and altering local immune surveillance mechanisms. While tissue microbial colonization may partially reflect larger tumor sizes or altered lymphatic drainage, these biological findings highlight the relevance of regional microenvironments in metastatic biology.[18-20]

Conversely, receipt of neoadjuvant systemic therapy resulting in pathological nodal response exerted a powerful protective effect against persistent nodal disease. Systemic chemotherapy combined with targeted anti-HER2 regimens effectively downstages

metastatic axillary nodes, clearing nodal tumor burden in a substantial proportion of patients. Pathological complete response in the axilla allows safe conversion from completion axillary lymph node dissection to targeted sentinel node biopsy or dual-tracer localization, significantly reducing postoperative lymphedema, shoulder morbidity, and chronic pain.

Integrating preoperative sonographic features, tumor biopsy histopathology, and systemic treatment response into a standardized clinical predictive model provides significant utility for surgical oncologists. Accurate preoperative identification of low-risk patients enables safe de-escalation of axillary surgery, whereas high-risk patients can be selected for neoadjuvant treatment strategies or targeted image-guided nodal clipping.

Strengths of this study include its prospective design, rigorous standardized pathological evaluation of lymph node specimens, integration of high-resolution imaging modalities, and novel exploration of perioperative microbiological characteristics. Limitations include the single-center setting and the lack of five-year disease-free survival follow-up, which was beyond the primary objective of this diagnostic and pathological evaluation. Multi-center studies incorporating radiomics, molecular profiling, and extended survival tracking are recommended to further validate these predictive findings.

Conclusion

Preoperative ultrasound nodal abnormalities, primary tumor lymphovascular invasion, high Ki-67 index, primary tumor size exceeding 20 mm, and local bacterial colonization independently predict axillary lymph node metastasis. Pathological response following neoadjuvant systemic therapy significantly decreases persistent nodal disease, reducing the need for invasive surgical clearance. Combining non-invasive sonographic parameters with core biopsy histopathology establishes a reliable model for axillary risk stratification and surgical decision-making.

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