

IMPACT OF PRIMARY TUMOR LOCATION ON AXILLARY BURDEN IN CLINICALLY NODE-NEGATIVE BREAST CANCER: A PROSPECTIVE OBSERVATIONAL STUDY

Surgical Oncology

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ABSTRACT

Background: Axillary lymph node status is the most important prognostic factor for breast cancer. While tumor size and biology are well-established determinants, the influence of tumor location on axillary burden is less defined. **Methods:** A prospective observational study was conducted on 150 clinically node-negative (cN0) breast cancer patients treated at a regional cancer institute (July 2022–January 2024). Quadrant-wise association with axillary nodal positivity was assessed. **Results:** The upper outer quadrant (40.6%) was the most common site. Axillary nodal positivity was detected in 22.6% (pN1–18.6%, pN2–3.3%, pN3–0.6%). Nodal positivity was highest in UOQ (27.8%) and central tumors (23.1%) and absent in LOQ tumors. Lymphovascular invasion (52.9%) and associated DCIS (47%) were significantly correlated with nodal involvement. No correlation was observed with menopausal status. **Conclusion:** Tumor location significantly impacts axillary burden in cN0 breast cancer, with UOQ and central tumors carrying the highest risk. Incorporating tumor location into preoperative risk stratification may optimize axillary staging decisions.

KEYWORDS

Breast Cancer, Axillary Burden, Tumor Location, Lymph Node Metastasis

INTRODUCTION

Although axillary staging has become less invasive with the advent of sentinel lymph node biopsy, the accurate prediction of nodal status remains crucial for treatment planning and prognosis. Tumor biology and size are well-established predictors, but the contribution of tumor location remains less clearly defined. Several large retrospective studies have suggested variable outcomes depending on whether the tumor is situated in the medial or lateral breast quadrants, with medial tumors potentially draining more frequently to the internal mammary nodes. However, quadrant-specific data on axillary burden in clinically node-negative breast cancer, particularly in the Indian population, are limited. Therefore, this study was designed to prospectively evaluate the impact of tumor location on axillary involvement, with the aim of improving preoperative risk stratification and guiding surgical decision-making.

Axillary lymph node (LN) involvement is the most important prognostic determinant [1] in breast cancer, influencing staging, adjuvant therapy, and survival. Advances in sentinel node biopsy [2] have reduced the need for routine axillary dissection; however, preoperative predictors of nodal positivity remain clinically relevant. While tumor size, grade, and biology are established predictors, the role of tumor location remains underexplored. Anatomical studies have confirmed that breast lymphatics drain variably [3] into the axillary, internal mammary, and supraclavicular nodes. Some reports suggest that medially located tumors may have worse outcomes [4] due to alternative lymphatic pathways, although axillary involvement is less frequent. Incorporating tumor location into predictive nomograms [6,7] (e.g., MSKCC, Chen et al.) has shown improved risk estimation. This study prospectively examined the impact of primary tumor location on axillary burden in clinically N0 breast cancer patients at a regional cancer institute.

MATERIALS AND METHODS

Study Design and Setting: A prospective observational study was conducted at the Kidwai Memorial Institute of Oncology, Bengaluru, between July 2022 and January 2024.

Eligibility Criteria: Inclusion: Adult patients (>18 years) with biopsy-proven invasive breast carcinoma, clinical and sonographic N0 axilla, T1–T3 tumors, and fit for curative surgery. Exclusion: Multicentric/bilateral cancers, metastatic disease, neoadjuvant chemotherapy, and palliative surgery.

Data Collection: Demographic, clinical, mammographic, operative, histopathological, and immunohistochemical parameters were recorded. Tumor quadrant assignment was based on sonomammography epicenter.

Surgery: Patients underwent either modified radical mastectomy (MRM), breast-conserving surgery with axillary dissection, or breast-conserving surgery with sentinel lymph node biopsy.

Pathology: Tumors were graded by Nottingham system, and staged per AJCC 8th edition. The axillary burden was stratified as pN0, pN1, pN2, or pN3. Statistical analysis: Descriptive analyses were performed using R. The associations between tumor location and nodal burden were analyzed. Statistical significance was set at $p < 0.05$.

RESULTS

Patient Demographics: A total of 150 patients with clinically node-negative (cN0) breast carcinoma were enrolled between July 2022 and January 2024. The mean age was 55.1 ± 11.6 years (range, 31–90 years). The largest age group was 51–60 years (31.3%), followed by 41–50 years (28.7%). Younger patients (≤ 40 years) accounted for 10% of the cohort, while elderly patients ≥ 70 years accounted for 10%. Menopausal status showed a slight predominance of postmenopausal women (56.7%) compared with premenopausal women (43.3%). Laterality was nearly balanced, with 52% left-sided and 48% right-sided tumors.

Tumor Characteristics: The upper outer quadrant (UOQ) was the most common tumor site (40.6%, $n=61$), followed by central (26%, $n=39$), upper inner quadrant (UIQ, 18.6%), lower inner quadrant (LIQ, 8.7%), and lower outer quadrant (LOQ, 6%). Most patients presented with clinical T2 tumors (84.7%), whereas T1 tumors were rare (0.7%), and T3 tumors accounted for 14.7% of the tumors. On mammography, BIRADS IV (55.3%) and BIRADS V (22%) were the most frequent categories, with 8% confirmed malignant (BIRADS VI).

Surgical Treatment: Most patients underwent modified radical mastectomy (MRM) (72.7%, $n=109$). Breast-conserving surgery (BCS) with axillary dissection was performed in 18.7% ($n=28$) of patients, sentinel lymph node biopsy (SLNB) alone was performed in 5.3% ($n=8$), and SLNB followed by axillary dissection was required in 2% ($n=3$). Two patients underwent simple mastectomy with SLNB.

Histopathology: The predominant histological subtype was invasive carcinoma of no special type (NST) (86%, $n=129$ cases). The special histological variants included mucinous carcinoma (4%), solid papillary carcinoma with invasion (3.3%), metaplastic carcinoma (2.7%), poorly differentiated carcinoma (1.3%), and rare lobular/papillary variants (0.7% each). The grading distribution revealed Grade 2 tumors in 60% of the cases, followed by Grade 3 (32%) and Grade 1 (8%) tumors.

Immunohistochemistry: Molecular subtyping revealed a predominance of Luminal B cancers (both HER2 negative and positive). Distribution was: Luminal B HER2-negative: 40% (n=60); Luminal B HER2-positive: 20.6% (n=31); Luminal A: 16.6% (n=25); HER2-enriched: 11.3% (n=17); Triple negative: 11.3% (n=17). The Ki-67 index was $\leq 40\%$ in 73% of patients. Among the LN-positive cases, 20.5% showed Ki-67 $> 50\%$, indicating higher proliferative activity. Axillary lymph node status: On final histopathology, 34/150 patients (22.6%) had axillary nodal involvement. Breakdown was: pN1:28 cases (18.6%); pN2:5 cases (3.3%); pN3:1 case (0.6%). Quadrant-wise LN positivity: UOQ: 17/61 (27.8%); Central: 9/39 (23.1%); UIQ: 4/28 (14.2%); LIQ: 4/13 (30.8%); LOQ: 0/9 (0%). These findings indicate that axillary burden is concentrated in UOQ and central tumors, while LOQ tumors carry negligible risk.

Adverse Pathological Features: Among LN-positive cases, several adverse features were overrepresented: Lymphovascular invasion (LVI): 52.9% vs. 20.7% overall; Ductal carcinoma in situ (DCIS): 47% vs. 40% overall; Perineural invasion (PNI): 5.8% vs. 2% overall; Lobular carcinoma in situ (LCIS): 2.9% vs. 0.7% overall. These findings reinforce the association between adverse histological factors and nodal metastasis.

Subset Analysis of LN-positive Disease: Menopausal status: Premenopausal 52.9% vs. postmenopausal 47.1% – no significant difference. Tumor size: pT2 predominated (76.4%), whereas pT1 and pT3 tumors accounted for 8.8% and 11.7%, respectively. Grade: Grade 2 tumors were the most frequent (70.6%), followed by grade 3 (29.4%). Biological subtype: Luminal B HER2-negative was most common (47%), followed by Luminal B HER2-positive (20.5%), triple negative (14.7%), HER2-enriched (11.7%), and Luminal A (5.8%). Histology: Nearly all were invasive carcinoma NST (97%), with one case of mucinous carcinoma (2.9%).

DISCUSSION

This prospective study provides important insights into the relationship between primary tumor location and axillary burden in clinically N0 breast cancer patients. With an overall nodal positivity rate of 22.6%, our findings are consistent with previously published series [5] that reported rates between 20% and 30% in clinically node-negative patients. The novelty of this study lies in the detailed quadrant-wise analysis, which revealed a clear variation in axillary involvement depending on the tumor location.

Quadrant-wise nodal involvement: The upper outer quadrant (UOQ) and central quadrant emerged as the highest-risk sites, with nodal positivity rates of 27.8% and 23.1%, respectively. In contrast, lower outer quadrant (LOQ) tumors showed no axillary metastasis in this cohort. These observations reinforce the long-recognized fact that lymphatic drainage of the breast is non-uniform. The UOQ has the densest concentration of glandular tissue and drains predominantly to levels I and II axillary nodes, explaining the higher incidence of axillary disease in this region. Central tumors, with proximity to the subareolar plexus of Sappey, have bidirectional drainage to both axillary and internal mammary nodes, which may also increase metastatic potential.

Comparison with published literature: Several large registry-based studies have attempted to correlate tumor location with prognosis and nodal involvement. Zucali et al. [4] reported that medially located tumors had a lower incidence of axillary positivity but paradoxically worse survival, likely due to internal mammary involvement. Kroman et al. [9], analyzing $> 35,000$ patients, demonstrated a 15–20% survival advantage for outer quadrant tumors compared with inner quadrants. Sohn et al. [8] similarly reported an independent survival benefit for UOQ cancers. Our results differ in some respects. Inner quadrant tumors (UIQ/LIQ) in this study had lower axillary positivity (14–12%) than UOQ/central tumors, supporting the anatomical hypothesis of preferential internal mammary drainage. However, unlike Western reports, we did not perform a survival analysis and thus cannot conclude whether the inner quadrant location confers a worse overall prognosis. These discrepancies may reflect population-specific biology, genetic differences in Indian patients, or differences in the stage at presentation.

Biological correlates: Among node-positive cases, Luminal B (both HER2-positive and negative) accounted for nearly 70% of the disease, highlighting its intermediate-aggressive nature. HER2-enriched and triple-negative cancers contributed to approximately 25% of nodal

metastases, consistent with their aggressive phenotype. Notably, Luminal A was rare (6%) among node-positive patients, reinforcing its indolent biology. The histopathological features were strongly correlated with nodal burden. Additional predictors include the tumor–nipple distance [14], MRI-based predictors [15], and histological subtype differences between ILC and IDC [16]. Lymphovascular invasion (LVI) was present in 53% of LN+ patients compared to only 21% overall, confirming its role as a surrogate marker for systemic spread. Similarly, the coexistence of ductal carcinoma in situ (DCIS) was higher in LN+ cases (47%), a finding that has been inconsistently reported in prior literature but may reflect an aggressive in situ–invasive interface.

Clinical implications: These findings have practical significance in the era of axillary de-escalation. Randomized trials such as ACOSOG Z0011, AMAROS, and SOUND [12], with long-term outcomes supported by Wanis [13], have supported the omission of axillary dissection in select early breast cancers. However, our data suggest that UOQ and central tumors should be approached with caution, as their higher nodal burden places them at risk for undertreatment if axillary surgery is omitted from the treatment plan. Conversely, LOQ tumors, with zero positivity in this cohort, may be considered for omission of axillary staging in carefully selected patients, pending further validation. Additionally, our results argue for the incorporation of tumor location into predictive nomograms. Existing tools, such as the MSKCC and Chen nomograms [6,7], include quadrant or medial versus lateral locations but without granularity. Our data support quadrant-specific risk estimates, which could be used to refine risk calculators and guide preoperative counseling.

Strengths and Limitations

The strengths of this study include its prospective design, uniform pathological review, and quadrant-wise analyses. Importantly, it addresses a gap in the Indian data, where breast cancer biology and presentation differ from those in Western populations. The limitations of this study must be acknowledged. This was a single-institution study with a modest sample size (n=150) compared to large registry analyses. Survival outcomes and internal mammary involvement were not assessed, which may underestimate the full burden of nodal disease in medial tumors. Furthermore, this study excluded patients who received neoadjuvant chemotherapy, limiting its applicability to this growing subgroup. Future research should focus on multi-institutional validation [10,11] of these findings, with the inclusion of sentinel mapping studies [10,11] to clarify the non-axillary drainage patterns. Longitudinal follow-up with survival outcomes is essential to determine whether quadrant-based differences in axillary burden translate into differences in disease-free or overall survival rates. Integration with genomic signatures (e.g., Oncotype DX, MammaPrint) may further refine risk stratification, particularly in identifying low-risk LOQ or inner-quadrant patients who can safely avoid axillary surgery.

CONCLUSION

Primary tumor location is a significant predictor of axillary involvement in clinically N0 breast cancer patients. UOQ and central tumors carry the greatest risk. Incorporating tumor location into clinical decision-making may optimize axillary management and minimize overtreatment.

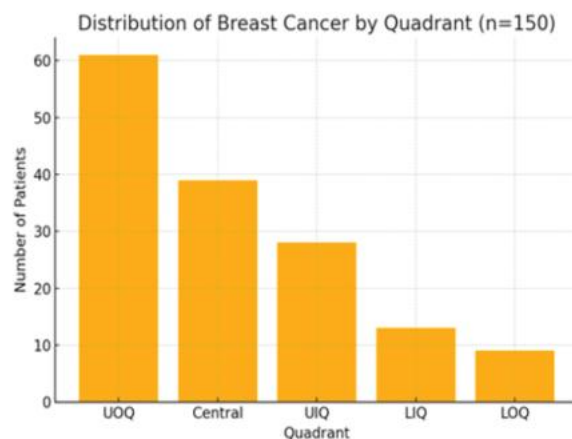


Figure 1: Distribution of Tumors by Quadrant (n=150).

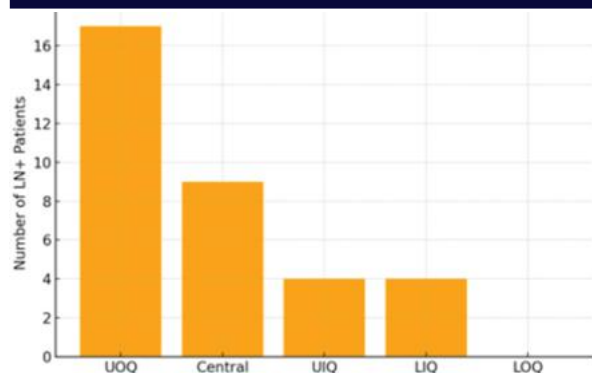


Figure 2: Axillary LN Positivity by Quadrant (n=34 Node-positive Cases).

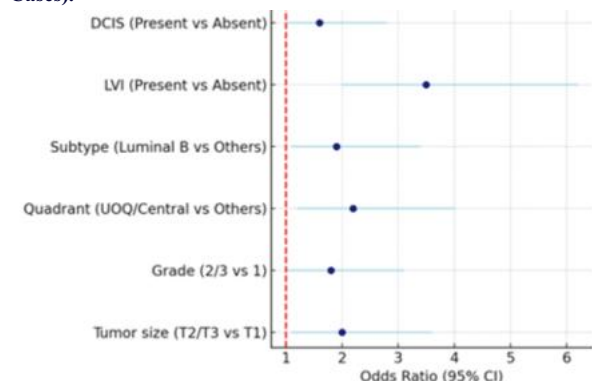


Figure 3: Forest Plot Showing Clinicopathological Factors Associated with Axillary LN Positivity (Odds Ratios with 95% CI).

Table 1: Age Distribution of Patients (n=150).

Age (years)	No. of Patients	%
31–40	15	10
41–50	43	28.7
51–60	47	31.3
61–70	30	20
71–80	14	9.3
81–90	1	0.7

Table 2: Quadrant-wise Axillary Lymph Node Positivity.

Quadrant	LN+ (n)	% within quadrant
UOQ	17	27.8
Central	9	23.1
UIQ	4	14.2
LIQ	4	11.7
LOQ	0	0

Table 3: Biological Subtype Distribution in Patients with LN-positive Disease (n=34).

Subtype	No. of LN+ cases	% of LN+ cases
Luminal A	2	5.9
Luminal B HER2-	16	47
Luminal B HER2+	7	20.5
HER2-enriched	4	11.7
Triple negative	5	14.7

Table 4: Association of Clinicopathological Factors with Axillary Lymph Node Positivity.

Factor	Category	LN+ (%)	p-value
Age	≤50 vs >50	45% vs 55%	0.62 (NS)
Menopausal status	Premenopausal vs Postmenopausal	52.9% vs 47.1%	0.78 (NS)
Tumor size (pT)	T1 vs T2 vs T3	8.8% vs 76.4% vs 11.7%	0.04*
Grade	Grade 1 vs Grade 2 vs Grade 3	0% vs 70.6% vs 29.4%	0.03*
Quadrant	UOQ vs Central vs Others	27.8% vs 23.1% vs 12%	0.01*
Histology	NST vs Others	97% vs 3%	0.45 (NS)
Subtype	Luminal B vs Others	67% vs 33%	0.02*

LVI	Present vs Absent	52.9% vs 20.7%	<0.001*
DCIS	Present vs Absent	47% vs 40%	0.04*
PNI	Present vs Absent	5.8% vs 2%	0.09 (NS)

Statements and Declarations

Ethical Approval

The study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Institutional Ethics Committee approval was obtained from Kidwai Memorial Institute of Oncology, Bangalore (KMIO/MEC/2022/PG/SO/05).

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Financial Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Dr Harish Kumar H and Dr Guru S Bharadwaj. All authors read and approved the final manuscript.

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

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