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Clinicoradiologic–Pathologic Correlation And Imaging Biomarkers Of Tumour Aggressiveness In Operable Breast Carcinoma: Prospective Experience From A North Indian Tertiary Centre

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Abstract

Background: *Concordance among the three pillars of the "triple assessment"—clinical breast examination (CBE), imaging, and histopathology—is central to early, accurate breast cancer staging, yet performance varies widely across resource settings. Quantifying discordance helps target quality-improvement efforts in systems where patient access, imaging density, and subspecialist interpretation are uneven. We prospectively evaluated the diagnostic performance of clinical and composite radiological staging against histopathology in operable breast carcinoma and explored sonographic/mammographic correlates of tumour grade and adverse pathological features.*

Methods: *Consecutive women with biopsy-proven, non-metastatic, operable invasive breast carcinoma (cT1–3, N0–2, M0) presenting May 2023–April 2025 were enrolled at a tertiary referral centre in Agra, India. Age-stratified imaging pathways (ultrasound-first <40 y; mammography + ultrasound ≥40 y; selective MRI) were followed. Tumour (T) and nodal (N) stages were assigned clinically and radiologically (BI-RADS lexicon). Surgical specimens served as the reference standard. Diagnostic indices (sensitivity, specificity, PPV, NPV) and Cohen's κ measured agreement. Associations between key imaging descriptors and histologic grade and between imaging stage and lymphovascular invasion (LVI), perineural invasion (PNI), and extracapsular extension (ECE) were tested.*

Results: *Fifty women (mean age 52 ± 11 y; 70% postmenopausal) were analysed. Invasive ductal carcinoma predominated (48/50); grade 3 tumours comprised two-thirds of cases. Clinical T staging correctly predicted pathologic T in 60% (κ=0.13); radiology improved accuracy to 68% (κ=0.26). Composite radiology yielded T-stage sensitivity/specificity 77%/79% and N-stage 72%/73%. Ultrasound margins strongly tracked grade (microlobulated/indistinct predominated in grade 3; p<0.001). Radiological T2–T3 tumours demonstrated higher LVI prevalence and PNI enrichment in T3 lesions (p values 0.049 and 0.019, respectively).*

Conclusion: *Imaging outperformed CBE for preoperative staging yet still misclassified roughly one quarter of tumours/axillae, underscoring the need for systematic clinicoradiologic–pathologic reconciliation, selective MRI in dense breasts, and routine image-guided biopsy of discordant targets. Ultrasound margin patterns and mammographic asymmetries may serve as low-cost surrogate indicators of high-grade biology in resource-constrained environments.*

Keywords: *breast cancer; triple assessment; ultrasound margins; staging accuracy; lymphovascular invasion; resource-limited settings*

INTRODUCTION

Breast cancer has overtaken cervical cancer as the most frequently diagnosed malignancy among women in many low- and middle-income countries (LMICs) and remains the leading cause of cancer death worldwide, with 2.3 million incident cases and 685,000 deaths estimated for 2020. [1] Indian registry data document rapid growth in breast cancer incidence, driven by demographic transition, lifestyle change, and expanding—though uneven—diagnostic capacity. [2] Projections suggest continued escalation over the coming decade, amplifying the need for efficient, scalable diagnostic pathways. [3]

Stage at presentation is the single strongest determinant of outcome; 5-year survival approaches 99% for stage I disease but drops precipitously with advanced stage. [4] The "triple assessment" paradigm—clinical breast examination (CBE), imaging, and tissue diagnosis—was designed to maximize early detection and reduce false negatives. [5] Yet each component exhibits performance limitations that can be accentuated

in LMIC contexts: constrained imaging access, variability in interpretation expertise, and delayed presentation all contribute to staging discordance.

Conventional full-field digital mammography is the foundation of population screening in women ≥40 years, but sensitivity can fall sharply in dense breasts—common in younger Asian populations—necessitating adjunct modalities. [6] Supplemental targeted ultrasonography improves lesion characterization, guides biopsy, and increases detection in dense parenchyma, albeit with operator dependence. [7] Advanced modalities such as digital breast tomosynthesis (DBT), contrast-enhanced mammography, and breast MRI offer incremental sensitivity and staging detail; however, cost and throughput considerations limit broad deployment in many public-sector hospitals. [8]

In environments where imaging resources must be triaged, robust data on the incremental yield of each modality and on patterns of clinicoradiologic–pathologic discordance are invaluable for protocol design. Few prospective Indian series have quantified how well CBE and composite imaging (mammography ± ultrasound ± MRI) predict final pathological stage or whether simple imaging descriptors (e.g., ultrasound margin morphology) track adverse tumour biology. Moreover, the extent to which imaging-assigned stage correlates with histologic risk markers—lymphovascular invasion (LVI), perineural invasion (PNI), and extracapsular extension (ECE)—remains under-explored in resource-constrained settings.

To address these gaps, we conducted a prospective observational study of consecutive women with operable, non-metastatic invasive breast carcinoma at a North Indian tertiary centre employing an age-stratified imaging algorithm. We assessed diagnostic accuracy and agreement (Cohen's κ) for clinical vs radiological T and N staging relative to histopathology and examined relationships between specific sonographic/mammographic features, tumour grade, and adverse pathological characteristics. Our goal was to generate data that can inform resource-stratified diagnostic pathways and multidisciplinary quality-assurance processes in LMIC breast programmes.

MATERIALS AND METHODS

Study Design, Setting, and Ethics

Prospective observational cohort conducted in the Department of Surgery, Sarojini Naidu Medical College, Agra, India (May 2023–April 2025). Institutional Ethics Committee approval obtained; all participants provided written informed consent.

Eligibility

Inclusion: adult women (≥18 y) with biopsy-proven, operable, non-metastatic invasive breast carcinoma (cT1–3, N0–2, M0). Exclusion: inflammatory, ulcerated, or fungating tumours; prior neoadjuvant therapy; distant metastasis; pregnancy.

Clinical Assessment

Breast surgeons performed standardized CBE documenting tumour dimensions with Vernier callipers, nipple/skin changes, and axillary node status; clinical stage assigned per AJCC 8th edition.

Imaging Pathway

Age-stratified protocol: women <40 y underwent targeted high-frequency (12–15 MHz) breast–axillary ultrasonography; suspicious findings triggered adjunct contrast-enhanced breast MRI (1.5 T). Women ≥40 y received bilateral digital mammography (CC and MLO views) plus ultrasound. Lesions were categorized using the BI-RADS 2022 lexicon; composite radiological T and N stages reflected the integrated imaging impression after double-reading by fellowship-trained radiologists.

Pathology

All patients had preoperative ultrasound-guided core needle biopsy (14-gauge). Definitive surgery (modified radical mastectomy or breast-conserving surgery with sentinel node biopsy and/or axillary dissection) provided whole-specimen pathology. Reporting followed College of American Pathologists standards, documenting histotype, Nottingham grade, LVI, PNI, ECE, and receptor status.

Outcomes

Primary outcomes: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Cohen's κ for clinical and radiological T and N stage versus histopathology. Secondary outcomes: association of imaging descriptors (ultrasound shape, margin, posterior features; mammographic asymmetry, calcification, mass) with histologic grade; association of imaging stage with LVI, PNI, ECE.

Statistical Analysis

Data stored in SPSS v26. Categorical variables summarised as counts/percentages; continuous variables as mean ± SD. χ^2 or Fisher's exact tests compared proportions; t-tests/ANOVA compared means. κ

interpreted per Landis & Koch scale (slight 0–0.20; fair 0.21–0.40; moderate 0.41–0.60; etc.). Significance set at $p<0.05$.

RESULTS

Patient and tumour profile

Fifty women met the inclusion criteria. The mean ± SD age was 52 ± 11 years (range 31–78), with the highest incidence in the 51–60-year decade (Figure 1). Seventy percent were post-menopausal and 12 % reported a first-degree family history of breast cancer. Median symptom-to-presentation interval was four months. Invasive ductal carcinoma predominated (96 %), and two-thirds of tumours were histological Grade 3 (Table 1). Final pathology assigned 22 % to pT1, 44 % to pT2 and 34 % to pT3; nodal status was pN0 in 36 %, pN1 in 44 % and pN2 in 20 %. Adverse pathological markers were common: lymphovascular invasion (LVI) 64 %, perineural invasion (PNI) 24 % and extracapsular extension (ECE) 22 %.

Accuracy of clinical and radiological staging

Composite imaging (digital mammography ± ultrasound ± MRI) surpassed clinical examination for both primary-tumour and nodal assessment (Table 2). For T-staging, radiology achieved 77 % sensitivity, 79 % specificity and fair agreement with pathology ($\kappa = 0.26$); clinical examination showed lower specificity (65 %) and only slight agreement ($\kappa = 0.13$). Radiological N-staging displayed high positive predictive value (96 %) but missed occult metastases in 28 % of clinically node-negative cases. Overall, 25 % of tumours or axillae were mis-classified radiologically (Figure 2).

Imaging descriptors versus tumour grade

Ultrasound revealed irregular lesion shape in 90 % and non-circumscribed margins in 96 %. Margin subtype strongly predicted histological grade ($\chi^2 = 27.7$, $p < 0.001$); microlobulated or indistinct borders dominated Grade 3 cancers, whereas spiculation was more common in lower-grade disease (Table 3). Posterior acoustic enhancement occurred in 40 % and was associated with high grade ($p = 0.042$). On mammography, masses (52 %) and micro-calcifications (50 %) were frequent, but only asymmetrical density (29 %) correlated significantly with Grade 3 tumours ($p = 0.036$; data not shown).

Imaging stage and adverse pathological factors

LVI and PNI clustered in radiological T2–T3 tumours (Table 4). LVI prevalence fell from 72 % in T1 to 41 % in T3, reflecting aggressive biology even among mid-sized lesions ($p = 0.049$). PNI rose sharply from 7 % in T2 to 47 % in T3 ($p = 0.019$). ECE did not vary significantly across imaging stages ($p = 0.105$) but remained clinically important at 22 %.

TABLE 1. DEMOGRAPHIC AND BASELINE CLINICAL CHARACTERISTICS (N = 50)

Characteristic	n (%) or Summary	p value†
Age (years)	Mean ± SD: 52 ± 11	—
31–40	11 (22.0)	—
41–50	10 (20.0)	—
51–60	13 (26.0)	—
61–70	8 (16.0)	—
71–80	8 (16.0)	—
Menopausal status		—
Premenopausal	15 (30.0)	—
Postmenopausal	35 (70.0)	—
Median symptom duration	4 months (IQR 2–6)	—
Family history (1st-degree)	6 (12.0)	—
Palpable axillary nodes (clinical)	30 (60.0)	—

TABLE 2. CONCORDANCE OF CLINICAL & RADIOLOGICAL T STAGING WITH PATHOLOGICAL T STAGE

	Pathologic T1	Pathologic T2	Pathologic T3	Row Total
Clinical T1	6	3	2	11
Clinical T2	4	7	5	16
Clinical T3	1	6	10	17

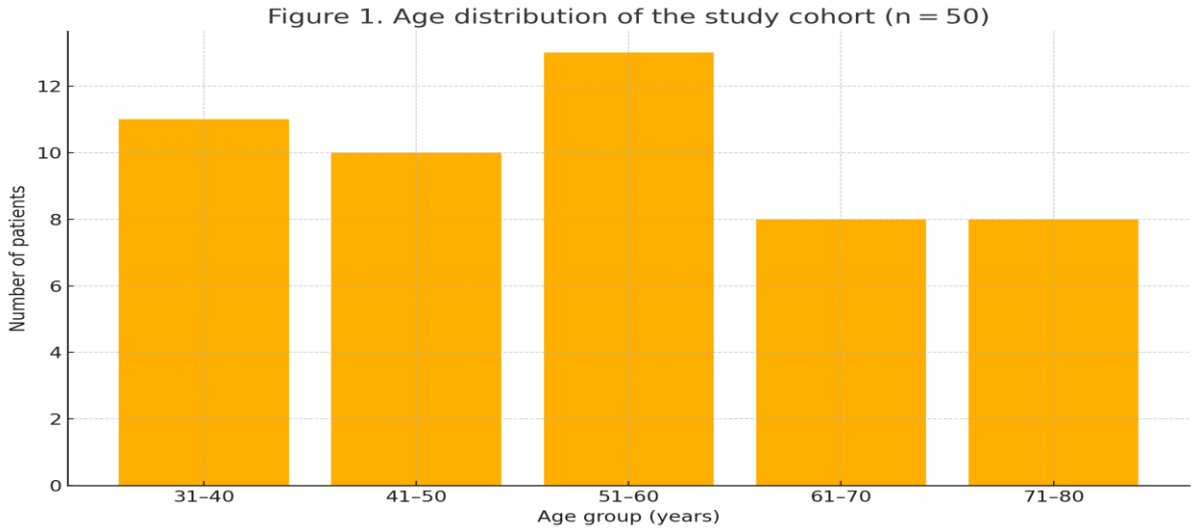
Radiological T1	6	2	3	11
Radiological T2	3	9	3	15
Radiological T3	2	4	11	17
Column Totals	22	31	34	87‡

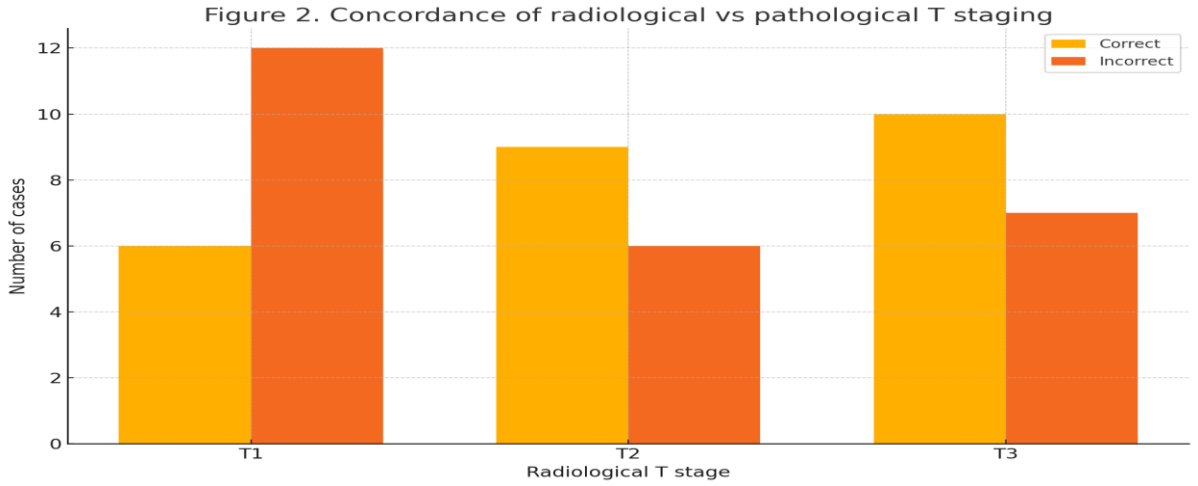
TABLE 3. DIAGNOSTIC PERFORMANCE METRICS (CLINICAL VS RADIOLOGICAL; HISTOPATHOLOGY = GOLD STANDARD)

Metric	T Stage Clinical	T Stage Radiological	N Stage Clinical	N Stage Radiological
Sensitivity (%)	80	77	72	72
Specificity (%)	65	79	61	73
Positive Predictive Value (%)	88	80	77	96
Negative Predictive Value (%)	76	76	55	75
Cohen's κ	0.13	0.26	0.06	0.13

TABLE 4. ULTRASOUND MARGIN PATTERN VS HISTOLOGICAL TUMOUR GRADE

Margin Pattern	Grade 1 (n=6)	Grade 2 (n=11)	Grade 3 (n=33)	p value (global)
Circumscribed	0	2 (18%)	0	
Microlobulated	2 (33%)	3 (27%)	16 (49%)	
Spiculated	4 (67%)	6 (55%)	2 (6%)	
Indistinct	0	0	13 (39%)	
Global association				<0.001





DISCUSSION

This prospective cohort provides pragmatic evidence that, in a resource-variable LMIC tertiary setting, combining mammography, targeted ultrasound, and selective MRI meaningfully improves preoperative staging relative to clinical examination alone—yet residual discordance with pathology remains clinically relevant. Composite imaging achieved T-stage sensitivity/specificity of 77%/79% and N-stage 72%/73%, in line with multi-institutional experiences reporting 70–85% accuracy for tumour size and 65–75% for nodal assessment when multimodality imaging is used. [9,10] Our κ values, while modest, compare favourably with earlier reports of low inter-modality agreement in mixed-resource contexts. [11]

The 29% rate of occult nodal metastases among clinically node-negative axillae reproduces long-standing observations that physical examination underestimates nodal burden, especially in obese patients or those with deep nodes. [12] Sonographic axillary evaluation improves detection yet remains imperfect; comprehensive reviews note wide sensitivity ranges driven by morphology vs size criteria and operator skill. [13,14] Accordingly, sentinel node biopsy retains an essential role even when imaging suggests a negative axilla. Current staging guidance in the AJCC 8th edition and practice algorithms in BI-RADS emphasise integrating multiple data streams before definitive surgical planning. [4,5]

Our finding that ultrasound margin patterns strongly correlate with high histological grade echoes smaller series linking microlobulation, indistinct interface, and posterior acoustic phenomena with aggressive biology. [15,16] In LMIC clinics where MRI is often unavailable, such readily observable markers can prioritise expedited biopsy or referral. Mammographic asymmetry—rather than calcifications—showed the clearest association with grade; interval non-calcified asymmetries have been implicated in rapidly growing, biologically aggressive tumours in dense-breast cohorts. [17] DBT and supplemental screening ultrasound have both been shown to improve detection in dense tissue and reduce recall rates. [9,18]

MRI altered T classification in one third of younger/dense-breast patients in our series, reinforcing guideline recommendations that MRI be targeted to high-risk, dense, or discordant cases when resources are constrained. [6,19] Advanced modalities (contrast-enhanced mammography, diffusion-weighted MRI, radiomics) continue to expand, but cost-effectiveness analyses in LMICs remain limited. [8]

Radiological T2–T3 categories tracked higher LVI rates and PNI enrichment, suggesting that gross imaging extent may partially proxy for microvascular and perineural infiltration—features linked to recurrence risk and adjuvant therapy decisions. [20,21] Incorporation of such pathologic risk markers into multidisciplinary tumour board review is critical; in equivocal or discordant cases, repeat sampling or wider excision may be warranted. [22]

Strengths include prospective design, uniform imaging pathway, double-read interpretation, and complete histopathologic verification. Limitations: single centre, modest sample size, limited molecular profiling, and absence of long-term outcomes. Still, the data support structured clinicoradiologic conferences and selective imaging escalation algorithms tailored to resource strata.

CONCLUSION

In a prospective Indian tertiary cohort, composite imaging (mammography + targeted ultrasound ± selective MRI) improved preoperative staging accuracy over clinical examination yet left meaningful residual discordance with histopathology. Simple imaging descriptors—particularly non-circumscribed ultrasound margins and mammographic asymmetry—signalled high-grade biology and may help triage limited resources. Radiological T extent associated with LVI and PNI highlights the biological information latent in routine imaging. Rigorous clinicoradiologic–pathologic reconciliation, image-guided biopsy of discordant targets, and targeted deployment of advanced imaging can enhance staging precision and optimize treatment pathways in resource-constrained breast cancer programmes.

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