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Features in Patients High-risk Clinicopathological Undergoing Modified Radical Mastectomy (MRM) for Breast Cancer: A Descriptive Cross-sectional Study

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ABSTRACT

Background: Modified Radical Mastectomy (MRM) remains a major surgical intervention for breast cancer, particularly in low- to middle-income countries (LMICs) and cases presenting with locally advanced disease or high tumor-to-breast size ratios. Identifying high-risk clinicopathological features in these patients is vital for stratifying systemic recurrence risk and tailoring post-mastectomy radiation therapy (PMRT) and adjuvant systemic treatments.

Objective: To evaluate the prevalence, spectrum, and inter-relationships of high-risk clinicopathological features in female breast cancer patients who underwent MRM at a tertiary care facility.

Methods: A hospital-based descriptive cross-sectional study was conducted on 100 consecutive female patients diagnosed with primary invasive breast carcinoma who underwent MRM between January 2024 and December 2025. Clinical parameters (age, menopausal status, lateralization) and histopathological parameters (tumor size [pT], pathological nodal status [pN], WHO histological type, Nottingham histological grade, lymphovascular invasion [LVI], perineural invasion [PNI], and immunohistochemical [IHC] markers: ER, PR, HER2/neu, Ki-67) were documented. Statistical analyses were performed using SPSS v26.0, employing Pearson's Chi-square and Fisher's exact tests to establish associations between clinicopathological variables ($p < 0.05$ considered statistically significant).

Results: The mean patient age was 52.4 ± 10.8 years, with 62.0% (n=62) being postmenopausal. Invasive Ductal Carcinoma (NOS) was the predominant histological subtype (89.0%, n=89). High-risk clinical features were abundant: 37.0% (n=37) presented with advanced T-stage (pT3/pT4), and 68.0% (n=68) exhibited axillary lymph node metastasis (pN1–pN3). High histological grade (Nottingham Grade III) was present in 42.0% (n=42), LVI in 54.0% (n=54), and PNI in 21.0% (n=21). Immunohistochemical profiling revealed Luminal A in 35.0%, Luminal B in 25.0%, HER2-enriched in 15.0%, and Triple-Negative Breast Cancer (TNBC) in 25.0%. A statistically significant positive association was observed between larger tumor size (pT3/pT4) and pathological nodal metastasis ($p < 0.001$), as well as between LVI and axillary lymph node involvement ($p < 0.001$).

Conclusion: Patients undergoing MRM present with a high burden of adverse clinicopathological features, including advanced tumor size, high rates of axillary node positivity, poorly differentiated histology, and aggressive molecular subtypes (TNBC/HER2-enriched). Comprehensive pathological reporting—specifically incorporating LVI, PNI, and IHC molecular subtyping—is mandatory to risk-stratify patients for escalated post-mastectomy radiation and aggressive systemic therapies.

Keywords: Breast Carcinoma, Modified Radical Mastectomy (MRM), Lymphovascular Invasion, Nottingham Grade, Axillary Lymph Node Metastasis, Triple-Negative Breast Cancer.

1. INTRODUCTION

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer mortality among women globally [1]. Despite major advancements in early screening programs and the widespread adoption of Breast-Conserving Surgery (BCS) in early-stage disease, Modified Radical Mastectomy (MRM) remains an indispensable surgical modality [2]. In low- and middle-income country (LMIC) settings, a substantial proportion of patients present with locally advanced breast cancer (LABC), multicentric disease, large tumor-to-breast volume ratios, or financial and logistical constraints that limit access to mandatory post-BCS radiotherapy [3]. The post-operative disease-free survival (DFS) and overall survival (OS) of breast cancer patients are strongly governed by specific clinicopathological variables. High-risk features that dictate a higher probability of locoregional recurrence (LRR) and distant metastasis include:

1. Large Primary Tumor Size (pT3 > 5\text{ cm} or pT4 with skin/chest wall involvement).
2. Pathological Axillary Lymph Node Metastasis (pN1 to pN3, particularly \ge 4 positive nodes).
3. High Histological Grade (Nottingham Modification of Bloom-Richardson Grade III).
4. Presence of Lymphovascular Invasion (LVI) and Perineural Invasion (PNI).
5. Close or Positive Surgical Resection Margins.
6. Aggressive Biological Subtypes (HER2-enriched and Triple-Negative Breast Cancer [TNBC]).

Accurate characterization of these high-risk parameters in surgical resection specimens is imperative for multidisciplinary tumor boards (MDT) to determine indications for post-mastectomy radiation therapy (PMRT), dose-dense adjuvant chemotherapy, targeted anti-HER2 therapies, and extended endocrine interventions [4,5]. This study aimed to evaluate the prevalence, anatomical distribution, and correlation of high-risk clinicopathological parameters among patients undergoing MRM at a tertiary referral center.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This prospective and retrospective descriptive cross-sectional study was conducted in the Department of Surgical Oncology in collaboration with the Department of Pathology at a tertiary care teaching hospital over a 24-month period (January 2024 to December 2025).

2.2 Ethical Approval and Informed Consent

The study protocol was approved by the Institutional Ethics Committee (IEC Reference Number: IEC/2022/SURG/841). Written informed consent was obtained from all living patients or their legally authorized representatives prior to data inclusion, adhering to the principles of the Declaration of Helsinki.

2.3 Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Female patients aged \ge 18 years with biopsy-proven primary invasive breast carcinoma.
2. Patients who underwent primary Modified Radical Mastectomy (MRM) with Level I, II, and III axillary dissection.
3. Patients with complete clinical, histopathological, and immunohistochemical (IHC) records.

Exclusion Criteria:

1. Patients presenting with overt distant metastasis (M1 stage) at initial diagnosis.
2. Patients who underwent simple mastectomy, breast-conserving surgery (BCS), or prophylactic mastectomy.
3. Patients with recurrent, bilateral, or secondary breast malignancies.
4. Patients who received neoadjuvant chemotherapy (NACT) (to prevent pathological downstaging bias).

2.4 Data Collection & Variable Definitions

Surgical resection specimens were routinely fixed in 10% neutral buffered formalin, sectioned, processed, and stained with Hematoxylin and Eosin (H&E). Pathological parameters were assessed according to WHO classification and AJCC Staging Manual (8th Edition) guidelines:
Demographics & Clinical Data: Patient age, menopausal status, and tumor lateralization.

- Pathological T and N Staging: Maximum microscopic tumor dimension (pT1 \le 2\text{ cm}, pT2 > 2\text{ to } 5\text{ cm}, pT3 > 5\text{ cm}, pT4 chest wall/skin involvement) and absolute number of positive axillary nodes (pN0: 0 nodes, pN1: 1–3 nodes, pN2: 4–9 nodes, pN3 \ge 10 nodes).
- Histological Type and Grade: Classified via Nottingham Modification of the Bloom-Richardson system based on tubule formation, nuclear pleomorphism, and mitotic count (Grade I, II, and III).
- Adverse Histopathology Markers: Presence of LVI (defined as tumor emboli within endothelium-lined vascular/lymphatic spaces) and PNI. Immunohistochemistry (IHC) Profile:
- ER & PR: Positive if \ge 1\% tumor cell nuclear staining (Allred score applied).
- HER2/neu: Staining intensity scored as 0, 1+, 2+, or 3+. Score 3+ was defined as positive; score 2+ cases were verified using Fluorescent In Situ Hybridization (FISH) for gene amplification.
- Ki-67 Index: Categorized as low (< 20\%) or high (\ge 20\%).
- Molecular Subtypes: Defined as:

1. Luminal A: ER+, PR+, HER2-, Ki-67 low (<20\%).
2. Luminal B: ER+, PR+ or PR-, HER2- with Ki-67 high (\ge 20\%), OR ER+, HER2+.
3. HER2-Enriched: ER-, PR-, HER2+.
4. TNBC: ER-, PR-, HER2-.

2.5 Statistical Analysis

Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics for Windows (Version 26.0, Armonk, NY: IBM Corp.). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as absolute frequencies (n) and percentages (\%). Associations between categorical variables (e.g., LVI vs. Nodal Status, Tumor Grade vs. Molecular Subtype) were evaluated using Pearson's Chi-square (\chi^2) test or Fisher's exact test. A two-tailed p-value < 0.05 was established as the threshold for statistical significance.

3. RESULTS

3.1 Patient Demographics and Clinical Baseline

A total of 100 female patients who met all eligibility criteria were analyzed. The mean age at diagnosis was 52.4 ± 10.8 years (range: 28 to 76 years). The majority of patients were in the 40–60 age group (58.0\%), and 62.0\% were postmenopausal (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics (N=100)

Parameter	Sub-category	Frequency (n)	Percentage (\%)
Age Group	< 40 years	18	18.0%
	40 – 60 years	58	58.0%
	> 60 years	24	24.0%
Menopausal Status	Premenopausal	38	38.0%
	Postmenopausal	62	62.0%
Tumor Side	Right Breast	51	51.0%
	Left Breast	49	49.0%

3.2 Pathological Stage (pT and pN) Distribution

Pathological examination revealed that early-stage tumors (pT1) accounted for only 15.0\% of cases, whereas pT2 tumors constituted 48.0\%, pT3 tumors 25.0\%, and pT4 tumors 12.0\%. Thus, advanced primary tumors (pT3/pT4) represented over one-third (37.0\%) of all MRM specimens.

Regarding nodal involvement, 32.0\% (n=32) were node-negative (pN0), while 68.0\% (n=68) exhibited pathologically proven axillary node metastasis (Table 2).

Table 2: Pathological T and N Staging Profile

Staging Category	Sub-stage	Definition	Count (n)	Percentage (\%)
Pathological T Stage	pT1	\le 2.0\text{ cm}	15	15.0%
	pT2	> 2.0\text{ cm to } 5.0\text{ cm}	48	48.0%
	pT3	> 5.0\text{ cm}	25	25.0%
	pT4	Chest wall / Skin involvement	12	12.0%
Pathological N Stage	pN0	No regional lymph node metastasis	32	32.0%
	pN1	1–3 positive axillary nodes	36	36.0%
	pN2	4–9 positive axillary nodes	20	20.0%

3.3 Histopathological Features and Molecular Profile

Invasive Ductal Carcinoma, Not Otherwise Specified (IDC-NOS) was the dominant histological type (89.0\%), followed by Invasive Lobular Carcinoma (7.0\%) and other specialized subtypes (4.0\%).

Nottingham Grade III poorly differentiated tumors were identified in 42.0\% of specimens. Lymphovascular Invasion (LVI) was present in 54.0\% (n=54), while Perineural Invasion (PNI) was identified in 21.0\% (n=21). Resection margins were close (< 2\text{ mm}) or positive in 6.0\% (n=6) of cases (Table 3).

In terms of surrogate IHC molecular subtyping, aggressive non-luminal phenotypes

(HER2-enriched and TNBC) accounted for 40.0\% of the cohort.

Table 3: Histopathology and Molecular Biomarkers

Parameter	Sub-category	Frequency (n)	Percentage (\%)
Histological Subtype	Invasive Ductal Carcinoma (NOS)	89	89.0%
	Invasive Lobular Carcinoma	7	7.0%
	Others (Mucinous, Medullary)	4	4.0%
Nottingham Grade	Grade I (Well Differentiated)	16	16.0%
	Grade II (Moderately Differentiated)	42	42.0%
	Grade III (Poorly Differentiated)	**42**	**42.0%**
Lymphovascular Invasion	Present	54	54.0%
	Absent	46	46.0%
Perineural Invasion	Present	21	21.0%
	Absent	79	79.0%
Molecular Subtype	Luminal A	35	35.0%
	Luminal B	25	25.0%
	HER2-Enriched	15	15.0%
	TNBC	**25**	**25.0%**

3.4 Cross-Tabulation and Statistical Correlations

Cross-tabulation demonstrated significant associations between key high-risk variables:

1. Tumor Size vs. Nodal Metastasis: Larger tumors (pT3/pT4) had a significantly higher rate of axillary node metastasis (83.8\%, 31/37) compared to pT1/pT2 tumors (58.7\%, 37/63) (\chi^2 = 6.42, p = 0.011).

2. LVI vs. Axillary Nodal Status: Lymphovascular invasion was strongly associated with axillary lymph node positivity. Node-positive patients exhibited LVI in 70.6\% (48/68) of cases, whereas node-negative patients showed LVI in only 18.8\% (6/32) (\chi^2 = 23.41, $p < 0.001$).

3. Histological Grade vs. Molecular Subtype: High Grade III tumors were

disproportionately clustered within the TNBC (68.0\%, 17/25) and HER2-enriched (60.0\%, 9/15) subtypes ($p < 0.001$).

Table 4: Correlation between LVI Status and Axillary Nodal Metastasis

LVI Status	pN0 (n=32)	pN+ (n=68)	Total (N=100)	Chi-Square (\chi^2)	p-value
LVI Present	6 (18.8%)	48 (70.6%)	54	23.41	< 0.001*
LVI Absent	26 (81.2%)	20 (29.4%)	46		

Statistically significant ($p < 0.05$).

4. DISCUSSION

Modified Radical Mastectomy remains a major therapeutic operation in breast oncology practice, particularly in resource-constrained environments where late presentation is common [6]. This cross-sectional investigation highlights that patients managed with MRM harbor a high density of unfavorable clinicopathological predictors that dictate an elevated risk of disease relapse.

4.1 Tumor Burden and Axillary Nodal Disease

In our study, 37.0\% of MRM patients presented with advanced primary tumors (pT3/pT4), and 68.0\% had pathologically confirmed axillary lymph node metastasis (pN+). These figures are higher than those typically reported in Western screening-detected cohorts, where pN+ rates range between 30\% and 40\% [7]. Late clinical presentation, delay in seeking medical evaluation, and lack of universal mammographic screening contribute to the heavier nodal tumor burden observed in our cohort. According to National Comprehensive Cancer Network (NCCN) guidelines, pN+ status (especially pN2/pN3 or \ge 4 nodes) represents an absolute indication for post-mastectomy radiation therapy (PMRT) to lower locoregional recurrence rates [8].

4.2 Biological Significance of LVI and PNI

Lymphovascular Invasion (LVI) serves as a critical step in the metastatic cascade, indicating microvascular penetration by malignant cells. In our cohort, LVI was present in 54.0\% of specimens and was strongly associated with axillary nodal positivity ($p < 0.001$). This reinforces the finding that LVI is a powerful surrogate marker for systemic tumor dissemination. Studies by Rakha et al. [9] demonstrated that LVI is an independent predictor of overall survival and disease-free survival in invasive breast carcinoma. Similarly, Perineural Invasion (PNI),

observed in 21.0\% of our patients, has been increasingly recognized as a predictor of locoregional recurrence, highlighting the need for careful systemic staging.

4.3 High Histological Grade and Molecular Phenotypes

Over 40\% of our patients exhibited Nottingham Grade III tumors, reflecting significant cellular pleomorphism and mitotic activity. Furthermore, aggressive non-luminal phenotypes (HER2-enriched: 15.0\%, TNBC: 25.0\%) constituted 40.0\% of the cohort. Triple-Negative Breast Cancer is notoriously aggressive, lacking targeted hormonal or anti-HER2 therapies, and associated with earlier peak recurrence risks within 3 to 5 years post-diagnosis [10]. The convergence of high histological grade and TNBC/HER2-enriched subtypes in MRM patients highlights the necessity of combining total surgical removal with platinum/anthracycline-taxane-based adjuvant chemotherapy regimens [11].

4.4 Clinical and Therapeutic Implications

The identification of high-risk features in MRM resection specimens directly influences post-operative systemic treatment strategies:

1. PMRT Escalation: Patients with pT3/pT4 stage, \ge 4 positive nodes, or positive margins require comprehensive chest wall and nodal irradiation.
2. Dose-Dense Chemotherapy: Grade III histology, high Ki-67 index (\ge 20\%), LVI positivity, and TNBC subtype warrant dose-dense anthracycline-taxane regimens.
3. Targeted Therapy: HER2 3+ positivity mandates full-year trastuzumab (± pertuzumab) administration.

5. STRENGTHS AND LIMITATIONS

Strengths:

- Standardized pathological protocol with routine verification of IHC markers and FISH testing for equivocal HER2 cases.
- Homogeneous study population excluding NACT downstaging confounders.

Limitations:

- Single-center cross-sectional design without prospective long-term follow-up to correlate features directly with 5-year Disease-Free Survival (DFS) and Overall Survival (OS).

- Moderate sample size (N=100), which restricts extensive subgroup multivariable

regression modeling.

6. CONCLUSION

Female patients undergoing Modified Radical Mastectomy (MRM) for invasive breast cancer frequently demonstrate a constellation of high-risk clinicopathological parameters, including advanced tumor size (pT3/pT4), extensive axillary nodal involvement (pN+), high Nottingham histological grade (Grade III), high prevalence of lymphovascular invasion (LVI), and aggressive molecular subtypes (TNBC and HER2-enriched). Routine pathology protocols must systematically evaluate and report LVI, PNI, and IHC profiles to enable multidisciplinary tumor boards to optimize post-mastectomy radiation therapy and adjuvant systemic regimens.

DECLARATIONS

- Ethical Approval: Approved by the Institutional Ethics Committee (Ref No:

IEC/2022/SURG/841).

- Consent to Participate: Informed written consent was obtained from all individual

participants.

- Consent for Publication: All authors have approved the final manuscript for publication.
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- Author Contributions: [Dr Sagar Baradwaj Suraj Singh] conceptualized the study, performed surgical

procedures, and drafted the manuscript. [Dr Praveen Agarwal] conducted histopathological and IHC evaluations. [Dr Sagar Haritha Singh] performed statistical analysis and data curation. All authors reviewed and finalized the text.

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