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Molecular Subtypes Of Breast Carcinoma And Their Propensity For Lymph-Node Metastasis: A Single-Center Retrospective Analysis From South India

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ABSTRACT

Background: Molecular heterogeneity is evident in the breast carcinoma with consequences for prognosis. Immunohistochemical subtyping, are used to classify the tumors as Luminal A, Luminal B, HER2 enriched and the Triple-Negative Breast Cancer (TNBC). LN metastasis continues to be a powerful prognosticator with possible-subtype specific metastatic propensities. In this retrospective analysis, the distribution of molecular subtypes and their correlation with LN metastasis of patients undergoing MRM was examined.

Methods: We reviewed records of 50 female patients treated with MRM for primary breast carcinoma at Chettinad Hospital and Research Institute between January 2023 and December 2024. Data collected included age, tumor size (TNM staging), histological type, molecular subtype (ER, PR, HER2 status), and LN involvement. Statistical analyses employed Chi-square tests and logistic regression via IBM-SPSS v21.0 to evaluate associations, with $p < 0.05$ denoting significance.

Results: The cohort included 36% Luminal A, 28% of Luminal B, 20% HRE2-enriched and 16% TNBC subtypes. Overall, 58% of patients were with LN metastasis. The most common form of metastasis was seen with HER2-enriched (80%) and Luminal B (71%) subtypes, but Luminal A had the least rate of metastasis (33%). Tumor size was highly correlated with nodal involvement ($p = 0.001$), and for LN metastasis, Luminal B (OR = 3.5, $p = 0.02$

Conclusion: Our findings confirm a significant association between molecular subtypes and LN metastasis, with HER2-enriched and Luminal B subtypes at elevated risk. Molecular subtyping thus provides valuable prognostic insight, informing tailored surgical and adjuvant strategies. Further multicentric studies with larger cohorts are warranted to validate these results.

Keywords: *breast carcinoma; molecular subtypes; lymph node metastasis; retrospective cohort; Luminal A; HER2-enriched*

1. INTRODUCTION

Globaly, women of all nations, the most prevalent form of cancer is breast carcinoma (19–34% of all female cancers) with median age for onset of approximately 47 years [1]. Even though they are hereditary in about 2-5%, most are sporadic, due to medical history of reproduction and exposure from hormones and such, obesity [1]. Pre-menarche, nulliparity and late menopause are risk factors; whereas pregnancy and breastfeeding are protective [1]. Histopathologically the most frequent invasive ductal carcinoma is also the most common, invasive lobular carcinoma followed by relatively less frequent variants.

Molecular classification by using the immunohistochemical expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2) has evolved as the staging rock in making prognosis and treatment pronouncements

This categorization grades tumor into; (Luminal A (ER+/PR+, HER2−, Low Ki-67), Luminal B (ER+/PR+ HER2−/+, high Ki-67), HER2-enriched (HER2

subtypes [2,3]. The Luminal A tumors are conventionally characterized by indolent behavior and promising results; the Luminal B, HER-enriched, and TNBC subtypes are seen as becoming more aggressive and characterized by poor outcomes [3,4].

LN status is still the strongest prognostic marker of breast cancer, dictating surgical treatment and selecting adjuvant therapy [1]. Lymphatic metastatic spread is one of the major mechanisms involved in disease progression with evidence of subtype specific nodal involvement. Luminal B and HER2-enriched tumors have been documented to demonstrate higher rates of LN metastases when compared to Luminal A and the predilection to nodal spread of the TNBC has been variably characterized [3,5].

Knowledge of the interrelationship between molecular subtypes and LN metastasis can lead to the refinement of the risk stratification framework and determine optimal personalized treatment. Whereas larger cohorts have previously examined this association, regional differences and single centre analyses continue to inform the clinical application of such studies in certain populations [5,6]. It was the purpose of this retrospective study was to determine the distribution of molecular subtypes in breast carcinoma patients receiving modified radical mastectomy (MRM) in our facility, and to test the relationship between such subtypes and LN metastasis. We hypothesize that HER2 enriched and Luminal B subgroups will have increased nodal involvement than Luminal A subtype and TNBC.

2. MATERIALS AND METHODS

Study Design and Setting: A retrospective observational cohort was carried out in Chettinad Hospital and research Institute Chennai looking back to cases from January 2023 to December 2024. Analysis of data was carried out from January through March 2025.

Study Population: Only female patients with a diagnosis of primary breast carcinoma who had undergone MRM, with accessible histopathologic and IHC reports outlining ER, PR, and HER2 status and recorded LN status, were eligible for inclusion. Exclusion criteria were male gender, a history of recurrent breast carcinoma, and cases in which histopathological or IHC data were insufficient or absent.

Data Collection: Patient records were systematically reviewed to retrieve demographics (age at diagnosis), and tumor information (size classified based on TNM staging: T1 ≤2, T2 2–5, T3 >5), histological subtype (ductal versus lobular carcinoma), molecular subtype (Luminal A-Luminal B, HER2-enriched, TNBC), LN involvement (number of

Statistical Analysis: Data were coded and analyzed using the computer package IBM-SPSS v21.0 Statistical software. Summary characteristics of patient and tumor were given using descriptive statistics (mean, standard deviation, frequencies). Correlations between discrete variables (categorical subtype v.s. LN metastasis, tumor size v.s. LN involvement) were observed using Chi-square tests. An odds ratio was obtained for LN metastasis with the confidence interval (95% CI) from a multivariate logistic regression for every class besides the Luminal A, which was used as the reference group. Statistical significance was evident for a two-tailed p value<0.05.

Ethical Considerations: The current research was approved by the Institutional Human Ethics Committee (IHEC Proposal ID: IHEC-I/3443/25). The confidentiality of a patient was observed by de-identifying all personal information. As a retrospective review of anonymized records, informed consent was waived.

3. RESULTS

All in all 50 female patients met inclusion criteria. The mean age of diagnosis was 47.6 ± 8.3 years, range: 30–70 years). The invasive ductal carcinoma was predominant, with the proportion of invasive lobular carcinoma coming in at the other 12%.

The most dominant molecular subtype was Luminal A (n = 18, 36%), Luminal B (n = 14, 28%), HER2-enriched (n = □□ Overall, 29 patients (58%) exhibited LN metastasis. In HER2-enriched group the highest nodal involvement rate was 80%, Luminal B had 71%, TNBC had 62% and Luminal A 33% (Table 2). The molecular subtype and LN metastasis was highly associated (Chi-square p = 0.003).

Age at diagnosis varied by subtype, with TNBC patients youngest (mean 42.5 ± 6.8 years) and Luminal A patients oldest (mean 50.3 ± 7.2 years). Larger tumors (T3 stage) had the highest LN metastatic rate (78%), compared to T2 (57%) and T1 (20%) (Table 3), with tumor size significantly associated with nodal involvement (p = 0.001).

On multivariate logistic regression, relative to Luminal A, the odds of LN metastasis were significantly elevated in Luminal B (OR = 3.5, 95% CI 1.4–8.7, p = 0.02), HER2-enriched (OR = 4.8, 95% CI 1.6–11.3, p = 0.01), and TNBC (OR = 2.7, 95%

CI 1.1–6.9, p = 0.04) (Table 4).

TABLE 1. DISTRIBUTION OF MOLECULAR SUBTYPES

Molecular Subtype	n (n = 50)	%
Luminal A	18	36%
Luminal B	14	28%
HER2-enriched	10	20%
Triple-Negative	8	16%

TABLE 2. MOLECULAR SUBTYPE VS. LYMPH NODE METASTASIS

Subtype	Total (n)	LN+ (n, %)	LN− (n, %)
Luminal A	18	6 (33%)	12 (67%)
Luminal B	14	10 (71%)	4 (29%)
HER2-enriched	10	8 (80%)	2 (20%)
Triple-Negative	8	5 (62%)	3 (38%)

TABLE 3. TUMOR SIZE (TNM) AND LN METASTASIS

Tumor Size	n (n = 50)	LN+ (n, %)	LN− (n, %)
T1 (≤2 cm)	10	2 (20%)	8 (80%)
T2 (2–5 cm)	28	16 (57%)	12 (43%)
T3 (>5 cm)	12	11 (78%)	1 (22%)

TABLE 4. LOGISTIC REGRESSION FOR LN METASTASIS

Subtype (ref: Luminal A)	OR	95% CI	p-value
Luminal B	3.5	1.4–8.7	0.02
HER2-enriched	4.8	1.6–11.3	0.01
TNBC	2.7	1.1–6.9	0.04

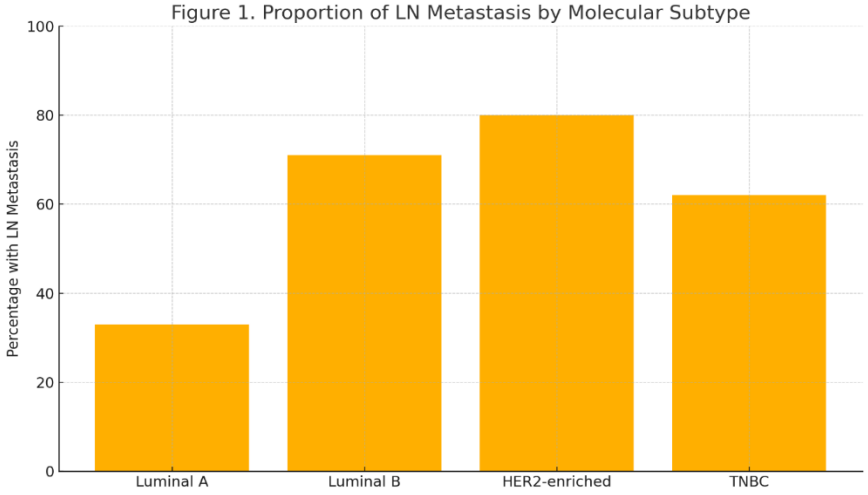

Figure 1. Bar chart illustrating the proportion of LN metastasis by molecular subtype.

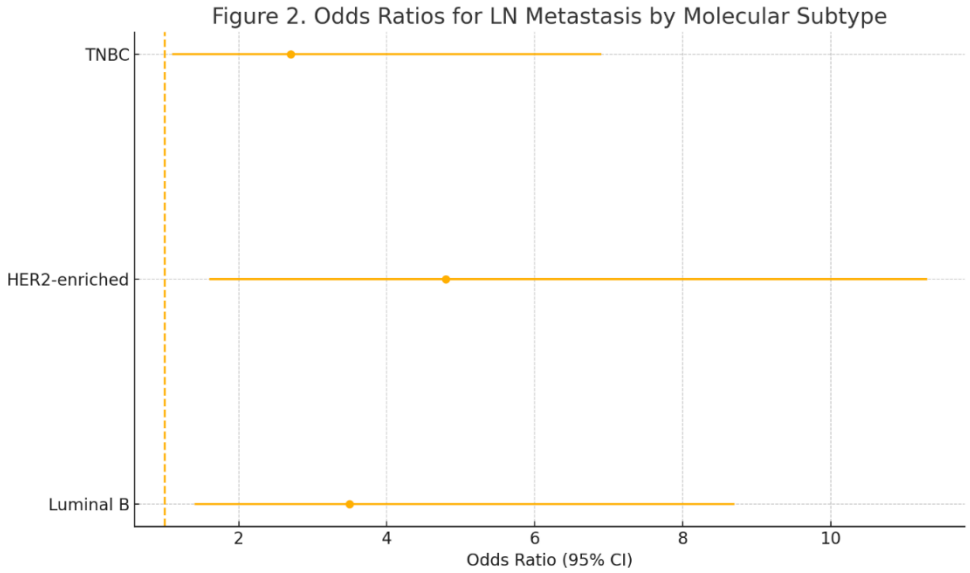

Figure 2. Forest plot of odds ratios for LN metastasis across molecular subtypes (reference: Luminal A).

4. DISCUSSION

This single-center retrospective analysis underscores a significant relationship between breast carcinoma molecular subtypes and LN metastasis. Consistent with global data, Luminal A was the most frequent subtype (36%), while HER2-enriched and TNBC comprised 20% and 16% of cases, respectively [5,7]. The observed subtype distribution aligns with multicenter cohorts reporting Luminal A prevalence exceeding 50% and combined Luminal B/HER2-positive subtypes representing 30–40% of diagnoses [6].

Our study's LN metastasis rate of 58% parallels reports ranging from 45–65% in similar surgical cohorts [5]. Notably, HER2-enriched (80%) and Luminal B (71%) subtypes exhibited the highest nodal involvement, corroborating prior findings that these subtypes harbor aggressive phenotypes and higher proliferation indices [6,8]. In contrast, Luminal A tumors demonstrated the lowest metastatic rate (33%), reinforcing their favorable biological behavior [4,7]. TNBC's intermediate nodal rate (62%) reflects heterogeneous metastatic patterns within this subtype, possibly influenced by variable tumor microenvironments and genetic heterogeneity [3].

Tumor size emerged as an independent correlate of LN involvement ($p = 0.001$), with T3 lesions (>5 cm) showing a 78% metastatic rate. This observation concurs with literature establishing tumor burden as a pivotal determinant of nodal spread irrespective of molecular subtype [8]. Age at diagnosis varied, with TNBC presenting earlier (mean 42.5 years) compared to Luminal A (mean 50.3 years), consistent with reports of TNBC's predilection for younger patients [9].

Logistic regression confirmed elevated odds of LN metastasis in Luminal B (OR 3.5), HER2-enriched (OR 4.8), and TNBC (OR 2.7) relative to Luminal A. These effect sizes are comparable to large-scale studies reporting ORs between 1.5 and 5.0 for HER2-positive and high-grade subtypes [6,7]. The heightened risk warrants consideration of more extensive nodal evaluation and aggressive systemic therapy for patients with high-risk subtypes.

Limitations include the retrospective design, single-institution scope, and modest sample size (n = 50), which may limit external validity. Selection bias cannot be excluded, and the absence of genomic profiling restricts subtype precision to IHC surrogates. Future prospective, multicentric studies integrating molecular assays (e.g., PAM50) could refine subtype-specific risk stratification and elucidate underlying mechanisms driving nodal dissemination.

In conclusion, our data reinforce the prognostic significance of molecular subtyping in predicting LN metastasis. Integrating subtype information with traditional clinicopathological factors can enhance personalized treatment planning, optimizing surgical and adjuvant strategies to improve patient outcomes.

5. CONCLUSION

This retrospective study demonstrates a clear association between breast cancer molecular subtypes and lymph node metastasis. HER2-enriched and Luminal B tumors exhibit significantly higher nodal involvement compared to Luminal A, while TNBC shows intermediate risk. Tumor size further influences metastatic propensity. These findings underscore the importance of molecular subtyping for prognostication and tailoring surgical and systemic therapies. Prospective multicenter investigations with larger cohorts and genomic profiling are recommended to validate and extend these observations, ultimately refining individualized breast cancer management.

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