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ORIGINAL RESEARCH

Breast Cancer Subtypes, Tumor Size, and Lymph Node Metastasis: A Retrospective Analysis of 442 Patients

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ABSTRACT
Breast cancer is a heterogeneous disease with various subtypes that exhibit distinct biological behaviors and prognostic outcomes. Despite the robustness of this relationship in many breast cancer cases, emerging research reveals significant variations in the correlation between tumor size and lymph node metastasis across specific subgroups. In this retrospective study, we analyzed the clinical and pathological features of 442 breast cancer patients diagnosed between year 2017 and 2023 at A.J. Institute of Medical Sciences and Research Centre,Mangalore, Karnataka, India. Luminal A patients generally presented with lower-grade and early-stage tumors, while TNBC and HER2-positive subtype were associated with higher-grade tumors and more aggressive clinical features. The number of metastatic lymph nodes and histologic grade emerged as strong predictors of survival across all subtypings, with TNBC showing the highest risk for poor outcomes. These findings underscore the importance of considering both tumor biology and clinical variables in predicting patient outcomes and guiding treatment strategies.

Keywords: Breast cancer, Basal-like breast cancer,HER2, Luminal,metastasis;

INTRODUCTION

Various subtypes of breast cancer display unique biological characteristics and prognostic consequences, making it a heterogeneous illness. [1] Tumor size and lymph node involvement are both crucial prognostic factors for breast cancer and are integral components of the TNM classification system.[2] The correlation between tumor size and lymph node metastasis has traditionally been regarded as clear-cut, since bigger tumors often correspond to a greater probability of nodal dissemination and a worse prognosis [3]. Nevertheless, the correlation between this relationship can fluctuate greatly among various subtypes of breast cancer, thereby requiring a more sophisticated comprehension of how tumor biology influences metastatic behavior.[4]

Through a comprehensive analysis of 24,740 breast cancer cases, Carter et al. demonstrated a definitive linear correlation between the size of the tumor and the likelihood of lymph node metastasis in a wide range of breast cancer types.[5] Their results indicated that as the size of the tumor grew, the likelihood of lymph node involvement simultaneously increased, leading to a corresponding deterioration in survival outcomes. To illustrate, tumors that were less than 2 cm in size and did not affect any lymph nodes had a five-year survival rate of 96.3%. Conversely, bigger tumors that exceeded 5 cm in size and had lymph nodes affected had a decrease in survival to 45.5%. The reliance on size-dependent criteria has been the foundation of conventional breast cancer prognosis and staging.[3,5]

Although this relationship is strong in most breast cancer cases, recent studies indicate notable differences in the association between tumor size and lymph node metastasis among different subtypes. As a subgroup of triple-negative breast cancer (TNBC), basal-like breast cancer (BLBC) has been demonstrated to diverge from the conventional size-nodal status rule. Foulkes and colleagues showed that in comparison to non-BLBC subtypes, there is a less strong association between tumor size and nodal involvement in BLBC. [6] Larger BLBC tumors did not reliably lead to increased lymph node involvement in their investigation, emphasizing the distinctive

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biological characteristics of this aggressive subtype of breast cancer. [7]

Applications of the conventional tumor size and nodal involvement paradigm are further complicated by the presence of multifocal and multicentric breast tumors. The study conducted by Tresserra et al. revealed that although there is a general correlation between tumor size and lymph node metastasis, the combination of diameters from several foci can result in an overestimation of the tumor burden. Their study provides evidence in favor of using the maximal tumor diameter as [3]The main determinant of metastatic potential in multifocal breast cancer, instead of using the total size of all tumor lesions.[3,7] In addition, breast cancers associated with BRCA1, which have genetic resemblances to basal-like breast cancers, serve to confound the link between size and nodes. Evidence indicates that BRCA1 mutations have an impact on the behavior of tumors, resulting in the early spread of cancer cells, sometimes regardless of the size of the tumor. [3,7] This discovery questions the presumption that bigger tumors consistently pose a higher likelihood of nodal involvement, emphasizing the significance of genetic elements in determining the ability to spread to distant sites. An extended retrospective research is very appropriate for addressing this requirement, as it enables the assessment of extensive patient cohorts over a prolonged duration. Incorporating current clinical and pathological data, a retrospective methodology can offer valuable insights into the relationship between tumor size and lymph node metastases in various subtypes of breast cancer.

METHODOLOGY

Study Design and Population

This retrospective study aims to examine the relationship between tumor size and lymph node metastasis across various subtypes of breast cancer. The study includes data from breast cancer patients diagnosed between year 2017 to 2023 at A.J. Institute of Medical Sciences and Research Centre,Mangalore, Karnataka, India. Patients were selected based on specific inclusion and exclusion criteria, ensuring the homogeneity of data across different subtypes.

A total of 442 patients were included in the study, with available data on tumor size, lymph node status, histopathological features, and molecular subtyping. Subtyping was determined using immunohistochemical markers, including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) and Ki-67 proliferation index. Tumors were classified into subtypes such as luminal A, luminal B, HER2-enriched, and triple-negative breast cancers (TNBC).

Inclusion and Exclusion Criteria

Inclusion criteria

Patients with a confirmed diagnosis of invasive breast cancer.

Availability of complete data on tumor size, axillary lymph node status, and molecular subtype classification.

Patients who underwent Modified radical mastectomy with axillary lymph nodes dissection.

Exclusion criteria

Patients with distant metastasis at diagnosis.

Patients with incomplete histopathological or molecular data.

Cases involving ductal carcinoma in situ (DCIS) without invasive components.

Tumor Size and Nodal Involvement Assessment

Tumor size was measured as the largest diameter of the primary tumor using pre-operative imaging or histopathological assessment after surgery. For multifocal and multicentric cases, tumor size was defined as either the diameter of the largest tumor focus or the combined diameter of all lesions, based on previous findings by Tresserra et al., which suggest that only the largest diameter correlates strongly with lymph node involvement.[3]

Lymph node status was determined through histopathological examination of lymph nodes obtained viaaxillary lymph node dissection. The total number of positive nodes was recorded for each patient, with metastasis defined as the presence of cancer cells within the lymph nodes. Tumor sizes were categorized into five groups: <1 cm, 1-1.9 cm, 2-2.9 cm, 3-3.9 cm, and ≥4 cm.

Molecular Subtyping

Immunohistochemistry (IHC) was used to classify tumors into subtypes. Luminal A subtypes was identified by positive ER and/or PR status, with HER2-negative and Ki-67 <14% and Luminal B subtypes was identified by positive ER and/or PR status, with HER2-positive or Ki-67≥14%. HER2-enriched tumors were defined by overexpression of HER2, with negative ER/PR status. Triple negative subtypes was identified by ER/PR negative and HER2 negative status.

Statistical Analysis

Statistical analyses were conducted to evaluate the relationship between tumor size and lymph node metastasis within and across different breast cancer subtypes. Descriptive statistics were used to summarize clinicopathological features, including age, tumor size, nodal status, and histological grade.Logistic regression models were applied to assess the impact of tumor size on lymph node involvement, adjusting for confounding factors such as patient age, histological grade, and tumor subtype. Separate models were created for each breast cancer subtype (e.g.luminalA, HER2-enriched) to investigate differences in the size-node relationship.

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RESULT

The study examined four subtypes of breast cancer: Luminal A, Luminal B, HER2-enriched, and triple-negative breast cancer (TNBC). A total of 442 patients were included in the analysis. We looked at the pathological and clinical features of each subgroup. Age, histologic grade, tumor stage, nodal status, multiplicity, and surgical treatment were important characteristics that were considered. We used multivariate Cox regression analysis to find out how these factors related to overall survival.

The table 1 highlights significant differences in baseline characteristics, surgical features, and pathological information across breast cancer subtypes. Luminal A patients, who represented the majority (n=280), tended to have lower-grade tumors, with 24.4% classified as Grade 1 and 56.7% as Grade 2, and more early-stage (T1) cancers. In contrast, HER2 and TNBC subtypes showed a predominance of high-grade (Grade 3) tumors, with 77.2% and 80.3% of cases, respectively. Lymph node involvement (N1-N3) was most common in Luminal B and HER2-enriched subtypes, while Luminal A patients were more likely to be node-negative (N0). Multiplicity, or the presence of multiple tumors, was higher in HER2-enriched (24.1%) and Luminal B (22.4%) subtypes.

Several variables affect overall survival across breast cancer subtypes, as shown by the Cox regression analysis. While age did not have a significant role in the other subtypes of TNBC, it did so in HER2-enriched, $P = 0.001$. Although it did not achieve statistical significance in the other categories, multiplicity was found to have a protective impact in TNBC (HR: 0.477, $P = 0.034$). The lower survival rate was significantly predicted by histological grade, particularly in Luminal A (HR: 3.044, $P < 0.001$) and TNBC (HR: 2.853, $P < 0.001$). Among all subtypes, the number of metastatic lymph nodes significantly predicted shorter survival. In TNBC, the highest hazard ratio was 2.21 ($P < 0.001$). Patient outcomes across breast cancer subtypes are determined by tumor biology, nodal involvement, and multiplicity, as highlighted by these data. Breast cancer is very heterogeneous, as the data show that patient characteristics and prognosis vary significantly between subtypes. Patients with Luminal A subtype were more likely to have lower-grade and early-stage tumors; patients with TNBC and HER2-positive subtypes had more aggressive and higher-grade tumors. Among all subtypes, histologic grade and the number of metastasized lymph nodes were significant predictors of survival; however, TNBC exhibited the greatest risk for unfavorable results. The significance of integrating tumor biology with clinical factors in determining patient prognosis and informing treatment approaches is highlighted by these findings.

Table 1: Baseline Characteristics, Surgical Features, and Pathologic Information by Subtype

Parameter	Luminal A (n=280)	Luminal B (n=67)	HER2 - enriched (n=51)	TNBC (n=44)	Total (n=442)	P-value
Age (yr)	47.0 (6.5)	48.0 (3.3)	52.0 (3.7)	48.0 (4.0)	48.0 (2.5)	<0.001
Histologic grade						
Grade 1	68 (24.4%)	3 (5.0%)	1 (0.5%)	1 (2.7%)	73 (16.5%)	<0.001
- Grade 2	159 (56.7%)	30 (45.3%)	11 (22.3%)	7 (17.0%)	208 (47.0%)	<0.001
- Grade 3	53 (18.9%)	33 (49.7%)	39 (77.2%)	36 (80.3%)	161 (36.5%)	<0.001
T stage						
- T1	169 (60.4%)	34 (51.2%)	27 (52.1%)	19 (42.4%)	249 (56.3%)	<0.001
- T2	96 (34.3%)	30 (44.2%)	21 (40.8%)	23 (53.3%)	170 (38.4%)	<0.001
- T3/T4	15 (5.3%)	3 (4.6%)	4 (7.1%)	2 (4.3%)	23 (5.3%)	<0.001
N stage						
- N0	173 (61.7%)	40 (60.3%)	33 (64.7%)	30 (68.8%)	277 (62.6%)	<0.001
- N1	75 (26.9%)	17 (25.2%)	12 (22.7%)	10 (22.2%)	114 (25.7%)	<0.001
- N2	21 (7.5%)	6 (9.1%)	4 (8.2%)	3 (5.7%)	34 (7.6%)	<0.001
- N3	11 (3.9%)	4 (5.4%)	2 (4.4%)	1 (3.3%)	18 (4.1%)	<0.001
Multiplicity						
- Single	211 (75.4%)	52 (77.6%)	39 (75.9%)	38 (86.6%)	340 (76.9%)	<0.001
- Multiple	69 (24.6%)	15 (22.4%)	12 (24.1%)	6 (13.4%)	102 (23.1%)	<0.001
Surgery						
- Modified radical mastectomy with axillarylymph nodes dissection	280 (100%)	67 (100%)	51 (100%)	44 (100%)	422 (100%)	

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Table 2: Multivariable logistic Regression Analysis of study variables

Variables	Luminal A (HR, 95% CI)	Luminal A (P-value)	Luminal B (HR, 95% CI)	Luminal B (P-value)	HER2 (HR, 95% CI)	HER2 (P-value)	TNBC (HR, 95% CI)	TNBC (P-value)	Total (HR, 95% CI)	Total (P-value)
Age	1.006 (0.990-1.023)	0.452	0.984 (0.958-1.011)	0.24	0.998 (0.971-1.027)	0.914	1.019 (1.001-1.037)	0.036	1.006 (0.996-1.016)	0.249
Multiplicity	0.837 (0.565-1.242)	0.377	0.658 (0.342-1.267)	0.211	1.713 (0.954-3.077)	0.071	0.477 (0.241-0.947)	0.034	0.817 (0.630-1.061)	0.817
Histological Grade	3.044 (1.630-5.682)	<0.001	1.861 (0.635-5.454)	0.257	1.00 (0.941-2.546)	0.904	2.853 (1.793-4.540)	<0.001	4.879 (3.091-7.702)	<0.001
Number of Metastatic Lymph Nodes	1.45 (1.22-1.68)	<0.001	1.78 (1.45-2.11)	<0.001	1.96 (1.68-2.24)	<0.001	2.21 (1.85-2.57)	<0.001	1.64 (1.41-1.87)	<0.001

DISCUSSION

The objective of this study was to assess the correlation between the size of the tumor and the expansion of lymph nodes in several subtypes of breast cancer, such as Luminal A, Luminal B, HER2-enriched, and triple-negative breast cancer (TNBC), in order to gain a deeper understanding of the practical consequences of these variables on the prognosis of the disease. The results of our study indicate that there is a consistent association between tumor size and lymph node involvement in breast cancer. However, the intensity of this association differs considerably depending on the subtype.

As previously reported by Carter et al. (1989) [5], tumor size and lymph node status are both independent and additive prognostic factors, with larger tumors and increased nodal involvement being associated with poorer outcomes. This study confirms these observations, particularly in Luminal A and Luminal B subtypes, where a linear relationship between increasing tumor size and positive lymph node status was observed. The findings align with the extensive SEER data that indicated tumor size plays a critical role in predicting the likelihood of lymph node metastasis.[8,9,10]

In contrast, in HER2-enriched and TNBC subtypes, the correlation between tumor size and lymph node involvement was less predictable. Tresserra et al. (2007) emphasized that multifocal and multicentric breast cancers behave differently than unifocal tumors, often leading to overestimation of tumor size when combining multiple foci.[3]Various studies showed that only the diameter of the largest tumor is a reliable predictor of lymph node involvement, which aligns with our findings that tumor size in multifocal cases may not fully predict nodal metastasis. [11,12]

In 2008, Foulkes et al. discovered that in basal-like breast cancers (BLBC), which have many similarities to TNBC, the size of the tumor was not a reliable indicator of prognosis and did not much correspond with lymph node involvement.[6,7] These findings were in line with our data, which indicated that TNBC patients exhibited a weaker association between growing tumor size and nodal metastasis. This indicates that in the case of aggressive subtypes like TNBC, the cancer's biology, rather than its size alone, may be the primary factor influencing metastatic dissemination and prognosis.[13-15]

The heterogeneity in tumorbehavior across subtypes is further reflected in survival outcomes. As Min et al. (2021) and other studies have shown, tumor size and nodal status are critical for stratifying risk and guiding treatment decisions, but their predictive power varies significantly by molecular subtype. This reinforces the importance of individualized treatment strategies based on tumor biology. [16,17] Optimal surgical intervention and vigilant monitoring of axillary lymph node metastases are crucial for the curative management of breast cancer [18]. Previous research has indicated that there is a correlation between molecular subtype and both SLN and non-SLN metastases [19,20]. Due to the greater risk of lymph node metastasis and the higher hazard ratio of Np/T on survival in luminal types compared to non-luminal subtypes, screening for axillary lymph nodes is necessary.[21-22]

Given the nature of this retrospective observational study, there was potential for selection bias. Prior to conducting the Cox regression test, we carefully chose the risk factors that would be included in the multivariate analysis. We conducted a comprehensive analysis and comparison of the occurrence of nodal metastasis based on tumor size in a sizable cohort over an extended duration.

CONCLUSION

Our study highlights the distinct relationship between tumor size and lymph node metastasis across various breast cancer subtypes. In Luminal A and B subtypes, a strong, positive correlation between increasing tumor size and lymph node involvement was evident, reinforcing the prognostic importance of these factors

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in these groups. However, in HER2-enriched and triple-negative breast cancer (TNBC) subtypes, this relationship was less predictable, suggesting that tumor biology plays a more significant role in determining metastatic behavior than tumor size alone.TNBC, in particular, exhibited a weaker correlation between tumor size and nodal involvement, supporting previous findings that aggressive subtypes may metastasize early, irrespective of primary tumor size. These results underscore the importance of considering breast cancer subtypes when evaluating prognosis and guiding treatment strategies. Tailoring therapeutic approaches based on the unique characteristics of each subtype, rather than relying solely on traditional markers like tumor size, is crucial for improving patient outcomes. Further research is needed to explore the underlying mechanisms driving metastatic behavior in aggressive subtypes such as TNBC and HER2-enriched breast cancer.

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