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Histopathological Study of Tumor Budding as Prognostic Marker in Invasive Breast Carcinoma

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Abstract: ***Background: Tumor budding (TB), defined as single cells or small clusters of up to five tumor cells at the invasive front, is an emerging histopathological marker associated with aggressive behavior in various cancers. Its prognostic significance in invasive breast carcinoma (IBC) remains underexplored. This study evaluates TB as a prognostic marker in IBC and its correlation with clinicopathological parameters. Methods: A retrospective analysis was conducted on 100 mastectomy specimens of histopathologically confirmed IBC, no special type (NST), from January 2022 to June 2023. Tumor budding was assessed using hematoxylin and eosin (H&E) stained slides, graded per the International Tumor Budding Consensus Conference (ITBCC) criteria. Associations with tumor size, lymph node metastasis, lymphovascular invasion (LVI), perineural invasion (PNI), hormone receptor status, and survival outcomes were analyzed using Chi-square tests and Kaplan-Meier survival analysis. Results: High-grade TB was observed in 38% of cases and was significantly associated with larger tumor size (p=0.012), lymph node metastasis (p<0.001), LVI (p=0.003), and worse overall survival (p<0.001). Hormone receptor-positive tumors showed a higher incidence of high-grade TB (p=0.008). Multivariate analysis confirmed TB as an independent prognostic factor (HR 3.85, p<0.001). Conclusion: Tumor budding is a significant and independent prognostic marker in IBC, correlating with adverse clinicopathological features and poorer survival. Its inclusion in routine histopathological reporting could enhance risk stratification and guide therapeutic decisions.***

Keywords: Tumor budding, invasive breast carcinoma, prognostic marker, epithelial-mesenchymal transition, histopathology

1. Introduction

Breast cancer remains a leading cause of morbidity and mortality among women globally, with an estimated 2.3 million new cases in 2022 (1). Invasive breast carcinoma (IBC), particularly of no special type (NST), constitutes the majority of cases, characterized by significant histological and molecular heterogeneity (2). Conventional prognostic markers, including tumor size, lymph node status, histological grade, and hormone receptor status, guide clinical management but may not fully capture the metastatic potential of tumors (3). Tumor budding (TB), defined as single tumor cells or clusters of up to five cells at the invasive front, has emerged as a promising histopathological marker in various cancers, including colorectal and gastric carcinomas (4; 5). TB is thought to represent epithelial-mesenchymal transition (EMT), a critical step in tumor invasion and metastasis (6).

In breast cancer, TB has been associated with adverse clinicopathological features, such as lymph node metastasis and lymphovascular invasion (LVI), but its prognostic role remains understudied (7; 8). The International Tumor Budding Consensus Conference (ITBCC) has standardized TB assessment in colorectal cancer, providing a framework that can be adapted for breast cancer (9). This study aims to evaluate TB as a prognostic marker in IBC and its correlation with established clinicopathological parameters and survival outcomes in a cohort of 100 patients.

2. Materials and Methods

2.1 Study Design and Population

This retrospective study included 100 mastectomy specimens from female patients diagnosed with IBC-NST at department of pathology, Acharya Shri Chander College of Medical Sciences, a tertiary care medical center in India between January 2022 and June 2023. Exclusion criteria included patients who received neoadjuvant chemotherapy, had distant metastases at diagnosis, or had incomplete clinical data. Clinical data, including age, tumor size, lymph node status, and hormone receptor status, were retrieved from medical records.

2.2 Histopathological Assessment

H&E-stained slides were prepared from formalin-fixed, paraffin-embedded tissue blocks. Tumor budding was assessed at the invasive front using a 20x objective (0.785 mm² field) as per ITBCC criteria (9). TB was graded as low (0–4 buds), intermediate (5–9 buds), or high (10 buds) based on the highest budding count in a single field. Two pathologists independently evaluated TB, with discrepancies resolved by consensus. Tumor grading was performed using the Nottingham modified Bloom-Richardson (BR) system, assessing tubule formation, nuclear pleomorphism, and mitotic count (10). Lymphovascular invasion (LVI) and perineural invasion (PNI) were evaluated on H&E slides. Hormone receptor status (estrogen receptor [ER], progesterone receptor [PR], and HER2/neu) was assessed using immunohistochemistry (IHC) per the Allred score and ASCO 2016 guide- lines (11).

2.3 Statistical Analysis

Associations between TB and clinicopathological parameters were analyzed using the Chi-square test. Survival outcomes were evaluated using Kaplan-Meier survival analysis and log-rank tests. Multivariate analysis was performed using Cox proportional hazards regression to identify independent prognostic factors. A p-value 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS version 25.0.

3. Results

3.1 Patient Characteristics

The study cohort comprised 100 female patients with a median age of 53 years (range 28–78 years). Invasive ductal carcinoma (NST) accounted for 96% of cases. Tumor characteristics and TB grades are summarized in Table 1.

Table 1: Patient and Tumor Characteristics (n=100)

Parameter	Category	n (%)
Age	50 years	42 (42%)
	>50 years	58 (58%)
Tumor Size	2 cm	25 (25%)
	2–5 cm	55 (55%)
	>5 cm	20 (20%)
Lymph Node Status	Negative (N0)	48 (48%)
	Positive (N1–N3)	52 (52%)
Histological Grade	Grade I	20 (20%)
	Grade II	50 (50%)
	Grade III	30 (30%)
LVI	Present	40 (40%)
	Absent	60 (60%)
PNI	Present	15 (15%)
	Absent	85 (85%)
ER Status	Positive	65 (65%)
	Negative	35 (35%)
PR Status	Positive	60 (60%)
	Negative	40 (40%)
HER2/neu	Positive	30 (30%)
	Negative	70 (70%)
Tumor Budding	Low (0–4 buds)	38 (38%)
	Intermediate (5–9 buds)	24 (24%)
	High (10 buds)	38 (38%)

3.2 Tumor Budding and Clinicopathological Correlations

High-grade TB was observed in 38 cases (38%) and was significantly associated with larger tumor size (p=0.012), lymph node metastasis (p<0.001), and LVI (p=0.003) (Table 2). A strong correlation was noted with hormone receptor-positive tumors (ER: p=0.008; PR: p=0.015), but no significant association was found with HER2/neu status (p=0.232) or PNI (p=0.762) (Table 3).

Table 2: Association of Tumor Budding with Clinicopathological Parameters

Parameter	Low/Intermediate TB (n=62)	High TB (n=38)	p-value
Tumor Size			
2 cm	20 (32.3%)	5 (13.2%)	0.012
2–5 cm	35 (56.5%)	20 (52.6%)	
>5 cm	7 (11.3%)	13 (34.2%)	
Lymph Node Status			
Negative	38 (61.3%)	10 (26.3%)	<0.001
Positive	24 (38.7%)	28 (73.7%)	
LVI			
Present	18 (29.0%)	22 (57.9%)	0.003
Absent	44 (71.0%)	16 (42.1%)	
PNI			
Present	9 (14.5%)	6 (15.8%)	0.762
Absent	53 (85.5%)	32 (84.2%)	

Table 3: Association of Tumor Budding with Hormone Receptor Status

Receptor	Low/Intermediate TB (n=62)	High TB (n=38)	p-value
ER			
Positive	34 (54.8%)	31 (81.6%)	0.008
Negative	28 (45.2%)	7 (18.4%)	
PR			
Positive	32 (51.6%)	28 (73.7%)	0.015
Negative	30 (48.4%)	10 (26.3%)	
HER2/neu			
Positive	16 (25.8%)	14 (36.8%)	0.232
Negative	46 (74.2%)	24 63.2%)	

3.3 Survival Analysis

Kaplan-Meier analysis revealed that high-grade TB was associated with significantly worse overall survival (OS) (p<0.001) (Table 4). The 3-year OS rate was 85% for low/intermediate TB versus 60% for high-grade TB. Multivariate Cox regression analysis identified high-grade TB (HR 3.85, 95% CI 2.10–7.06, p<0.001), lymph node metastasis (HR 2.52, 95% CI 1.45–4.38, p=0.001), and tumor size (HR 2.15, 95% CI 1.20–3.86, p=0.010) as independent prognostic factors.

Table 4: Survival Analysis and Multivariate Cox Regression

Parameter	HR	95% CI	p-value
Tumor Budding Low/Intermediate	Ref		
High	3.85	2.10–7.06	<0.001
Tumor Size			
2 cm	Ref		
>2 cm	2.15	1.20–3.86	0.01
Negative	Ref		
Positive	2.52	1.45–4.38	0.001
LVI			
Absent	Ref		
Present	1.78	0.98–3.24	0.058

4. Discussion

This study confirms that high-grade TB is a significant prognostic marker in IBC, associated with larger tumor size, lymph node metastasis, LVI, and worse OS, consistent with prior studies (7; 12; 13). The significant correlation

with hormone receptor-positive tumors (ER/PR) contrasts with some reports suggesting lower TB in triple-negative breast cancer (8). This discrepancy may reflect differences in TB assessment methods or cohort characteristics. The ITBCC scoring system, adapted from colorectal cancer, proved re- liable in our study, with good inter-observer reproducibility, supporting its potential for standardization in breast cancer (9).

TB is hypothesized to represent EMT, characterized by loss of E-cadherin and gain of vimentin, facilitating tumor invasion (6; 14). Our findings align with this, as high-grade TB correlated with features of aggressive tumor behavior. The lack of association with PNI suggests that TB may primarily reflect lymphatic dissemination rather than neural invasion (15). The strong prognostic value of TB in multivariate analysis underscores its independence from traditional markers like tumor size and lymph node status (7).

Limitations include the retrospective design, single-center setting, and lack of long- term survival data. The absence of immunohistochemical markers to enhance TB detection may have underestimated budding in some cases (16). Future studies should validate these findings in larger, multicenter cohorts and explore molecular mechanisms of TB in breast cancer, potentially integrating TB into routine histopathological reporting (17).

5. Conclusion

Tumor budding is a robust and independent prognostic marker in IBC, associated with adverse clinicopathological features and poorer survival. Its assessment is feasible us- ing H&E slides and the ITBCC scoring system, making it a cost-effective tool for risk stratification. Further research is needed to standardize TB evaluation and elucidate its molecular underpinnings in breast cancer.

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Conflicts of Interest
The authors declare no conflicts of interest.

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