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Evaluation of clinicopathologic significance of tumor budding in breast carcinoma

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Abstract
Background: Tumor budding is defined as small cluster of tumor cells located at the invasive edge of tumor and was assumed to be linked with epithelial-mesenchymal transition (EMT), which is an early event in metastasis.
Objective: This study aimed to evaluate clinicopathologic significance of tumor budding in carcinoma breast and to correlate with other molecular subtypes of breast cancer.
Method: We investigated 107 resected specimens of primary breast carcinoma. The number of foci (tumor budding) was counted in H&E slides under 100x magnification.
Result: Patient was categorized as low (0-10 buds) and high (≥11 buds) tumor budding group based on the count of foci. High tumor budding shared significant positive correlation with lymph nodal status and lymphatic invasion (LVI) and does not correlate with tumor grade and tumor size.
Conclusion: In conclusion, tumor budding in carcinoma breast is associated with undesirable pathologic factors, such as positive nodal status and lymphovascular invasion and may have supplementary independent prognostication value. In the future, standardized quantification criteria for tumor budding may further aid in its implementation as a prognostic marker.

Keywords: Tumor budding, breast cancer, nodal status, lymphatic invasion

Introduction
Tumor budding is a pathologic event linked with many cancers. It consists of a small group of cells, usually up to 5 cells, which had detached from the tumor bulk. Cancers in which tumor budding has been observed and studied include head and neck, lung, gastric and esophageal, colorectal and also breast cancers [1]. Tumor buds may be seen in areas near the margins of tumors at the invasive tumor front, called peritumoral buds, or inside the tumor mass and are called intratumoral buds [2]. In breast cancer (BC) and other tumors, high counts of tumor buds are associated with lymphovascular invasion (LVI) and/or lymph node metastasis [3]. Additionally, high counts of tumor buds are related with shorter overall and cancer-specific survival in BC [4] and in other tumor types as well [3]. This association of lymphovascular invasion and tumor budding led to the postulation that tumorbuds are involved in the early metastatic process by undergoing epithelial-mesenchymal transition (EMT) [5]. It is well-known that tumor cells undergoing EMT are more invasive and prone to metastasize that can lead to poor overall survival in cancer patients [6]. Inhibiting tumor cells involved in the early metastatic process would be of immense clinical value since metastatic disease remains the major cause of deaths with around 30% of BC patients developed metastasis [7]. Thus better understanding of the metastatic process is needed in order to invent novel targeted approaches for highly aggressive and invasive cancer. If tumor buds are involved in the early metastatic process, then it would be advantageous to determine whether and how they can be uniquely targeted.

Pathophysiologic Significance of Tumor Budding
Tumor budding from a pathophysiologic point of view, has been explained as a sign of cancer cell motility and as a first step in the process of metastatis [1] and hence assumed to represent cancer cells caught in the process of invasion. The process of metastatis begins with detachment of cells from the tumor bulk, infiltration through contiguous tissues into small blood vessels, and travel through the circulation to remote locations where they extravasate and may finally establish colonies of metastatic disease.

Paramount in metastasis is the process of epithelial to mesenchymal transition (EMT) and the reverse process of mesenchymal to epithelial transition (MET) [4]. These processes, collectively referred to as epithelial mesenchymal plasticity, are element of normal embryogenesis and physiologic wound healing, and have been usurped by cancer. During EMT, detached cancer cells partially or completely lose their epithelial characteristics, detach from adjacent epithelial cells and acquire mesenchymal characteristics, including expression of mesenchyme-associated proteins, to become motile. In metastatic sites, the reverse process occurs when arriving cells, facilitated by cues in their new microenvironment, regain epithelial properties and re-establish connections with adjacent cells [5].

Materials and Methods

This was a retrospective observational study conducted at Dhanalakshmi Srinivasan Medical College and was approved by the Institutional Ethical Committee. Whole tissue sections from 107 surgical resected specimens (SRS) of primary breast carcinoma were analyzed on H&E slide. The total count of tumor buds (TB) in ten high-power fields (HPF) was calculated. A bud was defined as a single tumor cell or a cluster of up to 5 tumor cells. The TNM classification was taken from the pathology reports, and the clinical data were obtained from the database of Medical record department, Dhanalakshmi srinivasan medical college. Estrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor 2 (HER2) and Ki-67 Immunohistochemical analysis were from immuno- histochemistry reports.

Evaluation of tumor budding

Tumor budding was defined as tiny cluster (1-5) tumor cells at the invasive front. The number of tumor budding was counted in H&E section. Tumors were considered as high tumor budding if the average number of tumor buds in 10 HPF was ≥10 buds. In contrast, tumors were considered to have low tumor budding if the average number of buds in 10 HPF was <10 buds. Chi Square test was used to calculate significant differences between categorical variables. A p value<0.05 was considered statistically significant.

Results

The clinico-pathological features for the sample cohort are summarized in Table 1.

Table 1: Distribution of clinico-pathological parameters of study sample.

Feature	Observation	Frequency N (%)
Age	Median (min, max)	53.7(32,80)
ER	Positive	61(57)
	Negative	46(43)
PR	Positive	58(54.2)
	Negative	49(45.8)
Her2	Positive	36(33.6)
	Negative	71(66.4)
Ki67	High (≥14%)	45(42.1)
	Low (<14%)	62(57.9)
Grade	G1	26(24.3)
	G2	62(57.9)
	G3	19(17.8)
pT	T1	5(4.7)
	T2	49(45.8)
	T3	37(34.6)
	T4	16(14.9)
pN	pN0	32(29.9)
	>pN0	75(70.1)
Molecular subtypes	Luminal A	42(39.3)
	Luminal B	19(17.7)
	Her 2 +	18(16.8)
	Basal like	28(26.2)
Lymphatic invasion	Yes	43(40.2)
	No	64(59.8)

Table 2 showed the correlation of tumor budding with other variables. 21 (19.6%) cases tumor budding density was lower than 10 and in 86 (80.4%) cases there were 10 or more tumor budding.

Table 2: Summary of significant results and tumor budding correlation

Features		TB n (%)		P value
		Low (< 10)	High (≥10)	
		21 (19.6)	86 (80.4)	
pN	Positive	11 (14.7)	64 (85.3)	< 0.05
	Negative	10 (31.3)	22 (68.7)	
Lymphatic invasion	Positive	4 (9.3)	39 (90.7)	< 0.05
	Negative	17 (26.6)	47 (73.4)	
Grading	G1	5 (26.3)	14 (73.7)	> 0.05
	G2	5 (19.2)	21 (80.8)	
	G3	11 (17.7)	51 (82.3)	
ER	Positive	9 (14.8)	52 (85.2)	> 0.05
	Negative	12 (26.1)	34 (73.9)	
PR	Positive	9 (15.5)	52 (84.5)	> 0.05
	Negative	12 (24.5)	34 (75.5)	
Her-2	Positive	2 (5.6)	34 (94.4)	< 0.05
	Negative	19 (26.8)	52 (73.2)	
Ki-67	Low	12 (26.6)	33 (73.4)	> 0.05
	High	9 (14.5)	53 (85.5)	
Subtypes	A	9 (21.4)	33 (78.6)	> 0.05
	B	1 (5.3)	18 (94.7)	
	C	2 (11.1)	16 (88.9)	
	D	9 (32.1)	19 (67.9)	

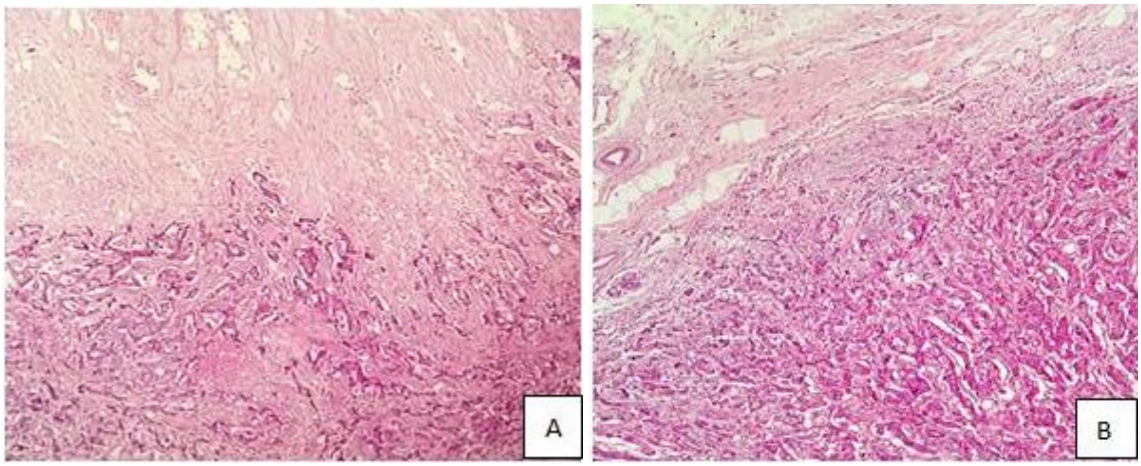

Fig 1: (A) Low grade (H & E, x 100), (B) and high grade tumor budding density (H & E, x 100)

Discussion

In the present retrospective study, we used a semi quantitative histologic scoring system to categorize 107 surgically resected, primary invasive BC. Study done by Liang *et al*. [8] and salhia *et al*. [9] demonstrated that high-grade budding was significantly related with the presence of LVI, larger tumor size, and worse clinical outcome. The present study also confirmed a significant association with LVI (p =<0.05).

Laedrach *et al*. [10] observed ER and Her2 status showed consistent expression between tumor buds and the main tumor mass. In the present study we observed consistent relation between Her 2 status and tumor budding. No significant association was observed between tumor buds and ER, PR and Ki 67 status and also with different molecular subtypes. The difference may be due to tumor heterogeneity [11]. A large cohort involving long-term follow up and survival data is needed to determine whether loss of ER and PR expression in tumor buds represents a change in tumor biology towards a more aggressive tumor phenotype. Although long-term follow-up data was not available in this study, the association of tumor budding with positive lymph nodes suggests that tumor budding is a poor prognostic marker of BC.

Conclusion

In conclusion, we identified that tumor buds associated with poor prognosis of BC. Inclusion of tumor budding into the histopathology report requires further standardization to define tumor buds and framing scoring parameters and cut-off criteria based on sensitivity and specificity. As per the data, tumor budding associated with an aggressive tumor phenotype and may enhance metastatic potential. The current study data revealed the utility of tumor budding in BC to potentially enhance prognostication and warrants further investigation.

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