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Original Research Article

Tumor budding in invasive breast carcinoma: an emerging prognostic factor

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ABSTRACT

Background: Tumor budding refers to single or small cluster of tumor cells detached from the main tumor mass in histological sections. In colon cancer high tumor budding is associated with worse prognosis and correlates with metastatic lymph nodes. We studied tumor budding in modified radical mastectomy specimens to evaluate its utility as a prognostic factor by correlating high tumor budding score with known prognostic markers of breast cancer like axillary lymph nodal metastasis, clinical staging, tumor size, lymphovascular invasion, hormonal status and pathological grading. Aim was to evaluate tumor budding in invasive breast carcinoma and to describe clinical features and histopathological spectrum of Invasive Breast Carcinoma with/without lymph node metastasis on H&E slides. Secondly, to find association between grades of tumor budding and various clinical, gross, microscopic and immunohistochemical variables.
Methods: The present study is a cross sectional study of 70 modified radical mastectomy specimens from June 2018 to Dec 2022. Along with tumor budding various prognostic parameters like hormonal markers, pathological grading and clinical grading were evaluated. Immunohistochemical marker Pancytokeratin was utilized for counting the tumor buds, wherever necessary. Statistical Analysis: Chi Square test was utilized to study significant differences between variables, $p<0.05$ was considered statistically significant.
Results: A high tumor budding score (≥4/HPF) had significant association with axillary lymph node involvement and clinical staging.
Conclusions: In our study we detected the association of high tumor budding, PTB in invasive breast carcinoma with axillary lymph node involvement and clinical staging. Hence our results highlight the importance of tumor budding as a prognostic factor and submit that this histological feature could be included in diagnostic protocols just as in carcinoma of the colon.

Keywords: Breast carcinoma, Tumor budding, Prognosis, Lymphovascular invasion, Hormonal status

INTRODUCTION

Breast carcinoma is a major health concern worldwide. It is globally the leading cause of death in women and ranks second in cancer related mortality.[1] Incidence rates of breast cancer in most regions of the world, especially in developing nations are increasing.[2] A woman who lives to age 90 has one in eight chances of developing breast cancer.[1] The mean age of occurrence is 42 years worldwide and in India it is 52-53 years.[3-4] Tumor budding refers to single or small clusters of tumor cells detached from the main tumor mass. A bud is defined as a single tumor cell or a cluster of up to 5 tumor cells.[5-12] Tumor budding is a sign of cancer cell motility and is a

first step in metastatic process. The metastatic process begins with detachment of cells from the tumor bulk, infiltration through surrounding tissues into small blood vessels and metastases to distant tissues. Paramount in metastasis is the process of epithelial to mesenchymal transition (EMT).[13] Epithelial mesenchymal transition is multistep dynamic cellular phenomenon in which epithelial cells lose their cell-cell adhesion resulting in migratory and invasive traits that are typical of mesenchymal cells. EMT involves loss of epithelial marker E-Cadherin and increase in vimentin, N-Cadherin, actin and fibronectin.[13] Tumor buds may be observed in areas near the margins of tumors at the invasive tumor front and are called peritumoral buds or inside the tumor mass and are thus called intratumoral buds.[13] Tumor budding can be identified on hematoxylin and eosin sections or by immunohistochemical staining. Tumor budding is measured in invasive tumor front also called 'hot spots' by calculating an average of tumor bud numbers seen in ten high power fields (HPF). Morphological investigations of the invasive front in colorectal carcinomas (CRC) have indicated the advent of tumor budding, which is the detachment of tumor cells into single cells or clusters of up to five cells.[14] Tumor budding is detected under high magnification and should not be confused with tumor border configuration, which is more visible under low magnification. Tumor budding is a biological mechanism that allows invasive cells to travel through peri-tumoral connective tissue, elude the host's defence mechanisms, and enter lymphatic and blood arteries, resulting in local and distant metastases.[14] Tumor budding also acts as a predictive marker for treatment with specific anticancer regimes. Tumor budding is best described as a histologic pattern associated with poor prognosis in early-stage colorectal adenocarcinoma and a predictor of nodal metastasis in T1 colorectal adenocarcinoma.[15-16] Some of the associations were also found in head and neck carcinoma, gastrointestinal carcinoma and pancreatic cancer.[17-18] Tumor budding in breast carcinoma is associated with other adverse pathologic factors such as age, tumor size, tumor grade and lymphovascular invasion.[19-20] Therefore, the present study aimed to examine the tumor budding in invasive ductal breast carcinoma (NOS).

METHODS

This cross-sectional analytical study was done on all the specimens of breast cancer received at tertiary care hospital of north India. This study included modified radical mastectomy, breast conserving surgery and simple mastectomy from June 2018 to December 2022, a minimum of 70 cases will be studied meeting the inclusion criteria. Cases with sufficient clinical data which include clinical history, history of previous chemoradiotherapy, duration of disease, ultrasonography and mammography findings, fine needle aspiration findings, any evidence of metastases or recurrence of disease are also included. Tumor budding was counted as per the procedure proposed by the (intra-tumoral bud count) ITBC 2016 for reporting tumor budding in breast cancer. Peripheral tumor budding are assessed in one hotspot (in a field measuring) at the invasive front and budding category are based on absolute bud count per HPF, by Olympus (MODEL U-MD0B3). High tumor budding equated to absolute bud scores ≥4 tumor buds per HPF, by Olympus (MODEL U-MD0B3) Low tumor budding equated to absolute bud score <4 tumor buds per HPF, by Olympus (MODEL U-MD0B3).

Salient histological findings such as grade, stage, nodal involvement are recorded as per the format attached. IHC staining for markers including ER, PR and Her2 Neu are carried out by standardized method of antigen retrieval by EnVision FLEX target retriever and staining by recommended IHC protocol on poly-L-lysine coated slides from suitable blocks.

RESULTS

A total of 70 participants were included, out of which 25 (62.5%) belong to clinical stage III and found to have significant association with ≥4 tumor budding score.

Table 1: Clinicopathological and statistical correlation of high tumor budding with various parameters.

Clinicopathological parameter	Low tumor budding (<4/HPF), N (%)	High tumor budding (≥4/HPF), N (%)	Remarks
Age (in years)	30 (30)	40 (35)	Not significant
Clinical stage III	28 (26)	42 (62)	Significant
Histological grade	14 (46.7)	23 (57.5)	Not significant
LVI	19 (60)	26 (65)	Not significant
DCIS	17 (56)	27 (68)	Not significant
Axillary lymph node	8 (27)	27 (68)	Significant
ER	18 (60)	30 (75)	Not significant
PR	18 (60)	28 (70)	Not significant
Her2 neu	7 (18)	9 (30)	Not significant

In our study, axillary lymph node involvement was seen in 35 (67.5%) patients and was found to have significant association with high tumor budding score. Present study also highlighted the strong clinicopathological and statistical association between the clinical staging (stage III) with high tumor budding score. 42 patients (62%) had high tumor budding score with p>0.002.

Table 2: Association of tumor budding score with clinical stage.

Clinical stage	<4		≥ 4		P value
	N	%	N	%	
Stage I	7	23.3	1	2.5	0.002
Stage II	15	50.0	14	35.0	
Stage III	8	26.7	25	62.5	
Total	30	100	40	100.0	

Table 3: Association of tumor budding with axillary lymph node involvement.

Lymph node status	<4		≥ 4		P value
	N	%	N	%	
Negative	22	73.3	13	32.5	0.002
Positive	8	26.7	27	67.5	
Total	30	100.0	40	100.0	

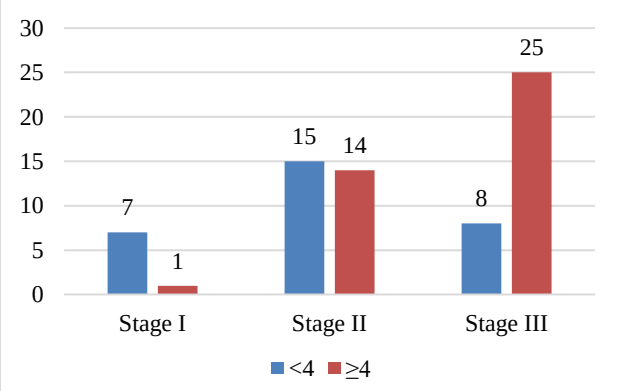

Figure 1: Association of tumor budding score with clinical stage.

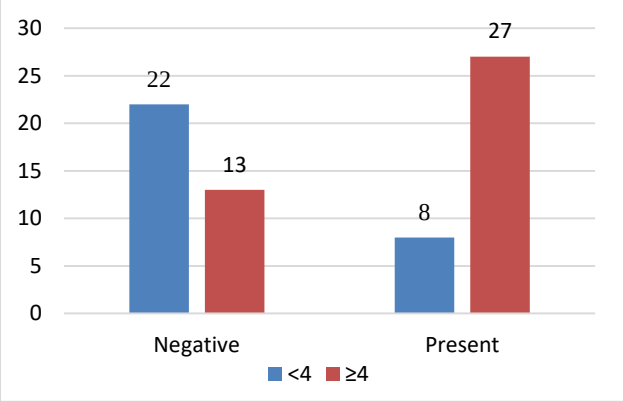

Figure 2: Association of tumor budding with axillary lymph node involvement.

Various parameters like age, quadrant, ductal carcinoma in situ, histological grade, molecular subtypes, lympho-vascular invasion, perineural invasion, pathological staging and associated features like fibroadenoma, medullary like features, sclerosing adenosis, hormonal receptor status like ER, PR, Her2neu were studied. But no significant statistical correlation was found. However, all these parameters have strong clinicopathological correlation with high tumor budding score.

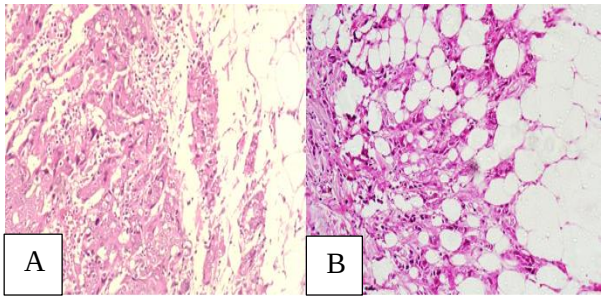

Figure 3: High peripheral tumor budding (H&E staining); (A) 100X, (B) 400 X.

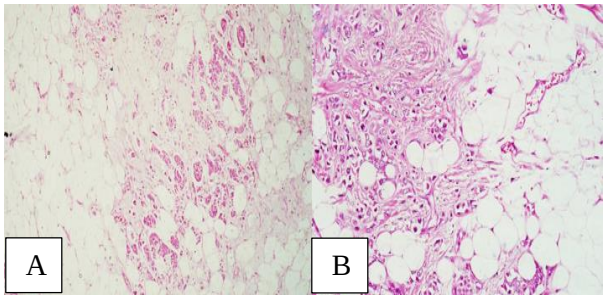

Figure 4: High peripheral tumor budding (H&E staining); (A) 100X, (B) 400 X.

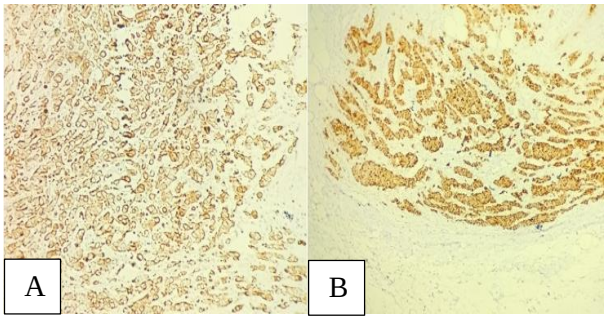

Figure 5 (A and B): Tumor buds using IHC marker (Pancytokeratin, 100X).

Statistically significant association was found between clinical stage and tumor budding score. Clinical stage III was found to be more among ≥4 budding score patients. Statistically significant association was found between lymph node status and tumor budding score. Positive lymph node was found to be statistically high among patients ≥4 tumor budding score.

DISCUSSION

The outcomes for breast cancer vary greatly depending on the patient's age, cancer type, extent of disease, lymph node invasion and immunohistochemical markers status of the tumor. The present study was a hospital-based, cross sectional observational study conducted amongst patients of breast carcinoma presented at tertiary hospital in northern India. The study aimed at Study of Tumor Budding in Breast Carcinoma. By following the consecutive sampling method, a total of 70 study participants were included. Out of which, 67.5% patients had positive axillary lymph node involvement along with strong statistical and clinicopathological correlation with high tumor budding score. Strong clinicopathological and statistical association between the clinical staging (stage III) with high tumor budding score. 42 patients (62%) had high tumor budding score with p>0.002 is highlighted by present study. Tumor budding is an emerging prognostic factor in invasive breast carcinoma. More extensive studies are still in progress. Due to the inconsistent quantification standards of tumor budding in breast carcinoma, different studies show different clinicopathological characteristics.[22-36]

Some study showed the association between tumor budding with lymphovascular invasion.[22,23] Only two studies showed correlation between tumor size and high tumor budding score.[22-24] Only one study showed correlation between high tumor budding score with ER and Her2.[24] But our present study showed no correlation. Present study included the participants from armed forces from Northern India with sample size of patients of 70. More pathological correlation between the tumor budding, clinical stage and axillary lymph node involvement can be studied on wide population from all over India. More sample size is required to study the correlation of tumor budding with more AJCC Prognostic stage group. There is need for a standardized method for assessment of tumor budding at invasive front. Tumor budding was counted as per the intra tumoral bud count (ITBC-2016) for reporting tumor budding in breast cancer. Our study highlights the strong statistical and pathological correlation between tumor budding and clinical staging and lymph node involvement. Present study is a step head as compared to previous study. More research work is going on between the assessment of variable variables. By evaluating the tumor budding as High tumor bud (>4/HPF) or low tumor bud (<4/HPF), it will help to develop novel targeted therapies. Better study of tumor budding would result in deeper understanding of metastatic process.

CONCLUSION

Our results support the correlation between high tumor budding score with clinical stage and axillary lymph node involvement.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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