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# Tumor Budding: A Novel Prognostic Marker in Breast Carcinoma with Correlation of Histopathological and Immunohistochemical Parameters

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## Abstract

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**Introduction** Breast cancer is a highly heterogenous tumor with different subtypes showing varying prognosis. Tumor budding is an unfavorable histological feature of many epithelial cancers. The purpose of this study is to analyze the association between tumor bud density with various histological and immunohistochemical characteristics and to explore its prognostic role in breast carcinoma.

**Materials and Methods** A retrospective analysis was performed on 100 patients of breast cancer diagnosed in our institute from January to December 2017. Hematoxylin and eosin (H&E) stained slides from tumors and immunohistochemical slides were reviewed independently by two pathologists, and clinical data were acquired from computerized records. Patients on neoadjuvant chemotherapy were excluded from the study.

**Results** The study comprised 100 patients of invasive breast carcinoma. The median age was 52 years, and 96% were invasive ductal carcinoma. The median follow-up was 34 months. High tumor bud density was substantially correlated with primary tumor staging (T3, T4; 73% [11/15] cases) and lymph node staging (N2, N3; 68% [13/19] cases) with *p*-values of 0.017 and 0.023, respectively. Systemic metastasis (85% [6/7] cases) was significantly associated with high tumor bud density ($p = 0.025$) but lymphovascular invasion (LVI) and perineural invasion (PNI) were not significantly associated with tumor bud density ($p = 0.762$ and 0.862, respectively). Patients with N2 nodal stage had low event-free survival rate than N0/N1 nodal stage irrespective of tumor bud status. Grade 3 tumors with high tumor bud density had worse event-free survival than any other grades. There was no association of tumor bud density with tumor staging, necrosis, PNI, LVI, estrogen receptor (ER), progesterone receptor (PR) and *Her2/neu*, and event-free survival.

**Conclusion** Strong relationships have been found between tumor bud density and poor prognostic variables such as primary tumor staging and lymph node staging. These results provide credence to the idea that tumor bud density can be an assessable

**Keywords**

- breast carcinoma
- event-free survival
- *Her2/neu*
- hormone receptors
- tumor bud

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prognostic feature that should be taken into account while reporting breast cancer cases. Tumor bud density evaluation has to be standardized nevertheless if it is to be widely adopted.

## Introduction

Breast carcinoma is the most common cancer in women, causing significant mortality worldwide. The International Agency for Research on Cancer (IARC) estimated approximately 685,000 deaths from this cancer and also predicted that by 2040 the breast cancer burden will increase to more than 3 million new cases per year (an increase of 40%) and more than 1 million deaths per year (an increase of 50%). With such a great prevalence, it is important to study its histological features, which may have prognostic or therapeutic impact. Tumor budding is one such assessable histological feature.[1] In general, tumor budding is defined as isolated or small cluster of tumor cells with ≤5 cells mainly seen in the most invasive front of tumor.[2] It was first described by Imai in gastric cancer.[3] Breast cancer is a highly heterogenous tumor having different morphological subtypes and with varying prognosis.[4] Invasion and early metastases are crucial indicators of poor prognosis in breast carcinoma. Furthermore, current pathological features, such as TNM (*t*umor size, *n*ode involvement, and *m*etastasis status) staging, tumor differentiation, and vascular involvement cannot accurately describe the biological behavior of early metastases in breast carcinoma. Hence to predict metastases and assess the prognosis, alternative histological parameters are necessary. Tumor budding is involved in the initial process of metastasis and it is highly associated with epithelial mesenchymal transition (EMT)/mesenchymal epithelial transition (MET). Tumor budding has been studied in various cancers like colorectal carcinoma, gastric carcinoma, lung carcinoma, and breast carcinoma.[5] In this study, we evaluated the significance of tumor budding and its association with various histological and immunohistochemical (IHC) parameters.

## Materials and Methods

Stained hematoxylin and eosin (H&E) slides of 100 cases of breast carcinoma diagnosed in our institute from January to December 2017 over the period of 1 year were analyzed retrospectively. Clinical parameters were retrieved from electronic records, and H&E slides from tumor sampled from breast conservation surgery/modified radical mastectomy specimens were examined independently by two pathologists. Patients who had neoadjuvant chemotherapy or hormonal therapy were excluded from the study.

All the slides were reviewed to assess the morphological tumor subtype and tumor grade. Other histological parameters like lymphovascular invasion (LVI), perineural invasion (PNI), and lymph node status were also evaluated. Tumor buds, either single cell or clusters with ≤5 cells were first identified under low power (10x) at the invasive front of the tumor. The morphological characteristics of the tumor bud were analyzed under high power (40x) and was compared with the main tumor. Other cells that mimic tumor buds like inflammatory cells, fibroblasts, and endothelial cells were examined carefully and were excluded. Tumor buds also have to be differentiated from necrotic debris. The necrotic and mucinous areas were excluded from the study field. Areas with maximum tumor buds were selected and the number of tumor buds (1–5 cells) were counted per high power field (hpf; 0.196 $mm^2$) by using the Olympus CX21i microscope with field number of 20 and 0.5-mm field of view (►Fig. 1). A two-tier system was used to categorize tumor bud density into low (≤5 tumor buds/hpf) and high (>5 tumor buds/hpf). IHC slides of ER, PR, and *Her2/neu* were also analyzed. Institutional ethical committee approval has been obtained.

## Statistical Analysis

Analyses were conducted using Epi Info software, which measures frequency distribution. The chi-squared test was used to assess the correlation of tumor bud density with its clinical, histopathological characteristics, and hormone receptor status. It was decided that a *p*-value of 0.05 was considered statistically significant. Event-free survival analyses for 5 years were done by the Kaplan–Meier method and significance value was calculated by log-rank test by using SPSS version 21.

## Results

One hundred cases of invasive breast carcinoma were included in the study. The median age of the study population

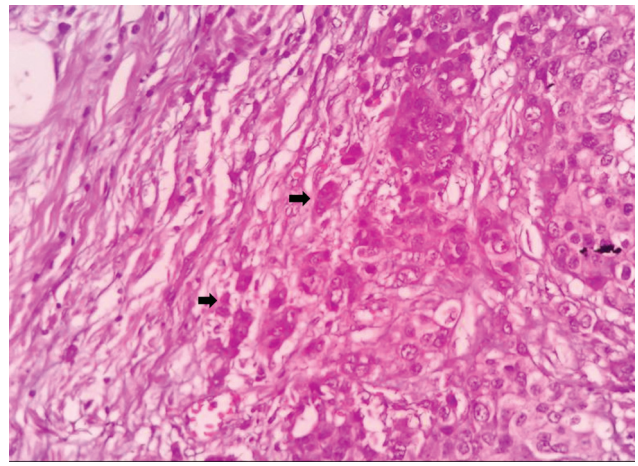

**Fig. 1** Tumor buds in invasive ductal carcinoma, hematoxylin and eosin (H&E), ×40 (shown in *arrows*).

 

was 52 years with minimum age of 26 years to maximum of 78 years. Invasive breast carcinoma, no special type (NST; ductal) accounted for 96% cases. Other carcinomas were mucinous carcinoma (2%), invasive ductal carcinoma with medullary differentiation (1%), and metaplastic carcinoma (1%). Tumors mostly involved the right breast ($n = 51$) and the commonest location was the upper outer quadrant ($n = 40$). The tumor bud density was assessed independently by two pathologists, which showed high interobserver agreement with an interobserver variability of 0.64 by employing descriptive statistics to calculate the standard deviation of respective variables. Among 100 cases, 45 cases showed high tumor bud density and 55 cases had low tumor bud density (►Table 1). The median follow-up of patients was 34 months (standard deviation of 21.88).

Forty-four percent (24/54) of patients with high tumor bud density were older than 50 years and 69% (9/13) patients with tumor size more than 5 cm had high tumor bud density. Grade 3 tumors constitute approximately 50% ($n = 50$) of total cases, of which 46% (23/50) cases showed high tumor bud density. LVI was seen in 55 cases and PNI in 14 cases.

**Table 1** Epidemiology of tumor characteristics

| | Categories | Cases ($n = 100$) |
|---|---|---|
| Age (y) | ≤50 | 46 |
| | >50 | 54 |
| Tumor grading (Nottingham score) | Grades 1 and 2 | 50 |
| | Grade 3 | 50 |
| Tumor staging (AJCC, 8th edition) | T1 | 16 |
| | T2 | 69 |
| | T3 | 12 |
| | T4 | 3 |
| Tumor bud density | High (>5 buds/hpf) | 45 |
| | Low (≤5 buds /hpf) | 55 |
| LVI status | Present | 55 |
| | Absent | 45 |
| PNI status | Present | 14 |
| | Absent | 86 |
| Lymph node status | N0 | 54 |
| | N1 | 27 |
| | N2 | 13 |
| | N3 | 6 |
| ER status | Positive | 57 |
| | Negative | 43 |
| PR status | Positive | 51 |
| | Negative | 49 |
| *Her2/neu* status | Positive | 35 |
| | Negative | 65 |

Abbreviations: ER, estrogen receptor; LVI, lymphovascular invasion; PNI, perineural invasion; PR, progesterone receptor.

Lymph node metastases were observed in 54 cases, of which only 21 cases (38%) showed high tumor bud density. Tumor necrosis was noted in 58 cases.

Most of the cases (85%) were in T1 and T2 stages, with 40% cases exhibiting high tumor bud density.

Primary tumor staging (T3, T4; 73%) and lymph node staging (N2, N3; 68%) were significantly associated with high tumor bud density with $p$-values of 0.017 and 0.023, respectively. Systemic metastasis (85% [6/7] cases) was significantly associated with high tumor bud density ($p = 0.025$). LVI and PNI were not statistically associated with tumor bud density and the $p$-values were 0.762 and 0.862, respectively (►Table 2).

Hormone receptors (estrogen receptor [ER], progesterone receptor [PR]) and *Her2/neu* status were not statistically associated with tumor bud density and the $p$-values were 0.887, 0.984, and 0.343, respectively (►Table 3).

Grade 3 tumors with high tumor bud density has statistically significant low event-free survival than any grades with high tumor bud density (►Figs. 2 and 3). In both low and high tumor bud densities, higher nodal stage (N2) patients have a significantly worse event-free survival (►Figs. 4 and 5). Other factors like tumor staging, necrosis, PNI, LVI, ER, PR, and *Her2/neu* were not associated with event-free survival. (►Table 4).

## Discussion

Tumor budding is considered an adverse prognostic parameter in various solid tumors like colorectal carcinoma, pancreatic carcinoma, and oral squamous cell carcinoma.[6] The International Tumor Budding Consensus Conference (ITBCC) 2016 recommends the application of tumor budding in colorectal carcinoma.[7] Tumor budding is mainly based on epithelial mesenchymal plasticity, which is involved in tumor invasion, progression, and metastasis. The presence of tumors bud at the invasive front of the tumor is likely to be the earliest step for invasion and metastasis. EMT is a dynamic process and its activation in tumor cells leads to loss of epithelial characteristics and acquiring of mesenchymal characteristics.[5] This process is supported by the tumor microenvironment where the tumor buds interact with the immune and stromal cells. The tumor's microenvironment is characterized by acidity, hypoxia, and inflammation. The immune cells will secrete various cytokines and chemokines to drive the EMT process.[8] Several transcription factors like Zinc finger E-box binding homeobox (ZEB), Twist1, Snail, and Slug are involved in EMT. These transcription factors are activated by transforming growth factor-β (TGF-β) signaling pathway, Neurogenic locus notch homolog protein 1 (NOTCH) signaling, WNT (wingless)/beta catenin signaling, and mitogen activated protein kinase (MAPK) pathway. EMT bestows the tumor cells with stem cell–like properties and is also responsible for immunosuppression and resistance to chemotherapy and endocrine therapy. In metastatic sites, the tumor cells regain the epithelial properties by undergoing MET.[9] In case of breast carcinoma, tumor stage, nodal stage, Nottingham score, hormone receptor, and *Her2/neu* status represent important prognostic markers. In this study, we evaluated the role of tumor bud

 

**Table 2** Tumor bud density and its association with clinical and histopathological parameters

| Parameters | | High tumor bud density = 45 cases | Low tumor bud density = 55 cases | *p* (chi-squared test) |
|---|---|---|---|---|
| Age (cutoff: 50) | ≤50 y | 21(46.7%) | 25 (45.5%) | 0.904 |
| | >50 y | 24 (53.3%) | 30 (54.5%) | |
| Tumor size (cm) | ≤5 cm | 36 (80%) | 51 (92.7%) | 0.060 |
| | >5 cm | 9 (20%) | 4 (7.3%) | |
| Tumor grade | 1 & 2 | 22 (48.9%) | 28 (50.9%) | 0.912 |
| | 3 | 23 (51.1%) | 27 (49.1%) | |
| Lymph node metastasis | Present | 21 (46.7%) | 33 (60%) | 0.183 |
| | Absent | 24 (53.3%) | 22 (40%) | |
| Tumor necrosis | Present | 24 (53.3%) | 34 (61.2%) | 0.414 |
| | Absent | 21 (46.7%) | 21(38.2%) | |
| Primary tumor staging | T1 and T2 | 34 (75.6%) | 51 (92.7%) | 0.017 |
| | T3 and T4 | 11 (24.4%) | 4 (7.3%) | |
| Regional lymph node staging | pN0 and pN1 | 32 (71.1%) | 49 (89%) | 0.023 |
| | pN2 and pN3 | 13 (28.9%) | 6 (11%) | |
| Systemic metastasis | Present | 6 (13.3%) | 1 (1.8%) | 0.025 |
| | Absent | 39 (86.7%) | 54 (98.2%) | |
| LVI | Present | 24 (53.3%) | 31 (56.4%) | 0.762 |
| | Absent | 21 (46.7%) | 24 (43.6%) | |
| PNI | Present | 6 (13.3%) | 8 (14.5%) | 0.862 |
| | Absent | 39 (86.7%) | 47 (85.5%) | |

Abbreviations: LVI, lymphovascular invasion; PNI, perineural invasion.

**Table 3** Tumor bud density and its association with immunohistochemical markers

| Parameters | | High tumor bud density = 45 cases | Low tumor bud density = 55 cases | *p* (chi-squared test) |
|---|---|---|---|---|
| ER status | Positive | 26 (57.8%) | 31 (56.4%) | 0.887 |
| | Negative | 19 (47.2%) | 24 (43.6%) | |
| PR status | Positive | 22 (48.9%) | 27 (49%) | 0.984 |
| | Negative | 23 (51.1%) | 28 (50%) | |
| *Her2/neu* status | Positive | 18 (40%) | 17 (30.9%) | 0.343 |
| | Negative | 27 (60%) | 38 (69.1%) | |

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

density and its association with other known prognostic parameters in invasive breast carcinoma.

In this study, most of the patients were in the age range of 50 to 60 years, which was comparable with Rathod et al[8] and Kumarguru et al.[10] H&E-stained slides were used in this study to calculate the tumor bud density, which is similar to Rathod et al[8] and Kumarguru et al.[10] IHC stains were used by Salhia et al,[11] Kundu et al,[12] and Liang et al[4] to identify and assess the number of tumor buds. Pancytokeratin IHC was used by Salhia et al[11] and Kundu et al[12] to count the tumor buds, while Liang et al[4] identified tumor buds showing increased cytoplasmic vimentin expression, reduced membrane E-cadherin expression, and decreased nuclear Ki67 expression as compared with tumor cells in the center areas.

Different tumor bud cutoffs were used in various studies across different parts of the world. Salhia et al[11] and Masilamani and Kanmani[13] both calculated the average tumor bud count in 10 hpfs, but Sahlia et al[11] selected more than 4 tumor buds as the threshold for high tumor budding, while Masilamani and Kanmani[13] applied ≥10 tumor buds as cutoff for high tumor budding. Liang et al[4] employed the receiver operating characteristic (ROC) curve to establish 7 tumor buds/0.950 $mm^2$ as high tumor budding. The Kaplan–Meier analysis was used by Gujam et al[14] to set a threshold of

 

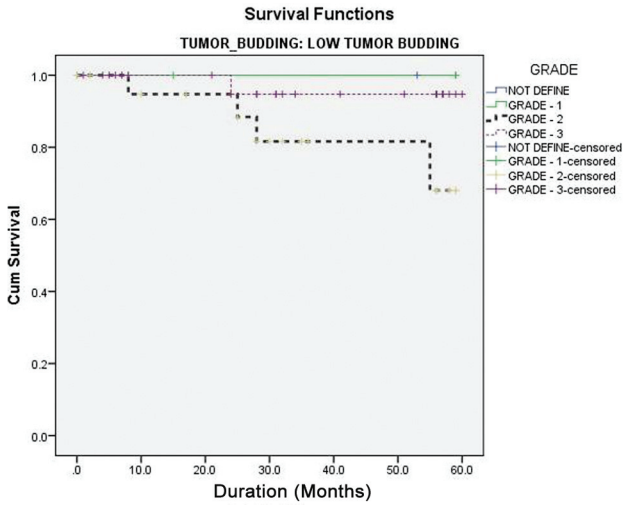


**Fig. 2** Correlation of low tumor bud density and event-free survival with tumor grade.

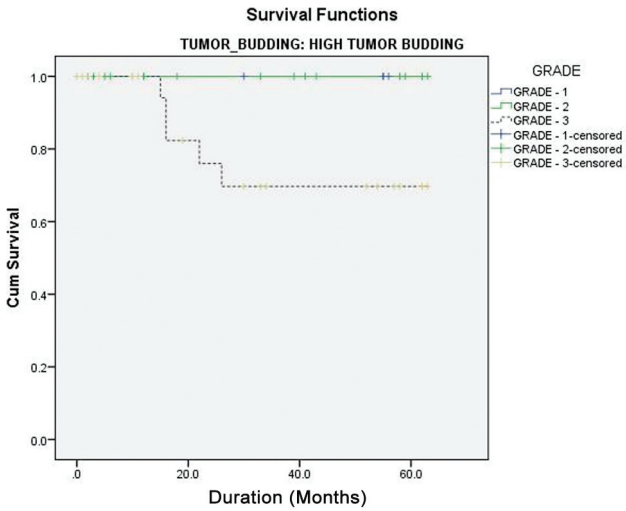


**Fig. 3** Correlation of high tumor bud density and event-free survival with tumor grade.

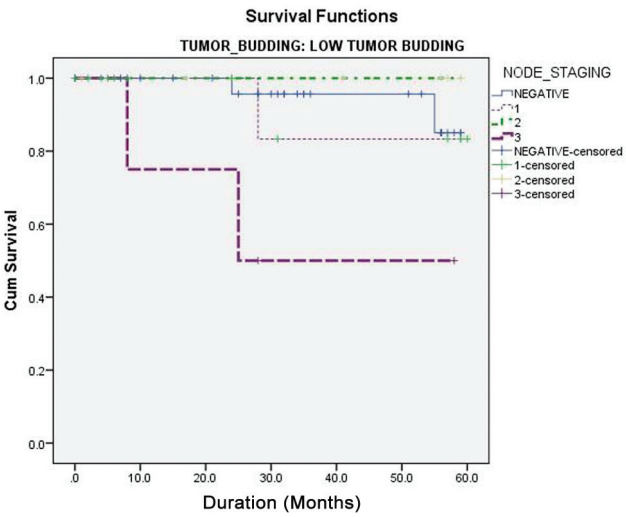


**Fig. 4** Correlation of low tumor bud density and event-free survival with nodal stage.

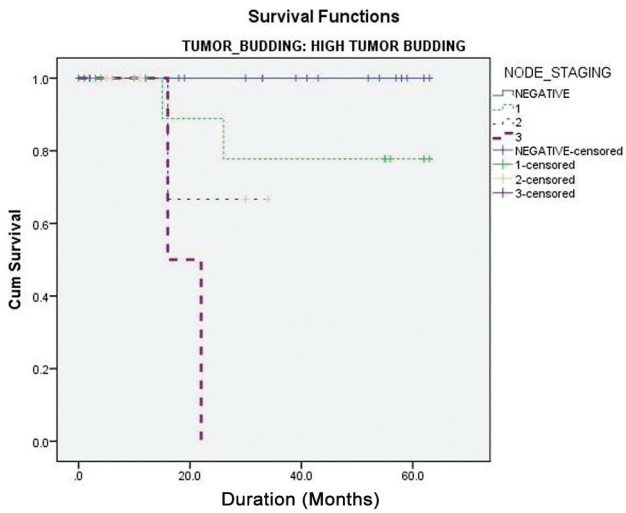


**Fig. 5** Correlation of high tumor bud density and event-free survival with nodal stage.

greater than 20 tumor buds/5 hpfs for evaluating high tumor budding. Agarwal et al[2] from India employed ≥10 tumor buds in the area of the highest tumor bud density. Renuka et al[15] counted tumor buds in one hotspot (0.785 $mm^2$) at the invasive front of the tumor and selected >4 tumor buds/ 0.785 $mm^2$ field as high tumor budding. In the present study, we used ≥5 tumor buds/hpf at the hotspot area as cutoff to classify it as high tumor bud density.

Tumor size (>5 cm) revealed no association with tumor bud density, which is similar to the observations by Gujam et al[14] and Singh et al.[16] However, Liang et al[4] and Agarwal et al[2] showed a positive correlation between tumor size and high-grade tumor buds.

Primary tumor staging and lymph node staging are highly correlated with high tumor bud density, which is consistent with the findings in Liang et al[4] and Patel and Gupta.[17] But no association was noted by Agarwal et al.[2]

Tumor necrosis was not associated with high tumor bud density, which is in line with the findings of Gujam et al.[15] Systemic metastases were observed in the liver, lung, brain, and bone and was significantly associated with high tumor bud density.

The ER, PR, and *Her2/neu* status does not correlate with high tumor bud density, which is consistent with the findings of Agarwal et al[2] and Xiang et al.[18] But Rathod et al[8] and Gujam et al[14] showed a correlation between ER positive tumors and high-grade tumor budding. Similarly significant association was observed between *Her2/neu* (Herceptin) and high-grade tumor budding by Masilamani and Kanmani.[13]

The event-free survival analysis and its correlation with tumor bud density were also analyzed. When compared with other grades with high tumor bud density, grade 3 tumors had a statistically significant worse event-free survival (►**Figs. 2** and **3**). Higher nodal stage (N2) patients have lower event-free survival in both low and high tumor bud densities (►**Figs. 4** and **5**). A meta-analysis from Lloyd et al[19] showed that there is significant association between high tumor bud density and poor survival factors like lymph node metastasis, LVI, and ER

 

**Table 4** Association of event-free survival (EFS) with immunohistochemical and histopathological parameters

| Variables | | Low tumor bud density | | | | Significance value: 0.342 | High tumor bud density | | | | Significance value: 0.08 | Odds ratio (confidence interval) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total | No. of events (metastasis or recurrence) | EFS | EFS rate | | Total | No. of events (metastasis or recurrence) | EFS | EFS rate | | |
| Grade | 1 | 7 | 0 | 7 | 100 | | 6 | 0 | 6 | 100 | | |
| | 2 | 22 | 4 | 18 | 81.8 | | 15 | 0 | 15 | 100 | | |
| | 3 | 26 | 1 | 25 | 96.2 | | 24 | 5 | 19 | 79.2 | | |
| Tumor stage | 1 | 8 | 0 | 8 | 100 | 0.418 | 8 | 1 | 7 | 87.5 | 0.957 | 1.230(0.267–5.661) |
| | 2 | 41 | 41 | 37 | 97.2 | | 28 | 3 | 25 | 89.3 | | |
| | 3 | 6 | 1 | 5 | 83.3 | | 9 | 1 | 8 | 88.9 | | |
| Nodal stage | 0 | 14 | 2 | 12 | 92.9 | 0.044 | 13 | 2 | 11 | 84.6 | 0 | 0.209(0.046–0.937) |
| | 1 | 6 | 0 | 6 | 100 | | 7 | 1 | 6 | 85.7 | | |
| | 2 | 4 | 2 | 2 | 50 | | 2 | 2 | 0 | 0 | | |
| Necrosis | Present | 22 | 2 | 20 | 90.9 | 0.592 | 19 | 3 | 16 | 0.15 | 0.278 | 1.744(0.218–3.945) |
| | Absent | 33 | 3 | 30 | 90.9 | | 26 | 2 | 24 | 92.3 | | |
| LVI | Present | 28 | 4 | 24 | 85.7 | 0.278 | 27 | 4 | 23 | 85.2 | 0.206 | 0.536(0.059–4.886) |
| | Absent | 27 | 1 | 26 | 96.3 | | 18 | 1 | 17 | 94.4 | | |
| PNI | Present | 5 | 0 | 5 | 100 | 0.404 | 9 | 2 | 7 | 77.8 | 0.24 | 0.794(0.042–5.158) |
| | Absent | 50 | 5 | 45 | 90 | | 36 | 3 | 33 | 91.7 | | |
| ER | Positive | 22 | 1 | 21 | 95.5 | 0.452 | 21 | 4 | 17 | 81 | 0.111 | 0.256(0.009–3.362) |
| | Negative | 33 | 4 | 29 | 87.9 | | 24 | 1 | 23 | 95.8 | | |
| PR | Positive | 28 | 2 | 26 | 82.9 | 0.667 | 23 | 4 | 19 | 82.6 | 0.152 | 3.947(0.125–5.345) |
| | Negative | 27 | 3 | 24 | 88.9 | | 22 | 1 | 21 | 95.5 | | |
| *Her2/neu* | Positive | 17 | 3 | 14 | 82.4 | 0.132 | 18 | 3 | 15 | 83.3 | 0.183 | 2.379(0.484–4.241) |
| | Negative | 38 | 2 | 36 | 94.7 | | 27 | 2 | 25 | 92.6 | | |

Abbreviations: ER, estrogen receptor; LVI, lymphovascular invasion; PNI, perineural invasion; PR, progesterone receptor.

status. In contrast, our study did not find any association of tumor staging, necrosis, PNI, LVI, ER, PR, and *Her2/neu* with event-free survival. This could be due to the low number of study population with high tumor bud density or it may be due to different tumor behaviors in the Asian subpopulation.

## Conclusion

Tumor bud density shows a significant association with adverse prognostic variables like primary tumor staging and lymph node staging. But significant association was not noted with other prognostic factors such as tumor grade, LVI, PNI, hormone receptors, and *Her2/neu* status. With these results, tumor bud density can be considered a prognostic parameter and may be included in the routine reporting system after conducting large-scale studies. However, the evaluation of tumor bud density has to be standardized in breast carcinoma to apply and employ it universally. The limitation of this study was the small sample size. There is need for proper consensus in the evaluation method of tumour bud density, thereby patients can be stratified and assigned to prognostic categories and to make appropriate treatment decisions.

Conflict of Interest
None declared.

## References

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70(01):7–30
2 Agarwal R, Khurana N, Singh T, Agarwal PN. Tumor budding in infiltrating breast carcinoma: correlation with known clinicopathological parameters and hormone receptor status. Indian J Pathol Microbiol 2019;62(02):222–225
3 Imai T. Growth patterns in human carcinoma. Their classification and relation to prognosis. Obstet Gynecol 1960;16:296–308
4 Liang F, Cao W, Wang Y, Li L, Zhang G, Wang Z. The prognostic value of tumor budding in invasive breast cancer. Pathol Res Pract 2013;209(05):269–275
5 Huang T, Bao H, Meng YH, et al. Tumour budding is a novel marker in breast cancer: the clinical application and future prospects. Ann Med 2022;54(01):1303–1312
6 Grigore AD, Jolly MK, Jia D, Farach-Carson MC, Levine H. Tumor budding: the name is EMT. Partial EMT. J Clin Med 2016;5(05):51
7 Lugli A, Kirsch R, Ajioka Y, et al. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Mod Pathol 2017;30(09):1299–1311
8 Rathod GB, Desai KN, Shrivastava A, Maru AM. Correlation of tumor budding with known clinicopathological, histomorphological and hormonal receptor status in patients with invasive breast carcinoma. Cureus 2022;14(09):e29637
9 Voutsadakis IA. Prognostic role of tumor budding in breast cancer. World J Exp Med 2018;8(02):12–17
10 Kumarguru BN, Ramaswamy AS, Shaik S, Karri A, Srinivas VS, Prashant BM. Tumor budding in invasive breast cancer: an indispensable budding touchstone. Indian J Pathol Microbiol 2020;63 (Supplement):S117–S122
11 Salhia B, Trippel M, Pfaltz K, et al. High tumor budding stratifies breast cancer with metastatic properties. Breast Cancer Res Treat 2015;150(02):363–371
12 Kundu T, Giri R, Hota SK, Sahu SK, Senapati U. Tumour budding in invasive breast carcinoma and its correlation with histopathological prognostic parameters and hormone receptor status. J Cancer Res Ther 2023;19(Suppl 2):S664–S668
13 Masilamani S, Kanmani P. Evaluation of clinicopathologic significance of tumor budding in breast carcinoma. Int J Clin Diagn Pathol 2019;2:171–173
14 Gujam FJ, McMillan DC, Mohammed ZM, Edwards J, Going JJ. The relationship between tumour budding, the tumour microenvironment and survival in patients with invasive ductal breast cancer. Br J Cancer 2015;113(07):1066–1074
15 Renuka IV, Madhavi K, Premalatha P, Krishnamacharyulu PAV, Vaishnavi R. Tumor budding in invasive carcinoma of breast of no special type (NST): value as a prognostic factor. IP J Diagn Pathol Oncol 2019;4:125–129
16 Singh T, Chandra K, Kumar N, et al. A retrospective study of association of tumor budding, tumor microenvironment, and clinicopathological characteristics of invasive breast carcinoma. J Lab Physicians 2022;14(04):485–490
17 Patel M, Gupta V. Evaluation of prognostic role of tumour budding in breast carcinoma and its correlation with known clinicopathological parameters. Indian Pathol Oncol 2022;9:238–242
18 Xiang Z, He Q, Huang L, Xiong B, Xiang Q. Breast cancer classification based on tumor budding and stem cell-related signatures facilitate prognosis evaluation. Front Oncol 2022;11:818869
19 Lloyd AJ, Ryan ÉJ, Boland MR, et al. The histopathological and molecular features of breast carcinoma with tumour budding-a systematic review and meta-analysis. Breast Cancer Res Treat 2020;183(03):503–514

 