

Tumor budding and tumor-infiltrating lymphocytes in invasive breast carcinoma: a single-centre cross-sectional observational histopathological study.

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Abstract

Background

Tumor budding reflects detachment of single malignant cells or small cell clusters from the main tumor and is increasingly recognized as a morphologic indicator of invasive potential. Tumor-infiltrating lymphocytes represent the host immune response within the tumor microenvironment and provide complementary biological information in breast carcinoma.

Objectives

To assess intratumoral budding, peritumoral budding, stromal tumor-infiltrating lymphocytes, and intratumoral tumor-infiltrating lymphocytes in invasive breast carcinoma and determine their associations with selected clinicopathological parameters.

Methods

This hospital-based observational histopathological study included 42 mastectomy specimens. Hematoxylin and eosin-stained sections were examined for tumor-budding hotspots. Intratumoral and peritumoral budding were categorized as high or low using the study-defined threshold of more than four buds across 10 high-power fields. Tumor-infiltrating lymphocytes were assessed morphologically and analyzed using the recorded low and high categories. Estrogen receptor, progesterone receptor, and HER2 results were available for a subset of cases. Associations were assessed using chi-square testing, with statistical significance set at $p < 0.05$.

Results

High ITB and PTB were each identified in 19/42 cases (45.2%). Both ITB ($p = 0.0001$) and PTB ($p = 0.0006$) showed statistically significant associations with lymph-node metastasis, which was present in 19/42 cases (45.2%). Low iTILs were observed in 34/42 cases (81.0%), while low sTILs were identified in 29/42 cases (69.0%). PTB showed no significant association with iTILs ($\chi^2 = 0.0905$; $p = 0.763$) or sTILs ($\chi^2 = 0.5631$; $p = 0.453$). Associations of tumor budding with age, lymphovascular invasion, histological grade, tumor size, and receptor status were not statistically significant (all $p > 0.05$).

Conclusion

Tumor budding, particularly its association with nodal metastasis, appears to identify an aggressive histomorphological phenotype in invasive breast carcinoma. The present series did not demonstrate a significant relationship between tumor budding and tumor-infiltrating lymphocyte categories.

Recommendations

Larger multicentre studies using standardized budding and lymphocyte-scoring systems, survival endpoints, and reproducibility assessment are recommended before routine incorporation into breast carcinoma reporting protocols.

Keywords: breast carcinoma; tumor budding; intratumoral budding; peritumoral budding; tumor-infiltrating lymphocytes; lymph-node metastasis; histopathology

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Introduction

Breast carcinoma is a heterogeneous malignancy in which prognosis and treatment decisions are shaped by an integrated assessment of tumor size, histological type and grade, lymph-node involvement, lymphovascular invasion, and biomarker expression. Histological grading by the Nottingham system remains a reproducible source of prognostic information when standardized criteria are applied [1,2]. Nevertheless, conventional variables do not fully capture the biological diversity of invasive breast cancer. There is continuing interest in additional tissue-based markers that are inexpensive, can be evaluated on routinely stained sections, and reflect the mechanisms responsible for local invasion, metastatic dissemination, and host antitumor response [3,4].

Tumor budding is defined morphologically as isolated tumor cells or small clusters detached from the main tumor mass. In breast carcinoma, both peritumoral budding at the invasive front and intratumoral budding within the tumor body have been investigated. Salhia et al. demonstrated that high budding could stratify invasive breast cancers according to metastatic properties, particularly nodal and lymphatic involvement [5]. Subsequent studies linked increased budding with lymphovascular invasion, lymph-node metastasis, distant spread, or inferior survival, although the strength of these associations has varied across cohorts and scoring methods [2-6]. This heterogeneity partly reflects differences in definitions, field size, staining method, hotspot selection, and cut-off values. Even so, tumor budding is biologically plausible as a marker of invasion because detached cells are considered to represent a phenotype related to epithelial-mesenchymal plasticity and early metastatic behavior [6].

The immune microenvironment provides a second, conceptually distinct dimension of tumor biology. Tumor-infiltrating lymphocytes (TILs) represent the host immune reaction within and around malignant tissue and are particularly relevant in triple-negative and HER2-positive breast cancers. Standardized evaluation of stromal TILs on hematoxylin and eosin sections has been proposed to improve reproducibility and clinical translation [8]. Higher lymphocytic infiltration has been associated with better response to neoadjuvant chemotherapy and favorable outcomes in selected breast-cancer subtypes [9-11]. Experimental and clinical observations also support the broader concept of cancer immunoediting, in which immune pressure can suppress, shape, or facilitate tumor progression [14]. The possible relationship between tumor budding and lymphocytic infiltration is therefore of interest because it brings together tumor-cell dissociation and host immune surveillance within the same histological field.

The present study was undertaken to evaluate these two routine histomorphological features in mastectomy specimens. The objectives were to score intratumoral budding and peritumoral budding, assess stromal and intratumoral TIL density, and examine their relationships with age, tumor size, Nottingham grade, lymphovascular invasion, lymph-node metastasis, and available ER, PR, and HER2 status. A further objective was to determine whether tumor budding was associated with the recorded TIL categories in invasive breast carcinoma.

Materials and Methods

Study Design and Setting

This hospital-based cross-sectional observational histopathological study was conducted in the Department of Pathology, Katuri Medical College and Hospital, Guntur, Andhra Pradesh, India, over a three-year period from November 2019 to October 2022. Katuri Medical College and Hospital is a tertiary-care teaching institution providing comprehensive diagnostic, medical, and surgical healthcare services to patients from Guntur and surrounding rural and urban areas. The hospital offers outpatient, inpatient, and emergency services across multiple specialties, including general medicine, general surgery, obstetrics and gynaecology, orthopaedics, radiodiagnosis, pathology, and surgical oncology. Additional specialty and superspecialty services include cardiology, neurology, nephrology, urology, and critical care. The institution is supported by laboratory diagnostic facilities, radiological imaging services, operating theatres, and histopathology laboratories that facilitate the diagnosis and management of benign and malignant diseases.

Participants and Specimen Selection

The study population comprised mastectomy specimens with histopathologically confirmed invasive breast carcinoma received by the Department of Pathology during the specified study period. A total-enumerative sampling method was employed, in which all eligible specimens available between November 2019 and October 2022 were considered for inclusion rather than selecting a predetermined sample. Specimens were eligible irrespective of the histological subtype of invasive breast carcinoma, provided that sufficient tumor tissue was available for evaluating the invasive tumor front, intratumoral regions, tumor budding, and lymphocytic infiltration.

A total of 42 eligible mastectomy specimens constituted the final study sample. Formalin-fixed, paraffin-embedded tissue sections were processed using routine histopathological techniques and stained with hematoxylin and eosin. The sections were evaluated for histological type,

Nottingham grade, lymphovascular invasion, lymph-node metastasis, intratumoral budding, peritumoral budding, and stromal and intratumoral lymphocytic infiltration. Available pathological records were reviewed to obtain clinicopathological information, including tumor size, lymph-node status, and estrogen receptor, progesterone receptor, and HER2 expression. Receptor status was available for 32 of the 42 cases, and analyses involving these biomarkers were restricted to cases with recorded results.

Eligibility criteria

Mastectomy specimens referred to the Department of Pathology during the study period were eligible irrespective of the histological type of breast carcinoma. The source protocol excluded specimens from women documented as smokers, women receiving hormone-replacement therapy or oral contraceptive pills, and pregnant women. Cases with tissue inadequate for histological assessment of the invasive tumor and its interface were not suitable for budding or TIL evaluation.

Histopathological assessment

Formalin-fixed, paraffin-embedded tissue was processed routinely, and hematoxylin and eosin-stained sections were reviewed. Histological type and grade were recorded, with grading based on the Nottingham modification of the Bloom-Richardson system [7]. Tumor size, lymphovascular invasion, and lymph-node status were retrieved from the pathological assessment. Tumor budding was assessed in areas with the highest concentration of buds. Peritumoral budding was evaluated at the invasive tumor front, whereas intratumoral budding was assessed within the tumor center. In keeping with the study protocol derived from the approach described by Salhia et al. [1], budding was counted across 10 high-power fields. Tumors with an average of more than four buds across 10 high-power fields were categorized as high budding; those at or below this threshold were categorized as low budding.

Tumor-infiltrating lymphocytes and biomarkers

TILs were assessed morphologically as the proportion of the relevant tumor-associated area occupied by lymphocytes and plasma cells. Stromal TILs represented lymphocytes within tumor stroma, while intratumoral TILs represented lymphocytes in direct association with tumor nests. Standardized principles for morphological TIL assessment were considered in interpretation [8]. Because the source analysis tables recorded the final TIL comparison as less than 10% versus greater than 10%, the present manuscript reports these recorded analytic categories. ER, PR, and HER2 results were available for 32 cases in the study

summary and were analyzed as recorded in the pathology reports.

Bias

Potential sources of bias included selection bias, measurement bias, observer variability, and information bias. Selection bias was minimized by including all eligible mastectomy specimens through a total-enumerative sampling approach. Measurement bias was reduced by using standardized hematoxylin and eosin staining, Nottingham grading, and predefined criteria for evaluating tumor budding and tumor-infiltrating lymphocytes. However, the absence of documented blinded assessment and interobserver agreement testing may have introduced observer-related variability. Information bias was addressed by restricting receptor-related analyses to the 32 cases with available immunohistochemical results. The small sample size and single-centre setting may have limited the representativeness of the findings. Furthermore, the absence of multivariable analysis prevented adjustment for potential confounding factors, necessitating cautious interpretation of the observed associations.

Statistical analysis

Categorical variables were summarized as frequencies and percentages. Associations of ITB, PTB, sTILs, and iTILs with clinicopathological variables were assessed using chi-square testing as reported in the source analysis. A two-sided *p* value below 0.05 was considered statistically significant. No multivariable modeling, survival analysis, or time-to-event analysis was performed; consequently, the results are interpreted as unadjusted histopathological associations rather than independent prognostic effects.

Ethical considerations

The study was conducted in the Department of Pathology, Katuri Medical College and Hospital, Guntur, Andhra Pradesh, India, between November 2019 and October 2022. Institutional permission was obtained before commencement of the study. Patient confidentiality was maintained throughout data collection, histopathological evaluation, and analysis, and identifying information was excluded from the research dataset.

Results

A total of 42 mastectomy specimens were included in the analysis. The largest age group was 51-60 years, comprising 16 cases, followed by 41-50 years with 15 cases. Right-sided tumors accounted for 23 cases (54.8%) and left-sided tumors for 19 (45.2%). The upper outer quadrant was the most

frequently reported site of involvement (42.4%). Invasive ductal carcinoma was the predominant histological type, present in 41 cases (97.6%), with one lobular carcinoma. Grade III tumors were reported in 36 cases, grade II in five, and grade I in one. Lymph-node metastasis was present in

19 cases (45.2%), and lymphovascular invasion was identified in 36 (85.7%). Most tumors were categorized as T2. Among the 32 cases with receptor results, ER positivity was present in 12, PR positivity in 11, and HER2 positivity in four (Table 1).

Table 1. Clinicopathological characteristics of the study population

Characteristic	Category	n (%)
Age group, years	31-40	4 (9.5)
	41-50	15 (35.7)
	51-60	16 (38.1)
	61-70	6 (14.3)
	71-80	1 (2.4)
Laterality	Right	23 (54.8)
	Left	19 (45.2)
Histological type	Invasive ductal carcinoma	41 (97.6)
	Lobular carcinoma	1 (2.4)
Nottingham grade	Grade I	1 (2.4)
	Grade II	5 (11.9)
	Grade III	36 (85.7)
Lymph-node metastasis	Present	19 (45.2)
	Absent	23 (54.8)
Lymphovascular invasion	Present	36 (85.7)
	Not identified	6 (14.3)
Tumor T category	T1	7 (16.7)
	T2	32 (76.2)
	T3	2 (4.8)
	T4	1 (2.4)
ER status (n=32)	Positive	12 (37.5)
	Negative	20 (62.5)
PR status (n=32)	Positive	11 (34.4)
	Negative	21 (65.6)
HER2 status (n=32)	Positive	4 (12.5)
	Negative	26 (81.3)
	Equivocal	2 (6.3)

Note. Percentages are based on n=42 unless otherwise stated; minor rounding differences are possible. ER, estrogen

receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

High ITB was recorded in 19 cases (45.2%), while 23 cases (54.8%) were categorized as low ITB. High PTB was likewise reported in 19 cases (45.2%), with 23 cases categorized as low PTB. ITB demonstrated a statistically significant association with lymph-node metastasis ($p=0.0001$). The reported tests for age, lymphovascular invasion, histological grade, tumor size, ER, PR, and HER2

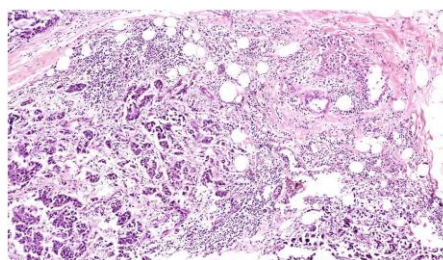
were not statistically significant. PTB was significantly associated with lymph-node metastasis ($p=0.0006$), while the reported p values for age, lymphovascular invasion, grade, tumor size, and receptor status were non-significant (Table 2). Representative budding patterns are illustrated in Figure 1, and representative nodal metastatic morphology is shown in Figure 2

Table 2. Reported associations of intratumoral and peritumoral budding with clinicopathological parameters

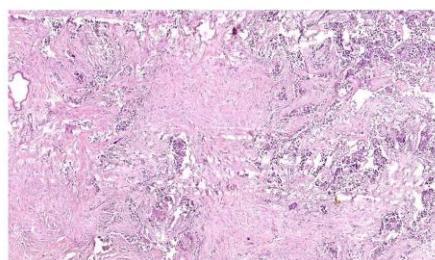
Parameter	ITB p value	PTB p value	Interpretation
Age	0.38	0.27	Not significant
Lymphovascular invasion	0.71	0.80	Not significant
Histological grade	0.63	0.69	Not significant
Tumor size/T category	0.71	0.47	Not significant
Lymph-node metastasis	0.0001	0.0006	Significant for ITB and PTB
ER status	0.98	0.47	Not significant
PR status	0.76	0.76	Not significant
HER2 status	0.45	0.45	Not significant

Note. P values reproduce the numerical values reported in the supplied analysis tables. Statistical significance was defined as $p<0.05$. ITB, intratumoral budding; PTB, peritumoral budding.

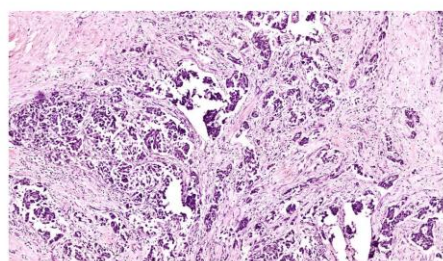
A



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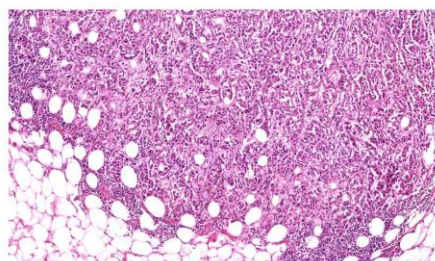


Figure 1. Representative histomorphological patterns of tumor budding and lymphocytic infiltration in invasive breast carcinoma. (A) Low peritumoral budding with stromal tumor-infiltrating lymphocytes (sTILs) >10% (H&E, ×40). (B) Desmoplastic stroma with high intratumoral budding (H&E, ×40). (C) Low intratumoral budding with stromal and intratumoral TILs <10% (H&E, ×40). (D) High peritumoral budding with stromal and intratumoral TILs >10% (H&E, ×40).

The TIL analysis showed a predominance of low lymphocytic infiltration. Low iTILs were recorded in 34 cases (81.0%) and high iTILs in eight (19.0%). Low sTILs were recorded in 29 cases (69.0%) and high sTILs in 13 (31.0%). When PTB was compared directly with TIL categories, 15 of 19 high-PTB cases had low iTILs and four had high iTILs. Among low-PTB cases, 19 had low iTILs and four had high iTILs. This association was not significant (chi-square=0.0905; p=0.763). Similarly, PTB was not significantly related to sTIL category (chi-square=0.5631; p=0.453) (Table 3). Representative stromal lymphocytic infiltration is shown in Figure 2A.

Table 3. Relationship of peritumoral budding with intratumoral and stromal tumor-infiltrating lymphocyte categories

TIL measure	PTB category	Low TIL	High TIL	p value
iTIL	High PTB	15	4	0.763
	Low PTB	19	4	
sTIL	High PTB	12	7	0.453
	Low PTB	17	6	

Note. TIL categories reproduce the recorded study analysis (<10% versus >10%). iTIL, intratumoral tumor-infiltrating lymphocytes; sTIL, stromal tumor-infiltrating lymphocytes; PTB, peritumoral budding.

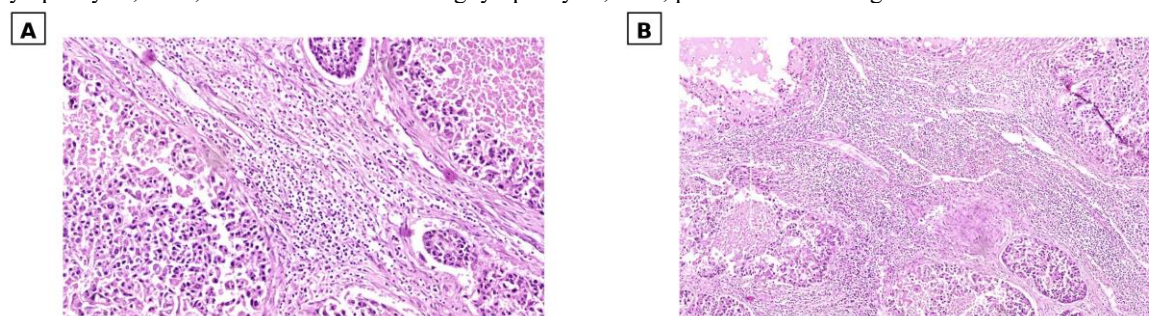


Figure 2. Representative tumor-associated immune and metastatic morphology. (A) Stromal tumor-infiltrating lymphocytes >10% (H&E, ×40). (B) Lymph-node metastasis (H&E, ×40).

No evaluated clinicopathological variable showed a statistically significant association with either sTIL or iTIL category. For sTILs, p values ranged from 0.2795 for tumor size to 0.8787 for HER2 status. For iTILs, p values ranged

from 0.2475 for tumor size to 0.9548 for lymph-node metastasis. The source analysis described low TIL categories as frequent among older patients, LVI-positive tumors, node-negative tumors, receptor-negative cases, and T2/grade II tumors; however, none of these comparisons reached the predefined level of statistical significance (Table 4).

Table 4. Reported associations of tumor-infiltrating lymphocyte categories with clinicopathological parameters

Parameter	sTIL p value	iTIL p value
Age	0.5552	0.7811
Lymphovascular invasion	0.6410	0.7259
Histological grade	0.3546	0.6307
Tumor size/T category	0.2795	0.2475

Parameter	sTIL p value	iTIL p value
Lymph-node metastasis	0.7725	0.9548
ER status	0.6422	0.7823
PR status	0.4507	0.7366
HER2 status	0.8787	0.5364

Note. All reported associations were non-significant at $p < 0.05$. sTIL, stromal tumor-infiltrating lymphocytes; iTIL, intratumoral tumor-infiltrating lymphocytes.

Discussion

The principal observation of this study was the relationship between tumor budding and lymph-node metastasis. Both ITB and PTB showed statistically significant associations with nodal involvement, whereas the reported associations with age, tumor size, histological grade, receptor status, and lymphovascular invasion were not significant. This pattern supports the concept that tumor budding captures a localized invasive phenotype that is closely linked to metastatic competence. Salhia et al. similarly found high PTB to be associated with lymph-node metastasis and lymphatic invasion in invasive breast cancer [1]. Gujam et al. reported associations between budding and adverse pathological characteristics and further demonstrated an independent relationship with cancer-specific survival in a substantially larger cohort [2].

Other breast-cancer studies have also described tumor budding as an unfavorable histological feature, although methods and thresholds differ. Li et al. associated high budding counts with distant metastasis, lymphovascular invasion, and poorer survival in selected molecular subgroups [3]. Agarwal et al. observed higher budding in tumors with larger size, advanced stage, and lymphovascular emboli [4], while Kumarguru et al. reported significant relationships with lymphovascular invasion, lymph-node metastasis, and pathological stage [5]. The present study did not reproduce all of these associations. Differences in sample size, case composition, receptor distribution, treatment exposure, slide selection, and budding cut-offs can materially influence statistical significance. This methodological variability is a major barrier to direct comparison across breast-cancer series and has been emphasized in reviews of tumor budding [6].

The second component of the study examined the lymphocytic tumor microenvironment. No statistically significant relationship was demonstrated between PTB and either iTILs or sTILs, and TIL categories were not significantly associated with the evaluated clinicopathological variables. These findings should be interpreted in the context of the small cohort and the use of a simplified dichotomous TIL classification. International guidance emphasizes standardized assessment of stromal

TILs, careful definition of the evaluable area, and attention to breast-cancer subtype [8]. In larger clinical datasets, TILs have shown predictive and prognostic relevance, especially in triple-negative and HER2-positive disease [9,10]. Meta-analytic evidence also indicates that higher pretreatment TIL levels are associated with increased pathological complete response after neoadjuvant chemotherapy [11], while CD8-positive and other lymphocyte subsets have demonstrated predictive or favorable prognostic associations [12,13].

Taken together, the findings suggest that tumor budding and TILs describe different aspects of tumor biology. Budding reflects dissociation and invasion, whereas lymphocytic infiltration reflects host-tumor immune interaction within the broader framework of cancer immunoediting [14]. Their combined assessment remains attractive, but the current data support tumor budding more strongly than TIL category as a marker associated with adverse nodal status in this cohort.

Generalizability

The findings are most applicable to mastectomy-based invasive breast carcinoma specimens evaluated in a tertiary-care pathology setting using routine hematoxylin and eosin sections. Because the cohort was small, single-centre, and heterogeneous, extrapolation to screening-detected cancers, core biopsies, specific molecular subtypes, or neoadjuvant-treated populations should be cautious. The simple microscopy-based approach is nevertheless feasible in resource-constrained laboratories and provides a practical basis for multicentre validation using harmonized budding and TIL scoring methods.

Conclusion

In this observational histopathological study of 42 mastectomy specimens, high intratumoral and peritumoral tumor budding showed significant associations with lymph-node metastasis, supporting tumor budding as a readily assessable marker of aggressive invasive behavior in breast carcinoma. No significant association was identified between budding and the evaluated TIL categories, and most other clinicopathological comparisons were statistically

non-significant. These findings indicate that budding provides morphological information distinct from routine TIL assessment in this cohort. Incorporating standardized tumor-budding assessment into future breast-cancer research could improve pathological risk stratification. Routine clinical adoption, however, requires larger multicentre cohorts, harmonized scoring thresholds, interobserver validation, and correlation with recurrence, treatment response, disease-free survival, and overall survival.

Limitations

This study was limited by its single-centre design, small sample size, and absence of follow-up or survival endpoints. Receptor data were unavailable for a proportion of cases, reducing the effective sample for biomarker comparisons. The study used study-specific budding and TIL categories without formal interobserver reproducibility testing. Multivariable analysis was not performed, so confounding by established pathological factors could not be assessed.

Recommendations

Future studies should evaluate tumor budding and TILs prospectively in larger, multicentre breast-cancer cohorts and apply clearly standardized definitions, field areas, hotspot selection, and reporting thresholds. Independent review by two pathologists should be incorporated to quantify interobserver agreement. Analyses should be stratified by molecular subtype and treatment setting, with complete ER, PR, and HER2 characterization. Multivariable models should determine whether budding adds prognostic information beyond tumor size, grade, lymphovascular invasion, and nodal status. Longitudinal follow-up should include recurrence, disease-free survival, overall survival, and treatment response. Digital pathology-assisted scoring could also be compared with conventional microscopy to improve reproducibility and clinical scalability.

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Abbreviations

ER, estrogen receptor; FFPE, formalin-fixed paraffin-embedded; H&E, hematoxylin and eosin; HER2, human epidermal growth factor receptor 2; HPF, high-power field;

IDC, invasive ductal carcinoma; iTIL, intratumoral tumor-infiltrating lymphocytes; ITB, intratumoral budding; LVI, lymphovascular invasion; MRM, modified radical mastectomy; PR, progesterone receptor; PTB, peritumoral budding; sTIL, stromal tumor-infiltrating lymphocytes; TB, tumor budding; TILs, tumor-infiltrating lymphocytes.

Conflict of Interest

The authors declare that there is no conflict of interest.

Source of Funding

The study received no external funding.

Data Availability

The data supporting the findings of this study are available from the corresponding author on reasonable request, subject to institutional and ethical requirements.

Author Contributions

Dr. Mounika Reddy Guntaka: Conceptualization, study design, histopathological evaluation, data interpretation, literature review, manuscript preparation, and overall coordination of the study. She also serves as the corresponding author and takes responsibility for communication with the journal.

Dr. Yerraguntla Divyaprabha: Histopathological assessment, data interpretation, literature review, critical revision of the manuscript, and intellectual input.

Dr. M.V.R.K. Prasanthi: Data collection, histopathological review, literature search, data organization, and assistance in manuscript drafting.

Dr. G. Hima Bindu: Supervision, methodological guidance, interpretation of pathological findings, critical intellectual review, and final refinement of the manuscript.

Dr. Mahathi Thotakura: Histopathological interpretation, validation of study findings, critical review of the manuscript, and contribution to the final approval of the article.

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