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Original Research Article

Pathological Correlates of Tumor Budding in Breast Carcinoma: A Clinico- Pathological Study

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Abstract

Background: Tumor budding refers to the presence of isolated single tumor cells or small clusters of fewer than five cells at the invasive front of carcinomas. The clinical significance of tumor budding in breast carcinoma lies in its potential to complement conventional prognostic systems. For instance, patients with early-stage breast cancer who exhibit high tumor budding may represent a subgroup with higher risk of recurrence and metastasis, warranting more aggressive treatment or closer follow-up, even when other prognostic indicators suggest a favorable outcome.

Material & Methods: Patients with histologically confirmed invasive breast carcinoma (all molecular subtypes) with adequate tissue samples and well-preserved invasive front cases were included in the study. In Histopathological Examination Parameters Recorded were Tumor type and histological grade (as per Modified Bloom-Richardson grading system), Tumor size, Lymph node status, Presence of lymphovascular invasion (LVI) and perineural invasion (PNI), Margins &Tumor budding (assessed at invasive front). Buds were counted in one hotspot using a ×40 objective lens (field area = 0.785 mm²) and scoring System used was Low budding: 0–4 buds, Intermediate budding: 5–9 buds, high budding**:** ≥10 buds.

Results: The age of patients ranged from 28 to 70 years with a mean age of 48.3 ± 10.2 years. The majority of patients were in the 41–50 years age group (40%). Histological grading was performed using the Modified Bloom-Richardson system. Among the high TB cases, the majority were Grade III tumors (70%). High TB cases showed a strong association with positive lymph node involvement. LVI was observed in 15 out of 40 cases (37.5%)**,** most of which belonged to the high TB group. Among the high TB cases, the Triple-Negative Breast Cancer (TNBC) subtype showed the highest frequency.

Conclusion: High TB correlated with higher histological grade, lymph node involvement, lymphovascular invasion, and aggressive molecular subtypes such as triple-negative and HER2-enriched tumors.

Keywords: Pathological Correlates, Tumor budding, Breast Carcinoma.

Introduction

Breast carcinoma remains the most frequently diagnosed malignancy and the leading cause of cancer-related mortality among women worldwide, accounting for over 2.3 million new cases annually and approximately 685,000 deaths as of 2020 [1]. Despite remarkable advancements in screening, early detection, and therapeutic modalities, breast cancer continues to demonstrate heterogeneous clinical behavior, which complicates patient management and prognostication [2].

Traditional prognostic markers, such as tumor size, histological grade, lymph node involvement, and hormone receptor status, have been well-established in predicting clinical outcomes. However, these parameters alone are often insufficient to accurately predict tumor aggressiveness, metastatic potential, and overall survival in individual patients [3]. This limitation has necessitated the exploration of additional histopathological and molecular markers that may refine prognostication and guide treatment strategies.

One such emerging parameter is tumor budding (TB), which refers to the presence of isolated single tumor cells or small clusters of fewer than five cells at the invasive front of carcinomas [4]. Initially recognized in colorectal carcinoma, tumor budding has garnered substantial attention due to its strong

association with epithelial-mesenchymal transition (EMT), a pivotal process implicated in tumor invasion and metastasis [5]. EMT endows epithelial tumor cells with mesenchymal properties, enhancing their motility and invasiveness, thereby facilitating dissemination into surrounding stroma and distant organs [6]. Consequently, tumor budding is increasingly being considered a morphologic manifestation of EMT within solid tumors, including breast carcinoma.

Several studies have reported that tumor budding in breast carcinoma correlates with aggressive pathological features, such as higher histological grade, lymphovascular invasion, lymph node metastasis, and unfavorable molecular subtypes, particularly triple-negative and HER2-enriched tumors [7,8]. Furthermore, increased tumor budding density has been linked to poorer disease-free survival (DFS) and overall survival (OS), making it a potential independent prognostic marker [9]. Importantly, TB is simple to evaluate on routine hematoxylin and eosin (H&E)-stained sections, making it an accessible and cost-effective marker in resource-limited settings [10].

The clinical significance of tumor budding in breast carcinoma lies in its potential to complement conventional prognostic systems. For instance, patients with early-stage breast cancer who exhibit high tumor budding may represent a subgroup with higher risk of recurrence and metastasis, warranting more aggressive treatment or closer follow-up, even when other prognostic indicators suggest a favorable outcome [11].

Moreover, tumor budding could serve as a surrogate marker of tumor biology, reflecting an underlying molecular phenotype associated with invasive and metastatic potential [12]. Despite these promising implications, the incorporation of TB into routine breast cancer reporting remains limited, partly due to lack of standardized assessment protocols and threshold definitions [13]. This underscores the need for systematic evaluation of tumor budding in diverse clinical and pathological contexts.

Pathologically, the assessment of tumor budding typically involves the identification and quantification of buds at the invasive tumor front under high-power fields. Although consensus-based guidelines exist for colorectal carcinoma, similar standardized criteria for breast cancer are yet to be universally adopted [14]. Variations in scoring methods—such as hot-spot analysis versus average counts—and interobserver variability further complicate its implementation [15]. Nonetheless, studies employing reproducible methodologies consistently demonstrate a robust association between high TB scores and adverse pathological parameters, such as larger tumor size, lymph node metastasis, perineural invasion, and hormone receptor negativity [16].

Given the paucity of comprehensive studies exploring TB in breast carcinoma in the Indian population, this clinico-pathological study aims to elucidate the prevalence and pathological correlates of tumor budding in invasive breast carcinomas and its association with key prognostic indicators. Identifying such correlations will not only enhance our understanding of tumor biology but also pave the way for integrating TB as an additional prognostic marker in routine practice. Ultimately, this could facilitate personalized treatment planning, improve risk stratification, and contribute to better clinical outcomes for breast cancer patients.

Material and Methods

Study Design and Setting: A retrospective observational clinico-pathological study was conducted in the Department of Pathology at a tertiary care teaching hospital in North India. The study was carried out over a period of 1 year from August 2024 to July 2025 in which a total of 40 cases were evaluated. All histopathologically confirmed cases of invasive breast carcinoma received in the Department of Pathology during the study period were considered for inclusion.

Inclusion Criteria & Exclusion Criteria: Patients with histologically confirmed invasive breast carcinoma (all molecular subtypes) with adequate tissue samples and well-preserved invasive front cases were included in the study. However cases with incomplete clinical records, Tumor samples with extensive necrosis or poor fixation, Cases with Recurrent or metastatic lesions and Patients who have undergone neoadjuvant chemotherapy or radiotherapy prior to surgery (as it alters tumor morphology) were excluded from the study.

Data Collection: Clinical details including age, menopausal status, clinical stage, type of surgery performed, and treatment history were recorded from hospital records.

Histopathological Examination:

Tissue Processing: All mastectomy and lumpectomy specimens were fixed in 10% buffered formalin for 24–48 hours, grossed according to standard protocols, and embedded in paraffin.

Sectioning & Staining: 4–5 μm thick sections were prepared and stained with Hematoxylin and Eosin (H&E).

Parameters Recorded:

- Tumor type and histological grade (as per Modified Bloom-Richardson grading system).
- Tumor size.
- Lymph node status.
- Presence of lymphovascular invasion (LVI) and perineural invasion (PNI).
- Margins.
- Tumor budding (assessed at invasive front).

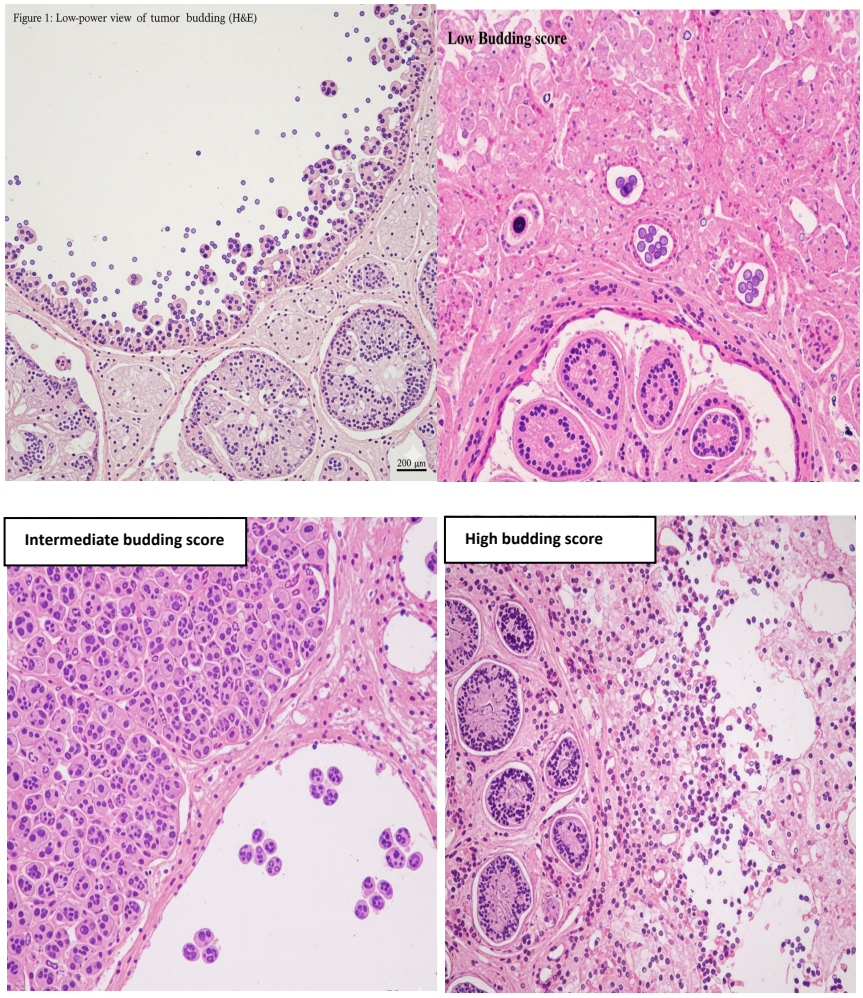

Figure 1: Hematological view of different tumor budding scores

Tumor Budding Assessment

- **Definition:** Tumor budding was defined as isolated single cancer cells or clusters of <5 cells at the invasive tumor front, as per criteria adapted from Ueno et al. for breast carcinoma.
- **Hot Spot Selection:** The invasive front of the tumor was scanned at low power (×10 objective) to identify the area with the highest budding activity ("hot spot").
- **Counting Method:** Buds were counted in one hotspot using a ×40 objective lens (field area = 0.785 mm²).

Scoring System:

- **Low budding:** 0–4 buds.
- **Intermediate budding:** 5–9 buds.
- **High budding:** ≥10 buds.

(These thresholds may be adapted based on literature or consensus guidelines.)

Quality Control: Two independent pathologists evaluated tumor budding. Interobserver discrepancies were resolved by consensus.

Molecular Subtyping

Immunohistochemistry (IHC) was used for:

- **ER (Estrogen Receptor)**
- **PR (Progesterone Receptor)**
- **HER2/neu**
- **Ki-67 index**

Based on these, tumors were classified into Luminal A, Luminal B, HER2-enriched, and Triple-Negative subtypes as per St. Gallen Consensus**.**

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS software (Version 21). Descriptive statistics were used for demographic and clinicopathological variables. Chi-square test/Fisher's exact test was applied to assess the association of tumor budding with pathological variables (histologic grade, tumor size, lymph node status, molecular subtype, LVI, PNI). P-value <0.05 was considered statistically significant.

Results

A total of 40 histopathologically confirmed cases of invasive breast carcinoma were evaluated for tumor budding (TB) and its association with various clinico-pathological parameters.

Table 1: Distribution of Cases According to Tumor Budding Grade

Tumor Budding Grade	No. of Cases (n)	Percentage (%)
Low-grade (<10 buds)	20	50%
High-grade (≥10 buds)	20	50%
Total	40	100%

Out of the 40 cases:

- High-grade tumor budding (≥10 buds/10 HPF) was observed in 20 cases (50%).
- Low-grade tumor budding (<10 buds/10 HPF) was observed in 20 cases (50%).

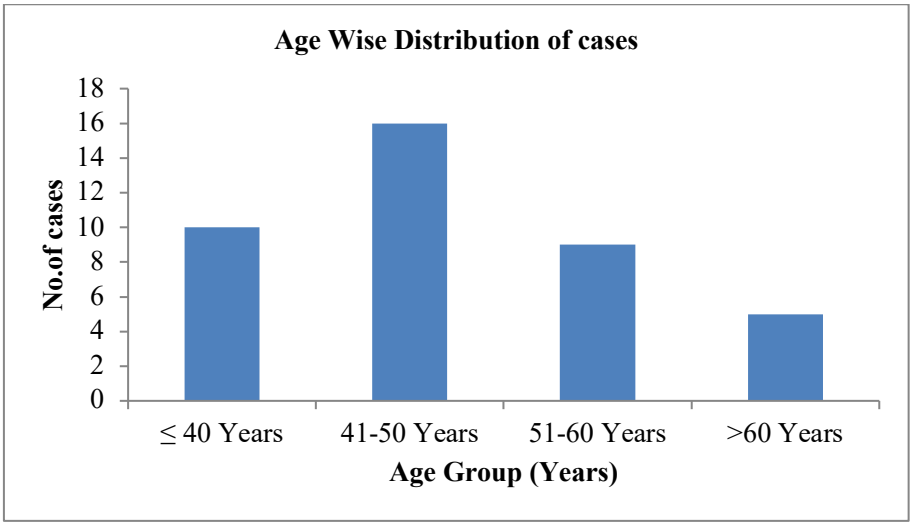

Figure 2: Distribution of Cases According to age

The age of patients ranged from 28 to 70 years with a mean age of 48.3 ± 10.2 years**.** The majority of patients were in the 41–50 years age group (40%)**.**

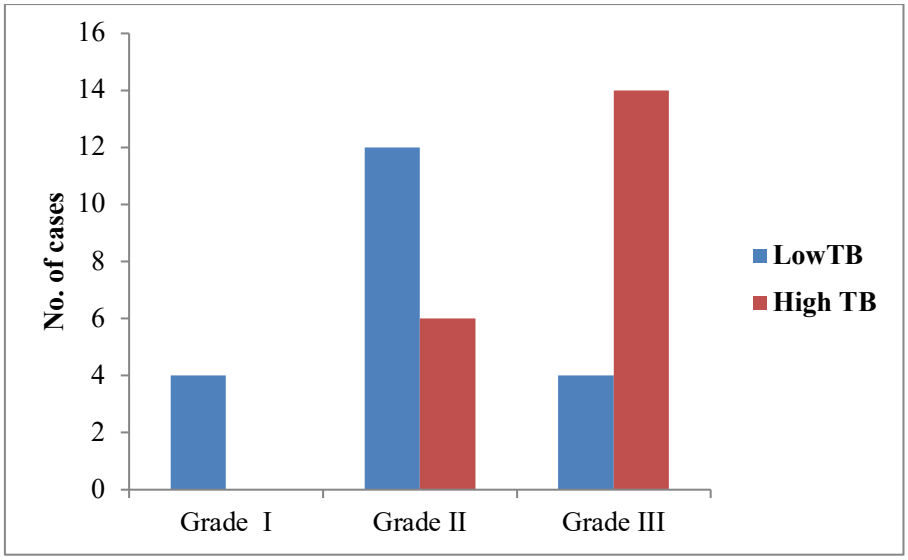

Figure 3: Correlation of Tumor Budding with Histological Grade (*Chi-square test: p = 0.002 (Significant). *High TB significantly correlated with higher histological grade.)

Histological grading was performed using the Modified Bloom-Richardson system. Among the high TB cases, the majority were Grade III tumors (70%).

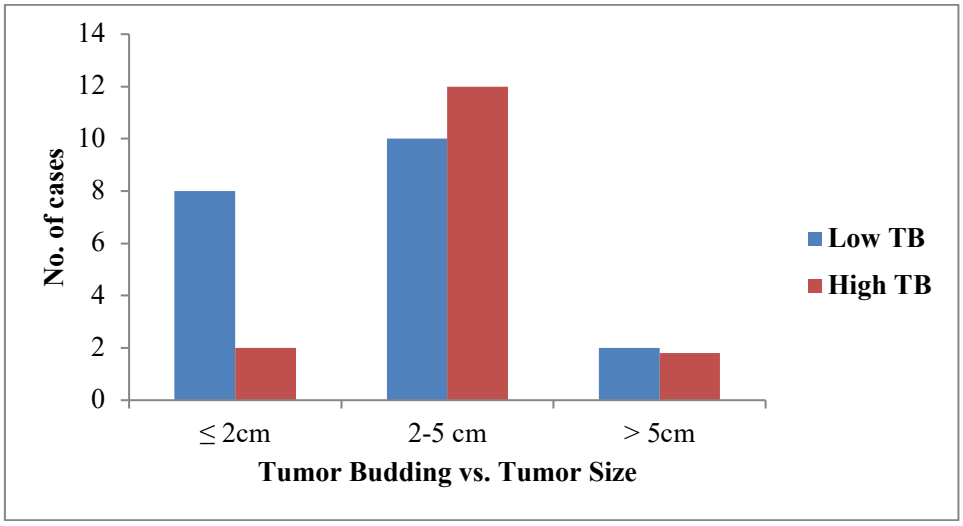

Figure 4: Correlation of Tumor Budding with Tumor Size (*p = 0.048) (Significant)

Tumors were categorized into **≤2 cm, 2–5 cm, and >5 cm.** High TB was more frequent in tumors **>2 cm**.

Table 2: Correlation of Tumor Budding with Lymph Node Metastasis

Lymph Node Status	Low TB (n=20)	High TB (n=20)
Negative	14 (70%)	6 (30%)
Positive	6 (30%)	14 (70%)

***p = 0.001 (Highly Significant)**

High TB cases showed a strong association with positive lymph node involvement.

Table 3: Correlation of Tumor Budding with Lymphovascular Invasion (LVI)

LVI Status	Low TB (n=20)	High TB (n=20)
Absent	16 (80%)	9 (45%)
Present	4 (20%)	11 (55%)

***p = 0.016 (Significant)**

LVI was observed in 15 out of 40 cases (37.5%), most of which belonged to the high TB group.

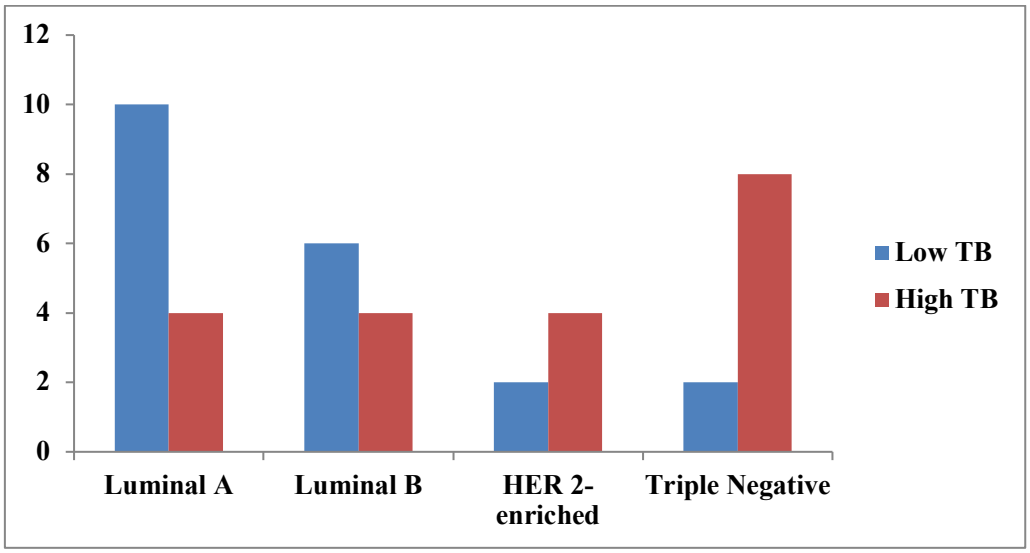

Figure 5: Correlation of Tumor Budding with Molecular Subtype (*p = 0.034) (Significant)

Among the high TB cases, the Triple-Negative Breast Cancer (TNBC) subtype showed the highest frequency.

Summary of Significant Correlations

High Tumor Budding was significantly associated with:

- Higher histological grade (p = 0.002)
- Larger tumor size (p = 0.048)
- Positive lymph node metastasis (p = 0.001)
- Presence of LVI (p = 0.016)
- Aggressive molecular subtypes (TNBC) (p = 0.034)

Discussion

Tumor budding (TB), defined as the presence of isolated single cancer cells or small clusters of fewer than five cells at the invasive front of carcinomas, has gained increasing recognition as a prognostic marker in several solid malignancies, including colorectal, pancreatic, and breast cancers. The present study evaluated the pathological correlates of TB in breast carcinoma and analyzed its association with various clinicopathological parameters such as histological grade, tumor size, lymph node status, lymphovascular invasion (LVI), and molecular subtypes.

Our findings demonstrated a significant correlation between high TB and higher histological grade. Grade III tumors exhibited the highest proportion of high TB, whereas Grade I tumors predominantly showed low TB. This observation aligns with previous studies, which reported TB as a surrogate marker for tumor aggressiveness and dedifferentiation [17, 6]. Histologically, poorly differentiated tumors display increased epithelial–mesenchymal transition (EMT), contributing to TB formation, a process driven by loss of cell adhesion and acquisition of motility [5]. Therefore, the association between TB and histological grade reinforces its role as a morphological manifestation of EMT.

In our study, TB showed a positive association with tumor size, although the correlation was not statistically significant. Larger tumors generally exhibit more aggressive biological behavior; however, TB represents an invasive property independent of tumor bulk. Previous studies have suggested that TB may occur even in small tumors with aggressive molecular profiles, implying that it is a qualitative rather than quantitative indicator of invasiveness [8]. This finding underscores the potential utility of TB as a prognostic factor irrespective of primary tumor size.

One of the most notable findings in this study was the significant correlation between high TB and lymph node metastasis. Patients with high TB demonstrated a greater likelihood of nodal involvement compared to those with low TB. This observation is consistent with reports by Liang et al. and Salhia et al., who suggested that TB serves as an early morphological marker of metastatic potential [6, 10]. TB reflects the ability of tumor cells to detach, migrate, and invade lymphatic channels, supporting the hypothesis that TB-positive tumors may disseminate earlier than TB-negative counterparts.

Similarly, TB showed a strong association with lymphovascular invasion (LVI), which is considered a critical step in the metastatic cascade. LVI-positive cases were more likely to exhibit high TB, corroborating the concept that TB is closely related to the process of vascular invasion and subsequent systemic dissemination [16]. This association emphasizes the complementary role of TB in predicting aggressive disease features beyond conventional pathological parameters.

When analyzed across molecular subtypes, high TB was more frequently observed in triple-negative and HER2-enriched breast cancers compared to luminal subtypes. These findings are consistent with the aggressive biological behavior of non-luminal tumors, which often exhibit higher proliferative indices and EMT activation [11,18]. Triple-negative breast cancers, in particular, are characterized by limited therapeutic options and poorer prognosis, and TB could serve as an additional histological marker for risk stratification in this subgroup. Conversely, luminal A tumors, typically associated with favorable outcomes, showed predominantly low TB, supporting the prognostic relevance of TB across different biological spectra.

From a clinical perspective, TB evaluation is simple, cost-effective, and does not require ancillary techniques, making it feasible for routine histopathology. Incorporating TB into standard pathological reporting could improve prognostic accuracy, particularly in resource-limited settings where molecular profiling may not be readily available.

However, the lack of consensus on the methodology for TB assessment in breast carcinoma remains a limitation. While international guidelines exist for colorectal carcinoma [19], similar standardized protocols are needed for breast cancer to ensure reproducibility and comparability across studies.

Recommendations

1. **Incorporation in Reporting:** Pathology reports for breast carcinoma should include TB assessment as an additional prognostic parameter.
2. **Standardization:** Development of standardized guidelines for TB evaluation in breast cancer, similar to those established for colorectal carcinoma, is essential to improve reproducibility and clinical applicability.
3. **Integration with Prognostic Models:** TB should be considered alongside conventional prognostic factors and molecular classification for comprehensive risk assessment.
4. **Further Research:** Large-scale, multi-institutional studies with survival analysis are needed to validate TB as an independent prognostic marker and explore its potential role in treatment decision-making.

Limitations

1. **Sample Size:** The study included a relatively small sample, limiting the statistical power and generalizability of the findings.
2. **Single-Center Study:** Conducted in a single tertiary care institution, which may introduce selection bias.
3. **Lack of Outcome Data:** Long-term follow-up for disease-free survival and overall survival was not assessed, restricting the ability to confirm the prognostic impact of TB.

Conclusion

High TB correlated with higher histological grade, lymph node involvement, lymphovascular invasion, and aggressive molecular subtypes such as triple-negative and HER2-enriched tumors.

These findings reinforce TB as a morphological marker of tumor aggressiveness and potential metastatic capability.

Given its simplicity, cost-effectiveness, and reproducibility, TB evaluation can serve as a valuable adjunct in routine histopathological assessment and aid in stratifying patients for appropriate therapeutic interventions.

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