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RESEARCH ARTICLE

Ozer et al: Tumor budding in breast cancer

Tumor budding in preoperative breast biopsies predicts sentinel lymph node metastasis

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ABSTRACT

Sentinel lymph node biopsy (SLNB) is a pivotal technique employed to assess the necessity for axillary lymph node dissection (ALND), evaluated during the preoperative phase through clinical and radiological findings. The preoperative identification of sentinel lymph node metastasis has gained paramount importance in the surgical management of breast cancer. Tumor budding (TB) has emerged as a significant prognostic marker across various cancers, including breast cancer, where it is instrumental in detecting lymph node metastasis. This study aims to investigate the role of tumor budding in predicting sentinel lymph node metastasis in preoperative breast biopsies. We included patients diagnosed with breast cancer, specifically those with invasive ductal carcinoma (IDC), who underwent preoperative needle biopsy and subsequent evaluation of postoperative surgical specimens, as well as SLNB at our medical center. The histological slides of these cases were reevaluated, and tumor cell clusters comprising up to four cells were classified as TB. Lymph nodes exhibiting tumor cell involvement, limited to macrometastasis, were classified as positive. A total of 65 patients were enrolled in the study. Among these, 36 patients exhibited TB in their preoperative biopsies, while 29 did not. The median tumor sizes were 20 mm (range: 6–50 mm) in the TB-positive group and 19 mm (range: 2–50 mm) in the TB-negative group (p=0.3). Sentinel lymph node metastasis was detected in 18 patients with TB, compared to only five patients without TB, a difference that was statistically significant (p=0.006). We conclude that evaluating tumor budding in breast tru-cut specimens, in conjunction with clinical and radiological findings, may enhance the preoperative assessment of breast cancer cases requiring SLNB.

Keyword: Breast cancer, tumor budding, sentinel lymph node biopsy.

INTRODUCTION

Breast cancer is still the most frequent cancer diagnosed in women and axillary lymph node metastasis is one of the prognostic factor in early breast cancer. Since William Halsted performed the first radical mastectomy in 1882, which consisted of removal of all breast tissue, all axillary lymph nodes, and both pectoralis muscles; minimally invasive treatment approaches are developing day by day [1]. Axillary lymph node dissection (ALND), however; has for a long time remained important for staging and local-regional control, ALND decision is still has importance due to its complications.

Sentinel lymph node biopsy (SLNB) is a surgical method with pathological assessment that used to assist in the decision-making for ALND, in addition to clinical and radiological evaluations performed in the preoperative period. ALND has maintained its importance for many years ensuring local-regional control and staging in breast cancer [2].

The selection of patients for axillary lymph node dissection has become increasingly meticulous due to the postoperative complications, such as mobility impairment, paresthesia, lymphedema, seroma, and pain, which affect the quality of life in 80% of patients. Additionally, it has been noted that axillary lymph node metastasis is not detected in approximately 80% of early-stage breast cancer cases [1,3,4]. Advanced radiological methods such as ultrasonography and PET/CT, as well as physical examination of the axilla through palpation, are not sufficiently sensitive, especially in the presence of micro-metastasis, which further emphasizes the importance of SLNB [3,5].

Tumor budding, first described in colorectal cancer and typically defined as the formation of single malignant cells or cell clusters of fewer than five malignant cells, which was standardized at the Tumor Budding Consensus Conference [6,7]. Over time, it has increasingly been recognized that TB is associated with epithelial-mesenchymal transition, as described in other organ tumors; studies have reported that TB is also a novel prognostic marker independent of tumor stage and grade in esophageal, gastric, and pancreatic tumors [7,8].

In breast cancer cases, it has been observed that TB is an important indicator of lymph node metastasis and is associated with poor outcomes and low survival [9]. In present

study, we aimed to assess the role of TB presence in preoperative breast biopsies in predicting sentinel lymph node metastasis.

MATERIALS AND METHODS

Present study included cases diagnosed with breast cancer at Bolu Izzet Baysal University Hospital between 2018 and 2023, who had invasive ductal carcinoma as the histological type, and whose preoperative needle biopsy and postoperative surgical specimens were evaluated at our center, and who underwent sentinel lymph node biopsy (SLNB). Cases with other histological types, those whose biopsies were performed at other medical centers but had surgery at our center, and those who underwent axillary lymph node dissection without SLNB, those who received neoadjuvant therapy were excluded from the study. The slides from the cases were re-examined. Tumor budding was first described in colorectal carcinomas and has been standardized through a consensus-based evaluation system [10].

Accordingly , isolated tumor cells separated from the main tumor mass or tumor cell clusters of up to 4 cells were classified as tumor budding. Since it was not possible to determine whether the biopsy material represented the peripheral or central areas of the tumor, tumor budding was not classified as intra- or peritumoral. In accordance with consensus recommendations, the area showing the highest tumor budding density was selected, and the number of buds was counted within an area of 0.785 mm^2 and routine immunohistochemical examination was not performed. We evaluated all tumor area in the specimens.

In biopsy specimens, tumor cell clusters consisting of up to four cells were classified as tumor budding (TB) (Figure 1). Single pathologist evaluated all tumor area in the specimens. She was not blinded to the study. The cases were subsequently divided into two groups: those with TB and those without TB.

Sentinel lymph node dissection was performed through the axilla following methylene blue injection into the nipple–areolar complex, including a total of three lymph nodes, at least two of which were stained. Excised sentinel lymph node counts were as follows: in TB present group median: 3 (min-max: 3-4); in TB absent group median: 3 (min-max: 3-4). The excised lymph nodes were examined in serial sections, and only cases with macrometastasis were included in the study and immunohistochemical examination was not performed.

A total of 82 subjects were initially enrolled, after exclusion of 17 according to the exclusion criteria, data of remaining 65 subjects were enrolled to the study.

Ethical statement

Ethical approval was obtained from institutional ethics committee (Abant Izzet Baysal University Ethics committee, approval date: 25 October 2023, approval number: 2023/345). The study strictly followed the principles outlined in the Declaration of Helsinki.

Statistical analysis

Statistical analyses were performed using IBM SPSS 20.0 software. Normality analysis was conducted with Shapiro Wilk test. Variables that fit into normal distribution were compared with independent samples t test and expressed as means (+/-SD). Other continuous variables were analyzed by Mann Whitney U test and expressed as medians (min-max). Categorical variables were compared with chi-square test and expressed as numbers and percentages. A receiver operative characteristics (ROC) curve analysis used to determine the sensitivity and specificity of tumor budding in detecting sentinel lymph node positivity. Youden index is employed to determination of cut off values in ROC analysis. Binary logistic regression analysis (considering patient age, tumor size, multicentricity and tumor budding) was conducted to find out whether tumor budding was an independent risk factor for sentinel lymph node metastasis. We employed Hosmer-Lemeshow calibration method during binary logistic regression analysis. A p-value of <0.05 was considered statistically significant for all analyses.

RESULTS

Among the patients, 36 (55.4%) had tumor budding (TB) in their preoperative biopsies, while 29 (44.6%) did not. The mean ages of the TB positive and negative groups were 53±12 years and 54 ±13 years, respectively (p=0.77). The average tumor size in patients with TB was 20 mm (6-50), whereas 19 (2-50) mm in patients without TB (p=0.3). Multicentricity was present in 4 (11%) patients with TB, while in 2 (7%) patients without TB (p=0.56). Sentinel lymph node positivity was observed in 18 (50%) patients with TB, while in 5 (17%) patients without TB. This difference was statistically significant (p=0.006), (Table 1).

In ROC analysis, a TB count higher than 3 had a 73% sensitivity and 62% specificity in detecting sentinel lymph node positivity (AUC: 0.69, p=0.01, 95%CI: 0.55-0.82). The positive and negative predictive value of tumor budding in detecting sentinel lymph node metastasis was 72%, and 57%, respectively. In binary logistic regression analysis, considering patient age, tumor size, multicentricity and tumor budding, absence of tumor budding independently reduced the presence of sentinel lymph node metastasis by 80% (p=0.013, OR=0.20, 95%CI=0.06-0.71) (Table 2).

DISCUSSION

Present study showed that sentinel lymph node positivity was more common in patients with TB compared to those without TB. Moreover, the results suggest that the presence of tumor budding in preoperative biopsies is not associated with age, tumor size, or multicentricity, but is associated with a markedly higher rate of sentinel node positivity. In other words, patients who already show TB in biopsy are more likely to have nodal metastasis. This finding suggests that TB is predictive of a more aggressive phenotype, even if tumor size and other factors are similar in patients with breast cancer. The results of present study align with the hypothesis that tumor budding represents a morphologic marker of early invasion / partial epithelial-mesenchymal transition (EMT) and early metastatic potential.

The concept of tumor budding has been better studied in colorectal cancer, but in recent years there's growing interest in breast cancer. A key study by Salhia et al. found that high peripheral tumor budding in surgical specimens was associated with lymph node metastases and lymphatic invasion [11]. In the matched preoperative biopsies in that study, high TB was associated with venous invasion [11]. Thus, our finding (of higher SLN positivity in TB-positive biopsies) is consistent with that prior association.

More broadly, Gujam et al. observed TB in a larger cohort of ductal breast cancers and found that higher tumor budding was associated with adverse pathologic features including lymph node involvement, lymphovascular invasion, and worse cancer-specific survival, independent of other factors [12]. Similarly, in 2023, Ozer also studied TB in invasive ductal breast carcinoma, examined correlations with clinicopathologic parameters and reported that higher tumor budding was often correlated with adverse features [13]. More recently, Ranaee et al. revealed a

significant relationship between the number of tumor buds (both intratumoral and peritumoral) and tumor size, stage, number of involved lymph nodes, and 5-year survival, though they did not find a significant association with age or tumor grade [14]. That is quite consistent with our observations, lack of association with age, but correlation with nodal involvement.

A study published in 2025 by Shah et al. similarly affirmed that high tumor budding was linked to poor prognostic features including higher tumor grade, negative hormone receptor status, and higher T stage [15]. The results of the present work were consisted with the literature data. TB is emerging as a morphologic predictor of nodal metastasis and worse outcome, independent of size, grade, or patient age. One nuance in the present study was that many prior studies examine TB in surgical specimens (after resection), while we analyzed preoperative biopsies. That is an important distinction. In case of TB could reliably be assessed on biopsy and predict nodal metastasis, that has real clinical implications for preoperative risk stratification (such as, decisions on axillary surgery or neoadjuvant therapy). Salhia et al's work already explored tumor budding in core biopsies versus resections and they found that high TB in biopsy was significantly associated with venous invasion, which supports that budding in biopsy was meaningful [11]. Our data extend that finding by linking biopsy TB to sentinel node positivity.

In a recent systematic review and meta-analysis by Buch et al., authors reported that high grade tumor budding was an independent risk factor of lymph node metastasis and lymphovascular invasion [16]. Another meta-analysis studied tumor budding in oral squamous cell carcinoma and revealed that TB was independent risk factor for overall survival but was not associated with lymph node metastasis [17]. Additionally, large observational studies consistently report that higher tumor-budding counts were associated with increased lymph node involvement and other adverse features [11,12,18]. Our data appears to be consistent with literature knowledge.

Tumor budding is recognized as a morphologic marker of early invasion/epithelial mesenchymal transition and is reproducibly associated with increased probability of nodal metastasis and worse outcomes across multiple studies and meta-analyses. These data support TB's potential role as a preoperative risk marker [19,20]. The literature, however, emphasized standardization of TB scoring (definition, field size,

cutoffs) and larger/validated cohorts before routine clinical adoption. Buch et al. specifically called out heterogeneity and the need for standardized reporting [16]. On the other hand, the behavior of TB may differ among molecular subtypes (ER/PR/HER2), some studies have noted associations or lack thereof depending on subtype. For example, Gujam et al. found TB's prognostic value was independent of molecular subtype [12]. However, due to small sample size, we could not perform such subgroup analyses in the present work.

Our study showed that absence of TB reduced the risk of sentinel lymph node metastasis by 80% independent of age, and size and multicentricity of the tumor. That means that, after adjusting for other covariates, patients without TB had one-fifth the odds of having sentinel lymph node metastasis compared to those with TB. According to the analysis, TB remained a strong independent predictor of nodal metastasis even when accounting for tumor size, multicentricity, and age. This observation is consistent with prior breast cancer series demonstrating that higher TB correlated with lymphatic invasion and nodal metastasis [11], and with larger cohorts showing an independent association between TB and adverse outcomes including nodal disease and reduced cancer-specific survival [12]. Meta-analytic data also support this relationship. Pooled estimates indicate that high TB increased the odds of lymph node metastasis roughly twofold (pooled OR was around 2.25), while also being linked to lymphovascular invasion across studies [16]. Our adjusted effect (inverse of OR: 0.20 around OR: 5 for presence of TB) is larger than pooled estimates. However, it remains biologically plausible. TB likely reflected epithelial–mesenchymal transition and an invasive cellular phenotype that is not captured by tumor size or multicentricity alone. Since there is heterogeneity in TB assessment and the modest sample size in the present work, these findings warrant validation in larger, standardized cohorts and inclusion of additional covariates (for example; lymphovascular invasion, grade, molecular subtype) to confirm independent prognostic utility in preoperative decision-making.

The increasing incidence of breast cancer, the growing adoption of minimally invasive approaches, and the complications associated with ALND have underscored the importance of sentinel lymph node biopsy (SLNB), particularly in early-stage patients [5,9]. Despite advancements in physical examination and radiological

imaging, the selection of patients for SLNB in the preoperative period has become increasingly critical.

The main issues in which SLNB will be applied are as follows; patients with clinically negative axillary lymph nodes, patients with clinically negative axillary lymph nodes even if they have multicentric disease, patients planned for breast-conserving surgery and radiotherapy. Also SLNB can be applied after neoadjuvant therapy to patients with clinically negative axillary lymph nodes before treatment or to patients with clinically positive axillary lymph nodes before treatment but who became negative with treatment [21,22].

Axillary lymph node dissection remains a major contributor to postoperative complications in breast cancer patients. Consequently, the decision to perform axillary lymph node dissection is now made with greater caution, with efforts to avoid it whenever possible. While clinical examination and radiological imaging play key roles in determining the need for axillary lymph node dissection, these methods are often insufficient, especially in the presence of micrometastasis, where SLNB becomes indispensable [3].

The main issues where axillary dissection is not recommended even if there are micrometastases in SLNB are as follows; patients with a tumor diameter of ≤5 cm, patients with micrometastases in 1–2 sentinel lymph nodes, patients with clinically negative axilla, patients who have undergone breast-conserving surgery (lumpectomy) and will receive radiotherapy (especially involving the axillary area), and patients who will receive systemic adjuvant therapy (hormonal or chemotherapy) [23,24].

In the context of SLNB, particularly for patients with early-stage tumors of smaller sizes, there is an emerging need for additional prognostic factors. Tumor budding (TB), similar to its growing recognition in various organ carcinomas, has increasingly been recognized as a significant prognostic factor in breast cancer [6]. A meta-analysis of 13 studies also showed that high tumor budding was significantly associated with the risk of lymph node metastasis (OR 2.25; 95% CI 1.52–3.34, $p<0.01$) [16]. Our study found that the presence of TB in preoperative biopsies correlates with a higher rate of sentinel lymph node positivity.

The finding that TB in biopsy correlates with SLN positivity may have several implications in clinical practice. If biopsy TB can reliably predict nodal metastasis,

surgeons might consider more aggressive axillary evaluation (or even sentinel node biopsy planning) in patients whose biopsies already show TB. Hence, TB could help in decision-making about whether to sample more nodes or plan sentinel node biopsy versus full axillary dissection. Moreover, the patients identified at high-risk (by budding) might be counseled differently regarding prognosis or adjuvant therapy. In addition, to translate these observations into clinical practice, there should be standardized protocols for assessing TB in biopsy specimens for example defining bud size/count, number of fields, cutoff thresholds, interobserver reproducibility, and etc.

Present study has some limitations. First, the groups in our work were relatively small (36 with TB, 29 without). Small sample size reduces power to detect differences in other parameters (size, multicentricity) and may inflate the risk of false negatives. In addition, the assessment method of TB (cutoff, number of fields, how buds are defined) may strongly influence reproducibility and comparability. Second, differences in methodology can lead to different results. Standardization is not yet fully established in breast cancer (as opposed to colorectal cancer, where tumor budding scoring is more standardized). Moreover, there may be other factors influencing both budding and nodal spread (such as tumor biology, grade, ER/PR/HER2 profile, Ki-67 index, lymphovascular invasion) that need to be accounted for in multivariable analysis. Third, in present study, our findings were observational and cross-sectional. TB may be a marker rather than a causal driver; the mechanism needs further elucidation (for example; via epithelial-mesenchymal transition, invasion, microenvironment). Another point is the association with nodal metastasis which is promising, however, whether TB in biopsy predicts long-term outcomes (disease-free survival, overall survival) would require prospective follow-up data. First, our study was retrospective so we cannot establish causality. We found only associations. We analyzed TB only with tru-cut biopsy. Another limitation could be evaluation of the TB by a single pathologist, exclusion of micrometastasis patients and lack of immunohistochemical staining which could detect small volume disease. Finally, single center nature of the work was another limitation.

CONCLUSION

Selection of patients for SLNB; still requires more additional prognostic factors. A specific study directly examining the relationship between tumor budding and sentinel lymph node metastasis in preoperative breast biopsies is currently limited in the literature, and studies are mostly conducted on postoperative histological evaluations. Therefore, incorporating TB evaluation in preoperative breast needle biopsy specimens, in addition to clinical and radiological findings, maybe useful in the preoperative identification of patients who would benefit from SLNB.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Characteristics of the study population

		TB present	**TB absent**	***p***
		Mean ± SD*		
Age (years)		53±12	54 ±13	0.77
		Median (min.-max.)**		
TB count (*n*)		11 (2-50)	0 (0-0)	**<0.001**
Size (mm)		20 (6-50)	19 (2-50)	0.3
		n, (%)***		
Multi-centricity	Positive (*n*, (%)	4 (11)	2 (7)	0.56
	Negative (*n*, (%)	32 (89)	27 (93)	
Sentinel LN	Positive (*n*, (%)	18 (50)	5 (17)	**0.006**
	Negative (*n*, (%)	18 (50)	24 (83)	

* Independent samples t test; ** Mann Whitney U test; *** Chi-square test. Abbreviations: TB: Tumor budding; SD: Standard deviation; LN: Lymph node.

Table 2. Results of regression analysis

	p	**OR**	**95% CI**
Age	0.68	1.01	0.963-1.059
Tumor size	0.33	0.98	0.926-1.026
Multicentricity	0.054	0.1	0.009-1.039
Tumor budding	0.01	0.2	0.056-0.712

Abbreviations: OR: Odds ratio; CI: Confidence interval.

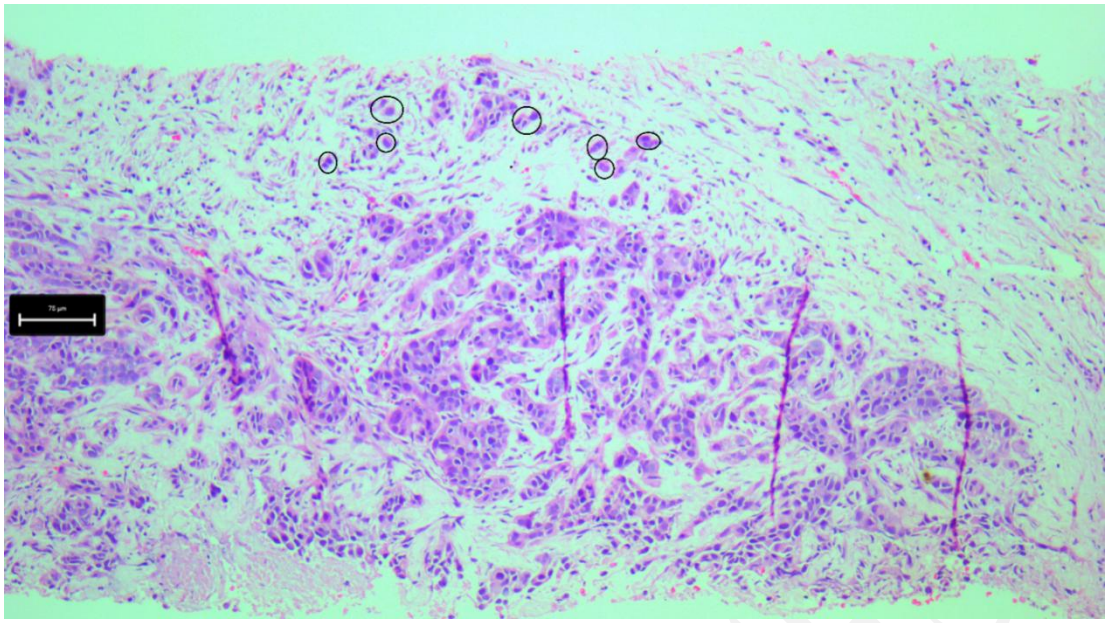

Figure 1. Tumor budding (TB) detached from the main tumor mass in biopsy specimens. Tumor cell clusters consisting of up to four cells were classified as TB; black circles indicate tumor buds (H&E stain, ×100).