Research Article

The Prognostic Value of Tumor Budding in Breast Biopsies and its Relationship with Survival: A Cross Sectional Study

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Abstract: Background: In 1954 Imai described Tumor Budding (TB), as a tumor sprouting at the invasive tumor front of colorectal carcinomas. TB is associated with poor prognosis. TB has prognostic importance in invasive ductal carcinoma of the breast.

Objective: The present study aims to examine TB in breast needle core biopsy specimens with invasive ductal type carcinoma, and its relationship with other clinicopathological parameters and overall survival.

Materials and Methods: From February 2015 to December 2022, patients who had undergone breast carcinoma surgery at the Bolu Abant Izzet Baysal Training and Research Hospital and had preoperative needle core biopsies at the same center were retrospectively analyzed. Needle core biopsy slides were re-evaluated for TB. Tumor size, and nodal status, were retrieved from pathology reports. Overall survival was considered. Analysis of the data was done with statistical software (SPSS 18.0 for Windows, IBM Inc., Chicago, IL, USA).

Results: 122 patients were enrolled in the study. The mean age of the study and control groups were 55±12 years and 54±11 years, respectively. TB was identified in 68 (55%) patients; the rest 54 (45%) patients didn't have any TB. The median value of the metastatic axillary lymph node in the TB absent group was 0 (0-51); in the TB group was 1 (0-21), and this was statistically significant (p=0.03). Lymphovascular invasion was detected in 33 patients (48.5%) in the TB present group and in 14 patients (25.9%) in the TB absent group. That was statistically significant (p=0.01). In the overall survival analysis, mean survival times were lower in the TB group compared to the TB absent group, but it was not statistically significant (p=0.33).

Conclusion: In conclusion, tumor budding is a robust prognostic indicator; therefore, assessing tumor budding especially in core needle biopsy specimens will be very helpful for individual treatment options.

Keywords: Tumor budding, Breast cancer, Biopsy, Size, Lymph node, Survival.

INTRODUCTION

In 1954 Imai described Tumor Budding (TB), as a tumor sprouting at the invasive tumor front of colorectal carcinomas [1]. At the International Tumor Budding Consensus Conference (ITBCC), it was defined as the formation of single malignant cells or cell clusters of up to four cells and evaluating method was standardized [2, 3]. Various studies were conducted on this subject in other organ carcinomas. They showed that TB is associated with poor prognosis, and some reported that TB is also a novel prognostic indicator independent of other prognostic factors [2, 4-6]. Breast carcinomas especially invasive ductal carcinoma is another area where the TB is frequently researched because of the necessity of individual treatment approaches; due to its incidence and clinical burden [7-9]. Inspite of availability of treatment protocols tailored on different patient groups, relapse and metastasis is known to occur. Therefore additional and more efficient prognostic markers are required to predict prognosis and survival [10-12]. Studies have showed that high number of tumor buds are associated with lymphovascular invasion (LVI), lymph node metastasis and shorter survival [13].

Although it is known that TB has prognostic impotance in invasive ductal carcinoma of the breast; due to lack of standardized scoring systems and large-scale studies, it requires further research.

Therefore, the present study aims to examine TB in breast needle core biopsy specimens with invasive ductal type carcinoma, and its relationship with other clinicopathological parameters, prognostic factors-especially tumor size, lypmhovascular invasion, perineural invasion, metastatic lymph node status, extranodal extension (ENE) and overall survival.

MATERIALS AND METHODS

From February 2015 to December 2022, patients who had undergone breast carcinoma surgery at the Bolu Abant Izzet Baysal Training and Research Hospital and have preoperative needle core biopsies at the same centre were retrospectively scanned from the electronic database. Among them some cases excluded for any of the following criterias: 1) those whose diagnosis was

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not invasive ductal carcinoma 2) those whose H&E stained slides were not reached or available for review 3) those whose needle core biopsy performed another centre 4) those whose needle core biopsy performed at our centre but operation performed at an another centre 5) those who received neoadjuvant chemotherapy or radiotherapy 6) those who died due to post-op complications in the first month after surgery 7) those whose clinical data were not reached. 122 patients included in the study.

Clinicopathologic information, including; age, tumor size, nodal status, was retrieved from pathology reports. Overall survival was considered the period after surgery until the death of the patient. Death records were completed on 31st December 2022.

All the H&E slides of the operation materials were re-evaluated for the histological type, lymphovascular invasion, perineural invasion, lymph node metastasis, extranodal extension, multicentricity. Needle core biopsy slides were re-evaluated for the histological type and TB. There is no standardized classification of tumor budding in breast cancer. In our study TB was considered as single tumour cells or cell clusters of up to four cells, as indicated at ITBCC 2016. First, the patients divided into two groups as 'tumor budding absent' or 'tumor budding present'. Then the whole biopsy material scanned for TB and the total number of buds counted (1-51). We grouped lymph nodes into three groups as negative, positive without ENE and positive with ENE. ENE length was not measured in ENE positive lymph nodes.

The study was approved by the Clinical Researches Ethics Committee of the Bolu Abant Izzet Baysal University (Decision number: 2023/27).

STATISTICAL ANALYSIS

SPSS 15.0 for Windows was used for statistical analysis. Kolmogorov Smirnov test was applied to the study variables for normality analysis. The variables with normal distribution were compared with independent samples t-test between 2 groups and with One Way ANOVA test for 3 or more groups. These variables were expressed as mean ±SD. Variables without normal distribution were compared by Mann Whitney U test in 2 groups and by Kruskall Wallis test in 3 or more groups. These variables were expressed as median (min-max). The comparison of categorical variables were conducted with chi-square test. These variables were expressed as numbers and percentages. Pearson's correlation analysis test was used to observe correlation between study variables. The sensitivity and specificity of study variables in determining tumor budding was analyzed with Receiver Operative Characteristics (ROC) curve analysis. It is considered significant when the p value was lower than 0.05.

RESULT

In this study, 122 samples of invasive ductal carcinoma were assessed. TB was identified in 68 (55%) patients and not identified in 54 (45%) patients. The average age of the TB present group was 54±11 years, of the TB absent group was 55±12 years and it was not statistically significant (p=0.91). TB median count was 10 (2-50). The average tumor size of the TB absent group was 19.5mm (2-70mm), of the TB present group 20mm (5-170mm) and it was not significant between the groups (p=0.13). However, the correlation of TB count and tumor size was statistically significant; tumor size increased as the TB count increased (p=0.01).

Metastatic lymph nodes were ranging between 0-51, and the mean metastatic lymph node number was 4. The median value of the metastatic axillary lymph node in the TB absent group was 0 (0-51); and in the TB present group was 1 (0-21). This finding was significant (p=0.03). In addition, the correlation of TB count and metastatic lymph node number was significant (p=0.02). In the ROC analysis performed with TB count and axillary lymph node metastasis, TB count cut-off was found to be 2.5, with 63% sensitivity and 57% specificity.

Multicentricity was seen in 9 patients (13.2%) in the TB present group and in 3 patients (5.6%) in the TB absent group; and that was not significant (p=0.15). Lymphovascular invasion was detected in 33 patients (48.5%) in the TB present group and in 14 patients (25.9%) in the TB absent group. That was statistically significant (p=0.01). Perineural invasion was seen in 13 patients (19.1%) in the TB present group and in 7 patients (13%) in the TB absent group; that was not significant (p=0.35).

ENE was detected in 16 patients (23.5%) in the TB present group and in 9 patients (16.7%) in the TB absent group; that was not significant (p=0.33).

The median follow-up period of the TB present group was 28 months, and the follow-up interval ranged from 3 to 91 months. The mean follow-up period of the TB absent group was 39,5 months, and the follow-up interval ranged from 2 to 95 months. 7 (10.3%) of the patients with TB died, and 61(89.7%) were still alive whereas 4 (7.4%) of the patients died in TB absent group and 50 (92.6%) were alive (p=0.58). In the overall survival analysis, mean survival times were lower in the TB present group compared to the TB absent group but it was not statistically significant (p=0.33), (Table **1**). However, in the ROC analysis performed with TB count, TB count cut-off was 3.5, with 63% sensitivity and 57% specificity (AUC:0.59, P=0.34, 95% CI:0.40 -0.77), (Fig. **1**).

DISCUSSION

Invasive ductal carcinomas are heterogeneus, thus have clinical behavior and therapeutic outcome. Therefore additional, more efficient prognostic markers are required to predict prognosis; also for individual treatment approaches [10-12]. Tumor budding is a histological process, that was described in colorectal carcinoma first by Imai in 1954 [1] From that day on, it was a subject of the studies in several malignancies as a prognostic factor [11,14,15]. Therefore TB was accepted as a more sensitive prognostic factor, prediction of aggressiveness and worse outcome [4,11,16].

Table 1. The Relationship between Tumor Budding and Clinicopathological Parameters.

		Tumor Budding Present n=68	Tumor Budding Absent n=54	p
Age (years)		54 ±11	55±12	0.91
Tumor size (mm)		20 (5-170)	19.5 (2-70)	0.13
Metastatic lymph nodes (median (min-max))		1(0-51)	0(0-51)	0.03
Multicentricity (n, %)		9 (13.2%)	3 (5.6%)	0.15
Lymphovascular invasion (n,%)		33 (48.5%)	14 (25.9%)	0.01
Perineural invasion (n,%)		13 (19.1%)	7 (13%)	0.35
Extranodal extension		16 (23.5%)	9 (16.7%)	0.33
Survival time (month) (median (min-max))		28(3-91)	39.5(2-95)	0.33
Survival (n,%)	dead	7 (10.3%)	4 (7.4%)	0.58
	alive	61(89.7%)	50 (92.6%)	

At the ITBCC the method of evaluating, scoring and reporting of TB was standardized in colorectal carcinomas [3]. For other organ malignancies this is still a subject for debate. Various studies conducted on TB assessment methods [7]. First of all, there has not been a consensus on the number of the cells of TB. Some authors accept the cell clusters of five cells or less and the others accept up to four cells. ITBCC had described TB; up to four cells. Adhering to ITBCC standards, we considered TB as single malignant cell or malignant cell groups up to four cells. We did not perform immunohistochemistry to be more applicable in reporting protocols and also as recommended at ITBCC. Some studies used immunohistochemistry for evaluating buds and some of them did not [9,11,13,14,17]. Despite the various evaluation methods, all these studies had showed that high TB scores was associated with poor prognosis and decreased survival [4,5,8].

In the present study, TB in the needle core biopsy specimens was statistically associated with tumor size, pT stage, angiolymphatic invasion, number of the metastatic axillary lymph nodes. However, in needle core biopsy specimens TB was not associated with overall survival, age, perineural invasion, extranodal extension, and multicentricity.

So many previous studies have found similar associations between TB and angiolymphatic invasion, axillary lymph node metastasis [4,5,8,11,16-20]. In line with them, we found a significant association. Although some of them have found an associations between TB and tumor size [4,17] ; the others have not [8,9,16]. In the current study we found a clear association with tumor size.

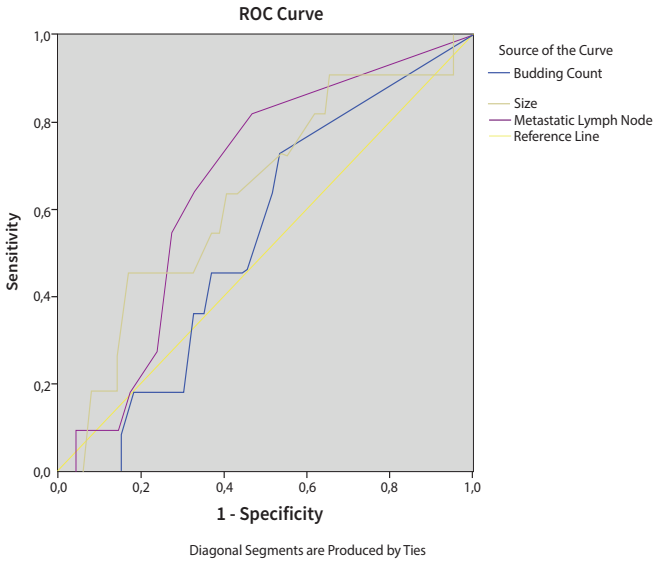

Fig. (1). Roc Curves in Determining the Relationships Tumor Budding Count, Size, Metastatic Lymph Node.

There was various studies that investigating the association of TB with survival. Survival evaluated as overall or as cancer specific survival. They have found strong relationship between TB and survival, especially high TB groups have had lower survival times [4,5,8,11]. Li, X. *et al*. have found that TB was a independent prognostic factor of cancer specific survival [4]. However, all of these studies conducted on surgery materials. There was not any study investigating TB in needle core biopsies. Therefore, in contrast with literature we could not find association between TB in biopsy specimen and survival. In the ROC analysis performed with TB count and overall survival data, TB count cut-off was 3.5, with 63% sensitivity and 57% specificity.

LIMITATIONS

Limitations of present study are small study cohort, single center nature of the work and short follow-up period.

CONCLUSION

The present study provides extensive assessment of the associations between tumor budding and the other clinicopathological parameters. Therefore, correlation of tumor budding and other poor prognostic factors such as tumor size, angiolymphatic invasion, number of the metastatic axillary lymph nodes was strong. With all these results we think that tumor budding is a strong prognostic indicator; therefore, assessment of tumor budding especially in core needle biopsy specimens will be very helpful for individual treatment options.

CONFLICT OF INTEREST

Declared none.

ACKNOWLEDGEMENTS

Declared none

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Received: May 16, 2023 Revised: July 26, 2023 Accepted: August 02, 2023