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ORIGINAL ARTICLE

Prognostic Importance of Tumor Deposits in the Ipsilateral Axillary Region of Breast Cancer Patients

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Abstract

Tumor deposits (TD) are irregular discrete tumor masses in adipose tissue, discontinuous from the primary tumor, that are described in various cancers. The incidence and/or prognostic value of TD in breast carcinomas have not been studied so far. We reevaluated 145 breast cancer patients, diagnosed and treated between 2001 and 2006 at our institution for the presence and incidence of TD. Histologic type, grade, size of the primary tumor, estrogen receptor, progesterone receptor, human epidermal growth factor receptor-2 status of the tumor, and presence of peritumoral lymphovascular invasion were included in the data. TD were detected in 42 cases (29.0%). The mean age of the patients was 52.2 years (27–82). Most patients (79.3%) had either invasive carcinoma of no special type (NST) or invasive lobular carcinoma, and most tumors (86.9%) were either grade 2 or 3. After excluding TD from the number of metastatic lymph nodes, the pN status of 9 patients changed. Univariate analysis of 110 patients with follow-up information revealed that the new pN status ($p = 0.036$), presence of local recurrence ($p = 0.016$) and TD ($p = 0.003$) were significantly correlated with distant metastases. The median follow-up of the patients was 84 months (5–161), 10-year disease-free survival and overall survival were 67.2% and 73.7%, respectively. In multivariate analysis, presence of TD remained independently associated with distant metastasis ($p = 0.002$). The probability of distant metastasis was 3.3 times higher in patients with TD. These results emphasize that TD are present in breast cancer patients, and that their presence should warn the clinician in terms of possible distant metastasis. Therefore, presence of TD, the evaluation of which is neither time consuming nor require sophisticated methods, should be included in pathology reports.

Keywords Breast cancer · Tumor deposits · Axillary dissection · Prognosis

Introduction

Tumor deposits (TD), that were originally recognized by Gabriel et al. in colorectal adenocarcinomas [1], have been described in various cancers since then, including gastric, biliary, pancreatic carcinomas and cholangiocarcinomas as well as head and neck carcinomas [2–5]. It has been reported by many studies that colorectal cancer patients with TD exhibit poor prognosis [6–14]. Although not as much, recent studies regarding TD in other organ systems emphasize the prognostic value of these deposits.

TD are described as irregular discrete tumor masses in adipose tissue, discontinuous from, but within the lymphatic drainage of the primary tumor. By definition, no residual lymph node tissue should be present in these tumor masses. The exact developmental mechanism is still controversial. However, tumor deposits are evaluated and classified according to the adjacent histologic structures; i.e. perineural, perivascular and perilymphatic.

Breast cancer is the most common malignancy in women worldwide. Breast cancer staging has been performed using the tumor, node and metastasis (TNM) staging system since late 1940's, and it is a major determinant of prognosis.

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According to the most recently updated Cancer Staging Manual published by the American Joint Committee on Cancer (AJCC), invasive tumor nodules within axillary adipose tissue not associated with definitive lymph node architecture, are classified as regional lymph node metastases (pN) [15]. However, such lesions seem to be similar to TD of carcinomas of other organs described above, and they may also be referred to as TD of breast carcinomas. To the best of our knowledge, there is no study evaluating the existance, incidence, and/or prognostic value of TD in breast carcinomas.

In this study, we aimed to re-evaluate our breast cancer patients in terms of presence of TD in the axillary adipose tissue, and to determine the prognostic value of TD by re-staging the lymph node status.

Materials and Methods

Lymph node positive breast cancer patients, diagnosed and treated at Dokuz Eylul University Faculty of Medicine between 2001 and 2006, were selected from the archives of our pathology department. One-hundred and forty-five patients, in whom the slides of the axillary dissection materials were obtained from the archive, were included in the study. The surgical process performed in all patients were either breast conserving surgery or simple mastectomy, accompanied by axillary dissection. None of the patients had received chemo/radiotherapy before surgery.

Patients' clinical and follow-up information, including survival data were obtained from medical charts and registry records. Disease-free survival (DFS) was defined as the time from the date of surgery to the date of disease recurrence or last follow-up. Overall survival (OS) was calculated as the time from the date of surgery to the date of death from any cause. Median follow-up was calculated for patients who were alive at the last follow-up visit.

The slides of the axillary dissection materials were re-evaluated by 3 pathologists (BY, NSS, SEK). Any tumor mass in the adipose tissue devoid of lymph node architecture, regardless of its shape, was identified as a tumor deposit (Fig. 1). In case of uncertainty, the slides were evaluated by 2 expert pathologists (MGD, SS), and consensus was provided. The total number of lymph nodes, metastatic lymph nodes, and the number of TD were documented. The lymph node classification of the TNM staging system was re-performed for each case according to the most recent WHO classification of breast tumors [16].

The histopathologic parameters included in the data were histologic type and grade, as well as size of the primary tumor, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2) status of the tumor, and presence of peritumoral lymphovascular invasion. Lymphatic and vascular invasion were evaluated separately on hematoxylin-eosin stained sections. Lymphatic invasion was defined as tumor cell nests in spaces and around the clump of tumor cell nests that were lined by flattened endothelium with no supporting smooth muscle or elastica, and/or were filled with lymphatic fluid. Vascular invasion was defined as tumor cell nests in spaces and around the clump of tumor cell nests that were lined by endothelium, that is, not flattened, and/or were filled with red blood cells. Tumor cell nests in spaces that were either not lined by endothelial cells or were lined by endothelial-like cells were classified as stroma-invasive tumor cell nests [17, 18].

Statistical Analysis

Statistical analyses were performed using SPSS 15.0 software (SPSS, Chicago, IL). The patients were grouped according to the presence or absence of tumor deposits. Comparisons between the groups were performed using chi-square and Mann-Whitney U tests. DFS and OS rates were estimated using the Kaplan-Meier method. The log-rank test was used to compare survivals of different groups. The Cox proportional hazards model was performed for multivariate analysis. The tests were two-sided. Results were considered to be significant at $p < 0.05$.

Results

A total of 145 breast cancer patients were included in this study. One-hundred and eight patients (74.5%) were both diagnosed and treated at Dokuz Eylul University Faculty of Medicine, whereas 37 patients (25.5%) were consultation cases, in whom the diagnoses were confirmed by our pathology department, and treatment processes proceeded in this institution. All of the patients had axillary lymph node metastasis. In 26 patients (17.9%) sentinel lymph node excision followed by axillary lymph node dissection was performed, while 118 patients (81.4%) had axillary lymph node dissection without sentinel lymph node biopsy. In 1 consultation case the type of axillary surgery could not be determined. Following surgery, all the patients had received adjuvant chemotherapy as well as adjuvant radiotherapy, both to the axillary and the supraclavicular regions, with a dose of 50Gy in 25 fractions. Additionally, 123 patients who had either ER and/or PR positive tumors received adjuvant endocrine therapy, and 29 patients received adjuvant targeted anti-HER2 treatment.

Most of the patients were female (99.3%), while there was only one male patient (0.7%). The mean age of the patients was 52.2 years, ranging between 27 and 82 years. Pathological T status of 40 patients (27.6%) was pT1, and 3 of these pT1 cancers were microinvasive breast carcinoma (pT1mi). The tumor size of 8 consultation cases (5.5%) could not be obtained. Nineteen patients (13.1%) had micrometastasis in their

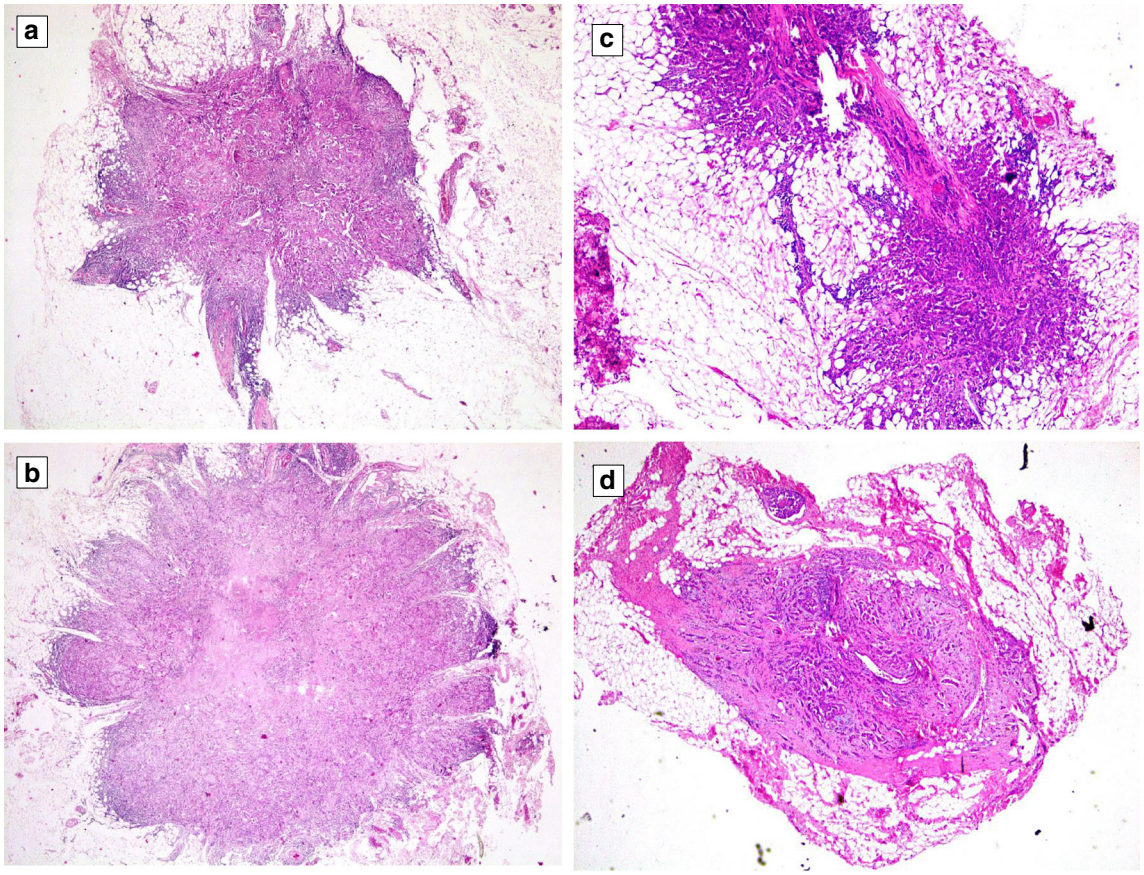

Fig. 1 Tumor deposits with irregular contours (**a**) (H&E staining, 20x), (**b**) (H&E staining, 40x), (**c**) (H&E staining, 20x), and (**d**) tumor deposit with regular contours (H&E staining, 20x) in the axillary adipose tissue. No lymph node structure is seen

lymph nodes; the number of lymph nodes with micrometastasis ranged between 1 and 3. The clinicopathologic features of the patients are summarized in Table 1.

TD were found in 42 of 145 patients (29.0%). The mean number of TD was 3.6, ranging between 1 and 22. After excluding TD from the number of metastatic lymph nodes and re-staging the N classification of cases, 9 patients had lower N stage. TD were detected in 3 (15.8%) out of 19 patients with micrometastasis, and in 39 (31.2%) out of 125 patients with macrometastases ($p = 0.169$). In one consultation case, presence of micrometastasis could not be evaluated properly, due to the quality of the section.

TD were present in 15 of 67 (22.4%) invasive carcinoma NST, 15 of 48 (31.3%) invasive lobular, and 12 of 30 (40.0%) mixed invasive breast carcinoma cases. Most of our cases were hormone receptor (ER and/or PR) positive. Among the cases with known HER2 status, HER2 positivity was detected in 20% of tumors. Insitu hybridization results of 19 HER2 score 2(+) cases could not be obtained, however according to the clinical files, none of these patients had received targeted anti-HER2 treatment. HER2 status of 1 consultation case could not be evaluated properly due to artificial defects. Lymphatic and vascular invasion were present in 138 (95.2%) and 63 (43.4%) patients, respectively.

Follow-up data of 35 patients (24.1%) could not be obtained. Locoregional recurrence was detected in 7 of 110 patients (6.4%), whereas distant metastasis was present in 30 patients (27.3%). The most common sites of distant metastasis were bone (18 patients), followed by liver (11 patients). Twenty-two of 110 patients (20.0%) were dead of either disease or other causes, and 88 patients (80.0%) were still alive. The median follow-up of the patients was 84 months (5–161), 10-year DFS and OS were 67.2% and 73.7%, respectively.

In univariate analysis, there was no significant correlation between the presence of TD and pT ($p = 0.089$), lymphatic ($p = 0.083$) or vascular invasion ($p = 0.197$), ER ($p = 0.521$), PR ($p = 0.668$) or HER2 status ($p = 0.726$). Presence of TD was not significantly correlated with presence of locoregional recurrence ($p = 0.517$) or OS ($p = 0.166$), either; 28.6% of patients with TD, and 17.1% of patients without TD were dead of disease or other causes. On the other hand, TD were found in most patients with pN3 status (71.1%), whereas most patients with pN1 status (90.0%) did not have TD ($p < 0.001$). This statistical significance remained the same in the new pN status of tumors. There was also significant correlation between presence of TD and distant metastasis ($p = 0.003$).

Table 1 Clinicopathologic features of the patients and their association with clinical outcome

Characteristics	No. of patients (%)	TD+ (%)	*P*
Histologic type			0.191
Invasive carcinoma of no special type (NST)	67 (46.2)	15 (35.7)	
Invasive lobular carcinoma	48 (33.1)	15 (35.7)	
Other*	30 (20.7)	12 (28.6)	
Histologic grade ǂ			0.646
1 (low)	11 (7.6)	2 (5.4)	
2 (intermediate)	74 (51.0)	19 (51.4)	
3 (high)	52 (35.9)	16 (43.2)	
Unknown	8 (5.5)		
Multifocality of tumor			0.669
Unifocal	113 (77.9)	32 (28.3)	
Multifocal	31 (21.4)	10 (32.3)	
Unknown	1 (0.7)		
pT ǂǂ			0.089
1	40 (27.6)	7 (16.7)	
2	63 (43.4)	20 (47.6)	
3	13 (9.0)	5 (11.9)	
4	21 (14.5)	10 (23.8)	
Unknown	8 (5.5)		
pN			<0.001
1	60 (41.4)	6 (14.3)	
2	47 (32.4)	9 (21.4)	
3	38 (26.2)	27 (64.3)	
Lymphatic invasion			0.083
Positive	138 (95.2)	42 (100.0)	
Negative	7 (4.8)	0 (0.0)	
Vascular invasion			0.197
Positive	63 (43.4)	22 (52.4)	
Negative	82 (56.6)	20 (47.6)	
Estrogen receptor status			0.521
Positive	110 (75.9)	30 (71.4)	
Negative	35 (24.1)	12 (28.6)	
Progesterone receptor status			0.668
Positive	111 (76.6)	31 (73.8)	
Negative	34 (23.4)	11 (26.2)	
HER2 status			0.726
Positive	29 (20.0)	9 (21.4)	
Negative	96 (66.2)	28 (66.7)	
Unknown ϕ	20 (13.8)	5 (11.9)	
Site of recurrence ϰ			
Local-regional	7 (6.4)	3 (8.6)	0.517
Distant	30 (27.3)	16 (45.7)	0.003

*Other histologic types include mixed invasive carcinoma NST and invasive lobular carcinoma, as well as mucinous, micropapillary and medullary carcinomas

ǂ Histologic grade of 3 microinvasive breast cancer patients are given as nuclear grade only

ǂǂ pT of 8 consultation cases (5.5%) are unknown

ϕ 19 of 20 patients with unknown status were scored as 2(+) immunohistochemically, the insitu hybridization results of the patients could not be obtained

ϰ Follow-up data of 35 patients (24.1%) could not be obtained

Table 2 Multivariate analysis of distant metastasis in breast cancer patients

Variable	Odds Ratio	95% CI	*P*
Histologic grade 2	0.6	0.1–3.8	0.630
Histologic grade 3	2.1	0.4–11.7	0.413
Locoregional recurrence	6.4	0.9–45.2	0.063
Tumor deposits	3.3	1.3–8.8	0.015

Of 110 patients with follow-up information, presence of distant metastasis was significantly correlated with the new pN status ($p = 0.036$) and presence of local recurrence ($p = 0.016$) using Kaplan-Meier analysis. There was limited significance between the presence of distant metastasis and histologic grade ($p = 0.052$). The proportion of distant metastasis in the new pN1, pN2 and pN3 patients were 17.4%, 27.9% and 47.6%, respectively. In addition, 73 of 88 patients (83.0%) still alive, did not have distant metastasis, whereas 15 of 22 patients (68.2%) who were dead, showed distant metastasis ($p < 0.001$). The probability of distant metastasis was 3.3 times higher in patients with TD. On the other hand, ER ($p = 0.449$), PR ($p = 0.310$), HER2 status ($p = 0.494$), presence of lymphatic ($p = 0.811$) or vascular invasion ($p = 0.516$) were not correlated with presence of distant metastasis.

Multivariate analysis was performed for parameters that were statistically significant in the univariate analysis, including the new pN status, presence of local recurrence and TD, as well as histologic grade (Table 2). Presence of TD remained independently associated with distant metastasis (Fig. 2). Although not statistically significant, the mean survival time among patients with and without TD was 116.264 vs 138.315 months, respectively (Fig. 3).

Discussion

TD were first described in colorectal carcinomas, and they are currently included as a parameter in AJCC classification. These lesions are observed in many types of carcinomas, including gastric, biliary, pancreatic carcinomas and cholangiocarcinomas, as well as head and neck carcinomas [2–5]. The incidence of TD in different types of cancers are variable, however, there are no series in the literature that could not find TD in a certain type of carcinoma. For instance, the incidence of TD in rectal carcinomas varies from 4.5% to 31.5%, in colon carcinomas from 16.6% to 25.5% [12, 19], and in gastric carcinomas from 17.8% to 24.0% [4, 20]. Sarioglu et al. have observed TD in 17.1% of 140 head and neck carcinoma cases [5].

Carcinomas in general disseminate following similar routes. Therefore, it should not be an unexpected finding to identify similar lesions in breast carcinomas. In our series, we have identified lesions which would be interpreted as TD in colorectal carcinoma cases, in 29.0% of our patients. The developmental mechanism of TD is still controversial. According to some authors, TD occur as a result of tumor growth inside or along lymphatic or vascular structures or nerves, while there are still some authors who believe that TD are potentially positive lymph nodes, that are no longer recognizable because of their replacement by tumor cells [7, 21, 22].

In some cases it may be difficult to distinguish TD from positive lymph nodes morphologically. Round shape, a peripheral rim of lymphocytes or lymphoid follicles, a possible subcapsular sinus, residual lymph node in the surrounding fibroadipose tissue and a thick capsule have been suggested to be the most useful features that favour a positive lymph node [23]. Care should be taken while evaluating such

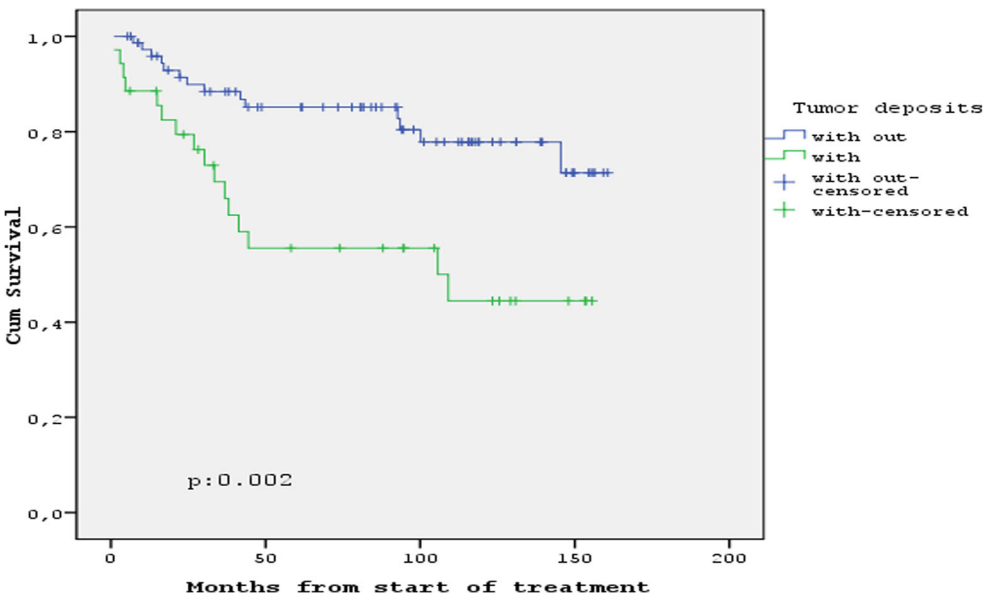

Fig. 2 Kaplan-Meier estimates of the presence of distant metastasis in breast cancer patients with and without tumor deposits

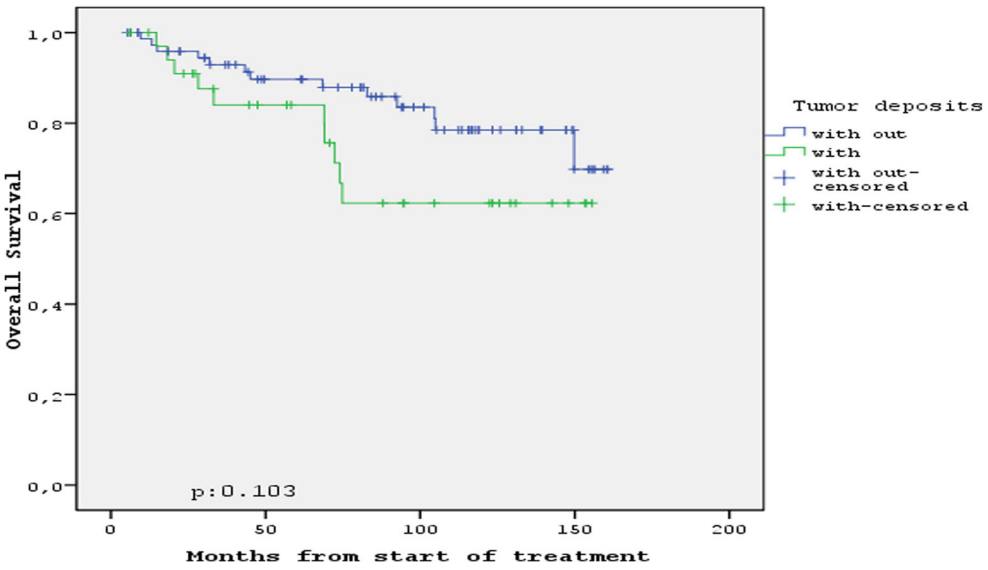

Fig. 3 Kaplan-Meier estimates of the overall survival of breast cancer patients with and without tumor deposits

neoplastic infiltrates, as TD may show either regular or irregular contours. The former is likely related to lymphatic/perilymphatic spread, whereas the latter is likely related to vascular/perivascular spread [12]. There are various studies in the literature that have categorized the morphologic patterns of TD [8, 24]. Basically, they can be classified according to the adjacent histologic structures, as perilymphatic, perivascular, or perineural. Nevertheless, as more than one pattern is present in most patients, in some, the origin cannot be determined. This, can best be defined as a journey along an "allocated highway", allowing escape from immune system surveillance, according to Sarioglu et al. [5].

Extensive perinodal invasion of metastatic lymph nodes, in which the whole lymph node architecture is obliterated, may mimic TD. Similarly, chemo/radiotherapy before surgery may also complicate evaluation, since chemotherapy may result in replacement of the lymph node with fibrosis, chronic mononuclear cell infiltration and histiocytes. TD have been reported in 17% to 48% of patients with colorectal carcinoma after NACT [7]. Nagtegaal suggests that special care is required in staging patients treated with neoadjuvant therapy, since they seem to have a different origin [7].

Various studies in the literature emphasize the adverse prognostic value of TD in colorectal cancers [6–9, 11–14], and currently TD are included in the TNM classification of colorectal carcinomas [15]. Although the prognostic implications of TD in gastric carcinoma patients have not been well emphasized in the literature, Ersen et al. have demonstrated prognostic impact of TD in intestinal type and vascular invasive gastric cancers, especially regarding the recurrence-free survival [4]. In addition, Sarioglu et al. have observed poor prognostic association of TD in head and neck cancers [5]. As might be expected, we have also recognized TD as a poor prognostic marker in breast carcinoma cases. In our series, the presence of TD was found to be an independent prognostic marker associated with distant metastasis ($p = 0.002$). The probability of distant metastasis was 3.3 times higher in patients with TD.

We believe that such a poor prognostic marker, probably reflecting a different pathway of metastasis, should be reported in breast carcinoma cases. The evaluation of the patients for these lesions is neither time consuming nor require other sophisticated methods. Prognostic markers, allowing extensive application seem to be very precious. Moreover, association of distant metastasis with TD in our series, deserves further investigation. We believe these findings suggest the possible value of further studies about TD in breast carcinomas, which has a potential to become an easily determined prognostic marker with a potential to be included in UICC T classification, like colorectal carcinomas.

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