Original Article

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Pure Tubular Breast Carcinoma: Clinicopathological Characteristics and Clinical Outcomes

Selman Emiroglu[1], Asmaa Mahmoud Abuaisha[2], Mustafa Tukenmez[1], Neslihan Cabioglu[1], Aysel Bayram[3], Vahit Ozmen[4], Mahmut Muslumanoglu[1]

[1]Breast Surgery Unit, Department of General Surgery, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey
[2]Department of Genetics, Institute of Health Sciences, Istanbul University, Istanbul, Turkey
[3]Department of Pathology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey
[4]Breast Surgery Unit, Department of General Surgery, Grup Florence Nightingale Hospital, Istanbul, Turkey

ABSTRACT

Objective: Tubular breast carcinoma (TBC) is a rare subtype of breast carcinoma (BC) with a good prognosis. In this study, we aimed to assess the clinicopathological characteristics of pure TBC (PTBC), analyze factors that may influence long-term prognosis, examine the frequency of axillary lymph node metastasis (ALNM), and discuss the need for axillary surgery in PTBC.

Materials and Methods: Fifty-four Patients diagnosed with PTBC between January 2003 and December 2020 at Istanbul Faculty of Medicine were included. Clinicopathological, surgical, treatment, and overall survival (OS) data were analyzed.

Results: A total of 54 patients with a mean age of 52.2 years were assessed. The mean size of the tumor was 10.6 mm. Four (7.4%) patients had not undergone axillary surgery, while thirty-eight (70.4%) had undergone sentinel lymph node biopsy and twelve (22.2%) had undergone axillary lymph node dissection (ALND). Significantly, four (33.3%) of those who had undergone ALND had tumor grade 2 (p = 0.020) and eight of them (66.7%) had ALNM. Fifty percent (50%) of patients who were treated with chemotherapy had grade 2 and multifocal tumors and ALNM. Moreover, the frequency of ALNM was higher in patients with tumor diameters greater than 10 mm. Median follow-up time was 80 months (12–220). None of the patients had locoregional recurrence, but one patient had systemic metastasis. Furthermore, five-year OS was 97.9%, while ten-year OS was 93.6%.

Conclusion: PTBC is associated with favorable prognosis, good clinical outcomes and high survival rate, with rare recurrences and metastases.

Keywords: Pure tubular breast carcinoma, clinicopathologic characteristics, axillary lymph node metastasis, and clinical outcomes

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Key Points

- Pure tubular breast carcinoma (PTBC) is associated with favorable prognosis and clinical outcomes.
- Fifty percent (50%) of PTBC patients who were treated with chemotherapy had grade 2 and multifocal tumors, and axillary lymph node metastasis (ALNM).
- The frequency of ALNM was higher in PTBC patients with tumor diameters greater than 10 mm.

Introduction

Tubular breast carcinoma (TBC) is a rare subtype, accounting for 1–2% of all breast carcinomas (BC) (1). TBC is a variant of invasive ductal carcinoma (IDC), characterized by well-formed tubular or glandular structures that are similar to structures seen in non-neoplastic mammary parenchyma (2). TBC is generally positive for estrogen receptors (ER) and usually positive for progesterone receptors (PR) and negative for human epidermal growth factor receptor-2 (HER2) overexpression (1). Histologically, TBC is classified into pure and mixed. Pure TBC (PTBC) contains a minimum of 90% tubular elements, and rare to no mitotic figures with low nuclear grade (G1) (3, 4). Generally, TBC has good biologic behavior and prognosis (3), with an incidence of metastasis of 8–20% compared with 50–60% for BC (5, 6). Even if metastasis occurs, TBC 15-year overall survival (OS) was as high as 100% for PTBC (6).

At the genetic level, genetic alterations in TBC are uncommon (7), and it's similar to that in low-grade luminal subtypes of BC (8). Genetic abnormalities mainly include chromosomal abnormalities, such as 16q loss (78–86%) and 1q gain (50–62%). In addition, other genetic abnormalities have been reported, including the loss of 17p, 8p and 3p and the gain of 16p and 11q (7). Based on gene expression profiling studies, it has been demonstrated that TBC belongs to the

Corresponding Author:
Selman Emiroğlu; selman.emirikci.82@istanbul.edu.tr

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luminal A subtype of BC. Moreover, no association was reported between *BRCA1* and *BRCA2* mutation carriers and non-carriers in TBC patients' families (9).

According to the National Comprehensive Cancer Network guidelines, TBC treatment is determined by the positivity of PR, ER, and HER2. The treatment protocol for patients with PR and ER negative or HER2 positive will be the same as in IDC. Adjuvant treatments for patients with PR and ER positive and HER2-negative tumors are determined by tumor size and axillary lymph node (ALN) status. Adjuvant endocrine therapy is considered the treatment protocol for tumors of less than 3 cm and is recommended for tumors greater than 3 cm or node positive tumors. For patients with node-positive tumors, adjuvant chemotherapy is an option (10).

Breast cancer surgery has evolved to become more conservative for both the breast and axilla. ALND is typically reserved for patients with significant axillary disease, since it is associated with significant morbidity (11). Therefore, patient selection must be carefully considered. In particular, if there is one or two lymph node positivity, there is no need for complete axillary dissection in axillary surgery, as suggested in the ACOSOG Z0011 study (11). Additionally, many studies have postulated that axillary staging may be unnecessary in TBC patients (12, 13).

Materials and Methods

Patients Selection

This study is based on our analysis of a large, mono-institutional series of PTBC patients treated in a high-volume reference center with widely standardized treatment and management. A multidisciplinary team had discussed each case individually after surgery, and all decisions about adjuvant treatment had been made. The study population was made up of patients diagnosed with PTBC between January 2003 and December 2020 at the Department of General Surgery, Breast Surgery Unit. The histological types of all cases were carefully evaluated. Multiple clinical and pathological factors were investigated.

Pathological Investigation

The pathological tumor stage was assessed according to the American Joint Committee on Cancer's 7th Staging System (14). Clinical features, demographic data and primary tumor characteristics were gathered from the institution digital records and pathology reports. Paraffin-embedded tissue obtained from excision specimen was microcut and stained with hematoxylin and eosin (H&E). ER (clone SP1, 1:100 dilution; Biocare Concord, CA, USA) and PR (clone SP2, 1:400 dilution; Spring Pleasanton, CA, USA), HER2 (clone SP3, 1:200 dilution; Thermo Waltham, MA, USA) and Ki67 (clone SP6, 1:100 dilution; Biocare Concord, CA, USA) were assessed by reviewing the archived glass slides. Either sentinel lymph nodes (SLNs) or lymph nodes cleared during axillary dissection were embedded in paraffin. The block of each lymph node was cut into 2 mm-thick sections and stained with H&E. Each slide was histopathologically reviewed under a light microscope for the presence of any metastatic cancer clusters (Figure 1).

Patient Follow-up and Treatment

Follow-up of patients was carried out at Istanbul Faculty of Medicine, Breast Surgery Unit. Patients came for follow-up every three months for the first two years, then every six months for the next two years, and later once a year. OS was defined as the number of months from the operation to the date of death. Patients were treated with either mastectomy or lumpectomy and ALND or sentinel lymph node biopsy (SLNB) with local radiotherapy. Hormone (PR/ER) receptor-positive patients received endocrine therapy.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS), version 25.0 (IBM Corp., Armonk, NY, USA) program was used for statistical analysis. Shapiro-Wilk test was used to test the normality of the data distribution of continuous variables with the statistical method. For data analysis, descriptive statistical methods (number, percentage, mean, standard deviation) were used, and for qualitative comparisons between groups, chi-square tests (Pearson chi-square, Continuity Correction, Fisher's Exact test) were used. Survival calculations were made using the Kaplan-Meier analysis method. A *p*-value less than 0.05 was considered to indicate statistically significant differences with a 95% confidence interval.

Results

Patients and Tumors Characteristics

During the study period, 6.849 patients were diagnosed with BC, and 0.7% (n = 54) were PTBC. The mean age of the PTBC patients was 52.2 years. Forty-four (81.5%) had undergone breast-conserving surgery (BCS), and ten (18.5%) patients had undergone mastectomy. Four (7.4%) patients had not undergone axillary surgery, while 38 (70.4%) had undergone SLNB and 12 (22.2%) had undergone ALND due to positive results. The mean size of tumors was 10.6 mm. Forty-eight (88.9%) of the tumors were unifocal and six (11.1%) were multifocal. There was no lymphatic vascular invasion (LVI) or necrosis in any of the patients. Forty-eight (88.9%) patients had grade 1 tumor and six (11.1%) patients had grade 2 (Table 1).

All the tumors were ER positive and HER2 negative, but forty-nine (90.7%) were PR positive and five (9.3%) were PR negative (Table 1). All patients received adjuvant endocrine therapy. Eight patients (14.8%) who had ALNM received both chemotherapy and radiotherapy. Radiotherapy was administered to all patients who underwent BCS (38/54; 70.4%) (Table 1).

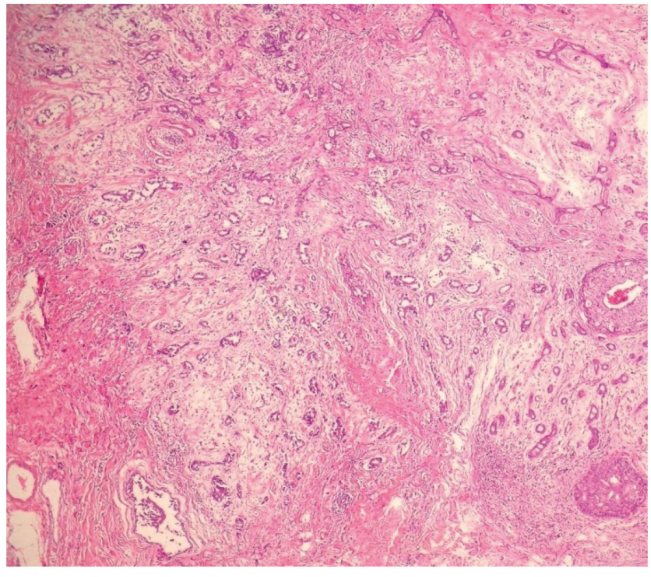

Figure 1. Well-defined glands with round, oval or angular contours, open lumina, and absence of myoepithelial cell layer in PTBC

PTBC: Pure tubular breast carcinoma

Comparison of the Different Characteristics of Patients and Tumors

Twelve patients had undergone ALND due to ALNM, and significantly, four of them (33.3%) had tumor grade 2 (p = 0.020) and eight (66.7%) had ALNM (p = 0.001). Moreover, fifty percent (50%) of patients who were treated with chemotherapy had grade 2, ALNM and multifocal tumors (p = 0.001, p = 0.007 and p = 0.031, respectively). Furthermore, the frequency of ALNM was higher in patients with tumor diameters greater than 10 mm (Table 2).

Patients Follow-up and Overall Survival

Median follow-up time was 80 (12–220) months. None of patients exhibited loco-regional recurrence, but one patient had systemic metastasis. Five-year OS was 97.9%, while ten-year OS was 93.6% (Figure 2).

Table 1. Patient and tumor characteristics

Characteristics (n = 54)	Category	n (%)
Age, mean (SD)	All	52.2 (10.7)
Age group	<50 years	23 (42.6)
	≥50 years	31 (57.4)
pT stage	pT1	53 (98.1)
	pT2	1 (1.9)
pN stage	pN0	46 (85.2)
	pN1-N2	8 (14.8)
Tumor focality	Unifocal	48 (88.9)
	Multifocal	6 (11.1)
Tumor diameter (mm), mean (SD)	All	10.6 (4.7)
	≤10 mm	32 (59.3)
	>10 mm	22 (40.7)
Breast surgery	BCS	44 (81.5)
	Mastectomy	10 (18.5)
	Not done	4 (7.4)
Axillary surgery	SLNB	38 (70.4)
	ALND	12 (22.2)
Grade	1	48 (88.9)
	2	6 (11.1)
LVI	Negative	54 (100)
Necrosis	Negative	54 (100)
ER	Positive	54 (100)
PR	Positive	49 (90.7)
	Negative	5 (9.3)
HER2	Negative	54 (100)
Adjuvant therapy	None*	8 (14.8)
	RT	38 (70.4)
	CT+RT	8 (14.8)
Median follow-up (months)	All	80 (4–220)
Type of recurrence	Locoregional	0 (0.0)
	Systemic	1 (1.9)
	No	53 (98.1)
Cause of death	Metastatic breast cancer	1 (1.9)
	Other	2 (3.7)
	No death	51 (94.4)

pT: pathologic tumor; pN: pathologic node; ER: estrogen receptor; PR: progesterone receptor; CT: chemotherapy; RT: radiotherapy; LVI: lymph vascular invasion; BCS: breast conserving surgery; SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; *: patients received only adjuvant endocrine therapy

Discussion and Conclusion

TBC is well known to be one of the less aggressive BCs, and histologically it is distinguished by tubule formation. In this study, cases were reported using the The American Joint Committee on Cancer criteria, and only cases of PTBC were included. These results showed that PTBC has a favorable prognosis, with good clinical outcomes and high survival rate. Furthermore, recurrences and metastases are rare.

Pathological tumor size is accepted as an independent factor in determining the frequency of lymph node involvement frequency. The presence of a small tumor diameter has been identified as a favorable prognostic factor for TBC. Lea et al. (15) investigated 146 cases of PTBC and the median tumor size was 10 mm (range 1-52 mm), with 93 of them being less than or equal to 20 mm. In addition, using a histological criterion of more than 90% tubule formation to define PTC, Papadatos et al. (16) showed that the median size of PTBC was small at about 10 mm. Dejode et al. (17) also reported a similar result, with a median tumor size of 9.59 (1–22) mm. Additionally, in line with the literature (18, 19), Metovic at al. (20) confirmed the small size (generally less than 10 mm) of PTBC tumors and the excellent outcomes. Moreover, there were no local or distant recurrences observed in the PTBC. Our findings are in keeping with

Table 2. Comparison of patients stratified by tumor grade, patient age, lymph node involvement and tumor focus (multifocal versus unifocal)

	All	Middle grade (II)		Young age (≤50)		LN (+)		Multifocal (Yes)	
Patients (n = 54)	n	n (%)	p	n (%)	p	n (%)	p	n (%)	p
Age			0.384[a]		NA		0.999[a]		0.073[a]
<50	23	4 (17.4)		NA		3 (13)		5 (21.7)	
≥50	31	2 (6.5)		NA		5 (16.1)		1 (3.2)	
Tumor diameter			0.211[a]		0.233[c]		0.051[a]		0.678[a]
≤10 mm	32	2 (6.3)		11 (34.4)		2 (6.3)		3 (9.4)	
>10 mm	22	4 (18.2)		12 (54.5)		6 (27.3)		3 (13.6)	
ALNM			0.213[a]		0.999[a]		NA		0.999[a]
No	46	4 (8.7)		20 (43.5)		NA		5 (10.9)	
Yes	8	2 (25)		3 (37.5)		NA		1 (12.5)	
Tumor focus			0.127[a]		0.073[a]		0.999[a]		NA
Unifocal	48	4 (8.3)		18 (37.5)		7 (14.6)		NA	
Multifocal	6	3 (33.3)		5 (83.3)		1 (16.7)		NA	
Breast surgery			0.070[a]		0.294[a]		0.632[a]		0.070[a]
BCS	44	3 (6.8)		17 (38.6)		6 (13.6)		3 (6.8)	
Mastectomy	10	3 (30)		6 (60)		2 (20)		3 (30)	
Axillary surgery			0.020[b*]		0.677[b]		<0.001[b*]		0.641[b]
Not done	4	0 (0)		1 (25)		0 (0)		0 (0)	
SLNB	38	2 (5.3)		16 (42.1)		0 (0)		4 (10.5)	
ALND	12	4 (33.3)		6 (50)		8 (66.7)		2 (16.7)	
Grade			NA		0.384[a]		0.213[a]		0.127[a]
1	48	NA		19 (39.6)		6 (12.5)		4 (8.3)	
2	6	NA		5 (66.7)		2 (33.3)		2 (33.3)	
PR			0.999[a]		0.380[a]		0.999[a]		0.999[a]
Positive	49	6 (12.2)		22 (44.9)		8 (16.3)		6 (12.2)	
Negative	5	0 (0)		1 (20)		0 (0)		0 (0)	
Adjuvant therapy			0.001[b*]		0.370[b]		0.007[b*]		0.031[b*]
Didn't receive*	8	1 (12.5)		5 (62.5)		0 (0)		1 (12.5)	
RT	38	1 (2.6)		14 (36.8)		4 (10.5)		2 (5.3)	
CT + RT	8	4 (50.0)		4 (50)		4 (50)		3 (37.5)	

*: p<0.05; [a]: Fisher's Exact testi; [b]: Pearson chi-square; [c]: continuity correction; NA: not available; LN: lymph node; ER: estrogen receptor; PR: progesterone receptor; CT: chemotherapy; RT: radiotherapy; BCS: breast conserving surgery; ALNM: axillary lymph node metastasis; SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; *: They received only adjuvant endocrine therapy

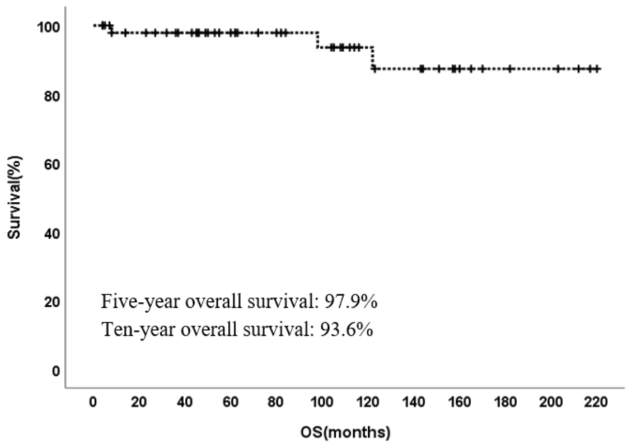

Figure 2. Overall survival in all PTBC patients (n = 54) in the present study

PTBC: Pure tubular breast carcinoma

these earlier studies; the mean tumor size was 10.6 mm, there was an absence of LVI and necrosis in the PTBC cases, and this result agrees with the findings of Rakha et al. (7). All of these findings suggest good prognosis and outcomes in PTBC.

ALNM is one of the most important prognostic factors in the staging and clinical management of BC. Many authors have found that PTBC patients have a lower incidence of ALNM and a better prognosis than patients with more poorly differentiated carcinomas (21, 22). Several studies have reported the association between tumor size and ALNM in TBC, especially in the pure subtype (12, 13, 16, 23). Nevertheless, there is a suggestion to perform SLNB on tumors larger than 10 mm, but this remains debatable (13, 18). Papadatos et al. (16) reported ALNM in only one of 22 cases, and they found no ALNM in PTBC when the tumor diameter was 10 mm or less (zero of 16). Furthermore, Cabral et al. (12) reported no ALNM in tumors less than or equal to 15 mm (zero of 20). Moreover, Winchester et al. (23) found no association between ALNM and tumor diameter in tumors smaller than 10 mm or tumors 10–20 mm. In the present study, ALNM occurrence was more likely in PTBC patients with tumor diameters greater than 10 mm.

Similar to our results, PTBCs in general are ER positive with a low-grade tumor (15, 24, 25). These characteristics result in a more favorable response to adjuvant endocrine treatment, leading to better prognosis and survival rate. None of the patients in the present study had a loco-regional recurrence, except for one patient who had multiple systemic metastasis (1.9%). The five-year OS was 97.9%, and the ten-year OS was 93.6%. In comparison to other study findings, Huang et al. (26) investigated the outcomes of TBC in 2.735 patients and showed that five-year OS was 97.2% and ten-year OS was 90.7%. In another study by Poirier et al. (27), it was reported that the 13-year OS of 223 PTBC patients was 95.8% for N0 PTBC patients, compared to 90.0% for N1-3 PTBC. Also, 13-year OS of PTBC was similar to that of grade 1 IDC (27). In the study of Lea et al. (15), 146 PTBC patients were investigated, and ALNM was uncommon. Eight (5%) patients had recurrent disease, and three of them died as a result. However, ten-year OS was 97%.

Peters et al. (21) found that as the non-tubular component increased, so did the tumor's biological aggressiveness. As we found no locoregional or systemic recurrence, with the exception of one patient in this study, we also suggest that PTBC tumors are less aggressive. As a result of our findings and those of others, it appears that PTBC patients may expect favorable prognosis, good clinical outcome and high survival rate, which may in part be due to the fact that PTBC are often ER positive and low grade, which leads to a good response to therapy. Surgical axillary investigation may not be warranted in PTBC patients who have a good initial prognosis.

Pure TBC is associated with favorable prognosis, good clinical outcomes and high survival rate and recurrences and shows rare recurrences and metastases.

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Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.E., A.M.A., M.T., N.C., M.M.; Concept: S.E., A.M.A., M.T., N.C., A.B., V.O., M.M.; Design: S.E., A.M.A., M.T., N.C., M.M.; Data Collection or Processing: S.E., A.M.A., M.T., N.C., A.B., V.O., M.M.; Analysis or Interpretation: S.E., A.M.A., M.T., N.C., A.B., V.O., M.M.; Literature Search: S.E., A.M.A., M.T., N.C.; Writing: S.E., A.M.A., M.T., N.C., A.B., V.O., M.M.

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