

Characteristics and clinical outcome of pT1a-b node-negative breast cancer

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ABSTRACT

OBJECTIVE: Tumor size, along with other clinicopathological characteristics, has a prognostic role in breast cancer. Recurrence risk tends to rise as tumor size increases. Early T-stage portends a good prognosis. We aimed to investigate the recurrence-free interval rates of T1abN0 group of early breast cancer.

METHODS: Patients diagnosed with pT1a and T1b, lymph node metastasis-negative breast cancer were included in the study. Clinicopathologic characteristics including recurrence, distant metastasis, and final status of the patients were obtained retrospectively from the patient files.

RESULTS: A total of 84 patients included. Twenty-six patients (31%) had T1a and 58 patients (69%) had T1b tumors. The 5-year distant relapse-free survival (DRFS) rate of T1ab tumors was 95.2%. The DRFS rate of T1a tumors was 96.2%, while the rate of T1b tumors was 94.8% ($p=0.555$). The 5-year RFS rate of T1ab tumors was 90.5%. The RFS rate of T1a tumors was 84.6%, whereas the rate of T1b tumors was 93.1% ($p=0.359$). The 5-year DRFS rate of hormone receptor positive group was 97%, Her-2 positive group was 81.8%, and triple negative group was 100% ($p=0.041$). The 5-year RFS rate of the hormone receptor positive group was 97%, Her-2 positive group was 72.7%, and triple negative group was 57.1% ($p=0.001$).

CONCLUSION: The results of the study provided that both T1a and T1b tumors have a good and similar prognosis.

Keywords: Distant relapse-free survival; early breast cancer; T1ab.

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The most common diagnosed type of cancer with the most frequent mortality in women worldwide is breast cancer. Early stage breast cancers include Stage 1, Stage 2a, and some Stage 2b tumors [1]. Early stage breast cancers have a very good prognosis and 5-year survival rates of about 90% [2]. As tumor size increases, the risk of lymph node metastasis increases and this situation was found to be associated with recurrence. In addition to tumor size, the biological and histological characteristics of the tumor (such as tumor grade, lymph node metastasis, estrogen and progesterone receptor sta-

tus, and the presence of human epidermal growth factor 2 [Her-2] expression) were found to be associated with recurrence [3–6]. In studies conducted in various centers, 5-year relapse-free survival (RFS) rate in patients with T1abN0M0 breast cancer was observed to be over 90% at 10-year follow-up [7–13].

According to the American Joint Committee on Cancer classification, tumors with a tumor diameter of 1–10 mm are called T1ab. The subgroup of tumors \leq or equal to 0.5 cm is called T1a tumors. On the other hand, tumors which are between 0.6 cm and 1 cm are classified as

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T1b tumors. Although tumors in this group have a good prognosis, systemic treatment is recommended for some tumors involving risk factors.

The 2019.3 version of the National Comprehensive Cancer Network (NCCN) guideline, systemic chemotherapy combined with an anti-Her-2 agent trastuzumab treatment is recommended at category 1 level for Her-2 positive tumors above 1 cm, and the same approach is recommended although evidence level is low in T1ab tumors. Adjuvant hormone therapy or systemic therapy is recommended in hormone positive, Her-2 negative group according to the characteristics of the tumor. In the triple negative group, adjuvant systemic treatment is recommended for the tumors above 0.5 cm.

Size of breast cancer tumors at diagnosis has decreased over the past 20-years as a result of early detection by mammography screening. Since detection limits of palpation are accepted to be 1 cm or bigger, small sub-centimeter invasive breast cancer tumors can be easily detected by mammography [14, 15].

In this study, we aimed to investigate distant invasive recurrence-free interval (DRFI) and recurrence-free interval (RFI) rates in the patients with T1abN0M0 breast cancer.

MATERIALS AND METHODS

Study Design

The study included 84 female patients diagnosed with T1abN0M0 breast cancer who were treated in the Medical Oncology Clinic of Dr. Lutfi Kirdar Kartal Training and Research Hospital and University of Health Sciences, Umraniye Research and Training Hospital, University of Health Sciences between 1998 and 2018. Clinicopathologic characteristics including recurrence, distant metastasis, and final status of the patients were obtained retrospectively from the patient files. Ethics committee approval of the study was received (date: 11.06.2020, number: 237).

Statistical Analysis

Descriptive statistics were used and patient characteristics were tabulated. The quantitative variables were analyzed using proportions and categorical variables were analyzed by Chi-square tests. For DRFI, follow-up ended at distant relapse, death as a result of non-breast cancer, or date of last medical record entry was considered an event. RFI was defined as the time beginning from the breast cancer

Highlight key points

- Both T1a and T1b tumors have a good and similar prognosis.
- Not only tumor size but also biological and histological characteristics of the tumor should be taken into consideration while individualizing prognosis and treatment decision.
- Triple-negative and Her-2 positive subtypes have worse prognosis compared with Luminal subtypes even in small breast tumors.

diagnosis to the diagnosis of local or regional recurrence, distant recurrence, death as a result of non-breast cancer, or date of last medical record entry, whichever came first. Time to recurrence and to distant recurrence were estimated according to the Kaplan–Meier method and compared between groups using the log-rank statistic. Two-sided $p < 0.05$ was considered statistically significant. All analyses were done utilizing the SPSS software package, version 17.0 (SPSS Inc., Chicago, Ill, USA).

RESULTS

A total of 84 patients were included in the study. Median age was calculated as 50-years. Forty patients (47.6%) were premenopausal and 44 patients (53.4%) were postmenopausal. Surgical treatment was applied to all patients. Mastectomy was performed in 32 patients (38%) and breast conserving surgery was performed in 52 patients (62%). According to TNM classification, 26 patients (31%) had T1a and 58 patients (69%) had T1b tumors in the pathological examination. The pathological characteristics of the tumors were examined. There were 22 patients (26.2%) with Grade 1 tumor and 62 patients (73.8%) with Grades 2–3 tumor. There were 73 (86.9%) patients who were estrogen receptor and/or progesterone receptor positive, while there were 11 (13.1%) patients who were hormone receptor negative. Expression of both receptors was observed in 11 patients (13.1%). Seven patients (8.3%) were observed as triple negative (triple negative).

17 patients (20.2%) were administered adjuvant systemic chemotherapy. Anti-Her-2 agent trastuzumab was administered to 10 (71.4%) of 14 patients in Her-2 positive group. In all, 66 (90.4%) of the hormone-positive patients received adjuvant hormone therapy. Distant metastasis occurred in total of six patients (7.2%). Five patients (6%) had loco regional recurrence. Clinicopathological characteristics of patients are presented in Table 1.

TABLE 1. Clinicopathological characteristics of patients (n=84)

Characteristic, n (%)	All patients	Tumor size	
		T1a	T1b
		26 (31.0)	58 (69.0)
Age			
Median (range), years	50 (30–77)	50 (42–56)	50 (46–59)
<65 years	77 (91.7)	25 (29.8)	52 (61.9)
≥65 years	7 (8.3)	1 (1.2)	6 (7.1)
Menopausal status			
Post	44 (52.4)	13 (15.5)	31 (36.9)
Pre	40 (47.6)	13 (15.5)	27 (32.1)
Surgery			
Mastectomy	32 (38.0)	12 (14.3)	20 (23.8)
Lumpectomy	52 (62.0)	14 (16.7)	38 (45.2)
Radiation therapy			
Yes	52 (62.0)	14 (16.7)	38 (45.2)
No	32 (38.0)	12 (14.3)	20 (23.8)
Chemotherapy			
Yes	17 (20.2)	4 (4.8)	13 (15.5)
No	67 (79.8)	22 (26.2)	45 (53.5)
Tumor grade			
Grade 1	22 (26.2)	3 (3.6)	19 (22.6)
Grades 2–3	62 (73.8)	23 (27.4)	39 (46.4)
HT among R-positive patients			
Yes	67 (78.5)	21 (25.0)	45 (53.5)
No	18 (21.5)	5 (6.0)	13 (15.5)
Distant metastasis			
M0	78 (92.8)	25 (29.8)	53 (63.0)
M1	6 (7.2)	1 (1.2)	5 (6.0)
Loco regional recurrence			
Yes	5 (6.0)	3 (3.6)	2 (2.4)
No	79 (94.0)	23 (27.4)	56 (66.6)
ER and/or PR status			
Positive	73 (86.9)	22 (26.2)	51 (60.7)
Negative	11 (13.1)	4 (4.8)	7 (8.3)
Her-2 status			
Positive	11 (13.1)	1 (1.2)	10 (11.9)
Negative	73 (86.9)	25 (29.8)	48 (57.1)

HT: Hormonal therapy; ER: Estrogen receptor; PR: Progesterone receptor; Her-2: Human epidermal growth factor receptor 2; *: Estimated using Pearson's Chi-square test.

The 5-year distant RFS (DRFS) rate of T1ab tumors was 95.2%. The DRFS rate of T1a tumors was 96.2%, while the rate of T1b tumors was 94.8% ($p=0.555$). The

5-year RFS rate of T1ab tumors was 90.5%. The RFS rate of T1a tumors was 84.6%, whereas the rate of T1b tumors was 93.1% ($p=0.359$). According to the breast cancer subtypes, the 5-year DRFS rate of hormone receptor positive group was 97%, Her-2 positive group was 81.8%, and triple negative group was 100% ($p=0.041$). The 5-year RFS rate of the hormone receptor positive group was 97%, Her-2 positive group was 72.7%, and triple negative group was 57.1% ($p=0.001$). Five-year RFS and DRFS rates of patients according to the tumor size and breast cancer subtype are shown in Table 2. Corresponding survival curves of 5-year RFS and DRFS are presented in Figures 1 and 2, respectively.

DISCUSSION

The frequency of early diagnosis in breast cancer has been increasing with the help of screening methods such as mammography [14, 15]. Early-stage breast cancers have a very good prognosis and 5–10 years survival rates of about 90% [2]. Reported 5-year relapse free survival in patients with T1abN0M0 breast cancer was observed to be over 90% in 10-year follow-up [7–13]. In our study, DRFS and RFS values were found to be over 90% in T1ab tumors.

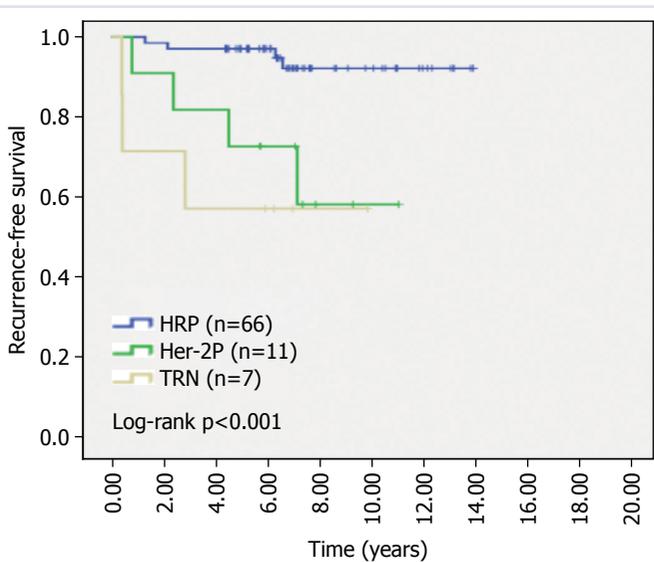
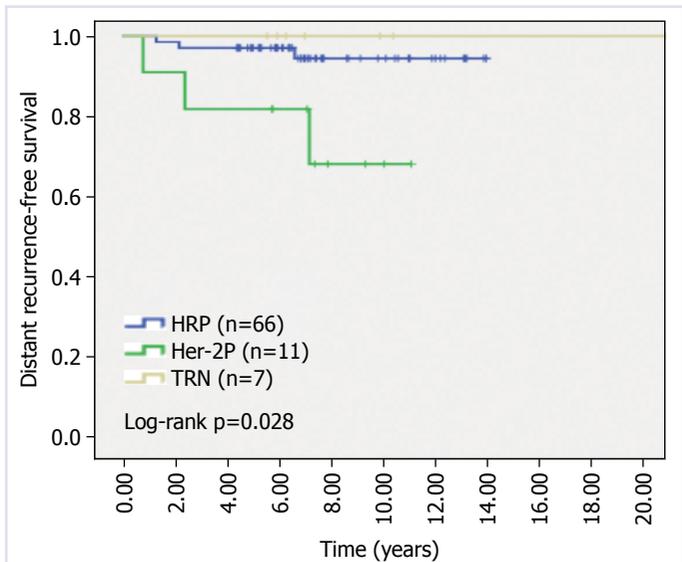
In the study conducted by Theriault et al. [16], only age and tumor subtype in T1ab breast cancer patients had significant impact on RFS and DRFS. Colleoni et al. [17], in their analysis, reported a similar 4-year DFS in T1a and T1b subgroups. In this study, ki-67 level was identified as an independent risk factor. In the study performed by Cancellato et al. [18], age and molecular subtype rather than tumor size was found to be significant in local recurrence, distant metastasis, and breast cancer-related deaths. In our study, no difference was observed between the 5-year DRFS and RFS rates in T1a and T1b groups. Multivariate analysis could not be performed due to the insufficient number of patients between the groups.

It is known that prognosis is not only related to increased tumor size but also grade, hormone receptor status, Her-2 status, and lymph node status are effective in breast cancer [19–21]. Her-2 positive breast cancers have more aggressive clinical characteristics. The addition of trastuzumab in the treatment of Her-2 positive breast cancer has a significant effect on both DFS and overall survival (OS). Similarly, triple negative breast cancers are also observed significantly more frequent in local and distant recurrence [22–27]. In our study, DRFS rates were found significantly lower in Her-2 positive group.

TABLE 2. Five-year RFS and DRFS of patients according to the tumor size and breast cancer subtype

	n (%)	Recurrences during first 5-year of follow-up					
		Distant			Total invasive		
		DRFS (%)	95% CI	p	RFS (%)	95% CI	p
Tumor size							
T1a	26 (31.0)	96.2	(89.9–100.0)	0.555	84.6	(73.0–96.3)	0.359
T1b	58 (69.0)	94.8	(90.0–99.6)		93.1	(87.6–98.6)	
T1ab	84 (100.0)	95.2	(91.4–99.1)		90.5	(85.2–95.7)	
Breast cancer subtype							
HRP	66 (78.6)	97.0	(93.5–100.0)	0.041	97.0	(93.5–100.0)	0.001
Her-2P	11 (13.1)	81.8	(62.7–100.0)		72.7	(50.6–94.8)	
TRN	7 (8.3)	100	(100–100)		57.1	(26.4–87.9)	

RFS: Recurrence-free survival; DRFS: Distant recurrence-free survival; CI: Confidence interval; HRP: Hormone receptor positive; Her-2P: Human epidermal growth factor receptor 2 positive; TRN: Triple negative.

**FIGURE 1.** Recurrence-free survival by breast cancer subtype.**FIGURE 2.** Distant recurrence-free survival by breast cancer subtype.

No distant metastasis was detected in the triple negative group and this may be because of small number of patients. Furthermore, RFS rates were significantly lower in Her-2 positive and triple negative groups.

Houvenaeghel et al. [28] in their large multicenter retrospective cohort study on clinical outcome of T1 breast cancer, after a median follow-up of 60.5 months, revealed that the OS rate was 97.6% at 60 months, 95.4% at 84 months, and 90.7% at the estimated 10-year outcome. No significant difference was observed between T1a,

T1b, and T1c tumors ($p=0.335$). Multivariate analysis identified AST, LVI, and grade but not tumor size as major determinants of relapse events. A decrease in the 5-year RFS rate from hormone-receptor-positive group to triple-negative group was observed which is consistent with our study. Similarly, in a more recent research regarding prognostic factors of T1a–T1b breast cancer, triple-negative breast cancer had a significantly poorer survival than the other subgroups [29]. In all, despite the institution of adjuvant systemic therapy, triple negative

T1N0 patients were shown to have greater recurrence and mortality risk.

Breast cancer is a highly heterogeneous disease involving a variety of subtypes each of which displays different biological behaviors. In this study, consisting of <1 cm, node negative tumors among early stage breast cancer, we found similar survival rates for T1a and T1b tumors. However, RFS rate was different for molecular subtypes with triple-negative having the worst. In clinical practice, utilization of both patient-related prognostic determinants such as age, race, menopausal status, and pathological features including histologic grade, tumor morphology, peritumoral lymphovascular invasion, hormone-receptor, and Her-2 amplification and/or overexpression status should be taken into consideration even if tumor size is <1 cm to achieve personalization of adjunctive treatment strategies.

Unable to perform multivariate analysis for DFS and RFS rates due to insufficient number of patients in terms of distribution of all groups, being a retrospective study, and insufficient sampling constitutes the limitations of our study.

Conclusion

Individualized treatment plays an important role in breast cancer. It would not be right for the clinician to decide only due to tumor size in the treatment decision. Especially age, molecular subtypes (e.g., Her-2 positive and triple negative) should be taken into consideration.

Ethics Committee Approval: The Health Sciences University, Umraniye Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 11.06.2020, number: 237).

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Authorship Contributions: Concept – AO; Design – AO, MO; Supervision – AO, MO; Fundings – AO; Materials – HO, MB; Data collection and/or processing – HO, AO; Analysis and/or interpretation – MB, MO; Literature review – AO; Writing – AO, MO; Critical review – AO, MO.

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