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Original Article

Prognostic factors of T1a-T1b breast cancer: a retrospective cohort study

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Abstract: *Objectives:* We aimed to analyze the clinicopathological features and prognostic factors of breast cancer patients with T1a-T1b, which was defined as tumor size was within 1 cm. *Methods:* From the Surveillance, Epidemiology, and End Results (SEER) database, we identified 39143 patients with T1a-T1b breast cancer who were diagnosed from January 1, 2010 to December 31, 2013. Clinicopathological features and prognosis were analyzed. Outcomes for breast cancer-specific survival (BCSS) and overall survival (OS) were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards models were used to determine independent factors relating to prognosis. *Results:* There were 10966 T1a and 28177 T1b breast cancer patients. The median follow-up was 15.78±10.54 months. The overall mortality rate was 1.38% (541/39143), and the breast cancer related mortality rate was 0.28% (108/39143). Multivariate analysis showed that age, histological grade, distant metastasis, HR status, surgery, and radiotherapy were independent factors of BCSS, while age, distant metastasis, HR status, surgery, and radiotherapy were independent factors of OS. Triple-negative breast cancer had a significantly poorer survival than the other three patient subgroups (P<0.001). Surgical approach (breast-conserving surgery or mastectomy) was unrelated to prognosis in T1a-T1b patients. Radiotherapy had a beneficial effect on both T1a-T1bN0 and T1a-T1bN1 patients who underwent mastectomy. *Conclusion:* Larger tumor size, HR^- and $Her\text{-}2^+$ status were associated with more aggressive tumor behavior. More aggressive treatment should be performed for T1a-T1b breast cancers with these prognostic risk factors: young age, high histological grade, distant metastasis, and HR-status, especially for triple-negative breast cancer. Breast-conserving surgery should be performed more commonly at the global level. Radiaotherapy should be considerable for T1a-T1b N0-N1 breast cancers even when mastectomy were performed.

Keywords: Small size breast cancer, prognosis, treatment

Introduction

Breast cancer is the most common non-skin cancer globally and is the second leading cause of cancer-related death in women. The frequency of small size breast cancer (tumor size ≤1 cm) has increased over time with the development of screening strategies. For instance, generalized mammography screening increased detection rate of small breast cancers [1]. T1 breast cancer, which includes T1a (tumor size ≤0.5 cm), T1b (tumor size >0.5 but ≤1 cm) and T1c (tumor size >1 but ≤2 cm) tumors has become the most frequently diagnosed invasive BC in developed countries. These small breast cancers have a good prognosis with a 5-10 year 90% or higher cancer-specific survival rate [2]. Previously, it was generally agreed that most of these tumors did not require adjuvant systemic therapy (AST), particularly T1ab breast cancer [3-7]. Even if small breast tumors are typically considered low risk, we have found that when they exhibit certain characteristics, the prognosis may be poor. Tumor size is an important prognostic factor, which is positively correlated with lymph node metastasis, distant metastasis, tumor recurrence, and prognosis [8]. In recent years, increasing evidence has demonstrated that it is not only the tumor size itself but also biological features, which are predictive for the outcome of patients, especially in T1a-T1b breast cancers. Young age, high tumor grade, adverse histological features and negative hormone recep-

Table 1. Baseline characteristics of the study group by tumor size

Feature (N/%)		Tumor Size		*P* value*
		T1a (n=10966)	T1b (n=28177)	
Age/Year	Median	61	63	**0.00**
	<65	6205 (56.6)	14983 (53.2)	
	≥65	4761 (43.4)	13194 (46.8)	
Tumor Grade	I	4437 (40.5)	10639 (37.8)	**0.00**
	II-III	6529 (59.5)	17538 (62.2)	
LN status	N0	10309 (94.0)	25305 (89.8)	**0.00**
	N1-N3	657 (6.0)	2872 (10.2)	
Distant metastasis	M0	10921 (99.6)	28010 (99.4)	**0.03**
	M1	45 (0.4)	167 (0.6)	
Surgery	Yes	10831 (98.8)	27546 (97.8)	**0.00**
	No	135 (1.2)	631 (2.2)	
Radiotherapy	Yes	5413 (49.4)	15449 (54.8)	**0.00**
	No	5553 (50.6)	12728 (45.2)	
HR	Positive	9576 (87.3)	25280 (89.7)	**0.00**
	Negative	1390 (12.7)	2897 (10.3)	
Her-2	Positive	1616 (14.7)	2833 (10.1)	**0.00**
	Negative	9350 (85.3)	25344 (89.9)	
BCSS	Other[a]	10938 (99.7)	28097 (99.7)	0.67
	Dead	28 (0.3)	80 (0.3)	
OS	Alive	10844 (98.9)	27758 (98.5)	**0.00**
	Dead	122 (1.1)	419 (1.5)	

*P values calculated by Pearson Chi squared testing; Bold if statistically significant, P<0.05. [a]Patients were alive at their last follow-up or died from non-breast cancer. HR: hormone receptor, LN: lymph node, BCSS: breast cancer-specific survival, OS: overall survival.

tor (HR) status were associated with recurrence or breast cancer-related mortality in T1a-T1b breast cancer in an early study [9]. Recent research has shown that human epidermal growth factor receptor 2 positive (HER-2$^+$) T1a-T1b N0 M0 tumors are associated with higher recurrence rates [10-12]. In fact, HER-2 overexpression and triple-negative tumors has been shown to be a significant unfavorable prognostic factor for patients with tumors of <1 cm [13-17]. Some clinical subgroups and molecular subtypes have been described as having a high risk of recurrence and metastasis. Patients with one or more significant risk factors in some small tumor patients relapsed and died. Furthermore, accumulating evidence regarding the underlying biology of aggressive subtypes indicates that it has prognostic value that is independent of tumor burden. For these reasons, adjuvant systemic therapy should be discussed with all of these patients and such prognostic factors should be taken into account in the treatment of small tumor patients. Previous studies have not provided strong evidence to date, therefore the purpose of this study was to evaluate prognostic factors in patients with small breast cancer (BC).

Materials and methods

Data source and study design

We obtained data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. The SEER Program collects cancer incidence and survival data from US population-based cancer registries. SEER started collecting information on HER2 status in 2010. Therefore, we used that year as the starting point for our study. We extracted data for all cases of invasive BC diagnosed between 2010 and 2013. We selected cases with known HR and HER2 statuses.

We used the SEER database to generate a case list. 39143 T1a-T1b breast infiltrating ductal carcinoma patients were identified according to the following inclusion criteria: time of diagnosis from January 1, 2010 to December 31, 2013; pathologically confirmed infiltrating duct carcinoma; tumor size from T1a to T1b; and female gender. Average age of diagnosis was 62.83±12.16 years (range from 19 to 100 years), we calculated follow-up durations from January 1, 2010 to December 31, 2013, with the median follow-up time of 15.78±10.54 months. Patients were categorized according to their tumor size (T1a and T1b), ER- and Her-2 status, respectively.

Cancer characteristics were classified according to age at diagnosis (<65, ≥65 years), grade (well, moderately, poorly, undifferentiated), tumor size (≤5 mm, 5-10 mm), lymph node metastasis and distant metastasis (no, yes), HR status and HER2 status (positive, negative). The subtypes were characterized according to the breast subtype variable as either HR$^+$/HER2$^-$, HR$^+$/HER2$^+$, HR$^-$/HER2$^+$ or triple-negative (TN).

Table 2. Baseline characteristics with HR and Her-2 status

Feature (N/%)		HR			Her-2		
		Positive (n=34856)	Negative (n=4287)	P	Positive (n=4449)	Negative (n=34694)	*P* value*
Age/Year	<65	18612	2576	0.00	2994	18194	**0.00**
	≥65	16244	1711		1455	16500	
Grade	I	14902	174	0.00	478	14598	**0.00**
	II-III	19954	4113		3971	20096	
Tumor Size	T1a	9576	1390	0.00	1616	9350	**0.00**
	T1b	25280	2897		2833	25344	
LN status	N0	31845	3769	0.00	3856	31758	**0.00**
	N1-N3	3011	518		593	2936	
Distant metastasis	M0	34688	4243	0.00	4401	34530	**0.00**
	M1	168	44		48	164	
BCSS	Other[a]	34784	4251	0.00	4435	34600	0.65
	Dead	72	36		14	94	
OS	Alive	34409	4193	0.00	4378	34224	0.22
	Dead	447	94		71	470	
HR	Positive	-	-		3168	31688	**0.00**
	Negative	-	-		1281	3006	
Her-2	Positive	3168	1281	0.00	-	-	
	Negative	31688	3006		-	-	

*P values calculated by Pearson Chi squared testing; Bold if statistically significant, P<0.05. [a]Patients were alive at their last follow-up or died from non-breast cancer. HR: hormone receptor, LN: lymph node, BCSS: breast cancer-specific survival, OS: overall survival.

Treatment characteristics included receipt of radiation therapy (no, yes) and surgery (no, yes). Patients were categorized according to whether they underwent BCS (surgery of primary site variable values of 20-24) or mastectomy (surgery of primary site variable values of 30-80). The two primary outcomes in our study were overall survival (OS) and breast cancer-specific survival (BCSS). BCSS was measured from the date of diagnosis to the date of breast cancer death. OS was defined as the time from the date of diagnosis to the date of death due to any cause (including breast cancer) or the last follow-up. Cases without survival times were classified as unknown and were removed from the study.

Statistical analysis

The clinical and pathological characteristics (age, histological grade, tumor size, lymph node metastasis, distant metastasis, HR status, Her-2 status, surgery and radiotherapy) of the included cases were compared for the two groups using a Chi-squared test. The Kaplan-Meier method was performed to depict the survival curves, with the log-rank test being performed to detect any significant difference in survival distribution. Multivariate analyses by Cox proportional hazards regression was carried out in order to determine the outcome-related elements. Two-sided *p*-values were reported and p<0.05 was considered statistically significant. All analyses were done utilizing the SPSS software package, version 21.0 (SPSS Inc., Chicago, Ill, USA).

Results

Baseline characteristics of the study population

As illustrated in **Table 1**, 39143 T1a-T1b BC patients were enrolled in the current study. Of these patients, 28.02% (n=10966) of the patients were classified as T1a and 71.98% (n=28177) were classified as T1b. The median follow-up was 15.78±10.54 months. The overall mortality rate was 1.38% (541/39143), and the breast cancer related mortality rate was 0.28% (108/39143). Compared with T1a patients, T1b patients tended to be older (the

Table 3. Multivariate Analysis of factors that Predict BCSS and OS

Variable	BCSS			OS		
	HR	95% CI	P	HR	95% CI	*P* value*
Age/Year						
<65	1			1		
≥65	2.08	1.40-3.09	0.00	3.17	2.62-3.85	**0.00**
Tumor Grade						
I	1			1		
II-III	2.15	1.23-3.77	0.01	1.08	0.89-1.31	0.43
Tumor size						
T1a	1			1		
T1b	0.86	0.55-1.33	0.50	1.22	0.99-1.50	0.06
LN metastasis						
Negative	1			1		
Positive	1.58	0.95-2.65	0.80	1.08	0.81-1.44	0.60
Distant metastasis						
M0	1			1		
M1	6.73	2.14-21.20	0.00	3.24	1.63-6.44	**0.00**
HR						
Negative	1			1		
Positive	0.35	0.23-0.0.53	0.00	0.66	0.52-0.84	**0.00**
Her-2						
Negative	1			1		
Positive	0.62	0.34-1.11	0.11	1.05	0.81-1.37	0.71
Surgery						
No	1			1		
Yes	0.19	0.10-0.35	0.00	0.17	0.13-0.22	**0.00**
Radiotherapy						
No	1			1		
Yes	0.37	0.23-0.60	0.00	0.32	0.26-0.40	**0.00**

**P* values calculated by Log-rank testing; Bold if statistically significant, P<0.05.
HR: hormone receptor, LN: lymph node.

median age of T1b-BC patients was 63 years, which of T1a-BC patients was 61 years; P< 0.001), presented with a higher histological grade (P<0.001) and were more likely to have more frequent lymph node metastasis and distant metastasis. In addition, HR-positive and Her-2 negative patients were more prevalent among T1b patients than T1a patients (both *P* values <0.001).

HR and HER-2 status in T1a-T1b BC patients

As illustrated in **Table 2**, the amount of $HR^+/Her\text{-}2^+$, $HR^+/Her\text{-}2^-$, $HR^-/Her\text{-}2^+$ and $HR^-/Her\text{-}2^-$ patients were 3168, 31688, 1281 and 3006, respectively. The majority (80.95%) of T1a-T1b patients were HR^+ and $Her\text{-}2^-$. Compared with HR-positive patients, HR-negative patients were younger (P<0.001), had a higher histological grade (P< 0.001), larger tumor size (P< 0.001), more frequent lymph node metastasis (P<0.001) and more frequent distant metastasis (P<0.001). In contrast, Her-2 positive patients tended to be younger (P< 0.001), had a higher histological grade (P<0.001), larger tumor size (P<0.001), more frequent lymph node metastasis (P<0.001) and more frequent distant metastasis (P< 0.001) than Her-2 negative patients. HR^- and $Her\text{-}2^+$ patients had similar clinical behavior, while being HR negative was associated with Her-2 positive status in T1a-T1b patients.

Analyses of outcome-related factors using the cox proportional hazard regression models

The results of the analyses of BCSS and OS using multivariate Cox proportional hazard regression models are shown in **Table 3**, respectively. In multivariate analysis, age, histological grade, distant metastasis, HR status, surgery and radiotherapy were independent prognostic factors of BCSS; age, distant metastasis, HR status, surgery and radiotherapy were independent prognostic factors of OS.

Subgroup survival analysis

As demonstrated in **Figure 1**, patients were divided into molecular subtype groups according to HR and Her-2 status. $HR^-/Her\text{-}2^-$ patients (also termed triple-negative breast cancer) had a significantly poorer BCSS and OS than the other three subgroups (P<0.001). As demonstrated in **Figure 2**, patients were divided into two groups according to surgery methods (breast-conserving surgery or mastectomy), and there was no significant difference in prognosis observed. In **Figure 3**, patients who underwent mastectomy were divided into two

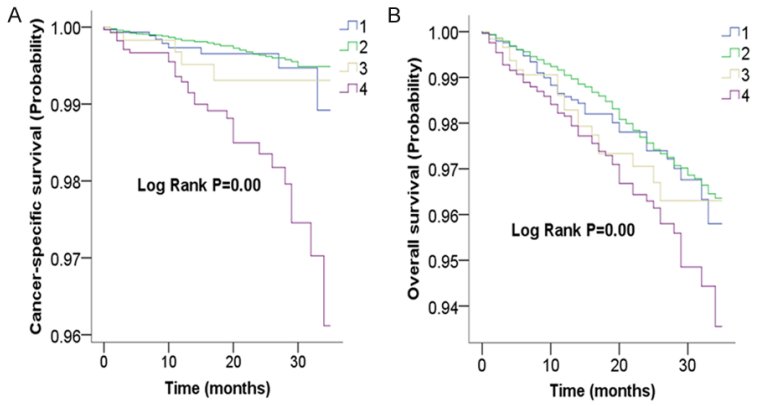

Figure 1. Impact of HR and Her-2 on prognosis of T1a-T1b BC. (1, 2, 3 and 4 in A, B represent $HR^+/Her\text{-}2^+$, $HR^+/Her\text{-}2^-$, $HR^-/Her\text{-}2^+$ and $HR^-/Her\text{-}2^-$, respectively).

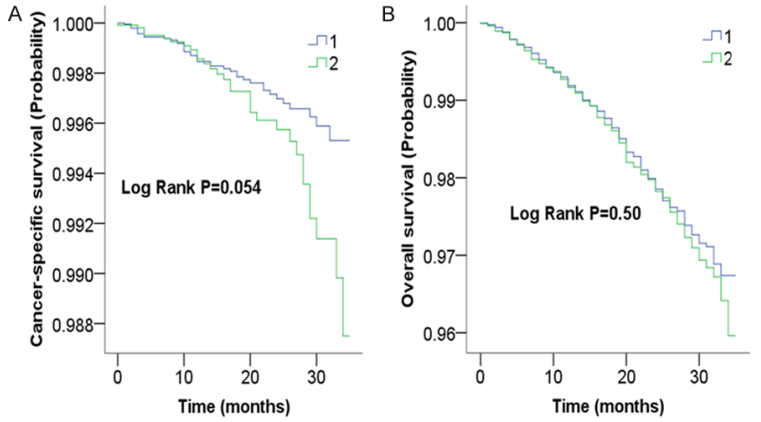

Figure 2. Impact of surgery on prognosis of T1a-T1b BC. (1 and 2 in A, B represent breast-conserving and mastectomy surgery, respectively).

groups according to receipt of radiation therapy (no, yes), radiotherapy was associated with a significantly better prognosis, with this effect even being observed in T1a-T1b lymph node negative patients ($P<0.001$).

Discussion

With clinical screening of breast disease becoming more prevalent, the early diagnosis rate of breast disease gradually increased. As a consequence, small breast cancer is being registered more commonly, and in this study, T1a and T1b accounted for 8.7% and 10.7% of all breast cancers, respectively, which is consistent with a number of other studies [18-19]. As far as we know, the prognosis of patients with small breast cancer is especially good, with 5-and 10-year survival rates that generally exceed 90% [2]. In our experience, we have also found that certain types of small breast cancer are associated with poorer prognosis, such as $Her\text{-}2^+$ and triple-negative breast cancer. Some patients experience local recurrence or distant metastasis very shortly after treatment. Small breast cancers typically have a greater proportion of well differentiated grade, less frequent lymph node metastasis, less frequent distant metastasis, hormone receptor-positive status, or HER-2-negative breast cancer status compared to large breast cancers. In this study, we compared T1a and T1b breast cancer and found that the larger the tumor size was, the more aggressive the disease in patients was, although prognosis was not significantly different. In all patients, the long-term survival rate of T1a and T1b breast cancer patients was similar but the treatment regimens of the two groups of patients were significantly different. According to a large study in the United States, 66% of T1a patients did not receive adjuvant therapy, while only 25% of T1b patients were treated using this regimen [20]. Therefore, the difference in adjuvant treatment between T1a and T1b breast cancer patients is likely to directly influence the survival time and is an important confounder. In this study, we also found differences in the type of therapy for T1a and T1b breast cancer; the proportion of T1b patients receiving surgery and radiotherapy was higher than that of T1a patients, and the rate of mastectomy in T1b patients was also higher than that of T1a patients.

There is increasing evidence that tumor size alone does not dictate prognosis but other biological factors such as grading, HR-status, HER2-status, and nodal-status of small tumors can also predicts patient prognosis. HER2-overexpressing and triple-negative cancer sub-

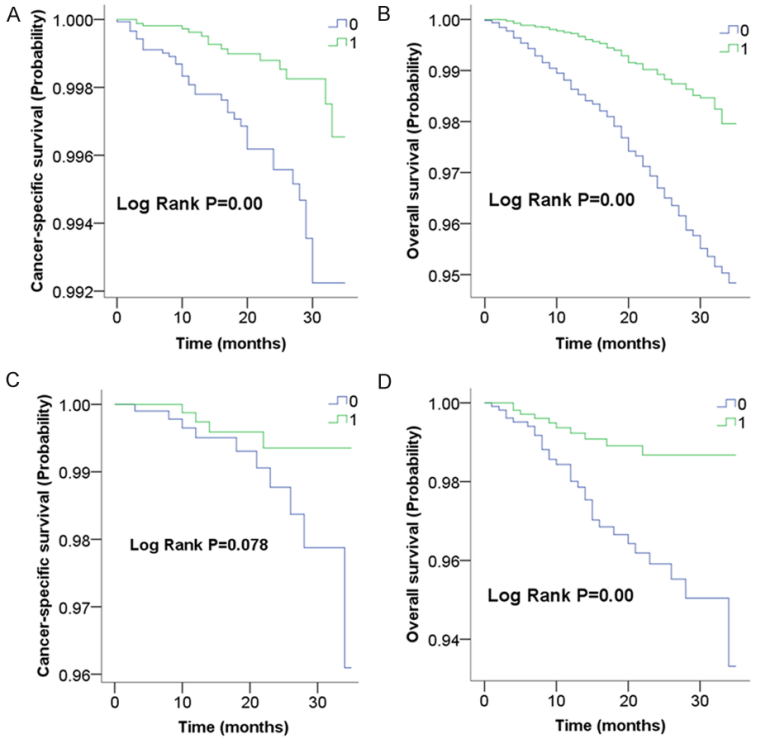

Figure 3. Impact of radiotherapy on prognosis of T1a-T1b No and T1a-T1b N1 BC. (1 and 0 in A-D represent radiotherapy and no radiotherapy, respectively. A, B was for N0 and C, D was for N1 patients).

types are especially associated with unfavorable outcomes in this subset [21-23]. Some investigators have suggested that the decision on when to use adjuvant chemotherapy in early stage breast cancer (T1mic, T1a, T1b, or T1c) can be based on the molecular subtype of breast cancer, and that the size of the tumor need not be considered [24]. The majority of breast cancer patients with hormone receptor-positive T1 N0 M0 do not require adjuvant chemotherapy, while triple-negative and HER-2 overexpressing breast cancers require adjuvant chemotherapy [24]. A total of 1012 patients with T1a-T1b N0 breast cancer from the Anderson Cancer Center were enrolled and analyzed from 1990 to 2002, and multivariate analysis of these showed that tumor type and age at first visit were significantly associated with recurrence-free survival (RFS) and distant relapse-free survival (DRFS) [25]. Cancello also performed a similar study with their multivariate analysis showing that only age and tumor molecular typing were associated with local recurrence, distant metastasis, and breast cancer-related survival (BCS). Furthermore, T stage, multifocal, and vascular infiltration were not significant predictors of prognosis for small breast cancer [13]. Both studies demonstrated that the age and tumor subtypes of patients with T1a-T1b N0 breast cancer were the only two prognostic factors associated with relapse and survival in patients. Our study also found that the size of the tumor was not a prognostic factor in small breast cancer outcomes. In addition, Her-2 status and lymph node metastasis were also not significant predictors of disease but age, histological grade, distant metastasis and HR status were independent prognostic factors for small breast cancer patients. Surgery and radiotherapy were also critically important for small breast cancer, and were independent factors affecting the prognosis of patients, radiotherapy was associated with a significantly better prognosis in T1a-T1b N0 and T1a-T1bN1 patients, suggesting that radiotherapy should be performed to T1a-T1b patients with or without lymph node metastasis. This study found that there was no statistical difference in surgery (breast-conserving or mastectomy) for prognosis among T1a-T1b breast cancer patients. A multicenter retrospective 10-year analysis of 900 patients with T1a-c N0 M0 breast cancer reported a breast conserving surgery (BCS) rate of 81.8%, with local therapy not related to breast cancer subtype [26]. However, Chinese clinical workers have demonstrated different findings, showing low BCS rates. Furthermore, a recent SEER review showed an increasing trend of mastectomies for patients with T1 tumors [27]. Currently, with advancements in breast surgery, the breast-conserving surgery rate are increasing year by year, especially for small breast cancer. In addition, radiotherapy offer significant survival benefit even in patients with small lymph node-negative breast cancer in this research.

In our study, TNBC patients had a poorer survival than the other three molecular typing, we

demonstrated a poorer prognosis of TNBC than Her-2$^+$ breast cancers. Clearly, there is a trend towards more aggressive adjuvant therapy of small breast cancers [31], especially for triple-negative and Her-2-positive breast cancer. According to current studies and guidelines, T1b, triple-negative, Her-2-positive breast cancer, or breast cancer with other risk factors require comprehensive treatment including chemotherapy or targeted therapy.

HER-2$^+$ and TNBC T1a-T1b breast cancers generally carry a higher risk of recurrence and death than other subtypes, especially in Her-2$^+$ patients [1, 12, 28]. According to data from retrospective studies, 6 to 10% of pT1ab N0 small tumors were positive for human epidermal growth factor receptor 2 (HER-2), with a 10-year recurrence rate of 7 to 33% and a 10-year specific breast cancer mortality rate of 7 to 32% [12, 29, 30]. Therefore, aggressive treatment of this type of breast cancer is imperative, and should include comprehensive treatment with Herceptin (trastuzumab). The consensus conference held in St Gallen, France, recommends the use of trastuzumab-based adjuvant chemotherapy in T1b HER2-overexpressing breast cancers [24], Nonetheless, there is no evidence that trastuzumab-based adjuvant chemotherapy in HER2-positive patients is beneficial for those with T1a node-negative breast cancers.

In summary, there are limitations to our study. For example, the database had a lack of detail relating to appropriate adjuvant therapy information, such as chemotherapy, endocrine therapy, and targeted therapy. As a consequence, we could not analyze the biases, which may affect prognosis of different small breast cancers. In addition, the prognosis of small breast cancers is generally so good that the short follow-up period also limits our analysis. Although overall prognosis of Tla-T1b small tumor breast cancer is good, there are still some patients who have a poor prognosis. When an adjuvant treatment decision is taken for triple-negative or HER-2-positive small breast cancer patients, prognosis-related factors should also be evaluated, such as tumor size (T1a/b), age, lymph node status, hormone receptor status, histological grade, and the Ki-67 expression. More aggressive treatment should be considered for patients with one or more adverse prognostic factors such as appropriate chemotherapy and anti-HER-2 therapy. All in all, further studies are still needed for T1a-T1b BC patients.

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Disclosure of conflict of interest

None.

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