The Breast 43 (2019) 97–104

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Effects of adjuvant chemotherapy in T1N0M0 triple-negative breast cancer

Yi-Xing Ren [a, b, 1], Shuang Hao [a, 1], Xi Jin [a], Fu-Gui Ye [a], Yue Gong [a, b], Yi-Zhou Jiang [a, **], Zhi-Ming Shao [a, c, *]

[a] Key Laboratory of Breast Cancer in Shanghai, Department of Breast Surgery, Fudan University Shanghai Cancer Center, Shanghai, 200032, China
[b] Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, 200032, China
[c] Institutes of Biomedical Science, Fudan University, Shanghai, 200032, China

ARTICLE INFO

Article history:
Received 17 October 2018
Received in revised form
24 November 2018
Accepted 27 November 2018
Available online 28 November 2018

Keywords:
Adjuvant chemotherapy
Triple-negative breast cancer
Recurrence-free survival
T1N0M0 breast cancer
Taxane

ABSTRACT

Objectives: Patients with T1N0M0 breast cancers are considered to have an excellent prognosis, even in triple-negative breast cancer (TNBC), which is often associated with diminished recurrence-free survival (RFS) and overall survival. Chemotherapy remains the only adjuvant treatment for TNBC, but evidence that adjuvant chemotherapy is beneficial for stage T1N0M0 TNBC patients is limited. In this study, we aimed to evaluate the effect of adjuvant chemotherapy and the benefit of taxanes in T1N0M0 TNBC patients.

Material and methods: A cohort of 354 consecutive patients with newly diagnosed T1N0M0 TNBC between January 2008 and December 2015 were included from the Fudan University Shanghai Cancer Center. Univariate and multivariate survival analyses were performed to compare patients treated with adjuvant chemotherapy with/without taxane addition.

Results: Median follow-up was 45 months. Chemotherapy was used in 92.4% of patients. The 5-year estimated RFS rates of patients with and without adjuvant chemotherapy were 94.5% and 83.6%, respectively. In multivariate analysis, adjuvant chemotherapy and a lack of lymphovascular invasion were associated with a significant benefit for RFS. A significant RFS benefit from adjuvant chemotherapy was observed in T1c (hazard ratio, HR = 0.24, 95% CI [0.08–0.76], P = 0.014) but not in T1b (HR = 0.32, 95% CI [0.03–3.18], P = 0.330) subgroups. Addition of taxane to an anthracycline-based regimen was not significantly associated with improved RFS in T1N0M0 TNBC patients.

Conclusion: Adjuvant chemotherapy improves recurrence-free survival in T1c TNBC patients but not in T1b. Anthracycline-based taxane-free regimens might be sufficient to achieve RFS benefits in T1N0M0 TNBC patients.

1. Introduction

Breast cancer is the most commonly diagnosed cancer in women and the leading cause of cancer-related deaths among women worldwide. With an increase in breast cancer awareness and development of screening strategies, early-stage breast cancer has been diagnosed with increasing frequency [1,2]. These small tumors usually show good prognosis with a 5-year survival rate as high as 85%–95%, even without adjuvant therapy.

Recent studies suggest that breast cancer is a heterogeneous disease comprising several molecular profiles with distinct clinical outcomes and therapeutic responses. The reported outcomes of breast cancer vary greatly between different subtypes [3]. In clinical practice, breast cancer is classified by histological characteristics, including hormonal receptor (HR) and growth factor receptor 2 (HER2) status. One of these is triple-negative breast cancer (TNBC), which accounts for approximately 15%–20% of all breast cancers, characterized by no/low expression of estrogen receptor (ER),

* Corresponding author. Key Laboratory of Breast Cancer in Shanghai, Department of Breast Surgery, Fudan University Shanghai Cancer Center, Shanghai, 200032, China.
** Corresponding author.
E-mail addresses: renyixingsh@163.com (Y.-X. Ren), hzz50@hotmail.com (S. Hao), 15111230037@fudan.edu.cn (X. Jin), yefugui87@163.com (F.-G. Ye), garykung_jscs@163.com (Y. Gong), yizhoujiang@fudan.edu.cn (Y.-Z. Jiang), zhimingshao@yahoo.com (Z.-M. Shao).
[1] These authors contributed equally to the work.

https://doi.org/10.1016/j.breast.2018.11.011
0960-9776/

progesterone receptor (PR) and HER2 by immunohistochemical analysis. TNBC is often associated with a high risk of early relapse and disease progression compared to other subtypes [3,4]. Because of the absence of endocrine and other targeted therapies, chemotherapy remains the only systemic treatment option for patients with early-stage TNBC. The survival benefits of chemotherapy for TNBC patients are well established. Compared to other breast cancer subtypes, TNBC benefits most from chemotherapy [5]. Currently, the administration of chemotherapy for TNBC patients depends on clinical parameters, such as tumor size, lymph node status and comorbidities, patient preference and cost of therapy. In some clinical practices, chemotherapy is considered even in patients with T1a-bN0 TNBC to ensure the highest possibility for cure. Despite extensive study, there is still a high degree of uncertainty about choosing patients who might benefit from adjuvant chemotherapy and selecting the best chemotherapy regimens. To avoid overtreatment with chemotherapy, studies of gene expression profiling are underway, aiming to identify early-stage TNBC patients who may benefit from chemotherapy, but these data have not changed the clinical management of early-stage TNBC thus far.

Anthracyclin- and/or taxane-based regimens have been mainstay systemic treatments for TNBC. Adjuvant regimen with taxane improves the outcomes of TNBC patients. Breast Cancer International Research Group (BCIRG) 001 trial compared the regimen of docetaxel, doxorubicin, and cyclophosphamide (TAC) with the regimen of fluorouracil, doxorubicin, and cyclophosphamide (FAC), which showed improvement in both risk of recurrence and survival with TAC in the TNBCs [6]. However, most taxane trials have focused on patients with advanced or node-positive TNBCs. Although early-stage breast cancer has been diagnosed with increasing frequency, to date, the value of taxanes in the treatment of early-stage node-negative breast cancer is still uncertain [7–9]. Whether there is an opportunity for minimizing standard systemic therapy in T1N0M0 TNBC patients is unknown.

In this study, we aimed to evaluate the effect of adjuvant chemotherapy on recurrence-free survival (RFS) in a retrospective cohort of 354 T1N0M0 TNBC patients and to assess the benefit of taxanes in this particular group (Table A).

2. Material and methods

2.1. Patient recruitment

All patients aged ≥18 years with newly diagnosed TNBC underwent surgery (breast-conserving surgery or mastectomy) and were selected between January 2008 and December 2015 at our institution. In this retrospective study, ER, PR and HER2 status of all patients were defined by the following standard procedures and guidelines. Briefly, the hematoxylin-eosin (HE) staining of tumor tissue slides were reviewed to determine breast carcinoma by two independent pathologists. The ER, PR, and HER2 immunohistochemistry (IHC) staining procedures were performed on a Ventana Benchmark automated immunostainer (Tucson, Arizona, USA) by the standard streptavidin-biotin staining method (Antibodies: ER, Roche Ventana, Clone SP1; PR, Roche Ventana, Clone IE2; HER2, Roche Ventana, Clone 4B5) [10]. Mammary tumors were considered negative for ER or PR if strong immunoreactivity was observed in less than 1% of tumor nuclei, according to the 2010 ASCO/CAP guidelines [11]. HER2 status was initially evaluated by IHC on a scale of 0–3, combining the intensity of membranous staining and the percentage of staining of invasive tumor cells, according to the 2013 ASCO/CAP guidelines [12]. Cases with scores of 0–1+ were identified as negative. Tumors with HER2 expression status (IHC, score equals to 2+) were further subjected to fluorescence in situ hybridization (FISH) test to determine the HER2 gene amplification with the FDA- approved PathVysion HER2/Neu DNA Probe Kit (Abbott Molecular, Abbott Park, IL, USA). HER2 negativity was defined as FISH negative or IHC staining score equals to 0–1+. All TNBC patients with confirmed T1 pathology and no lymph node infiltration were included, and patients with isolated tumor cells (N0i+) and micro metastases (N1mi) were excluded as their prognosis has been described to be close to that of N1 disease [13]. Since bilateral breast cancer shows a different pathological profile and significantly worse overall survival compared to unilateral breast cancer [14], patients with bilateral breast cancer were excluded. Patients with pathological types other than invasive ductal carcinomas (IDCs) were also excluded because IDCs are the most common type, and prognoses between different pathological types have been proven to vary substantially [15]. Male patients and patients who received prior treatment with neoadjuvant chemotherapy were also excluded. Thus, a total of 354 T1N0M0 TNBC patients were included in this analysis (Fig. 1). The electronic medical records for these patients were then reviewed to confirm their clinical and histopathological details, including age, tumor size, menstruation status, date and type of surgery, vascular invasion, radiation therapy, adjuvant chemotherapy and date of recurrence or death. Menopause is defined as amenorrheic for 12 or more months and it is considered at the beginning of the chemotherapy.

Our study was approved by the independent ethics committee/institutional review board of FUSCC (Shanghai Cancer Center Ethics Committee). All patients provided written informed consent before inclusion.

2.2. Statistical analysis

The present analysis was performed to assess RFS. RFS was defined as the absence of any locoregional (within the confines of the ipsilateral breast, chest wall, or regional lymph nodes) or distant breast cancer recurrence after initial therapy. For patients who were alive and recurrence-free at the last follow-up, data were censored. Clinical and biological characteristics between patients who received chemotherapy and those who did not were described by counts of subjects and percentages, and tested by Pearson's chi-square test or Fisher's exact test as appropriate. The 5-year survival rate was estimated using the Kaplan-Meier method, and differences in survival curves were determined by the Log-rank test. The 5-year survival rate and hazard ratios (HRs) estimations are provided along with their bilateral confidence intervals. Prognostic scores (PS) of chemotherapy were estimated by logistic regression and included the following variables: age, menstruation status, tumor size, grade, type of surgery, and lymphovascular invasion (LVI). The Cox proportional hazards model was used for the univariate and multivariate survival analyses, and hazard ratios and 95% confidence intervals (CIs) were calculated. Subsequently the model was adjusted for PS as a continuous variable. P-values below 0.05 were considered statistically significant. Statistical analyses were performed using SPSS statistical version 22.0 (IBM Corporation, Armonk, NY).

3. Results

3.1. Clinical features

From January 2008 to December 2015, a total of 354 patients with T1N0M0 TNBC were enrolled. Patient, tumor, and treatment characteristics are listed in Table 1. The median follow-up was 45.5 months (range 12–119 months). The median age was 51 years (range 28–82 years) with 42.1% of patients under 50 years of age and 52.8% being postmenopausal. The majority of patients (n = 303,

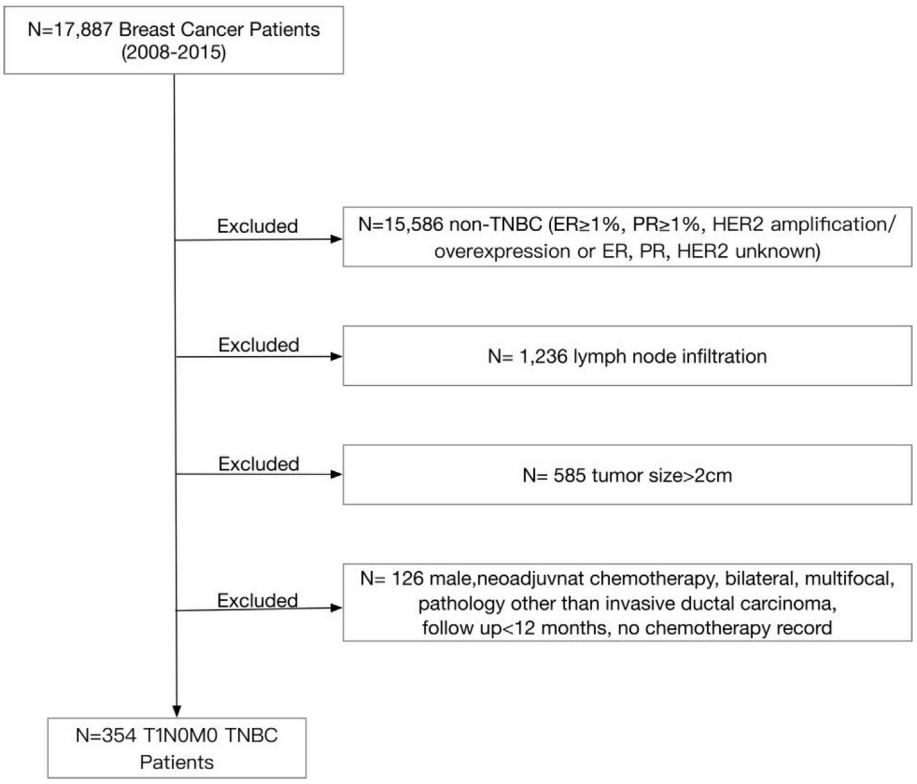

Fig. 1. Patient selection flow chart. (2-column). ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2.

Table 1
Clinical features associated with chemotherapy in T1N0M0 TNBC patients.

	Overall (N = 354)	Chemotherapy		P value
		Not received (N = 27) (%)	Received (N = 327) (%)	
Age, years (median)	51	66	51	<0.001
<50	149 (42.1)	2 (7.4)	147 (45.0)	
≥50	205 (57.9)	25 (92.5)	180 (55.0)	
Menstruation status				<0.001
Pre	167 (47.2)	2 (7.4)	165 (50.4)	
Post	187 (52.8)	25 (92.5)	162 (49.6)	
Tumor size				<0.001
T1a	7 (2.0)	4 (14.8)	3 (0.9)	
T1b	44 (12.4)	4 (14.8)	40 (12.2)	
T1c	303 (85.6)	19 (70.4)	284 (86.9)	
LVI				0.71
Yes	28 (7.9)	1 (3.7)	27 (8.3)	
No	326 (92.1)	26 (96.3)	300 (91.7)	
Grade				<0.001
1-2	140 (39.5)	21 (77.8)	119 (36.4)	
3	214 (60.5)	6 (22.2)	208 (63.6)	
Surgery				
Breast-conserving	137 (38.7)	5 (18.5)	132 (40.4)	0.025
Mastectomy	217 (61.3)	22 (81.5)	195 (59.6)	
Radiotherapy				<0.001
Yes	128 (36.2)	2 (7.4)	126 (38.5)	
No	226 (63.8)	25 (92.5)	201 (61.5)	

Abbreviations: LVI, lymphovascular invasion; N, No. of patients.

85.6%) were T1c. Vessel invasion occurred in 28 patients. One hundred and thirty-seven patients (38.7%) underwent lumpectomy, 88 patients (24.9%) underwent total mastectomy and 129 patients underwent modified radical mastectomy. All patients underwent surgical axillary staging or sentinel-node biopsy. Of the 137 patients who underwent lumpectomy, 87.6% (n = 120) had radiation therapy, which is only 3.7% (n = 8) of the mastectomy group. Two hundred and seventy-eight patients received an anthracycline/taxane-based adjuvant chemotherapy, including 16 treated with EC (epirubicin/cyclophosphamide), 21 with EC-T (docetaxel), 28 with EC-P (paclitaxel), 125 with FEC-T (5-fluorouracil/epirubicin/cyclophosphamide followed by docetaxel), 54 with FEC, 30 with TC (docetaxel/cyclophosphamide) and 4 with FTC (5-fluorouracil/docetaxel/cyclophosphamide). Forty-nine patients received PC

(paclitaxel/cyclophosphamide). Three hundred and twenty-seven patients received adjuvant chemotherapy, while 27 did not.

3.2. Recurrence-free survival (RFS)

Compared to patients not receiving chemotherapy, patients treated with chemotherapy were more likely to experience adverse clinical and pathological features, such as larger tumor size ($P < 0.001$), higher tumor grade ($P < 0.001$), and younger age (66 versus 51, $P < 0.001$), which is in line with some other studies [16,17]. (Table 1). Factors associated with chemotherapy administration were analyzed by multivariate logistic regression followed by estimation of propensity score (Table 2). The results showed that, compared to patients with T1a disease, patients with T1b and T1c were more likely to receive adjuvant chemotherapy with odds ratios (OR) of 11.03 (95% confidence interval [CI] [1.29–94.31], $P = 0.028$) and 11.25 (95% CI [1.64–76.90], $P = 0.014$), respectively. Higher grading was also associated with chemotherapy (grade 3 versus grade 1–2, OR = 4.33; 95% CI [1.63–11.52], $P = 0.003$), while age, menstruation status, surgery and LVI were not associated with receipt of chemotherapy (Table 2).

Overall, 24 RFS events (6.8%) were observed. Five of these patients (20.8%) did not receive chemotherapy, while 19 (79.2%) did. Five-year estimated RFS was 93.7% (95% CI [89.0%–96.4%]) in the overall population. Adjuvant chemotherapy was associated with a better RFS benefit but not reaching statistical significance (HR = 0.41, 95% CI [0.15–1.11], $P = 0.078$), with a 5-year estimated RFS of 94.5% (95% CI [89.6%–97.1%]) versus 83.6% (95% CI [56.3%–94.6%]) in the absence of adjuvant chemotherapy ($P = 0.069$, log-rank test) (Fig. 2). Only LVI was associated with a significantly increased risk of recurrence on univariate analysis (Table 3). Multivariate Cox regression analysis, including LVI and adjuvant chemotherapy, revealed that the presence of LVI (HR = 5.26, 95% CI [1.99–13.89], $P = 0.001$) and adjuvant chemotherapy (HR = 0.31, 95% CI [0.11–0.87], $P = 0.027$) were statistically significant independent predictors of RFS (Table 4). With the adjustment of propensity score, estimated RFS was significantly impacted by adjuvant chemotherapy (HR = 0.16, 95% CI [0.05–0.53], $P = 0.003$) (Table 4).

Subgroup analysis showed that patients with T1c who received chemotherapy appeared to gain an RFS benefit from chemotherapy compared to their counterparts not receiving chemotherapy (HR = 0.24, 95% CI [0.08–0.76], $P = 0.014$) ($P = 0.008$, log-rank test). In contrast, chemotherapy had no impact on estimated RFS in T1b patients (HR = 0.32, 95% CI [0.03–3.18], $P = 0.330$) ($P = 0.305$, log-rank test), although the number of events and patients in this subgroup were very small (Table 5) (Fig. 3). Table 6 shows the results of univariate survival analyses of RFS in patients with T1b and T1c. The benefit of RFS remained in T1c patients with adjuvant chemotherapy (HR = 0.18, 95% CI [0.06–0.58], $P = 0.004$). Results were consistent when the propensity score was considered (HR = 0.17, 95% CI [0.04–0.73], $P = 0.017$) (Table 7).

Table 2
Characteristics predictive for receipt of chemotherapy.

	Odds Ratio (95% CI)	P value
Age		
≥50 versus <50	0.64 (0.07–5.77)	0.690
Menopause		
Post versus Pre	0.15 (0.02–1.36)	0.092
Tumor size		
T1a	1	
T1b	11.03 (1.29–94.31)	0.028
T1c	11.25 (1.64–76.90)	0.014
Grade		
3 versus 1-2	4.33 (1.63–11.52)	0.003
Surgery		
Breast conserving versus Mastectomy	0.47 (0.16–1.36)	0.164
LVI		
Yes versus No	1.99 (0.24–16.76)	0.527

Abbreviations: CI, confidence interval; LVI, lymphovascular invasion.

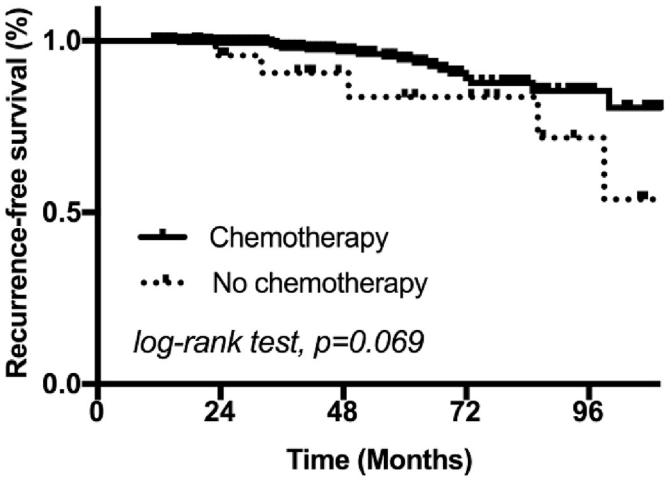

Fig. 2. Estimated RFS according to chemotherapy for Cox analysis in T1N0M0 TNBC patients. (single-column).

Table 3
Univariate survival analyses for recurrence-free survival (RFS).

	Hazard Ratio (95% CI)	P value
Age		
≥50 versus <50	1.10 (0.49–2.51)	0.815
Menopause		
Post versus Pre	0.72 (0.31–1.65)	0.435
Tumor size		
T1a-b versus T1c	1.79 (0.71–4.55)	0.220
Grade		
3 versus 1-2	1.38 (0.61–3.15)	0.439
Surgery		
Breast conserving versus Mastectomy	1.55 (0.68–3.55)	0.299
LVI		
Yes versus No	4.32 (1.67–10.98)	0.002
Radiotherapy		
Yes versus No	1.04 (0.44–2.44)	0.938
Adjuvant chemotherapy		
Yes versus No	0.41 (0.15–1.11)	0.078

Abbreviations: CI, confidence interval; LVI, lymphovascular invasion.

3.3. Taxane therapy

In groups with the same EC*4-containing regimen, the 5-year estimated RFS rates were 92.7% and 87.1% in groups with and without docetaxel, respectively (HR = 2.13; 95% CI [0.29–15.52]; P = 0.456). In groups with the same courses of treatment, the 5-year estimated RFS rates were 91.8% for patients with FEC*3-T*3 vs. 97.3% for FEC*6 (HR = 2.47; 95% CI [0.65–9.40]; P = 0.185). Recently, several trails suggested that four cycles of chemotherapy might be as good as six cycles as they exhibited similar rate of RFS or overall survival [18,19]. In addition, some studies with the same anthracycline-based regimens in control showed that adding fluorouracil provided no significant survival benefit [20,21]. Thus, through indirect comparison, evidences indicate that four cycles of EC might be equivalent to six cycles of FEC. In univariate analysis, no statistically significant difference was observed between FEC*3-T*3 and EC*4 (HR = 0.55; 95% CI [0.12–2.61]; P = 0.455) or between EC*4-T/P and FEC*6 (HR = 4.10; 95% CI [0.52–32.50]; P = 0.182). In

Table 4
Cox multivariate analysis of factors for recurrence-free survival (RFS).

	Hazard Ratio (95% CI)	P value	Adjusted HR* (95% CI)	P value
LVI				
Yes versus No	5.26 (1.99–13.89)	0.001	4.67 (1.77–12.33)	0.002
Adjuvant chemotherapy				
Yes versus No	0.31 (0.11–0.87)	0.027	0.16 (0.05–0.53)	0.003

Abbreviations: CI, confidence interval; HR, Hazard ratio; LVI, lymphovascular invasion.
*Adjusted Hazard Ration was derived from Cox regression analysis for chemotherapy, LVI and propensity score.

Table 5
Impact of chemotherapy on RFS according to tumor size.

Tumor Size	Events	HR (95% CI)	P value
T1a			
No chemotherapy	0/4	–	–
Chemotherapy	0/3	–	–
T1b			
No chemotherapy	1/4	1	
Chemotherapy	6/40	0.32 (0.03–3.18)	0.330
T1c			
No chemotherapy	4/19	1	
Chemotherapy	13/284	0.24 (0.08–0.76)	0.014

Abbreviations: CI, confidence interval; HR, Hazard ratio.

multivariate analysis including the covariates that were most significant in the univariate analysis (Table B.$_1$), RFS was also not significantly impacted by addition of docetaxel (Table B.$_{2\text{-}5}$). Adding taxane wasn't associated with shorter RFS, regardless of any clinical and pathological features in this study (Table B.$_6$).

4. Discussion

In this retrospective cohort study, adjuvant chemotherapy was administered to 92.3% of patients with IDC, T1N0M0, TNBC, and it significantly improved RFS in T1c patients but not in T1b patients (Table 5). In addition, no prognostic benefit was derived from the administration of taxane in this cohort.

Recently, a large study including 104,499 node-negative breast cancer patients showed that the TNBC subtype exhibited higher risk of mortality than all other subtypes [3]. Higher recurrence was observed in Her-2 positive and TNBC subsets among patients with small node-negative breast cancers not receiving adjuvant chemotherapy or trastuzumab [22]. These results indicate that TNBC represents a higher risk subtype, even in early stages [23]. Currently, chemotherapy is the only adjuvant therapy that may be effective for TNBC patients. Our study showed that receiving chemotherapy significantly improved estimated RFS, which is consistent with the results of a former study [21].

Recent knowledge suggests that TNBC is a heterogeneous disease. With the development of gene sequencing technology, increasing molecular differences were observed within TNBC. Studies have been conducted to identify models that could predict chemotherapy benefit of TNBC [24]. Unfortunately, no reliable model has been established as of yet. Several clinical and pathological features, such as high grade, young age, and vascular invasion, are considered adverse prognostic factors and used as indicators for more aggressive therapy [24]. Our study revealed a trend in receiving chemotherapy in high-grade or T1b-c tumors. The current NCCN (National Comprehensive Cancer Network) guidelines recommend adjuvant chemotherapy for node-negative TNBC patients based on tumor size, suggesting that adjuvant chemotherapy should be considered for T1bN0 patients and should be administered to T1cN0 patients [25]. Subgroup analysis in this study demonstrated that patients with T1cN0 who received

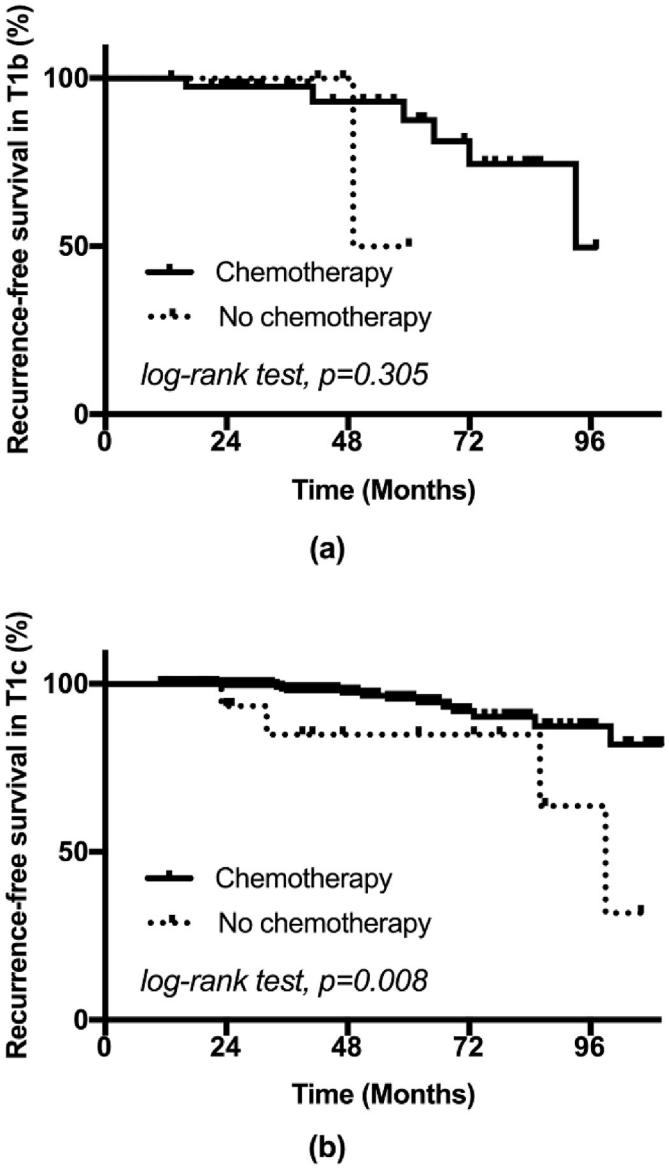

Fig. 3. Estimated RFS according to chemotherapy for Cox analysis in (a) T1bN0M0 and (b) T1cN0M0 TNBC patients. (single-column).

chemotherapy appeared to gain an RFS benefit from chemotherapy, while no benefit was observed in T1bN0 patients, although the number of patients in this subgroup was very small. These results are partially in favor of the NCCN guideline and in line with several studies. Most recently, in a study examining a cohort of 284 patients with T1a-bN0 TNBC, chemotherapy was not associated with a benefit for disease-free survival [26]. In our study, in addition to adjuvant chemotherapy, LVI was reported as a prognostic factor for

Table 6
Univariate analysis of factors for recurrence-free survival (RFS).

	T1b		T1c	
	Crude HR (95% CI)	P value	Crude HR (95% CI)	P value
Age				
≥50 versus <50	0.29 (0.03–2.52)	0.263	1.63 (0.62–4.28)	0.326
Menopause				
Post versus Pre	0.27 (0.03–2.34)	0.236	1.04 (0.40–2.72)	0.932
Grade				
3 versus 1-2	2.41 (0.44–13.26)	0.313	0.82 (0.31–2.13)	0.680
Surgery				
Breast conserving versus Mastectomy	2.24 (0.45–11.17)	0.325	1.28 (0.49–3.37)	0.618
LVI				
Yes versus No	1.37 (0.10–19.63)	0.816	4.37 (1.53–12.43)	0.006
Radiotherapy				
Yes versus No	2.54 (0.46–13.92)	0.285	0.60 (0.20–1.84)	0.37

Abbreviations: CI, confidence interval; HR, Hazard ratio; LVI, lymphovascular invasion.

Table 7
Cox multivariate analysis of factors for estimated recurrence-free survival (RFS) in T1c patients.

	Hazard Ratio (95% CI)	P value	Adjusted HR* (95% CI)	P value
Chemotherapy	0.18		0.17	
Yes versus No	(0.06–0.58)	0.004	(0.04–0.73)	0.017
LVI	5.66		5.62	
Yes versus No	(1.89–16.91)	0.002	(1.84–17.13)	0.002

Abbreviations: CI, confidence interval; HR, Hazard ratio; LVI, lymphovascular invasion.
*Adjusted HR was derived from Cox regression analysis for chemotherapy and propensity score.

RFS among patients with T1c node-negative TNBC, in that the presence of LVI was associated with an increased hazard of a RFS event. However, among patients with T1b node-negative TNBC, the prognostic effect of LVI was absent. Although presence of LVI, in most cases, is considered as an early metastatic event, to our knowledge, it has not yet been utilized in selecting breast cancer patients who should be treated with adjuvant therapies. In fact, the prognostic value of LVI in breast cancer is controversial. In a retrospective analysis of 2754 patients with node- negative breast cancer, the presence of LVI in patients with ER-negative disease was significantly associated with poorer disease-free survival among the premenopausal subgroup, but not among the postmenopausal subgroup [27]. Another prospective population-based study including 16172 patients with operable breast cancer indicated that invasive disease-free interval might only be associated with LVI within the high-risk group (patients with positive lymph nodes, tumor size > 2 cm, high grade, hormone receptor-negative tumor, or younger than 35 years) [28]. More recently, in two retrospective studies, data suggested that TNBC patients with LVI might be at an increased risk of recurrence compared with TNBC patients without LVI [29,30]. Despite the existence of all these studies, the prognostic impact of LVI among patients with early node-negative TNBC remains to be determined. Our study provided new evidence to the prognostic value of LVI, however, due to the limited number of cases, especially in the T1b subgroup, the results of our study could be due to chance.

To date, for TNBC patients requiring adjuvant chemotherapy, there is no evidence to recommend a specific chemotherapy regimen. Early-stage node-negative breast cancers show relatively low rates of recurrence, even in high-risk subtypes such as TNBC [4]. In fact, the majority of patients with early-stage TNBC never experience a distant metastatic recurrence or die from their disease [31,32]. However, the current preferred adjuvant regimens for early-stage and late-stage TNBC patients are the same. Whether there is an opportunity to de-escalate chemotherapy in T1N0M0 TNBC patients remains unclear. Efforts have been made to address this question. Some studies evaluated the omission of adjuvant chemotherapy in low risk TNBC [33]. De Nonneville et al. identified no advantage for chemotherapy in estimated RFS or metastasis-free survival in T1a-b, N0 TNBC patients [26]. Furthermore, the data from the CALGB 40101 trial (with AC and T) and the recent PACS 05 trial (with FEC) showed that four cycles of chemotherapy were as good as six cycles in terms of RFS and OS [18,19]. In addition, less toxic or aggressive adjuvant chemotherapy complexes have been considered for patients with small node-negative tumors [21,34]. In the GIM 2 trial, addition of fluorouracil did not provide a significant RFS benefit over a sequential EC-P regimen [20]. Similarly, the effect of fluorouracil was obtained in a retrospective study, which included 4033 patients with T1-2N0 triple-negative breast cancer, and reported no difference in survival benefit among AC, FAC and CMF regimens [21].

Anthracycline- and/or taxane-based regimens are recommended for adjuvant treatment of women with operable breast cancer. Taxanes were introduced for the treatment of breast cancer in the 1990s, which led to benefits in RFS and OS in node-positive or advanced breast cancer [35]. Current trials of taxane-based versus non-taxane-based chemotherapy vary greatly, with the same or more of each non-taxane component in control regimens. However, due to limited data and varied treatment comparisons, adjuvant treatment with taxanes in patients with early-stage node-negative breast cancer remains controversial. The GEICAM 9805 trial showed that in a subgroup of patients with high-risk node-negative disease, adjuvant TAC (docetaxel/doxorubicin/cyclophosphamide) was associated with significant improvements in disease-free survival compared to FAC (5-fluorouracil/doxorubicin/cyclophosphamide) [9]. Meanwhile, the TACT UK trial compared four cycles of FEC followed by four cycles of docetaxel with eight cycles of FEC and found no overall gains from addition of docetaxel [7]. Furthermore, to our knowledge, almost all current studies have cohorts comprising mixed ER, HER2 or node status. The benefit of taxane in the treatment of T1N0M0 TNBC patients is still unclear. The results from our study showed no significant improvements in RFS from addition of taxane to anthracycline-based adjuvant chemotherapy.

An advantage of this study is that, while most studies focusing on early node-negative breast cancer have cohorts of mixed ER and HER2 status, making it difficult to detect prognostic factors and evaluate the effects of chemotherapy in early-stage TNBC, our study only included patients who have T1N0M0 TNBC with pathology of IDCs from a large cohort. Because of the relatively low incidence of

T1N0M0 TNBC and the predictable good prognosis, this group of patients is not usually included in clinical trials and retrospective studies.

This study has some limitations. First, this study may have been underpowered for subgroup analysis given the small sample size of T1a-b patients; further randomized prospective studies need to be performed in the future. Second, lying mainly in the observational nature of the study, potential indication bias was observed, as chemotherapy treatments were provided depending on the prognostic features of patients. Therefore, we used propensity scores to adjust the baseline differences arising from known prognostic factors between groups and to minimize the impact of confounding. Third, we had a limited follow-up time and low numbers of events in the overall study population. However, TNBC has a trend of quick recurrence within the first 3–5 years after diagnosis [36], and the TNBC survivors who have been disease free for 5 years have a low probability of experiencing recurrence over the subsequent 10 years [37].

In conclusion, our results suggest that adjuvant chemotherapy improves recurrence-free survival in T1cN0M0 TNBC patients but may not in T1b, in agreement with many studies, though current consensus guidelines recommend consideration of chemotherapy in T1b TNBC patients. Therefore, T1b patients might not be suitable for chemotherapy, which may make chemotherapy reduction strategies possible for these patients. Moreover, our study also illustrates that adjuvant use of taxane in T1N0M0 TNBCs may not confer a significant RFS advantage. Thus, even though it remains common to propose taxane treatment for such patients, we should carefully choose chemotherapy regimens considering the yet unproven benefits and side effects of taxane.

Conflicts of interest

The authors have stated that they have no conflicts of interest.

Acknowledgements

This study was funded by grants from the National Natural Science Foundation of China (81874112, 81502278, 81572583, and 81372848), the Training Plan of Excellent Talents in Shanghai Municipality Health System (2017YQ038), the “Chen Guang” project supported by Shanghai Municipal Education Commission and Shanghai Education Development Foundation (17CG01), Shanghai Pujiang Program (18PJD007), and the Training Plan of Excellent Talents of Fudan University Shanghai Cancer Center (YJYQ201602). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2018.11.011.

References

[1] Li J, Zhang BN, Fan JH, Pang Y, Zhang P, Wang SL, et al. A nation-wide multicenter 10-year (1999-2008) retrospective clinical epidemiological study of female breast cancer in China. BMC Canc 2011;11:364. https://doi.org/10.1186/1471-2407-11-364.

[2] Welch HG, Prorok PC, O'Malley AJ, Kramer BS. Breast-cancer tumor size, overdiagnosis, and mammography screening effectiveness. N Engl J Med 2016;375:1438–47. https://doi.org/10.1056/NEJMoa1600249.

[3] Parise CA, Caggiano V. Risk of mortality of node-negative, ER/PR/HER2 breast cancer subtypes in T1, T2, and T3 tumors. Breast Cancer Res Treat 2017;165:743–50. https://doi.org/10.1007/s10549-017-4383-5.

[4] Leon-Ferre RA, Polley MY, Liu H, Gilbert JA, Cafourek V, Hillman DW, et al. Impact of histopathology, tumor-infiltrating lymphocytes, and adjuvant chemotherapy on prognosis of triple-negative breast cancer. Breast Cancer Res Treat 2018;167:89–99. https://doi.org/10.1007/s10549-017-4499-7.

[5] Houssami N, Macaskill P, von Minckwitz G, Marinovich ML, Mamounas E. Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy. Eur J Canc 2012;48:3342–54. https://doi.org/10.1016/j.ejca.2012.05.023.

[6] Ahluwalia MS, Daw HA. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 2005;353:954–5. author reply -5, https://doi.org/10.1056/NEJMc051802.

[7] Ellis P, Barrett-Lee P, Johnson L, Cameron D, Wardley A, O'Reilly S, et al. Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT): an open-label, phase III, randomised controlled trial. Lancet 2009;373:1681–92. https://doi.org/10.1016/S0140-6736(09)60740-6.

[8] Buyukhatipoglu H, Babacan T, Kertmen N, Balakan O, Suner A, Ates O, et al. A retrospective analysis of adjuvant CAF, AC-T and TAC regimens in triple negative early stage breast cancer. J BUON 2015;20:22–7.

[9] Martin M, Segui MA, Anton A, Ruiz A, Ramos M, Adrover E, et al. Adjuvant docetaxel for high-risk, node-negative breast cancer. N Engl J Med 2010;363:2200–10. https://doi.org/10.1056/NEJMoa0910320.

[10] Shaoxian T, Baohua Y, Xiaoli X, Yufan C, Xiaoyu T, Hongfen L, et al. Characterisation of GATA3 expression in invasive breast cancer: differences in histological subtypes and immunohistochemically defined molecular subtypes. J Clin Pathol 2017;70:926–34. https://doi.org/10.1136/jclinpath-2016-204137.

[11] Hammond MEH, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American society of clinical oncology/College of American pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 2010;28:2784–95. https://doi.org/10.1200/jco.2009.25.6529.

[12] Wolff AC, Hammond MEH, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American society of clinical oncology/College of American pathologists clinical practice guideline update. J Clin Oncol 2013;31:3997–4013. https://doi.org/10.1200/jco.2013.50.9984.

[13] Houvenaeghel G, Sabatier R, Reyal F, Classe JM, Giard S, Charitansky H, et al. Axillary lymph node micrometastases decrease triple-negative early breast cancer survival. Br J Canc 2016;115:1024–31. https://doi.org/10.1038/bjc.2016.283.

[14] Vuoto HD, Garcia AM, Candas GB, Zimmermann AG, Uriburu JL, Isetta JA, et al. Bilateral breast carcinoma: clinical characteristics and its impact on survival. Breast J 2010;16:625–32. https://doi.org/10.1111/j.1524-4741.2010.00976.x.

[15] Wu Y, Zhang N, Yang Q. The prognosis of invasive micropapillary carcinoma compared with invasive ductal carcinoma in the breast: a meta-analysis. BMC Canc 2017;17:839. https://doi.org/10.1186/s12885-017-3855-7.

[16] Kwon J, Eom K-Y, Koo TR, Kim BH, Kang E, Kim S-W, et al. A prognostic model for patients with triple-negative breast cancer: importance of the modified Nottingham prognostic index and age. J Breast Canc 2017;20:65. https://doi.org/10.4048/jbc.2017.20.1.65.

[17] Liu Y, Xin T, Huang D-y, Shen W-x, Li L, Lv Y-j, et al. Prognosis in very young women with triple-negative breast cancer: retrospective study of 216 cases. Med Oncol 2014;31. https://doi.org/10.1007/s12032-014-0222-2.

[18] Shulman LN, Cirrincione CT, Berry DA, Becker HP, Perez EA, O'Regan R, et al. Six cycles of doxorubicin and cyclophosphamide or Paclitaxel are not superior to four cycles as adjuvant chemotherapy for breast cancer in women with zero to three positive axillary nodes: cancer and Leukemia Group B 40101. J Clin Oncol 2012;30:4071–6. https://doi.org/10.1200/JCO.2011.40.6405.

[19] Kerbrat P, Desmoulins I, Roca L, Levy C, Lortholary A, Marre A, et al. Optimal duration of adjuvant chemotherapy for high-risk node-negative (N-) breast cancer patients: 6-year results of the prospective randomised multicentre phase III UNICANCER-PACS 05 trial (UCBG-0106). Eur J Canc 2017;79:166–75. https://doi.org/10.1016/j.ejca.2017.03.004.

[20] Del Mastro L, De Placido S, Bruzzi P, De Laurentiis M, Boni C, Cavazzini G, et al. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2 x 2 factorial, randomised phase 3 trial. Lancet 2015;385:1863–72. https://doi.org/10.1016/S0140-6736(14)62048-1.

[21] Kim HA, Seong MK, Kim EK, Kang E, Park S, Hur MH, et al. Evaluation of the survival benefit of different chemotherapy regimens in patients with T1-2N0 triple-negative breast cancer. J Breast Cancer 2015;18:271–8. https://doi.org/10.4048/jbc.2015.18.3.271.

[22] Gonzalez-Angulo AM, Litton JK, Broglio KR, Meric-Bernstam F, Rakkhit R, Cardoso F, et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. J Clin Oncol 2009;27:5700–6. https://doi.org/10.1200/JCO.2009.23.2025.

[23] Vaz-Luis I, Ottesen RA, Hughes ME, Mamet R, Burstein HJ, Edge SB, et al. Outcomes by tumor subtype and treatment pattern in women with small, node-negative breast cancer: a multi-institutional study. J Clin Oncol 2014;32:2142–50. https://doi.org/10.1200/JCO.2013.53.1608.

[24] Sonnenblick A, Fumagalli D, Azim Jr HA, Sotiriou C, Piccart M. New strategies in breast cancer: the significance of molecular subtypes in systemic adjuvant treatment for small T1a,bN0M0 tumors. Clin Canc Res 2014;20:6242–6. https://doi.org/10.1158/1078-0432.CCR-14-1086.

[25] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

[26] de Nonneville A, Goncalves A, Zemmour C, Cohen M, Classe JM, Reyal F, et al.

Adjuvant chemotherapy in pT1ab node-negative triple-negative breast carcinomas: results of a national multi-institutional retrospective study. Eur J Canc 2017;84:34–43. https://doi.org/10.1016/j.ejca.2017.06.043.
[27] Viale G, Giobbie-Hurder A, Gusterson BA, Maiorano E, Mastropasqua MG, Sonzogni A, et al. Adverse prognostic value of peritumoral vascular invasion: is it abrogated by adequate endocrine adjuvant therapy? Results from two International Breast Cancer Study Group randomized trials of chemo-endocrine adjuvant therapy for early breast cancer. Ann Oncol 2010;21:245–54. https://doi.org/10.1093/annonc/mdp317.
[28] Ejlertsen B, Jensen MB, Rank F, Rasmussen BB, Christiansen P, Kroman N, et al. Population-based study of peritumoral lymphovascular invasion and outcome among patients with operable breast cancer. J Natl Cancer Inst 2009;101:729–35. https://doi.org/10.1093/jnci/djp090.
[29] Ahn KJ, Park J, Choi Y. Lymphovascular invasion as a negative prognostic factor for triple-negative breast cancer after surgery. Radiat Oncol J 2017;35:332–9. https://doi.org/10.3857/roj.2017.00416.
[30] Alcantara VS, Lim GH, Lim SH, Sultana R, Lee JA. Incidence and prognosis of non-metastatic triple negative breast cancer (TNBC) among different races in Southeast Asia. J Surg Oncol 2017;115:523–37. https://doi.org/10.1002/jso.24559.
[31] Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, et al. Race, breast cancer subtypes, and survival in the Carolina breast cancer study. JAMA 2006;295:2492–502. https://doi.org/10.1001/jama.295.21.2492.
[32] Urru SAM, Gallus S, Bosetti C, Moi T, Medda R, Sollai E, et al. Clinical and pathological factors influencing survival in a large cohort of triple-negative breast cancer patients. BMC Canc 2018;18. https://doi.org/10.1186/s12885-017-3969-y.
[33] Colonna SV, Higgins AK, Alvarez J, Saville BR, Lawrence J, Abramson VG. Analysis of risk of recurrence by subtype in </= 1-cm breast tumors. Clin Breast Canc 2016;16:223–31. https://doi.org/10.1016/j.clbc.2015.10.001.
[34] Carey LA. De-escalating and escalating systemic therapy in triple negative breast cancer. Breast 2017;34(Suppl 1):S112–5. https://doi.org/10.1016/j.breast.2017.06.041.
[35] Mavroudis D, Saloustros E, Boukovinas I, Papakotoulas P, Kakolyris S, Ziras N, et al. Sequential vs concurrent epirubicin and docetaxel as adjuvant chemotherapy for high-risk, node-negative, early breast cancer: an interim analysis of a randomised phase III study from the Hellenic Oncology Research Group. Br J Canc 2017;117:164–70. https://doi.org/10.1038/bjc.2017.158.
[36] Lin NU, Vanderplas A, Hughes ME, Theriault RL, Edge SB, Wong YN, et al. Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network. Cancer 2012;118:5463–72. https://doi.org/10.1002/cncr.27581.
[37] Reddy SM, Barcenas CH, Sinha AK, Hsu L, Moulder SL, Tripathy D, et al. Long-term survival outcomes of triple-receptor negative breast cancer survivors who are disease free at 5 years and relationship with low hormone receptor positivity. Br J Canc 2018;118:17–23. https://doi.org/10.1038/bjc.2017.379.