Original Article

Exploration of prognostic factors and the value of adjuvant chemotherapy in T1a,bN0M0 triple-negative breast cancer: a prospective cohort study based on the SEER database

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Background: There are limited published studies on the prognostic predictors and the value of adjuvant chemotherapy (CT) in T1a,bN0M0 triple-negative breast cancer (TNBC) after local therapy. Therefore, the aim of the present study was to explore the prognostic predictors and the value of adjuvant CT in this population.

Methods: We identified T1a,bN0M0 TNBC cases registered in the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2015. We analyzed associations between patient characteristics and overall survival (OS) and breast cancer-specific mortality (BCSM), and differences in OS and BCSM in a CT and no chemotherapy (no CT) cohort before and after propensity score matching.

Results: Of the 3,065 SEER patients, 1,534 (50.0%) received adjuvant CT. The median follow up was 57 months (interquartile range: 39–75 months). The 5-year OS and cumulative BCSM were 93.6% and 3.3%, respectively. Younger age was not associated with lower OS or higher BCSM in the total and no CT cohorts. Higher histologic grade was associated with lower OS in the no CT cohort, and T1b tumors were associated with higher BCSM in the total cohort. Multivariable analysis showed no association between adjuvant CT and OS or BCSM.

Conclusions: Patients with T1a,bN0M0 TNBC had an excellent prognosis with or without adjuvant CT. For this population, higher histologic grade and larger tumor size were predictors of poor prognosis, although the effect of age was complex. Our data did not support using adjuvant CT in patients with T1a,bN0M0 TNBC.

Keywords: Chemotherapy; triple-negative breast cancer (TNBC); prognosis; Surveillance, Epidemiology, and End Results (SEER); T1a,bN0M0

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Introduction

Triple-negative breast cancer (TNBC) is a highly aggressive breast cancer (BC) subtype and has a poor prognosis, which is characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2)/neu (1-5). In TNBC, chemotherapy (CT) remains the cornerstone of treatment, despite its toxic side-effects. Mammographic screening and adjunctive ultrasonography have led to an increase in the number of newly diagnosed BCs with tumor size of

≤1 cm (T1a,b), no lymph node involvement (N0), and no distant metastases (M0) (6-9). Most studies suggest that T1a,bN0M0 TNBC has an excellent long-term prognosis (10-13). According to the National Comprehensive Cancer Network (NCCN) guidelines (14), adjuvant CT is not recommended for patients with T1aN0M0 TNBC, but could be considered for subgroups with high-risk factors, such as young age and high histologic grade. In contrast, for patients with T1bN0M0 TNBC, the NCCN recommends adjuvant CT. Due to the low prevalence of, and limited evidence for, T1a,bN0M0 TNBC, information regarding clinical prognostic factors and the value of adjuvant CT in these patients is limited. Therefore, recommending optimal adjuvant systemic therapy in this patient population remains challenging (10,13).

To better analyze the prognosis of patients with T1a,bN0M0 TNBC and assist physicians with adjuvant systemic therapy decisions, we reviewed all T1a,bN0M0 TNBC cases registered in 2 large database and analyzed their overall survival (OS) and BC-specific mortality (BCSM). We further analyzed the effects of age, tumor size, histologic grade, and adjuvant CT on OS and BCSM in patients with T1a,bN0M0 TNBC. We present the following article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-409/rc) (15).

Methods

Study population

In this cohort study, we retrospectively reviewed patient data from the Surveillance, Epidemiology, and End Results (SEER) database between January 1, 2010, and December 31, 2015. All included patients fulfilled the following inclusion criteria: female, unilateral BC, BC as the first and only cancer diagnosis, pathologically confirmed invasive BC, ER negative, PR negative, HER2 negative, American Joint Committee on Cancer (AJCC) stage T1a,bN0M0, and reception of definitive surgery. Patients were excluded if they had distant metastasis, received neoadjuvant CT, or had missing data regarding treatment or follow up. Positive ER and PR statuses were defined as >1% of tumor cells with nuclear staining, while positive HER2 status was defined as a score of 3+ with immunohistochemistry staining or a score of 2+ and a positive fluorescence *in situ* hybridization result. Patients with BC diagnosed before 2010 were not included, because the SEER database did not record data on HER2 status until 2010. Additionally, patients with BC diagnosed after 2015 were not included to ensure adequate follow-up time. Patient demographics, treatment modalities, tumor pathology, and survival characteristics were obtained. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Variables

The following variables were extracted from the SEER databases: age at diagnosis, year of diagnosis, race, marital status, laterality, tumor size, TNM stage (AJCC stage, 7th edition), histologic subtype, histologic grade, ER status, PR status, HER2 status, type of surgery performed, regional nodes examined, radiation treatment status, adjuvant CT treatment status, BCSM, and OS.

To clarify the effect of age at diagnosis on BCSM and OS, we treated age as a categorical variable and divided it into the following age groups: ≤39, 40–49, 50–59, 60–69, and ≥70 years. Regarding histologic grade, patients were divided into grade I (well differentiated), grade II (moderately differentiated), and grade III (poorly differentiated) + IV (undifferentiated; anaplastic) groups. Regarding tumor size, patients were divided into T1a and T1b groups. Patients were divided into the CT and no CT cohorts based on whether adjuvant CT was performed. The extent of axillary staging was classified as 0, 1–5, or ≥6 examined lymph nodes (16).

Statistical analyses

We used SEER Research Plus data submitted in November 2019 with a final follow-up date of December 31, 2018. Data were analyzed in May 2021. The median follow-up time was calculated using the reverse Kaplan-Meier method (17).

A logistic regression model was used to investigate which variables (including demographic, clinical, and pathological) were associated with adjuvant CT treatment in patients with T1a,bN0M0 TNBC in actual clinical practice. OS was measured as the time from the date of BC diagnosis to the date of death from any cause or the date of the last follow up. Cox proportional hazards models were used to evaluate the association between variables (including demographic, clinicopathological, and treatment) and OS. BCSM was measured as the time from the date of BC diagnosis to the date of death due to BC (SEER cause-specific death classification). In the analysis of BCSM, deaths from other

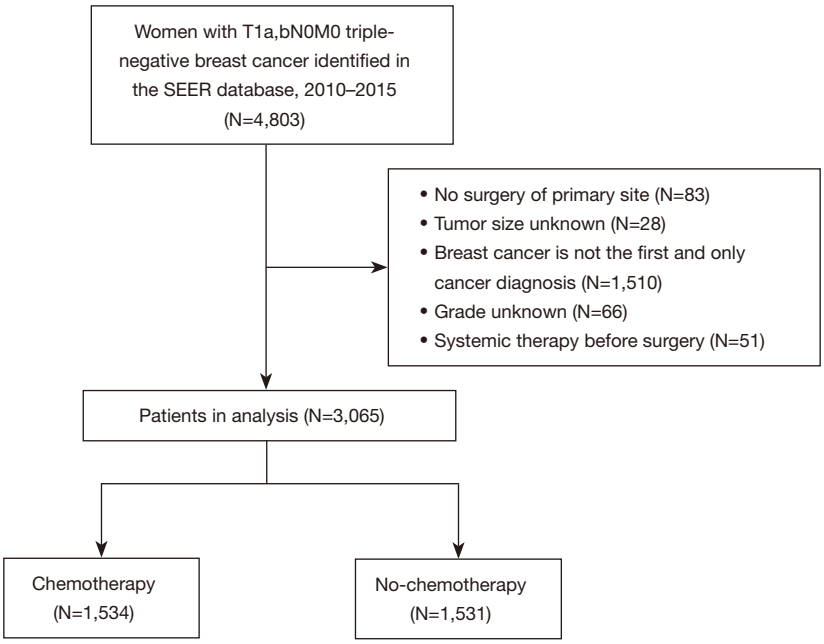

Figure 1 Flow diagram of SEER database patient selection. SEER, Surveillance, Epidemiology, and End Results.

causes were considered competing risks. The cumulative incidence function for competing risks method was used to calculate the crude cumulative probabilities of BCSM in the presence of competing risks of non-BC mortality (18,19). We used the Fine-Gray model to evaluate the association between variables (especially age, tumor size, and histologic grade) and BCSM in the total and no CT cohorts (20).

Propensity score matching (PSM) of the CT and no CT cohorts was conducted for baseline characteristics. The CT and no CT cohorts were matched at a ratio of 1:1 using the nearest neighbor method, with a caliper of 0.05 (21). Before and after PSM, we analyzed whether the use of adjuvant CT affected OS and BCSM in patients with T1a,bN0M0 TNBC, and performed an exploratory subgroup analysis on BCSM after PSM. The Kaplan-Meier estimator was used to calculate the 5-year OS of the CT and no CT cohorts, which was then compared using the log-rank test. The Nelson-Aalen estimator was used to calculate the 5-year BCSM of the CT and no CT cohorts, which was then compared using Gray's test (22,23).

All statistical analyses were performed using R software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria), and differences with a P value of <0.05 were considered statistically significant.

Results

SEER patient characteristics and predictors of CT

Between 2010 and 2015, 3,065 women with T1a,bN0M0 TNBC were enrolled in the SEER database (*Figure 1*). Patient demographics, and their clinical and pathological characteristics, are shown in *Table 1*. Of the 3,065 patients, 1,534 (50.0%) received adjuvant CT, 2,215 (72.3%) had T1b tumors, and 1,926 (62.8%) had grade III + IV tumors.

Younger age at diagnosis, higher histologic grade, larger tumor size, more recent treatment periods, infiltrating ductal carcinoma, breast-conserving surgery, and adjuvant radiotherapy were all associated with an increased probability of receiving adjuvant CT (P<0.05 for each predictor) (Table S1).

OS of SEER patients

Of the 3,065 T1a,bN0M0 TNBC cases in the SEER database, 96 and 103 deaths resulted from BC and other causes, respectively. The median follow up was 57 months (interquartile range: 39–75 months). The 5-year OS estimates for the patient subgroups are presented in *Table 2*. For the total cohort, the 5-year OS of patients with T1a or

Table 1 Characteristics of women with T1a,bN0M0 triple-negative breast cancer (Surveillance, Epidemiology, and End Results database 2010–2015)

Characteristics	Total cohort (n=3,065), n (%)	CT cohort (n=1,534), n (%)	No CT cohort (n=1,531), n (%)
Age at diagnosis (years)			
≤39	105 (3.4)	87 (5.7)	18 (1.2)
40–49	395 (12.9)	279 (18.2)	116 (7.6)
50–59	808 (26.4)	500 (32.6)	308 (20.1)
60–69	963 (31.4)	505 (32.9)	458 (29.9)
≥70	794 (25.9)	163 (10.6)	631 (41.2)
Year of diagnosis			
2010–2012	1,522 (49.7)	726 (47.3)	796 (52.0)
2013–2015	1,543 (50.3)	808 (52.7)	735 (48.0)
Race			
White	2,326 (75.9)	1,150 (75.0)	1,176 (76.8)
Black	513 (16.7)	275 (17.9)	238 (15.6)
Others	226 (7.4)	109 (7.1)	117 (7.6)
Marital status			
Married	1,817 (59.3)	971 (63.3)	846 (55.3)
Not married	1,248 (40.7)	563 (36.7)	685 (44.7)
Laterality			
Right	1,494 (48.7)	735 (47.9)	759 (49.6)
Left	1,571 (51.3)	799 (52.1)	772 (50.4)
Histologic type			
Infiltrating duct carcinoma	2,721 (88.8)	1,411 (92.0)	1,310 (85.6)
Other	344 (11.2)	123 (8.0)	221 (14.4)
Histologic grade			
I	182 (5.9)	32 (2.1)	150 (9.8)
II	957 (31.2)	373 (24.3)	584 (38.2)
III + IV	1,926 (62.8)	1,129 (73.6)	797 (52.1)
Tumor size			
T1a	850 (27.7)	212 (13.8)	638 (41.7)
T1b	2,215 (72.3)	1,322 (86.2)	893 (58.3)
Breast surgery strategies			
Mastectomy	548 (17.9)	249 (16.2)	299 (19.5)
Breast-conserving surgery	2,188 (71.4)	1,099 (71.6)	1,089 (71.1)
Reconstruction	329 (10.7)	186 (12.1)	143 (9.3)

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total cohort (n=3,065), n (%)	CT cohort (n=1,534), n (%)	No CT cohort (n=1,531), n (%)
Regional nodes examined (n)			
0	130 (4.2)	36 (2.4)	94 (6.1)
1–5	2,553 (83.3)	1,304 (85.0)	1,249 (81.6)
≥6	382 (12.5)	194 (12.7)	188 (12.3)
Radiation therapy			
Yes	1,899 (62.0)	989 (64.5)	910 (59.4)
No	1,166 (38.0)	545 (35.5)	621 (40.6)
Vital status			
Alive	2,866 (93.5)	1,466 (95.6)	1,400 (91.4)
Breast cancer-specific mortality	96 (3.1)	53 (3.5)	43 (2.8)
Other cause-specific mortality	103 (3.4)	15 (1.0)	88 (5.8)

CT, chemotherapy.

T1b tumors not treated with adjuvant CT exceeded 90%. For patients aged ≤39 years, the 5-year OS exceeded 93%, regardless of whether they received adjuvant CT. Among the grade III + IV patients, the 5-year OS was 94.9% and 91.3% for patients receiving and not receiving adjuvant CT, respectively.

For the total cohort (n=3,065), Cox multivariable analysis revealed several predictors of worse OS, including age ≥60 years at diagnosis, breast mastectomy surgery, unmarried status, and 0 axillary nodes examined (P<0.05 for each predictor) (*Table 3*). In the no CT cohort (n=1,531), another Cox multivariable analysis revealed several predictors of worse OS, including age ≥60 years at diagnosis, unmarried status, omission of radiotherapy, and higher histologic grade (P<0.05 for each predictor) (*Table 3*).

After PSM, the baseline characteristics of the CT and no CT cohorts were balanced (Table S2). Before PSM, the estimated 5-year OS was 95.3% in the CT cohort and 91.9% in the no CT cohort [hazard ratio (HR): 0.53; 95% confidence interval (CI): 0.39–0.71; P<0.001] (*Figure 2A*). After PSM, the estimated 5-year OS was 96.7% in the CT cohort and 93.8% in the no CT cohort (HR: 0.55; 95% CI: 0.34–0.88; P=0.012) (*Figure 2B*).

BCSM in SEER patients

Table 2 lists the 5-year cumulative BCSM estimates for the SEER patients treated/not treated with adjuvant CT. In all patients, the 5-year cumulative BCSM did not exceed 3.9%. In the no CT cohort, the 5-year cumulative BCSM was the highest in the 40–49-year group (5.7%), and similar within the 50–59-, 60–69-, and ≥70-year groups (2.8%, 2.0%, and 2.9%, respectively). There were no BCSM events in the ≤39-year group. In the no CT cohort, the 5-year cumulative BCSM was 1.9%, 2.3%, and 3.3% for histologic grades I, II, and III + IV, respectively. In the no CT cohort, among the different subgroups with tumor diameters of 2–10 mm, the 10-mm subgroup had the highest 5-year cumulative BCSM (7.0%).

For the total cohort (n=3,065), the Fine-Gray model revealed only 2 predictors of lower cumulative BCSM, which were smaller tumor size (P=0.039) and breast-conserving surgery (P=0.001) (*Table 4*). For the no CT cohort (n=1,531), the Fine-Gray model also revealed 2 predictors of lower cumulative BCSM, which were married status (P=0.012) and breast-conserving surgery (P=0.008) (*Table 4*).

Before PSM, the estimated 5-year cumulative BCSM was 3.9% in the CT cohort and 2.8% in the no CT cohort (HR: 1.27; 95% CI: 0.86–1.88; P=0.247) (*Figure 3A*). After PSM, the estimated 5-year cumulative BCSM was 2.3% in the CT cohort and 2.8% in the no CT cohort (HR: 0.86; 95% CI: 0.46–1.60; P=0.463) (*Figure 3B*). For the post-PSM population, an exploratory subgroup analysis also did not find a statistically significant improvement in BCSM with adjuvant CT in any subgroup (Figure S1).

Table 2 Overall survival (OS) and cumulative probabilities of breast cancer-specific mortality (BCSM) in patients with T1a,bN0M0 triple-negative breast cancer (Surveillance, Epidemiology, and End Results database 2010–2015)

Characteristics	5-year OS (%) and 95% CI			5-year cumulative probabilities of BCSM (%) and 95% CI		
	Total cohort (n=3,065)	CT cohort (n=1,534)	No CT cohort (n=1,531)	Total cohort (n=3,065)	CT cohort (n=1,534)	No CT cohort (n=1,531)
All patients	93.6 (92.6–94.6)	95.3 (94.1–96.6)	91.9 (90.4–93.5)	3.3 (2.6–4.1)	3.9 (2.8–5.0)	2.8 (1.9–3.7)
Age at diagnosis (years)						
≤39	94.0 (88.8–99.4)	93.1 (87.2–99.3)	100.0 (100.0–100.0)	6.0 (0.7–11.4)	6.9 (0.8–13.0)	0.0 (0.0–0.0)
40–49	95.7 (93.3–98.2)	96.9 (94.3–99.5)	93.2 (88.0–98.7)	3.9 (1.6–6.3)	3.1 (0.5–5.7)	5.7 (0.7–10.6)
50–59	96.1 (94.5–97.6)	95.9 (93.9–98.0)	96.3 (94.0–98.8)	3.5 (2.0–4.9)	3.9 (1.9–5.9)	2.8 (0.7–4.9)
60–69	94.6 (93.0–96.3)	95.1 (93.0–97.3)	94.1 (91.6–96.6)	2.9 (1.8–4.1)	3.8 (1.9–5.7)	2.0 (0.6–3.4)
≥70	88.8 (86.3–91.4)	92.6 (88.1–97.2)	87.9 (85.0–90.9)	3.1 (1.8–4.4)	3.8 (0.4–7.2)	2.9 (1.5–4.4)
Histologic grade						
I	97.1 (94.2–100.0)	100.0 (100.0–100.0)	96.4 (93.0–100.0)	1.5 (0.0–3.8)	0.0 (0.0–0.0)	1.9 (0.0–4.6)
II	93.5 (91.7–95.3)	96.2 (94.1–98.4)	91.7 (89.1–94.4)	2.7 (1.5–3.8)	3.2 (1.2–5.2)	2.3 (0.9–3.7)
III + IV	93.3 (92.1–94.6)	94.9 (93.4–96.4)	91.3 (89.1–93.5)	3.8 (2.8–4.8)	4.2 (2.8–5.6)	3.3 (2.0–4.7)
Tumor size (stage)						
T1a	95.3 (93.6–96.9)	98.5 (96.9–100.0)	94.2 (92.1–96.3)	1.8 (0.8–2.8)	1.5 (0.0–3.1)	1.9 (0.7–3.2)
T1b	93.0 (91.8–94.3)	94.8 (93.5–96.2)	90.5 (88.3–92.7)	3.9 (3.0–4.8)	4.2 (3.0–5.5)	3.4 (2.1–4.7)
Tumor size (mm)						
2	90.9 (85.9–6.1)	100.0 (100.0–100.0)	89.4 (83.8–95.4)	3.8 (0.4–7.3)	0.0 (0.0–0.0)	4.5 (0.5–8.4)
3	98.1 (96.0–100.0)	100.0 (100.0–100.0)	97.7 (95.1–100.0)	0.6 (0.0–1.8)	0.0 (0.0–0.0)	0.7 (0.0–2.2)
4	95.3 (92.2–98.6)	97.9 (93.8–100.0)	94.4 (90.4–98.6)	1.1 (0.0–2.5)	2.1 (0.0–6.3)	0.7 (0.0–2.1)
5	96.1 (93.6–98.7)	98.0 (95.2–100.0)	95.2 (91.7–98.8)	1.9 (0.2–3.6)	2.0 (0.0–4.9)	1.9 (0.0–4.0)
6	93.5 (90.5–96.7)	96.1 (93.0–99.3)	90.9 (85.8–96.3)	2.8 (0.9–4.8)	3.9 (0.7–7.1)	1.7 (0.0–3.9)
7	94.7 (92.0–97.4)	95.1 (91.5–98.9)	94.1 (90.1–98.2)	3.2 (1.1–5.3)	4.3 (0.8–7.8)	2.1 (0.0–4.4)
8	93.6 (91.0–96.2)	93.8 (90.5–97.2)	93.2 (89.4–97.3)	4.1 (2.0–6.1)	4.9 (1.9–8.0)	2.9 (0.3–5.6)
9	94.2 (91.7–96.8)	96.8 (94.7–99.0)	90.2 (85.0–95.8)	2.7 (1.0–4.3)	2.8 (0.7–4.9)	2.3 (0.0–5.1)
10	90.4 (87.7–93.1)	93.4 (90.6–96.3)	85.1 (79.8–90.7)	5.7 (3.6–7.8)	4.9 (2.4–7.4)	7.0 (3.3–10.8)

CI, confidence interval; CT, chemotherapy.

Discussion

In the present study, we explored the prognostic predictors and the value of adjuvant CT in patients with T1a,bN0M0 TNBC in the SEER database. The findings of the study indicated that 50% of patients with T1a,bN0M0 TNBC underwent adjuvant CT, and subtypes with larger tumors, younger age, and higher histologic grade were more likely to receive adjuvant CT. These findings are consistent with the NCCN recommendations. The findings of the present study also indicated that higher histologic grade and larger tumor size are predictors of poor prognosis, although the effect of age was complex. We did not identify a significant BCSM advantage for adjuvant CT in patients with T1a,bN0M0 TNBC. We found that the overall T1a,bN0M0 TNBC population had an excellent prognosis, with a 5-year OS of 93.6% and 5-year cumulative BCSM

Table 3 Univariable and multivariable Cox proportional hazards analyses for predictive factors of overall survival (Surveillance, Epidemiology, and End Results database 2010–2015)

Variables	Total cohort				No CT cohort			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age at diagnosis (years)								
≤39	1.768 (0.730–4.281)	0.207	1.477 (0.599–3.641)	0.397	–	–	–	–
40–49	1.094 (0.574–2.087)	0.784	1.032 (0.538–1.978)	0.924	1.490 (0.542–4.101)	0.44	1.452 (0.525–4.012)	0.472
50–59	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
60–69	1.655 (1.043–2.627)	0.033	1.688 (1.059–2.690)	0.028	2.019 (0.987–4.129)	0.054	2.181 (1.065–4.467)	0.033
≥70	3.790 (2.475–5.804)	<0.001	3.178 (2.014–5.016)	<0.001	4.356 (2.262–8.389)	<0.001	4.081 (2.112–7.885)	<0.001
Year of diagnosis								
2010–2012	1 (Reference)		–		1 (Reference)		–	
2013–2015	0.900 (0.639–1.267)	0.545	–	–	0.848 (0.545–1.320)	0.466	–	–
Race								
White	1 (Reference)		–		1 (Reference)		–	
Black	1.307 (0.925–1.846)	0.129	–	–	1.298 (0.837–2.013)	0.244	–	–
Others	0.634 (0.323–1.242)	0.184	–	–	0.743 (0.345–1.599)	0.447	–	–
Marital status								
Married	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Not married	1.862 (1.407–2.463)	<0.001	1.582 (1.189–2.106)	0.002	2.034 (1.428–2.898)	<0.001	1.766 (1.232–2.532)	0.002
Laterality								
Right	1 (Reference)		–		1 (Reference)		–	
Left	1.216 (0.919–1.608)	0.171	–	–	1.177 (0.835–1.659)	0.353	–	–
Histologic type								
Infiltrating duct carcinoma	1 (Reference)		–		1 (Reference)		–	
Others	0.877 (0.558–1.379)	0.57	–	–	0.708 (0.413–1.212)	0.208	–	–

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Total cohort				No CT cohort			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Histologic grade								
I	1 (Reference)		–		1 (Reference)		1 (Reference)	
II	2.686 (1.083–6.662)	0.033	–	–	2.991 (1.197–7.473)	0.019	2.810 (1.123–7.035)	0.027
III + IV	2.459 (1.006–6.012)	0.048	–	–	2.720 (1.098–6.737)	0.031	2.698 (1.088–6.692)	0.032
Tumor size (mm)								
T1a (2–5)	1 (Reference)		–		1 (Reference)		–	
T1b (6–10)	1.274 (0.911–1.781)	0.157	–	–	1.424 (0.983–2.061)	0.061	–	–
Breast surgery strategies								
Mastectomy	1 (Reference)		1 (Reference)		1 (Reference)		–	
Breast-conserving surgery	0.498 (0.364–0.683)	<0.001	0.528 (0.382–0.728)	<0.001	0.619 (0.423–0.904)	0.013	–	–
Reconstruction	0.679 (0.419–1.101)	0.117	1.107 (0.662–1.852)	0.699	0.398 (0.178–0.890)	0.025	–	–
Regional nodes examined (n)								
0	1 (Reference)		1 (Reference)		1 (Reference)		–	
1–5	0.335 (0.208–0.541)	<0.001	0.468 (0.287–0.764)	0.002	0.423 (0.241–0.740)	0.003	–	–
≥6	0.432 (0.242–0.770)	0.004	0.513 (0.283–0.931)	0.028	0.550 (0.275–1.097)	0.09	–	–
CT					–		–	
Yes	1 (Reference)		1 (Reference)		–		–	
No	1.895 (1.414–2.540)	<0.001	1.201 (0.867–1.664)	0.271	–	–	–	–
Radiation therapy								
Yes	1 (Reference)		–	–	1 (Reference)		1 (Reference)	
No	1.698 (1.286–2.242)	<0.001	–	–	1.463 (1.039–2.061)	0.029	1.589(1.125–2.246)	0.009

In the ≤39-year subgroup of the no CT cohort, there were no death. Therefore, when we performed the univariable and multivariable analyses in the no CT cohort, the ≤39- and 40–49-year subgroups were combined into 1 group. CT, chemotherapy; HR, hazard ratio; CI, confidence interval.

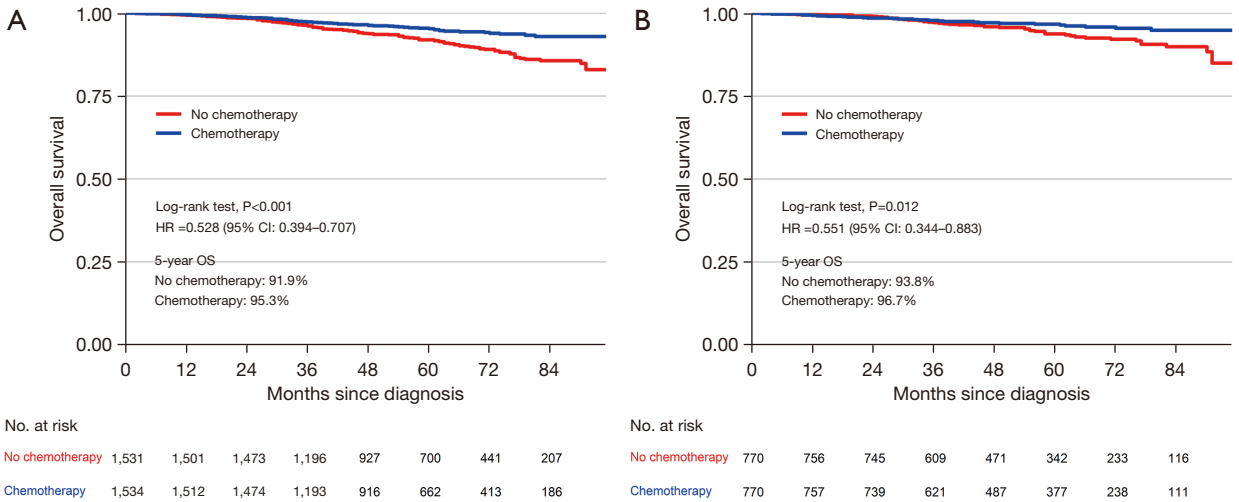

Figure 2 Kaplan-Meier curves comparing overall survival for the chemotherapy versus no chemotherapy cohorts in patients with T1a,b N0M0 triple-negative breast cancer (Surveillance, Epidemiology, and End Results database 2010–2015). (A) Whole cohort (n=3,065) before propensity score matching. (B) Exact matched cohort (n=1,540) after propensity score matching.

of only 3.3%. For patients with T1a,bN0M0 TNBC, both undertreatment and overtreatment should be avoided.

In both the total and no CT cohorts, we did not find a statistical association between younger age and worse OS or increased BCSM, which conflicts with the findings of previous studies (10,24-26). Two retrospective studies found that in patients with TNBC, age <40 years at diagnosis was an independent adverse prognostic factor in a multivariable analysis (24,25). Conversely, our study found that the risks of all-cause mortality were higher in the 60–69- and ≥70-year groups when the 50–59-year group was used as the reference group, whereas the risks of all-cause mortality in the ≤39- and 40–49-year groups were similar to those of the reference group. Interestingly, the 5-year cumulative BCSM was only 2.9% and 3.1% for the 60–69- and ≥70-year subgroups, respectively, both being lower than the average for the overall population (3.3%). Therefore, worse OS in patients with T1a,bN0M0 TNBC aged ≥60 years is mainly caused by increased non-BCSM (cardiovascular death and others). In some younger subgroups, the 5-year cumulative BCSM could reach twice the mean, but did not reach a statistical difference, which adds to the complexity of the effect of age on survival. In summary, the findings of our study did not fully elucidate the effect of age on T1a,bN0M0 TNBC, and further prospective, large-scale studies are needed to explore the underlying mechanism.

Regarding the effect of age on the prognosis of T1a,bN0M0 TNBC, current studies tended to reach different conclusions, with the following possible explanations for these discrepancies. First, the study enrollment criteria were inconsistent. We enrolled only patients with T1a,bN0M0 TNBC, whereas most previous studies enrolled patients with non-metastatic TNBC and did not consider T and N staging. TNBC is a very heterogeneous subtype. Younger patients with TNBC have a higher proportion of higher histologic grade, increased nodal involvement, and larger tumor size, which present as confounding factors when assessing the effect of age on survival (24,26-28). Second, the proportion of young patients varied. In our study, the ≤39-year group represented only 3.4% of the total population, which might also have influenced the statistical analysis. Third, the study endpoints were different. When examining the effect of age on survival, BCSM is a more appropriate endpoint than OS due to the influence of non-BC mortality events (20). Fourth, the statistical methods used were different. When BCSM is the study endpoint and the frequency of competing events is high, the Cox proportional hazards model is not an appropriate analytical method, and the Fine–Gray model should be used (20,29). Fifth, the confounding effects of adjuvant CT were excluded. We performed statistical analyses mainly in the no CT cohort, expecting to observe the direct effect of age on BCSM and to identify the true prognostic factors.

Consistent with previous studies (10,12,13,30), our study also found that patients with T1a,bN0M0 TNBC with

Table 4 Univariable and multivariable analyses for predictors of breast cancer-specific mortality based on the Fine-Gray model in the total and no CT cohort (Surveillance, Epidemiology, and End Results database 2010–2015)

Variables	Total cohort (n=3,065)				No CT cohort (n=1,531)			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age at diagnosis (years)								
≤39	1.893 (0.744–4.815)	0.180	–	–	–	–	–	–
40–49	1.090 (0.479–2.481)	0.836	–	–	1.562 (0.533–4.580)	0.416		
50–59	1 (Reference)		–		1 (Reference)		–	
60–69	1.001 (0.575–1.742)	0.998	–	–	1.006 (0.375–2.695)	0.991	–	–
≥70	1.059 (0.571–1.967)	0.855	–	–	1.350 (0.578–3.153)	0.488	–	–
Year of diagnosis								
2010–2012	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
2013–2015	0.496 (0.290–0.850)	0.011	0.548 (0.293–1.026)	0.060	0.341 (0.162–0.716)	0.004	0.398 (0.158–1.002)	0.051
Race								
White	1 (Reference)		–		1 (Reference)		–	
Black	1.624 (0.933–2.829)	0.087	–	–	1.539 (0.687–3.447)	0.295	–	–
Others	0.576 (0.212–1.571)	0.282	–	–	0.544 (0.129–2.287)	0.406	–	–
Marital status								
Married	1 (Reference)		–		1 (Reference)		1 (Reference)	
Not married	1.431 (0.927–2.209)	0.106	–	–	1.940 (1.060–3.550)	0.032	2.644 (1.239–5.642)	0.012
Laterality								
Right	1 (Reference)		1 (Reference)		1 (Reference)		–	
Left	1.498 (1.071–2.096)	0.018	1.503 (0.964–2.343)	0.072	1.604 (0.867–2.967)	0.132	–	–
Histologic type								
Infiltrating duct carcinoma	1 (Reference)		–		1 (Reference)		1 (Reference)	
Others	0.494 (0.227–1.075)	0.075	–	–	0.246 (0.062–0.972)	0.045	0.361 (0.063–2.080)	0.254

Table 4 (*continued*)

Table 4 (*continued*)

Variables	Total cohort (n=3,065)				No CT cohort (n=1,531)			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Histologic grade								
I	1 (Reference)		–		1 (Reference)		–	
II	2.407 (0.571–10.141)	0.231	–	–	1.870 (0.422–8.283)	0.410	–	–
III + IV	3.349 (0.838–13.391)	0.087	–	–	2.468 (0.596–10.229)	0.213	–	–
Tumor size (mm)								
T1a (2–5)	1 (Reference)		1 (Reference)		1 (Reference)		–	
T1b (6–10)	2.099 (1.255–3.509)	0.005	1.806 (1.030–3.168)	0.039	1.898 (0.981–3.673)	0.057	–	–
Breast surgery strategies								
Mastectomy	1 (Reference)		1 (Reference)		1 (Reference)			
Breast–conserving surgery	0.376 (0.216–0.654)	<0.001	0.390 (0.221–0.688)	0.001	0.383 (0.179–0.818)	0.013	0.328 (0.144–0.747)	0.008
Reconstruction	1.146 (0.599–2.195)	0.681	1.243 (0.660–2.341)	0.501	0.654 (0.253–1.689)	0.380	1.079 (0.368–3.161)	0.890
Regional nodes examined (n)								
0	1 (Reference)		–		1 (Reference)		–	
1–5	0.458 (0.151–1.389)	0.168	–	–	0.427 (0.139–1.312)	0.137	–	–
≥6	0.551 (0.142–2.131)	0.388	–	–	0.510 (0.128–2.025)	0.339	–	–
CT					–		–	
Yes	1 (Reference)		–		–		–	
No	0.788 (0.532–1.168)	0.236	–	–	–	–	–	–
Radiation therapy								
Yes	1 (Reference)		–		1 (Reference)		–	
No	1.912 (0.956–3.824)	0.067	–	–	2.000 (0.940–4.257)	0.072	–	–

In the ≤39-year subgroup of the no CT cohort, there were no deaths. Therefore, when we performed the univariable and multivariable analyses in the no CT cohort, the ≤39- and 40–49-year subgroups were combined into 1 group. CT, chemotherapy; HR, hazard ratio; CI, confidence interval.

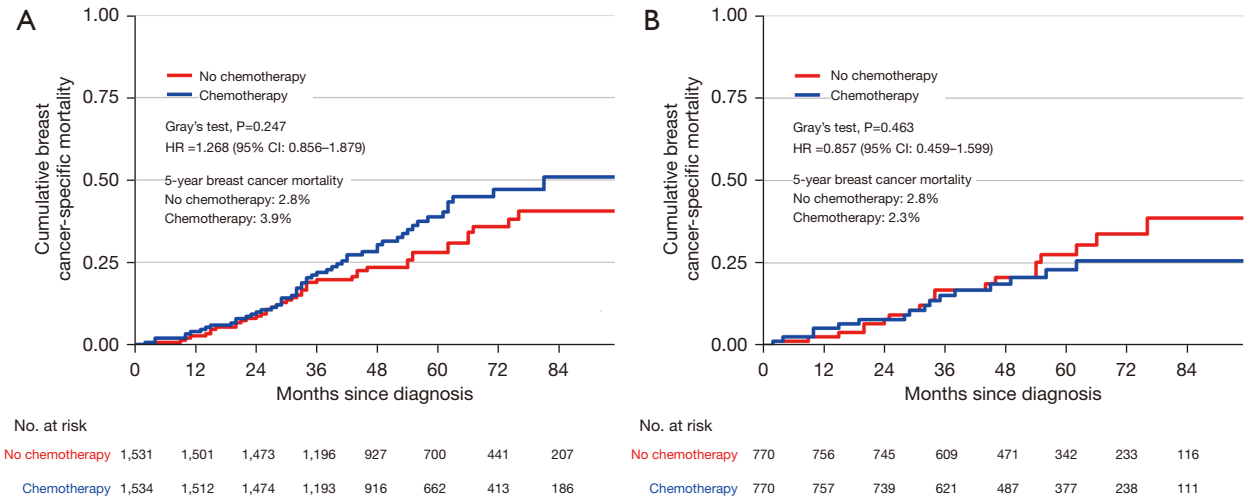

Figure 3 Comparison of the cumulative probability of breast cancer-specific mortality in patients with T1a,b N0M0 triple-negative breast cancer according to the use of adjuvant chemotherapy (Surveillance, Epidemiology, and End Results database 2010–2015). (A) Whole cohort (n=3,065) before propensity score matching. (B) Exact matched cohort (n=1,540) after propensity score matching.

lower histologic grade and smaller tumors tended to have a better prognosis. A review found that, among the several possible negative prognostic predictors of T1a,bN0M0 BC, a high histologic grade was most consistently shown to be associated with poor long-term prognosis (13). Similar to a previous study (31), we found that, among patients with T1a,bN0M0 BC, tumors with a 1-cm diameter were associated with an overwhelmingly poor prognosis. This could be because, as the tumor diameter increases, the tumor volume increases significantly, and larger tumor volumes are theoretically more likely to develop distant metastases (31). Also, due to inadvertent "rounding down" of tumor size by the pathologist when measuring the tumor diameter, a portion of tumors with true diameters >1 cm were incorrectly recorded as 1 cm (31). Our findings of the present study indicate that 1-cm T1bN0M0 TNBC tumors should be treated differently from the remaining subtypes.

Consistent with previous studies (32,33), the findings of the present study showed no association between adjuvant CT and OS or BCSM in the multivariable analysis. However, this outcome could be influenced by a number of confounding factors, such as life expectancy, comorbidities, and socioeconomic factors. Therefore, we should be careful when interpreting and applying this conclusion. In addition, we performed a direct comparison of 5-year OS and BCSM between the CT and no CT cohorts before and after PSM. Our findings indicated that the CT cohort had a significantly better 5-year OS than the no CT cohort, both before and after PSM. However, no statistical difference was observed in the 5-year cumulative BCSM between the CT and no CT cohorts, both before and after PSM. While contradictory, this result was inevitable. In our study, the selection of adjuvant CT was not randomized; patients with a higher risk of recurrence were more likely to receive adjuvant CT. This resulted in a particularly high risk of recurrence at baseline in the CT cohort. Although adjuvant CT theoretically improved BCSM, the final data showed a higher rate of BCSM in the CT cohort than in the no CT cohort (3.9% *vs.* 2.8% before PSM). After PSM, the baseline risk of recurrence was balanced between the CT and no CT cohorts, allowing us to explore the true role of adjuvant CT (34). The baseline risk of recurrence in the CT cohort was somewhat diluted after PSM, as corroborated by the difference in the 5-year cumulative BCSM in the CT cohort before and after PSM (3.9% *vs.* 2.3%). After PSM, we found a 0.5% absolute reduction in the 5-year cumulative BCSM with adjuvant CT, although this did not reach statistical significance, most likely due to the sample size.

Overall, our study does not fully elucidate whether adjuvant CT is beneficial in patients with T1a,bN0M0 TNBC. To date, we lack tools, such as genetic testing, to accurately predict the extent of adjuvant CT benefit in T1a,bN0M0 TNBC; therefore, we rely heavily on traditional clinicopathological indicators, such as histologic grade and tumor size. Therefore, when decisions regarding

adjuvant CT are made for patients with T1a,bN0M0 TNBC, baseline risk of recurrences, benefits and risks of adjuvant CT, patient preferences, life expectancy, and comorbidities need to be taken into consideration.

The present study has some limitations. First, the CT variable was categorized as either "yes" or "no/unknown" in the SEER database. The increasing number of patients undergoing CT outside the hospital settings has resulted in the CT treatment not being accurately recorded in the SEER database, but only registered as "no/unknown" (35). Therefore, we must acknowledge that conclusions based on CT variables and related analyses could be inaccurate and misleading. Second, this study had a relatively short follow-up time, and the median follow-up was only 5 years. Nevertheless, previous studies have found that recurrences and metastases in TNBC occur mainly in the first 5 years after diagnosis (36-38). Third, the SEER database does not contain information regarding Ki-67. Furthermore, the SEER database does not provide detailed information on the adjuvant CT regimens used, and we were unable to analyze the risk–benefit ratio for the different CT regimens. Fourth, the results could be affected by selection bias from excluded and incomplete data. Finally, the sample size of the CSCO BC database was too small to validate the analytical results of the SEER database.

Conclusions

Women with T1a,bN0M0 TNBC had an excellent prognosis, with or without adjuvant CT. In this population, higher histologic grade and larger tumor size were found to be predictors of poor prognosis, although the effect of age was complex. Further studies are needed to explore the underlying mechanisms. Our data did not support using adjuvant CT in patients with T1a,bN0M0 TNBC. However, due to the limitations of the present study, we must approach this result with caution. When considering adjuvant CT for high-risk T1a,bN0M0 TNBC patients, a risk–benefit discussion should be undertaken on a case-by-case basis.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-409/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-409/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 Univariable and multivariable logistic regression analyses for predictive factors of CT use (SEER database 2010–2015)

Characteristics	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age at diagnosis, years				
≤39	1.0 (reference)		1.0 (reference)	
40–49	0.498 (0.279–0.846)	0.013	0.476 (0.254–0.853)	0.016
50–59	0.336 (0.193–0.556)	<0.001	0.291 (0.159–0.510)	<0.001
60–69	0.228 (0.131–0.376)	<0.001	0.183 (0.100–0.320)	<0.001
≥70	0.053 (0.030–0.089)	<0.001	0.039 (0.021–0.070)	<0.001
Year of diagnosis				
2010–2012	1.0 (reference)		1.0 (reference)	
2013–2015	1.205 (1.046–1.389)	0.01	1.336 (1.129–1.582)	<0.001
Race				
White	1.0 (reference)		–	
Black	1.182 (0.976–1.432)	0.088	–	–
Others	0.953 (0.724–1.252)	0.728	–	–
Marital status				
Married	1.0 (reference)		1.0 (reference)	
Not married	0.716 (0.620–0.827)	<0.001	0.861 (0.725–1.023)	0.088
Laterality				
Right	1.0 (reference)		–	
Left	1.069 (0.928–1.231)	0.358	–	–
Histologic type				
Infiltrating duct carcinoma	1.0 (reference)		1.0 (reference)	
Others	0.517 (0.408–0.651)	<0.001	0.718 (0.544–0.946)	0.019
Histologic grade				
I	1.0 (reference)		1.0 (reference)	
II	2.994 (2.026–4.550)	<0.001	3.336 (2.152–5.298)	<0.001
III + IV	6.640 (4.547–9.991)	<0.001	6.003 (3.907–9.455)	<0.001
Tumor size (mm)				
T1a (2–5)	1.0 (reference)		1.0 (reference)	
T1b (6–10)	4.455 (3.738–5.327)	<0.001	5.633 (4.615–6.903)	<0.001
Breast surgery strategies				
Mastectomy	1.0 (reference)		1.0 (reference)	
BCS	1.212 (1.005–1.463)	0.045	0.668 (0.499–0.894)	0.007
Reconstruction	1.562 (1.187–2.059)	0.002	0.725 (0.519–1.012)	0.059
Regional nodes examined				
0	1.0 (reference)		–	
1–5	2.726 (1.860–4.082)	<0.001	–	–
≥6	2.694 (1.760–4.197)	<0.001	–	–
Radiation therapy				
Yes	1.0 (reference)		1.0 (reference)	
No	0.808 (0.698–0.934)	0.004	0.575 (0.449–0.736)	<0.001

CT, chemotherapy; SEER, the Surveillance, Epidemiology, and End Results; CI, confidence interval; BCS, breast-conserving surgery.

Table S2 Demographic, clinical, and pathological characteristics of patients with T1a,bN0M0 triple-negative breast cancer before and after propensity score matching (SEER database 2010–2015)

Characteristic	Before PSM			After PSM		
	CT cohort (n=1,534) No./Total No. (%)	No-CT cohort (n=1,531) No./Total No. (%)	P value	CT cohort (n=770) No./Total No. (%)	No-CT cohort (n=770) No./Total No. (%)	P value
Age at diagnosis (years)*			<0.001			0.317
≤39	87 (5.7)	18 (1.2)		20 (2.6)	16 (2.1)	
40–49	279 (18.2)	116 (7.6)		91 (11.8)	86 (11.2)	
50–59	500 (32.6)	308 (20.1)		233 (30.3)	204 (26.5)	
60–69	505 (32.9)	458 (29.9)		263 (34.2)	298 (38.7)	
≥70	163 (10.6)	631 (41.2)		163 (21.2)	166 (21.6)	
Year of diagnosis*			0.011			0.284
2010–2012	726 (47.3)	796 (52.0)		406 (52.7)	384 (49.9)	
2013–2015	808 (52.7)	735 (48.0)		364 (47.3)	386 (50.1)	
Race*			0.198			0.138
White	1,150 (75.0)	1,176 (76.8)		554 (71.9)	582 (75.6)	
Black	275 (17.9)	238 (15.6)		146 (19.0)	137 (17.8)	
Others	109 (7.1)	117 (7.6)		70 (9.1)	51 (6.6)	
Marital status*			<0.001			0.127
married	971 (63.3)	846 (55.3)		496 (64.4)	466 (60.5)	
Not married	563 (36.7)	685 (44.7)		274 (35.6)	304 (39.5)	
Laterality*			0.377			0.508
Right	735 (47.9)	759 (49.6)		394 (51.2)	380 (49.4)	
Left	799 (52.1)	772 (50.4)		376 (48.8)	390 (50.6)	
Histologic type*			<0.001			0.415
Infiltrating duct carcinoma	1,411 (92.0)	1,310 (85.6)		691 (89.7)	680 (88.3)	
Others	123 (8.0)	221 (14.4)		79 (10.3)	90 (11.7)	
Histologic grade*			<0.001			0.36
I	32 (2.1)	150 (9.8)		31 (4.0)	28 (3.6)	
II	373 (24.3)	584 (38.1)		264 (34.3)	240 (31.2)	
III + IV	1,129 (73.6)	797 (52.1)		475 (61.7)	502 (65.2)	
Tumor size* (mm)			<0.001			0.812
T1a (2–5)	212 (13.8)	638 (41.7)		190 (24.7)	185 (24.0)	
T1b (6–10)	1,322 (86.2)	893 (58.3)		580 (75.3)	585 (76.0)	
Breast surgery strategies*			0.006			0.778
Mastectomy	249 (16.2)	299 (19.5)		138 (17.9)	133 (17.3)	
BCS	1,099 (71.6)	1,089 (71.1)		540 (70.1)	552 (71.7)	
Reconstruction	186 (12.1)	143 (9.3)		92 (12.0)	85 (11.0)	
Regional nodes examined*			<0.001			0.634
0	36 (2.3)	94 (6.1)		22 (2.9)	17 (2.2)	
1–5	1,304 (85.0)	1,249 (81.6)		660 (85.7)	658 (85.5)	
≥6	194 (12.7)	188 (12.3)		88 (11.4)	95 (12.3)	
Radiation therapy*			0.005			1.0
Yes	989 (64.5)	910 (59.4)		477(61.9)	476 (61.8)	
No	545 (35.5)	621 (40.6)		293(38.1)	294 (38.2)	
Vital status			–			–
Alive	1,466 (95.6)	1,400 (91.4)		743 (96.5)	722 (93.8)	
Breast cancer-specific mortality	53 (3.5)	43 (2.8)		16 (2.1)	20 (2.6)	
Other cause-specific mortality	15 (1.0)	88 (5.8)		11 (1.4)	28 (3.6)	

*, based on these variables, propensity score matching was performed for the CT and no-CT cohorts. SEER, the Surveillance, Epidemiology, and End Results; PSM, propensity score matching; CT, chemotherapy; CI, confidence interval; BCS, breast-conserving surgery.

Subgroup	Breast cancer-specific mortality, No./total No. CT	no-CT	HR (95%CI)	P value
Age (years)				
20-49 years	2/111	4/102	0.53(0.10 to 2.94)	0.469
50-59 years	3/233	5/204	0.42(0.10 to 1.82)	0.245
60-69 years	6/263	6/298	1.28(0.40 to 4.10)	0.674
70+ years	5/163	5/166	0.93(0.27 to 3.24)	0.908
Year of diagnosis				
2010–2012	8/406	16/384	0.49(0.20 to 1.21)	0.124
2013–2015	8/364	4/386	2.36(0.68 to 8.18)	0.174
Race				
White	9/554	13/582	0.76(0.32 to 1.82)	0.539
Others	7/216	7/188	0.88(0.30 to 2.59)	0.821
Marital status				
Married	8/496	8/466	0.78(0.28 to 2.16)	0.634
Not married	8/274	12/304	0.82(0.34 to 2.03)	0.674
Histological grade				
I + II	5/295	9/268	0.53(0.18 to 1.60)	0.262
III + IV	11/475	11/502	1.07(0.45 to 2.51)	0.883
Laterality				
Right	10/394	7/380	1.57(0.58 to 4.25)	0.376
Left	6/376	13/390	0.50(0.19 to 1.34)	0.170
Histological type				
IDC	15/691	18/680	0.85(0.45 to 1.59)	0.604
Others	1/79	2/90	0.41(0.04 to 4.59)	0.470
Tumor size (mm)				
T1a (2-5)	2/190	1/185	1.90(0.17 to 20.92)	0.602
T1b (6-10)	14/580	19/585	0.78(0.38 to 1.60)	0.496
Breast surgery strategies				
Mastectomy	7/138	8/133	0.91(0.32 to 2.56)	0.857
BCS	5/540	10/552	0.55(0.17 to 1.76)	0.318
Reconstruction	4/92	2/85	1.67(0.30 to 9.18)	0.554
Regional nodes examined				
≤5	14/682	16/675	0.86(0.45 to 1.65)	0.653
≥6	2/88	4/95	0.44(0.08 to 2.45)	0.349
Radiation therapy				
Yes	4/477	7/476	0.64(0.19 to 2.21)	0.480
No	12/293	13/294	0.94(0.42 to 2.08)	0.872

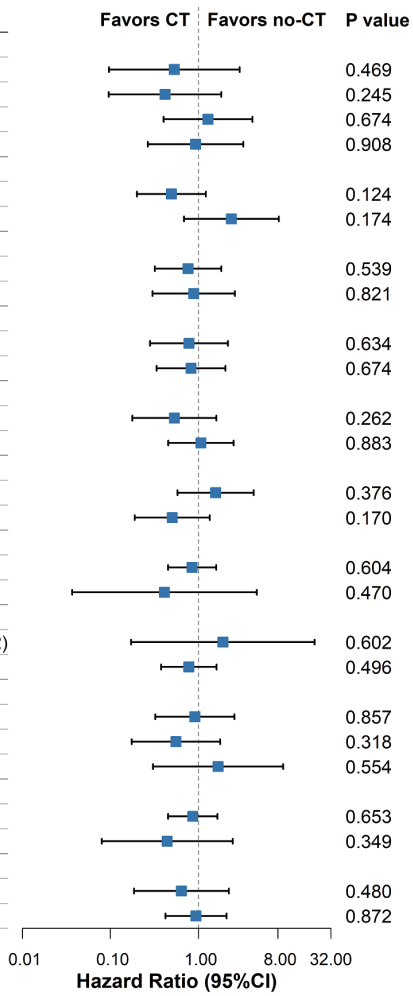

Figure S1 Exploratory subgroup analysis of breast cancer-specific mortality in the exact matched cohort (n=1,540) after propensity score matching. IDC, infiltrating duct carcinoma; BCS, breast-conserving surgery; CT, chemotherapy; CI, confidence interval.

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