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ORIGINAL ARTICLE

Survival outcomes of neoadjuvant versus adjuvant therapy in patients with T1c, node-negative, human epidermal growth factor receptor 2–positive breast cancer: A Surveillance, Epidemiology, and End Results population-based study

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Abstract

Background: Persistent debates exist regarding the superiority of neoadjuvant therapy (NAT) over adjuvant therapy (AT) for patients with T1c, node-negative, human epidermal growth factor receptor 2–positive (HER2+) breast cancer, and relevant guidelines for these patients are lacking.

Methods: Data on patients with T1cN0M0-stage HER2+ breast cancer who received chemotherapy and surgery were extracted from 2010 to 2020 from the Surveillance, Epidemiology, and End Results database. Propensity score matching (PSM) was used to create well-balanced cohorts for the NAT and AT groups. Kaplan–Meier (KM) analysis and Cox proportional hazards models were used to assess the differences between NAT and AT in terms of overall survival (OS) and breast cancer–specific survival (BCSS). Additionally, logistic regression models were used to explore factors associated with response to NAT.

Results: After PSM, 2140 patient pairs were successfully matched, which achieved a balanced distribution between the NAT and AT groups. KM curves revealed similar OS and BCSS between patients receiving NAT and those undergoing AT. A multivariate Cox model identified achieving pathological complete response (pCR) after NAT, compared with AT, as a protective prognostic factor for OS (hazard ratio, 0.52; 95% CI, 0.35–0.77; $p < .001$) and BCSS (hazard ratio, 0.60; 95% CI, 0.37–0.98; $p = .041$). A logistic regression model revealed that White race and hormone receptor–negative status independently predicted pCR.

Conclusions: For patients with T1cN0M0-stage HER2+ breast cancer, NAT demonstrated comparable OS and BCSS to AT. Patients who achieved pCR after

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NAT exhibited significantly better survival outcomes compared with those who received AT.

KEYWORDS
early-stage breast cancer, human epidermal growth factor receptor 2–positive (HER2+), neoadjuvant therapy, Surveillance, Epidemiology, and End Results (SEER), survival outcomes

INTRODUCTION

Breast cancer is the most common malignancy that affects women's survival and quality of life globally, with an estimated 297,790 new cases and 43,170 new deaths in the United States in 2023.[1–3] Overexpression of human epidermal growth factor receptor 2 (HER2) occurs in 14% of patients with breast cancer, and was previously associated with high recurrence rates and poor survival.[4,5] However, the addition of trastuzumab to chemotherapy has dramatically improved outcomes for patients with both early and advanced HER2-positive (HER2+) disease.[6,7] Beyond trastuzumab, several other HER2-targeted drugs, including the monoclonal antibody pertuzumab, tyrosine kinase inhibitors, and antibody–drug conjugates such as trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan, have been approved, which allows for escalation of treatment in high-risk HER2+ patients.[8–10]

Systemic therapy, including chemotherapy combined with surgery, HER2-targeted therapy, radiotherapy, and endocrine therapy tailored to hormone receptor (HR) status, constitutes the standard of care for HER2+ breast cancer.[11,12] Chemotherapy and HER2-targeted therapy can be administered in either the neoadjuvant or adjuvant setting. However, neoadjuvant therapy (NAT) offers the advantages of improving eligibility for breast-conserving surgery (BCS) and avoiding excessive axillary dissection.[13] HER2+ breast cancer shows a notably favorable response to NAT, which achieves the highest rate of pathological complete response (pCR) among all breast cancer subtypes.[14–16] In recent years, there has been a substantial increase in NAT for patients with small tumors in T1-stage HER2+ breast cancer.[17–19] For these patients, NAT provides information about tumor response in vivo. Several trials and meta-analyses have demonstrated a robust correlation between pathological response and prognosis after NAT. Achieving pCR after NAT is associated with improved survival, particularly in patients with HER2+ and triple-negative breast cancer.[15,16,20] For patients with residual disease after NAT, escalation therapy with adjuvant regimens, such as HER2 antibody–conjugated chemotherapy (T-DM1), has been proven to enhance disease-free survival (DFS), which highlights the utility of NAT in identifying patients who may benefit from more aggressive therapeutic approaches.[21,22]

On the other hand, adjuvant therapy (AT) has also shown excellent survival outcomes in patients with node-negative, HER2+ breast cancer with small tumors. The phase 2 single-arm adjuvant paclitaxel and trastuzumab trial (N = 406) demonstrated that in patients with stage I HER2+ breast cancers, 12 weeks of adjuvant paclitaxel combined with trastuzumab for 1 year resulted in favorable outcomes: 7-year overall survival (OS) of 95.0% (95% CI, 92.4%–97.7%) and 7-year DFS of 93.3% (95% CI, 90.4%–96.2%), and 10-year OS of 94.3% (95% CI, 91.8%–96.8%) and 10-year invasive disease–free survival (iDFS) of 91.3% (95% CI, 88.3%–94.4%).[23,24] Initial surgery and pathology assessment for small tumors often guide the selection of appropriate systemic therapy regimens, and potentially facilitate the deescalation or avoidance of chemotherapy. NAT carries the risk of overtreating patients who might achieve excellent survival with lower toxicity with taxane/trastuzumab regimens in the adjuvant setting. Conversely, upfront surgery risks undertreating patients with residual disease who could benefit from intensified AT. According to American Society of Clinical Oncology guidelines, patients with T1aN0M0- and T1bN0M0-stage HER2+ disease should not be routinely offered NAT. Nevertheless, the optimal sequence of chemotherapy and surgery for patients with T1cN0M0-stage HER2+ breast cancer remains unclear.[25] To date, limited data compare the outcomes of NAT versus upfront surgery with AT in T1cN0M0-stage HER2+ disease.

Therefore, by using the Surveillance, Epidemiology, and End Results (SEER) database, we aimed to compare the survival outcomes of patients with HER2+ breast cancer at the T1cN0M0 stage who underwent NAT with those who received AT. Furthermore, the correlation between pCR and prognosis, as well as the clinicopathological features associated with pCR, was investigated to provide insights into the management of early-stage HER2+ breast cancer.

MATERIALS AND METHODS

Data source and study population

The SEER database stands as the largest publicly accessible cancer database, which encompasses data from 18 states that collectively represent all regions of the United States.[26] In this retrospective cohort study, we extracted data from 17 SEER database registries released in April 2023. A total of 8768 female patients diagnosed with primary T1cN0M0-stage HER2+ breast cancer between 2010 and 2020 who underwent surgery and chemotherapy were included in the analysis. Exclusion criteria included patients aged 80 years and older and those with bilateral breast cancer, multiple primary cancers, and incomplete essential parameters (Figure 1).

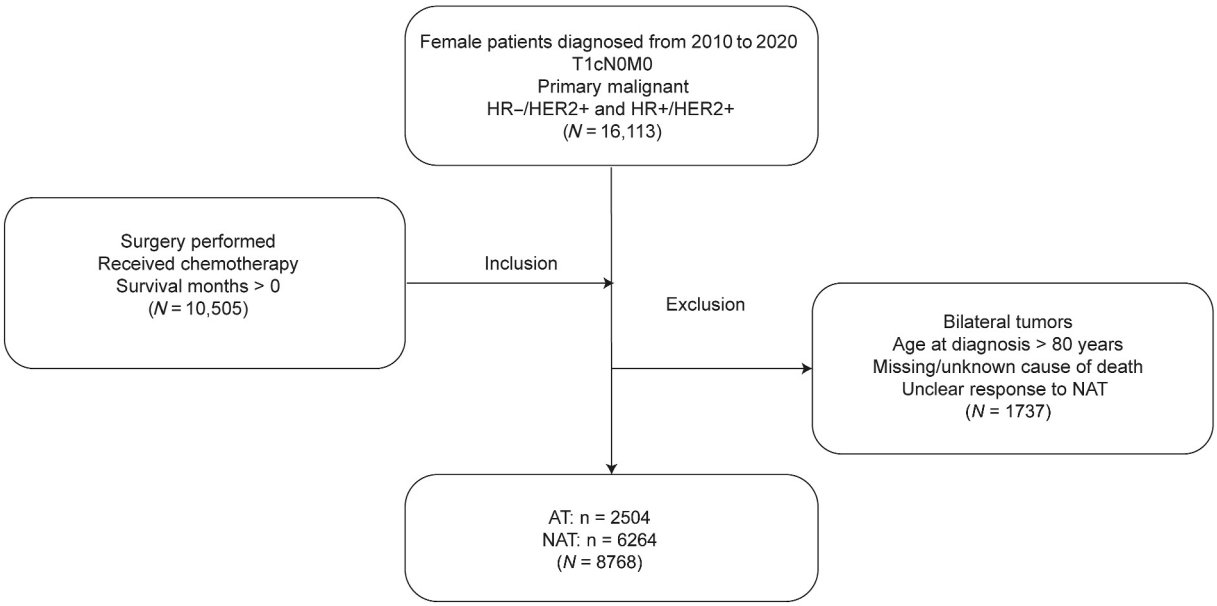

FIGURE 1 Flowchart of data extraction. AT indicates adjuvant therapy; HER2+, human epidermal growth factor receptor 2–positive; HR–, hormone receptor–negative; HR+, hormone receptor–positive; NAT, neoadjuvant therapy.

Ethical approval

Informed consent was not required for this study because personally identifiable information was not accessed. Similarly, institutional review board permission was unnecessary because the SEER database is a national database that has already been deidentified.

Demographic and clinicopathological information

Information on age at diagnosis (15–79 years), year of diagnosis (2010–2020), marital status (married, single, divorced/separated, widowed, and unknown), race (White, Black, other [American Indian/Alaska Native and Asian/Pacific Islander], and unknown), histology (invasive ductal carcinoma, invasive lobular carcinoma, and other), grade (1–4), N stage (N0), surgery (breast surgery and axillary surgery), systemic therapy (NAT and AT), response to NAT (NAT not given, complete response, partial response, no response, and response but not noted whether complete or partial), and follow-up were extracted from the SEER database. According to the "breast subtype (2010+)" in the SEER database, HR+ was defined as a positive status for the estrogen receptor (ER) and/or progesterone receptor (PR). Pathological ER, PR, and HER2 status were defined according to the guidelines of the American Society of Clinical Oncology and the College of American Pathologists.[27,28] On the basis of the surgery codes of the SEER program, breast surgical procedures were categorized as BCS or mastectomy. Similarly, axillary surgical procedures were classified as no surgery or axillary lymph node dissection. Age at diagnosis was divided into two groups on the basis of a threshold of 50 years. Grades 1 and 2 were categorized as low, whereas grades 3 and 4 were categorized as high. Unknown race was included in the "other" category. The term "response to neoadjuvant therapy" refers to the impact of NAT on the breast. "Neoadjuvant therapy not given" was equated to AT in our study. To ensure a conservative estimate, cases labeled as "response but not noted whether complete or partial" were reclassified as "partial response." Records of "partial response" and "no response" were considered as not achieving pCR (non-pCR).

Exposures

The research intervention was NAT, with the control group receiving AT. Systemic therapy administered before surgery was defined as NAT, whereas systemic therapy given after surgery was referred to as AT.

Outcomes

OS and breast cancer–specific survival (BCSS) were adopted as outcomes. OS was defined as the duration from diagnosis to death from any cause or to the most recent follow-up. BCSS was measured as the time from diagnosis to death specifically from breast cancer or to the last follow-up for patients who were alive or had died from other causes. The "SEER cause-specific death classification" was used to determine the patient's cause of death.

Statistical analysis

All feature variables and clinical parameters in this study were categorical. Baseline comparisons between the NAT and AT groups were

assessed via χ^2 tests. A 1:1 nearest-neighbor propensity score matching (PSM) analysis with a caliper of 0.01 was conducted with a logistic regression model, including all variables as covariates. Kaplan–Meier (KM) curves were used to depict the OS and BCSS of study participants, with a log-rank test used to assess the statistical differences between the groups. Additionally, univariate and multivariate Cox proportional hazards regression models were applied to estimate the hazard ratios and 95% confidence intervals (CIs) for OS and BCSS. Both univariate and multivariate logistic regression analyses were performed to identify factors potentially associated with achieving pCR after NAT.

Statistical significance was set at two-sided $p < .05$. All analyses were performed with R, version 4.3.1.

RESULTS

Patient characteristics

Altogether, 8768 cases met the study criteria (Figure 1). Of these, 2504 patients received NAT, whereas 6264 patients received AT. A pCR rate of 47.8% was obtained among patients treated with NAT. Patients receiving NAT were generally younger than those receiving AT (aged <50 years; 41.7% vs. 30.8%; $p < .001$). Patients with invasive ductal carcinoma (90.8% vs. 87.7%; $p < .001$), negative HR status (34.2% vs. 29.1%; $p < .001$), and those who were single (19.6% vs. 16.3%; $p < .001$) or divorced/separated (12.1% vs. 11.1%; $p < .001$) were more likely to receive NAT (Table 1).

Survival analysis of patients after PSM

During a median follow-up of 79 months (interquartile range, 61–103 months), 594 deaths were recorded, including 317 deaths from breast cancer and 277 deaths from other causes. To minimize baseline characteristic differences between the NAT and AT groups, PSM analysis was used. A total of 2140 patient pairs were successfully matched, with well-balanced demographic and clinicopathological characteristics between the groups (Table 1). KM plots and log-rank tests were used to illustrate and compare survival curves for patients with OS and BCSS (Figure 2A,B). Patients who underwent NAT and AT exhibited comparable OS (5-year: 96.5% vs. 95.5%; 10-year: 90.0% vs. 89.2%; $p = .230$) and BCSS (5-year: 97.4% vs. 97.0%; 10-year: 94.3% vs. 94.9%; $p = 1.000$). To evaluate the prognostic impact of NAT response, patients who underwent NAT were divided into pCR and non-pCR groups. Patients who achieved pCR after NAT had the best OS and BCSS (Figure 2C,D). Cox proportional hazards models demonstrated that compared with patients undergoing AT, achieving pCR with NAT significantly improved both OS (hazard ratio, 0.52; 95% CI, 0.35–0.77; $p < .001$) and BCSS (hazard ratio, 0.60; 95% CI, 0.37–0.98; $p = .041$) (Table 2).

Predictive factors of pCR

Given the considerably improved impact of NAT on survival among patients who achieved pCR, a logistic regression model was used to identify the predictive factors for pCR in patients with T1cN0M0-stage HER2+ breast cancer after undergoing NAT. Statistically significant variables ($p < .05$) in univariate analysis were included in the multivariate logistic regression model. The outcomes revealed that White race (odds ratio [OR], 0.76; 95% CI, 0.59–0.99; $p = .040$) and negative HR status (OR, 0.49; 95% CI, 0.41–0.58; $p < .001$) were significantly associated with pCR (Table 3).

DISCUSSION

This study retrospectively assessed the survival outcomes of individuals diagnosed with HER2+ breast cancer at the T1cN0M0 stage who received either NAT or AT. The findings revealed that there was no significant difference in survival between NAT and AT. However, patients achieving pCR after NAT exhibited superior outcomes compared with those treated with AT.

Consistent with our study, several clinical trials have confirmed that patients treated with NAT and AT have similar prognoses. For example, landmark trials such as National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18, NSABP B-27, European Organisation for Research and Treatment of Cancer 10902, and Institut Bergonié Bordeaux Groupe Sein demonstrated no significant differences in survival between NAT and AT.[29–32] Additionally, a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group also found no significant differences in survival and overall disease progression between the two groups.[33] However, none of these trials differentiated between breast cancer molecular subtypes or considered the impact of response to NAT on prognosis. A study conducted by Chang et al. compared the survival outcomes of patients with T1c-stage HER2+ breast cancer receiving NAT and AT. The results indicated that patients who underwent NAT had inferior BCSS compared with those who received AT.[34] We observed that this study included patients with T1c-stage HER2+ breast cancer across stages N0–N3, with a significantly higher proportion of lymph node–positive individuals receiving NAT than AT. Because lymph node metastasis is a well-established adverse prognostic factor in breast cancer, this discrepancy could contribute to a poorer prognosis for the entire T1c-stage cohort undergoing NAT in comparison with those receiving AT.[20,35]

In our research, we specifically focused on HER2+ patients with T1cN0M0-stage tumors to assess the survival outcomes with NAT compared with AT. A balanced cohort for comparing the NAT and AT groups was created with PSM. Our results showed no significant difference in survival between the two therapies. Previous studies indicated that patients with HER2+ breast cancer had the highest rates of pCR after NAT, with pCR considered a surrogate end point

TABLE 1 Baseline characteristics of the study population according to systemic treatment before and after PSM.

	Total before PSM (n = 8768)			Total after PSM (n = 4280)		
Variables	**AT (n = 6264)**	**NAT (n = 2504)**	***p***	**AT (n = 2140)**	**NAT (n = 2140)**	***p***
Age at diagnosis, No. (%), years			<.001			.418
<50	1932 (30.8)	1043 (41.7)		881 (41.2)	854 (39.9)	
≥50	4332 (69.2)	1461 (58.3)		1259 (58.8)	1286 (60.1)	
Marital status, No. (%)			<.001			.828
Married	3895 (62.2)	1511 (60.3)		1308 (61.1)	1322 (61.8)	
Single	1024 (16.3)	490 (19.6)		410 (19.2)	404 (18.9)	
Divorced/separated	694 (11.1)	304 (12.1)		234 (10.9)	237 (11.1)	
Widowed	407 (6.5)	108 (4.3)		92 (4.3)	96 (4.5)	
Unknown	244 (3.9)	91 (3.6)		96 (4.5)	81 (3.8)	
Race, No. (%)			.163			.710
White	4663 (74.4)	1864 (74.4)		1630 (76.2)	1636 (76.4)	
Black	716 (11.4)	289 (11.5)		218 (10.2)	228 (10.7)	
Other	853 (13.6)	328 (13.1)		292 (13.6)	276 (12.9)	
Histology, No. (%)			<.001			.726
IDC	5494 (87.7)	2274 (90.8)		1952 (91.2)	1947 (91.0)	
ILC	168 (2.7)	50 (2.0)		36 (1.7)	43 (2.0)	
Other	602 (9.6)	180 (7.2)		152 (7.1)	150 (7.0)	
Grade, No. (%)			<.001			.634
Low	2345 (37.4)	695 (27.8)		657 (30.7)	686 (32.1)	
High	3474 (55.5)	1082 (43.2)		1092 (51.0)	1071 (50.0)	
Unknown	445 (7.1)	727 (29.0)		391 (18.3)	383 (17.9)	
Breast cancer subtype, No. (%)			<.001			.949
HR−/HER2+	1824 (29.1)	857 (34.2)		742 (34.7)	739 (34.5)	
HR+/HER2+	4440 (70.9)	1647 (65.8)		1398 (65.3)	1401 (65.5)	
Axillary surgery, No. (%)			<.001			.462
No	5663 (90.4)	2120 (84.7)		1877 (87.7)	1860 (86.9)	
ALND	601 (9.6)	384 (15.3)		263 (12.3)	280 (13.1)	
Breast surgery, No. (%)			<.001			.951
BCS	3454 (55.1)	1181 (47.2)		1067 (49.9)	1064 (49.7)	
Mastectomy	2810 (44.9)	1323 (52.8)		1073 (50.1)	1076 (50.3)	
Radiotherapy, No. (%)			<.001			.284
No/unknown	3190 (50.9)	1064 (42.5)		1043 (48.7)	1007 (47.1)	
Yes	3074 (49.1)	1440 (57.5)		1097 (51.3)	1133 (52.9)	

Note: $p < .05$ was considered statistically significant.

Abbreviations: ALND, axillary lymph node dissection; AT, adjuvant therapy; BCS, breast-conserving surgery; HER2+, human epidermal growth factor receptor 2–positive; HR−, hormone receptor–negative; HR+, hormone receptor–positive; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; NAT, neoadjuvant therapy; PSM, propensity score matching.

for improved survival outcomes.[15,36,37] Consistent with these findings, our study revealed that patients achieving pCR demonstrated the best OS and BCSS. Logistic regression analysis further identified White people and those with negative HR status as more likely to attain pCR. Consequently, NAT may be a more suitable option for these individuals.

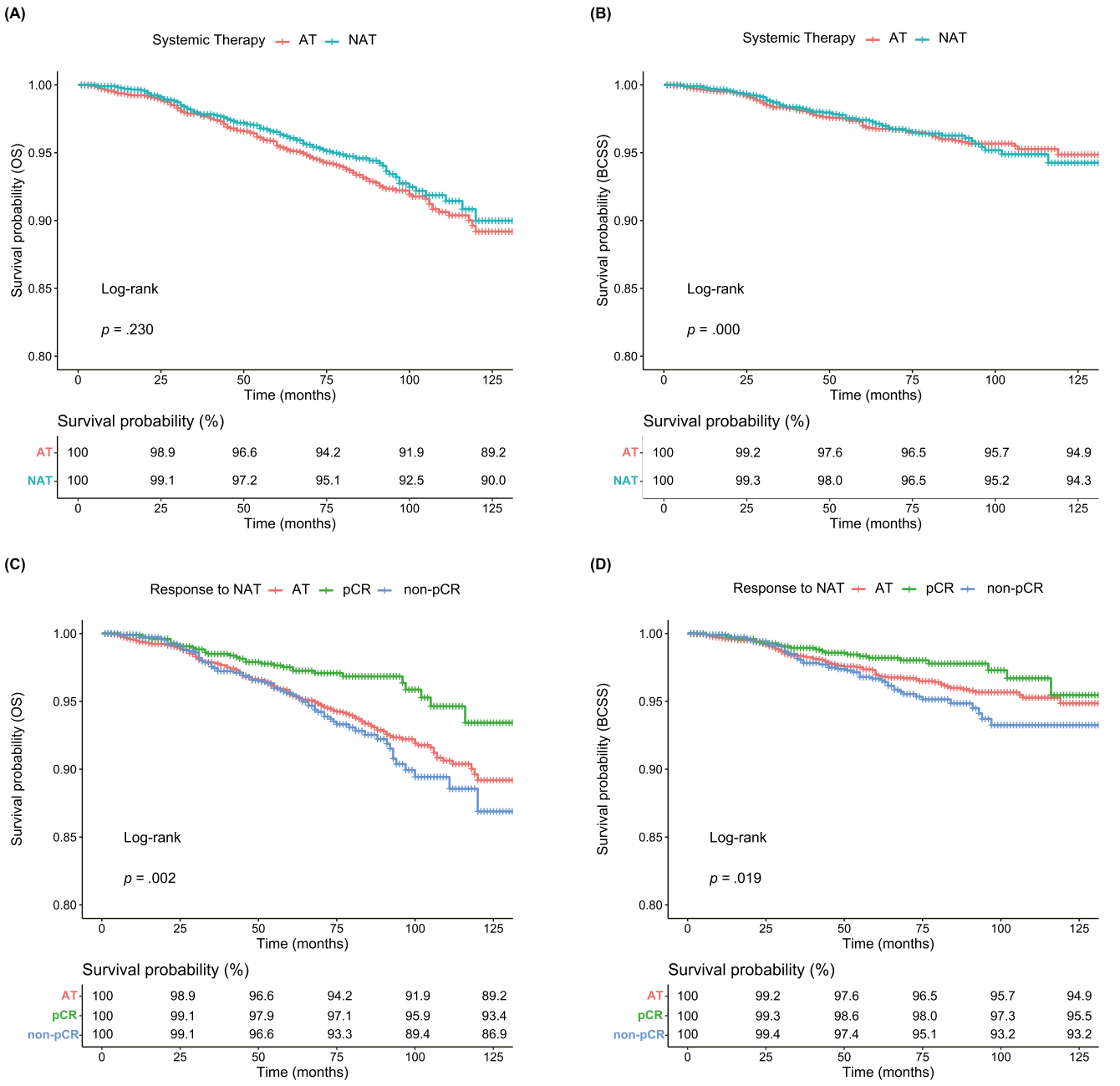

FIGURE 2 Kaplan–Meier survival curves for OS (A) and BCSS (B) after PSM in patients treated with AT and those treated with NAT. Kaplan–Meier survival curves for OS (C) and BCSS (D) after PSM in patients treated with AT, populations achieving pCR, and those not achieving pCR after NAT. AT indicates adjuvant therapy; BCSS, breast cancer–specific survival; NAT, neoadjuvant therapy; non-pCR, not achieving pathological complete response; OS, overall survival; pCR, pathological complete response; PSM, propensity score matching.

Aside from downstaging disease in both the breast and axilla, the benefits of NAT compared with AT include evaluating the in vivo response to therapy, particularly for patients with HER2+ and triple-negative breast cancer with small tumors. This facilitates timely modifications to treatment regimens or the administration of intensified postoperative therapy for patients who fail to achieve pCR. Results from the randomized phase 3 KATHERINE trial ($N = 1486$) showed that postsurgical T-DM1 significantly enhanced iDFS (hazard ratio, 0.50; 95% CI, 0.39–0.64; $p < .001$) compared with trastuzumab in patients with early-stage HER2+ breast cancer with residual disease after NAT, although OS (hazard ratio, 0.70; 95% CI, 0.47–1.05; $p = .080$) did not differ significantly.[21] Additionally, our study demonstrated that patients who did not achieve pCR had comparable survival to those receiving AT. NAT allows for the evaluation of individual drug sensitivity without compromising survival for patients who may not achieve pCR, and thereby guides subsequent treatment decisions. Hence, for patients with HER2+ breast cancer at the T1cN0M0 stage, NAT may represent a preferable treatment option over AT.

TABLE 2 Univariate and multivariate Cox regression analyses of OS and BCSS for patients after PSM.

	OS				BCSS			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Age at diagnosis, years								
<50	Ref		Ref		Ref			
≥50	1.96 (1.47–2.59)	<.001	1.97 (1.47–2.64)	<.001	1.25 (0.90–1.76)	.188		
Marital status								
Married	Ref		Ref		Ref		Ref	
Single	1.83 (1.34–2.51)	<.001	1.78 (1.29–2.46)	<.001	1.70 (1.13–2.54)	.010	1.50 (1.00–2.27)	.053
Divorced/ separated	1.47 (0.98–2.21)	.060	1.28 (0.85–1.92)	.236	1.55 (0.94–2.55)	.084	1.34 (0.81–2.22)	.252
Widowed	3.15 (2.02–4.90)	<.001	2.26 (1.44–3.56)	<.001	1.85 (0.92–3.71)	.082	1.60 (0.79–3.21)	.19
Unknown	2.86 (1.79–4.56)	<.001	2.82 (1.76–4.51)	<.001	2.59 (1.40–4.78)	.002	2.57 (1.39–4.75)	.003
Race								
White	Ref		Ref		Ref		Ref	
Black	1.94 (1.41–2.68)	<.001	1.70 (1.22–2.36)	.002	2.04 (1.36–3.06)	.001	1.76 (1.16–2.67)	.008
Other	0.60 (0.37–0.96)	.032	0.63 (0.39–1.02)	.060	0.36 (0.17–0.78)	.009	0.36 (0.17–0.78)	.009
Histology								
IDC	Ref		Ref		Ref			
ILC	1.29 (0.57–2.91)	.535	1.17 (0.51–2.67)	.707	1.06 (0.34–3.34)	.917		
Other	1.51 (1.00–2.27)	.048	1.45 (0.97–2.19)	.073	1.14 (0.63–2.05)	.669		
Grade								
Low	Ref				Ref			
High	0.91 (0.69–1.21)	.530			1.15 (0.79–1.66)	.466		
Unknown	1.15 (0.79–1.68)	.468			1.27 (0.77–2.12)	.348		
Breast cancer subtype								
HR−/HER2+	Ref		Ref		Ref			
HR+/HER2+	0.74 (0.57–0.95)	.019	0.73 (0.57–0.95)	.019	0.7 (0.50–0.97)	.030	0.64 (0.46–0.89)	.008
Axillary surgery								
No	Ref		Ref		Ref		Ref	
ALND	1.99 (1.48–2.68)	<.001	1.71 (1.22–2.39)	.002	2.55 (1.77–3.67)	<.001	2.08 (1.38–3.14)	<.001
Breast surgery								
BCS	Ref		Ref		Ref		Ref	
Mastectomy	1.46 (1.13–1.89)	.004	1.42 (1.06–1.89)	.019	1.79 (1.27–2.51)	.001	1.46 (1.00–2.14)	.051
Radiotherapy								
No/unknown	Ref				Ref			
Yes	1.19 (0.92–1.53)	.180			1.28 (0.92–1.78)	.139		
Systemic therapy								
AT	Ref						Ref	
pCR	0.55 (0.37–0.81)	.002	0.52 (0.35–0.77)	.001	0.65 (0.40–1.05)	.076	0.60 (0.37–0.98)	.041
Non-pCR	1.15 (0.86–1.53)	.353	1.10 (0.82–1.47)	.527	1.33 (0.93–1.92)	.123	1.28 (0.89–1.84)	.190

Note: $p < .05$ was considered statistically significant.

Abbreviations: ALND, axillary lymph node dissection; AT, adjuvant therapy; BCS, breast-conserving surgery; BCSS, breast cancer–specific survival; CI, confidence interval; HER2+, human epidermal growth factor receptor 2–positive; HR−, hormone receptor–negative; HR+, hormone receptor–positive; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; non-pCR, not achieving pathological complete response; OS, overall survival; pCR, pathological complete response; PSM, propensity score matching; Ref, reference.

TABLE 3 Univariate and multivariate logistic regression analyses of factors associated with pCR.

	Univariate		Multivariate	
Variables	**OR(95% CI)**	***p***	**OR(95% CI)**	***p***
Age at diagnosis, years				
<50	Ref			
≥50	1.11 (0.94–1.30)	.218		
Marital status				
Married	Ref		Ref	
Single	0.80 (0.65–0.98)	.029	0.82 (0.66–1.02)	.071
Divorced/ separated	0.86 (0.67–1.10)	.237	0.88 (0.68–1.13)	.304
Widowed	0.94 (0.63–1.39)	.745	0.88 (0.59–1.32)	.547
Unknown	0.66 (0.43–1.01)	.060	0.63 (0.40–0.98)	.041
Race				
White	Ref			
Black	0.76 (0.59–0.98)	.035	0.76 (0.59–0.99)	.040
Other	0.91 (0.72–1.14)	.403	0.90 (0.71–1.14)	.376
Histology				
IDC	Ref			
ILC	0.60 (0.33–1.06)	.086		
Other	0.82 (0.60–1.11)	.193		
Grade				
Low	Ref		Ref	
High	1.37 (1.13–1.66)	.001	1.20 (0.99–1.47)	.068
Unknown	1.18 (0.96–1.46)	.116	1.14 (0.92–1.41)	.234
Breast cancer subtype				
HR−/HER2+	Ref		Ref	
HR+/HER2+	0.48 (0.41–0.57)	<.001	0.49 (0.41–0.58)	<.001

Note: $p < .05$ was considered statistically significant.

Abbreviations: CI, confidence interval; HER2+, human epidermal growth factor receptor 2–positive; HR−, hormone receptor–negative; HR+, hormone receptor–positive; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; OR, odds ratio; pCR, pathological complete response; Ref, reference.

In recent years, research into biomarkers for HER2+ breast cancer has continued to advance. It was found that PAM50 subtypes, tumor-infiltrating lymphocytes, HER2 gene mutations, and alterations in the *PI3K/Akt/mTOR* pathway are linked to response to NAT or survival of HER2+ breast cancer.[38–40] Furthermore, the HER2DX genomic test, a classifier based on both clinicopathological and genomic features, demonstrated prognostic value and the ability to predict pCR, independent of chemotherapy type, anti-HER2 therapy, and HR status.[41,42] This test may further aid in selecting suitable candidates for NAT among patients with T1cN0M0-stage HER2+ breast cancer.

To our knowledge, this is the first population-based retrospective study investigating the prognosis of patients with HER2+ breast cancer at the T1cN0M0 stage undergoing NAT or AT. Leveraging a large sample size and an extended follow-up duration, our findings carry significant credibility. Furthermore, we used PSM to minimize the influence of confounding variables. Our results offer valuable insights for guiding treatment decisions in T1cN0M0-stage HER2+ diseases. Inevitably, some limitations in our study should not be ignored. First, as a retrospective study, inherent selection biases and uncontrolled confounding factors are unavoidable; however, we minimized confounding factors by PSM. Additionally, the SEER database lacked detailed information on systemic regimens. Further analyses of different regimen subgroups are warranted.

In conclusion, NAT and AT demonstrated comparable survival outcomes in patients with T1cN0M0-stage HER2+ breast cancer, whereas pCR after NAT was a significant prognostic factor for favorable survival. For patients who did not achieve pCR, NAT could be a valuable indicator for potential treatment escalation. Therefore, NAT should be considered the preferred treatment approach for patients with T1cN0M0-stage HER2+ breast cancer. Further prospective trials are needed to corroborate these findings and refine treatment strategies for this specific patient subgroup.

AUTHOR CONTRIBUTIONS

Xuelian Wang: Conceptualization, writing–original draft, writing–review and editing, investigation, formal analysis, data curation, methodology, validation, and visualization. **Yuhang Shang**: Conceptualization, investigation, methodology, writing–original draft, writing–review and editing, data curation, validation, visualization, and formal analysis. **Jiayang Zhang**: Writing–review and editing, supervision, and project administration. **Jiangwei Liu**: Validation, data curation, and writing–review and editing. **Zhengbo Fang**: Writing–review and editing and formal analysis. **Yansong Liu**: Writing–review and editing and data curation. **Weilun Cheng**: Writing–review and editing and formal analysis. **Yunqiang Duan**: Formal analysis and writing–review and editing. **Anbang Hu**: Supervision and writing–review and editing. **Jiarui Zhang**: Methodology and writing–review and editing. **Mingcui Li**: Visualization and writing–review and editing. **Yanling Li**: Software and writing–review and editing. **Hanyu Zhang**: Data curation and writing–review and editing. **Zhiyuan Rong**: Writing–review and editing and resources. **Suborna S. Shakila**: Visualization and writing–review and editing. **Fanjing Kong**: Writing–review and editing and resources. **Baoliang Guo**: Writing–review and editing, funding acquisition, and project administration.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data sets analyzed during the current study are available from the Surveillance, Epidemiology, and End Results database (https://seer.cancer.gov/).

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