Benefits of neoadjuvant therapy compared with adjuvant chemotherapy for the survival of patients with HER2-positive breast cancer: A retrospective cohort study at FUSCC

Shuyue Zheng a,b, Lun Li a,b,d, Ming Chen a,b, Benlong Yang a,b, Jiajian Chen a,b, Guangyu Liu a,b, Zhimin Shao a,b, Jiong Wu a,b,c,*

a Department of Breast Surgery, Fudan University Shanghai Cancer Center, Shanghai, China
b Department of Oncology, Fudan University, Shanghai Medical College, Shanghai, China
c Collaborative Innovation Center for Cancer Medicine, Shanghai, China
d Department of Breast Surgery, The Second Xiangya Hospital, Central South University, Changsha, China

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ABSTRACT

Purpose: Neoadjuvant therapy (NAT) is considered the standard of care for patients with HER2-positive breast cancer (BC). However, there is no proven survival benefit of NAT compared to adjuvant therapy for the survival of patients with early-stage HER2-positive BC. This study aimed to compare the prognosis of HER2-positive BC patients treated with NAT to that of patients treated with adjuvant therapy.

Methods: This was a single-center real-world retrospective study. This study analyzed the disease-free survival (DFS) and overall survival (OS) of 538 HER2-positive BC patients treated with neoadjuvant therapy and 2684 patients treated with adjuvant therapy at Fudan University Shanghai Cancer Center (FUSCC) between 2012 and 2016. Patients with a clinical tumor size (cT) \( \leq 5 \) cm or \( >5 \) cm were matched using the propensity score matching (PSM) method to prevent selection bias.

Results: After PSM, among patients with cT \( \leq 5 \) cm, there was no significant difference in DFS (\( P = 0.08 \)) or OS (\( P = 0.11 \)) between the two groups. The analysis of survival outcomes of patients treated with neoadjuvant and adjuvant therapy in the different chemotherapy subgroups yielded consistent results. According to multivariate analysis, lymph node status and response to NAT showed independent prognostic value for OS and DFS. Among patients with cT \( >5 \) cm, the DFS (\( P = 0.25 \)) and OS (\( P = 0.57 \)) of patients treated with NAT were similar to those of patients treated with adjuvant therapy after PSM.

Conclusion: We confirmed the equivalent effects of adjuvant therapy and NAT in HER2-positive BC patients. Neoadjuvant therapy should be used for patients with HER2-positive BC.

1. Introduction

Neoadjuvant therapy (NAT) has gradually become the standard treatment for patients with inoperable locally advanced breast cancer and inflammatory breast cancer [1,2]. NAT can decrease tumor sizes and allow more patients to undergo breast-conserving surgery. NAT can also facilitate the monitoring of treatment responses in vivo via observations of pathological findings that indicate residual disease in the breast and axilla [3,4].

Human epidermal growth factor receptor (HER2)-positive breast cancer is a unique type of breast cancer in which the oncogene ERBB2 is overexpressed [5]; HER2-positive breast cancer that is not treated with HER2-targeted therapies is associated with a worse prognosis. Previous trials have shown that HER2-positive breast cancer is more chemo-sensitive than other subtypes of breast cancer [6,7]. Pathological complete response (pCR) is commonly defined by the absence of invasive cancer in both the breast and/or lymph nodes after NAT. pCR can also provide information regarding the responsiveness of a tumor to NAT. A meta-analysis by Rouzier R et al. showed that the pCR rates among patients with HER2-positive breast cancer who receive HER2-targeted therapies and neoadjuvant therapies can reach 60% or higher [5].

Previous clinical trials have shown that NAT is equally as effective as
adjuvant therapy in terms of overall survival (OS) and disease-free survival (DFS) [2,8]. A meta-analysis of the long-term outcomes of patients with early breast cancer who were treated with neoadjuvant chemotherapy versus adjuvant chemotherapy was conducted by Early Breast Cancer Trialsists’ Collaborative Group (EBCTCG) [9], and the analysis showed that the distant recurrence rate and OS were similar in patients who received NAT and patients who received adjuvant therapy. However, the studies that addressed the equal efficacy of these two therapies did not routinely evaluate HER2 status. According to the St. Gallen international expert consensus conference in 2017, the panel favored the preference for neoadjuvant therapy in HER2 positive breast cancer [10]. A recent study indicated that NAT is more beneficial than adjuvant therapy, particularly in cN-positive and postmenopausal patients with HER2-positive breast cancer [11]. However, these studies ignored the important prognostic factor pCR. Although the meta-analysis by EBCTCG showed that responders to NAT had lower distant recurrence rates and breast cancer-related mortality than non-responders, the authors did not compare the distant recurrence rate and breast cancer-related mortality between responders to NAT and respondents to adjuvant therapy. We conducted this retrospective study to confirm the equal efficacy of NAT and adjuvant therapy in patients with HER2-positive breast cancer in the real world and to further compare the outcomes of patients who respond to NAT and patients who are treated with adjuvant therapy.

The primary aim of our study was to determine the OS and DFS of HER2-positive breast cancer patients treated with NAT versus patients treated with adjuvant therapy in a single-center cohort of Chinese breast cancer patients. In addition, we aimed to identify the population of patients with HER2-positive breast cancer who are most likely to benefit from treatment with neoadjuvant therapy. The secondary aim was to evaluate the current regimens for the treatment of patients with HER2-positive breast cancer with NAT or adjuvant therapy.

2. Methods

2.1. Study design and eligibility

This was a single-center, retrospective study. Patients with primary invasive HER2-positive breast cancer and who were treated with neoadjuvant or adjuvant therapy at Fudan University Shanghai Cancer Center (FUSCC) between 2012 and 2016 were analyzed. This study was approved by the Ethics Committee of Fudan University Shanghai Cancer Center (1905202-7) and conducted in accordance with the Declaration of Helsinki. This was a retrospective cohort study, so informed consent of the patients was not required.

Consecutive female patients aged 18–85 years with invasive HER2-positive breast cancer diagnosed by core-needle aspiration were analyzed in the study. Pathological HER2 status was defined according to the ASCO/CAP 2007 guidelines [12]. A HER2 expression score of 3+ by immunohistochemical staining was considered positive; a score of 2+ required verification by fluorescence in situ hybridization (FISH), and FISH positivity was considered to indicate HER2 amplification. Patients with other cancers or recurrent breast cancer when they were first diagnosed in our center were not eligible for this study. Other exclusion criteria included metastatic disease before surgery and male breast cancer. Targeted therapy refers to the completion of one year of trastuzumab treatment, and the patients did not receive other targeted therapies, such as pertuzumab and lapatinib, during this retrospective study.

2.2. Follow-up

All the patients were followed up through outpatient interviews or telephone calls. Local relapse was defined as relapse at the breast, chest wall, pectoral muscles, ipsilateral supraclavicular nodes, and internal mammary nodes. Distant metastasis was considered if it was observed in clinical and imaging studies. OS was calculated from the date of diagnosis to the date of death or last follow-up. DFS was calculated from the first date of no disease, i.e., date of surgery, to the date of disease relapse (local relapse, metastasis, or death from any cause). pCR was defined by the absence of invasive cancer in both the breast and lymph nodes after NAT.

2.3. Statistics

The clinical and pathological stages of the patients included in the analysis were classified according to the AJCC 8th edition guidelines. Because there were only 68 patients with a clinical tumor size (cT) larger than 5 cm in the adjuvant therapy group, the patients were divided into two groups: those with a clinical tumor size smaller than 5 cm and those with a clinical tumor size larger than 5 cm. The propensity score matching (PSM) methodology was used to reduce the treatment selection bias in the nonrandom assignment. Matching was performed with the use of a 1:3 or 3:1 matching protocol with a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score for patients with clinical tumor size ≤5 cm or >5 cm who received NAT and adjuvant therapy, respectively. Patients were stratified according to age (<35 years, 35–65 years, or >65 years), clinical tumor size (<2.0 cm, 2.1–5.0 cm, or >5.0 cm), clinical lymph nodal status (negative or positive), estrogen receptor (ER) status, progesterone receptor (PR) status, and Ki-67 status (0–20% or >20%). Positive clinical lymph nodal status was identified by axillary lymph node aspiration cytology. For ER and PR status, samples with ≥1% of cells with strongly stained tumor nuclei were considered positive, and samples with <1% of cells with strongly stained tumor nuclei were considered negative [13].

Continuous variables are expressed as the mean values or median values, while categorical variables are expressed as frequencies. We conducted a survival analysis of patients who received and did not receive neoadjuvant therapy. Patients without adverse events or who did not die were censored at the last follow-up. Comparability of the NAT and adjuvant therapy groups at baseline was assessed using t tests and chi-square tests. Univariate and multivariate survival analyses were performed using the Cox regression model. Survival curves were estimated using the Kaplan–Meier method, and the log-rank test was used to analyze differences between groups. All the P values reported were two-sided and were calculated at a significance level of 0.05. All the statistical procedures were carried out using SPSS and R software.

3. Results

3.1. Patient characteristics

A total of 3222 consecutive patients were analyzed in our study, including 538 (16.7%) patients treated with NAT and 2684 (83.3%) patients treated with adjuvant therapy. The median age of these patients was 50 years (range 21–78 years, interquartile range, IQR 43–57 years). The patient characteristics are listed in Table 1. Patients received trastuzumab at FUSCC or their local hospital. The patients who received NAT and those who received adjuvant therapy differed in terms of clinical tumor stage (cT, P < 0.0001), pretreatment clinical nodal status (cN, P < 0.0001), estrogen receptor status (ER, P < 0.0001) and progesterone receptor (PR) status (P = 0.008). The patients who received NAT were characterized by higher clinical-stage distributions and lower HR-positive rates. The proportion of patients with clinical tumors larger than 5 cm in the NAT group was higher than that in the adjuvant treatment group (34.9% vs. 2.5%). For clinical nodal status, 73.8% of patients in the NAT group had lymph node metastasis at baseline, and only 42.8% of patients in the adjuvant therapy group had lymph node metastasis at baseline. In the NAT group, the overall pCR rate was 40.1% (216/538). Compared with the patients who did not achieve pCR, the patients who achieved pCR had a higher rate of HR-negative status (P < 0.0001). More patients received endocrine therapy in the adjuvant
therapy group than in the NAT group due to the hormone receptor status
(P < 0.0001).

Comparing the systemic treatment of patients who received neo-adjuvant therapy with patients who received adjuvant therapy, the results showed that the regimen including anthracycline was mostly used for adjuvant chemotherapy (71.8%), and the regimen without anthracycline was mainly used for NAT (78.8%). The primary regimen for NAT for adjuvant chemotherapy (71.8%), and the regimen without anthracycline was mainly used for NAT (78.8%) than in the adjuvant therapy group (69.7%), P < 0.0001.

3.2. Survival analysis for all patients

The median follow-up time was 54.1 months (IQR 40.8–68.9 months). The 5-year OS rate was lower in patients treated with NAT than in those treated with adjuvant therapy (86.5% vs. 95.6%, P < 0.0001, Fig. 1 A). The multivariate Cox regression analysis suggested that patient age, cT, cN, and PR status were independent predictors of OS (Table 2). Achieving pCR after NAT was associated with significantly improved OS compared to not achieving pCR (5-year OS rate 98.5% vs. 78.6%, P < 0.0001). After adjusting for the patient’s age, cN, and PR status, multivariate analysis showed that patients who achieved pCR had the best OS, resulting in an 83% reduction in the relative risk of death, and the relative risk of death for patients who did not achieve pCR after NAT was increased 2.57-fold. Similar results were observed for DFS (Table 2).

For these patients, 70.8% of the patients who were treated with adjuvant therapy received taxane combined with anthracycline. A total of 74.9% of patients who were treated with NAT received taxane and carboplatin without anthracycline. There was no significant difference between patients treated with NAT and those treated with adjuvant therapy in terms of the proportion of patients who received trastuzumab-based targeted therapy. For the patients with cT1 or cT2 at baseline, the proportion of patients treated with NAT who received adjuvant radiotherapy was 68.8%, which is higher than the proportion of patients treated with adjuvant therapy who received adjuvant radiotherapy (50.5%, P < 0.0001). Separate survival curves for HER2-positive patients treated with or without NAT are shown in Fig. 2A (OS) and Fig. 2C (DFS). There was no significant difference between the groups in terms of DFS (P = 0.08) or OS (P = 0.11). Data about the pathological response to NAT was available for 135 patients out of 346 patients, and the pCR rate was equal to 39%. Achieving pCR after NAT was significantly related to improved OS (HR 0.13, 95% CI 0.02–0.92; P = 0.04) and DFS (HR 0.37, 95% CI 0.16–0.85, P = 0.02) compared to receiving adjuvant therapy. Patients who did not achieve pCR after NAT had the worst survival outcomes, with a 5-year OS of 83% and a 5-year DFS of 76.7% (Fig. 2B; Table 4). Among patients who were treated with trastuzumab, there were no significant differences between the NAT group and the adjuvant therapy group in terms of patients who were treated with taxanes without anthracycline or patients who were treated with taxanes combined with anthracyclines (Supplement Fig 4). Multivariate analysis

| Table 1 | Patient characteristics according to treatment group. |
|---------|-------------------------------------------------------|
| Number of patients(%) | NAT N = 538 | Adjuvant N = 2684 |
| Age | | |
| <35 | 54 (10.9%) | 229 (8.5%) |
| 36-64 | 460 (85.5) | 2284 (85.1%) |
| >65 | 24 (4.5%) | 171 (6.4%) |
| Age | 3.87 | 0.15 |
| Tumor stage | | |
| T1 | 42 (7.8%) | 1433 (53.4%) |
| T2 | 308 | 1183 (44.1%) |
| T3/4 | 188 (34.9%) | 68 (2.5%) |
| Tumor stage | 812.65 | <0.0001 |
| Nodal status | | |
| N0 | 141 | 1536 (57.2%) |
| N+ | 397 | 1148 (42.8%) |
| ER positive | 226 (42.0%) | 1388 (51.8%) |
| PR positive | 176 (32.7%) | 1042 (38.8%) |
| Ki-67 | | |
| <20% | 480 (91.1%) | 2451 (91.3%) |
| >20% | 0 | 180 (7.0%) |
| Unknown | 207.01 | <0.0001 |
| Chemotherapy | | |
| Taxane | 407(75.7%) | 640 (23.8%) |
| Anthracycline | 163(3.0%) | 320 (11.9%) |
| Taxane and anthracycline | 115(21.4%) | 1607 (59.9%) |
| Others | / | 177(4.4%) |
| Radiotherapy | 207.01 | <0.0001 |
| Yes | 379 | 1001 (37.3%) |
| No | 128 | 1499 (55.8%) |
| Unknown | 31 | 184 (6.9%) |
| Trastuzumab | 21.36 | <0.0001 |
| yes | 424 | 1870 (69.7%) |
| No | 79 | 635 (23.6%) |
| Unknown | 35 | 181 (6.7%) |
| Endocrine treatment | 17.44 | <0.0001 |
| Yes | 191(35%) | 121(4.5%) |
| No | 316(58.7%) | 1328(49.5%) |
| Unknown | 31(5.8%) | 142(5.3%) |

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showed that cN and response to treatment were independent predictors of OS and DFS. Patients who were younger and had negative clinical nodal status showed improved OS and DFS.

Stratified survival analysis according to the patient’s clinical nodal status at baseline showed that achieving pCR after NAT was not a significant independent predictor of OS ($P = 0.96$) or DFS ($P = 0.42$) in patients with no lymph node metastasis (Table 5). However, patients who did not achieve pCR after NAT had the worst prognosis, with a 2.21-fold relative risk of death and a 1.87-fold relative risk of disease progression. Among patients with positive nodal status, achieving pCR after NAT was associated with improved survival outcomes compared to receiving adjuvant therapy, which reduced the relative risk of death by 88%. Patients who did not achieve pCR had the worst OS and DFS (Fig. 3).

Fig. 1. Kaplan-Meier survival curves for OS (A) and DFS (C), in patients treated with adjuvant therapy (blue) and those treated with NAT (red). Kaplan-Meier survival curves for OS (B) and DFS (D), in patients treated with adjuvant therapy (blue), populations achieving pathologic complete response (pCR) at surgery (green) and those with residual disease at time of surgery (red). NAT = Neoadjuvant therapy.

Table 2

Cox regression analysis of OS, and DFS in all patients.

| Variable                  | OS Univariate analysis |  | OS Multivariate analysis | DFS Univariate analysis |  | DFS Multivariate analysis |
|---------------------------|------------------------|  |--------------------------|-------------------------|  |--------------------------|
|                           | HR 95% CI P            |  | HR 95% CI P              | HR 95% CI P            |  | HR 95% CI P              |
| Age                       |                        |  |                          |                         |  |                          |
| ≤35                       | 1 Ref                  |  | 1 Ref                    | 1 Ref                  |  | 1 Ref                    |
| 36–64                     | 1.03 0.58–1.82 0.93    |  | 1.00 0.56–1.78 1.00     | 0.92 0.62–1.36 0.67   |  | 0.93 0.63–1.37 0.70     |
| ≥65                       | 2.62 1.31–5.23 0.01    |  | 2.52 1.25–5.08 0.01     | 1.76 1.05–2.93 0.03   |  | 1.78 1.07–2.97 0.03     |
| Tumor stage               |                        |  |                          |                         |  |                          |
| T1                        | 1 Ref                  |  | 1 Ref                    | 1 Ref                  |  | 1 Ref                    |
| T2                        | 2.45 1.66–3.61 <0.0001 |  | 1.71 1.14–2.56 0.01     | 2.10 1.61–2.73 <0.0001 |  | 1.56 1.18–2.06 0.002    |
| T3/T4                     | 6.43 4.04–10.22 <0.0001|  | 3.26 1.87–5.67 <0.0001  | 4.42 3.14–6.20 <0.0001 |  | 2.70 1.79–4.05 <0.0001  |
| Nodal status              |                        |  |                          |                         |  |                          |
| N0                        | 1 Ref                  |  | 1 Ref                    | 1 Ref                  |  | 1 Ref                    |
| N+                        | 4.20 2.88–6.13 <0.0001 |  | 3.15 2.12–4.68 <0.0001  | 3.22 2.50–4.15 <0.0001 |  | 2.56 1.97–3.34 <0.0001  |
| ER Status                 |                        |  |                          |                         |  |                          |
| +                         | 1.18 0.86–1.60 0.31    |  | – – –                    | 1.08 0.87–1.36 0.48   |  | – – –                    |
| –                         | 1.58 1.12–2.23 0.01    |  | 1.75 1.24–2.48 0.001    | 1.20 0.95–1.52 0.12   |  | – – –                    |
| PR positive               |                        |  |                          |                         |  |                          |
| +                         | 1 Ref                  |  | 1 Ref                    | 1 Ref                  |  | 1 Ref                    |
| –                         | 1.05 0.59–1.85 0.87    |  | – – –                    | 0.78 0.49–1.24 0.29   |  | – – –                    |
| Ki-67 ≥20%                |                        |  |                          |                         |  |                          |
| ≥20%                      | 1 Ref                  |  | 1 Ref                    | 1 Ref                  |  | 1 Ref                    |
| <20%                      | 2.09 1.27–3.44 0.001   |  | 2.47 1.47–4.06 0.001    | 2.79 1.65–4.68 0.001  |  | 2.18 1.30–3.65 0.001    |
| Timing of chemotherapy    |                        |  |                          |                         |  |                          |
| Adjuvant therapy          |                        |  |                          |                         |  |                          |
| 1 Ref                     | – – –                  |  | – – –                    | – – –                  |  | – – –                    |
| NAT                       | 3.08 2.23–4.25 <0.0001 |  | – – –                    | 2.34 1.84–2.98 <0.0001 |  | – – –                    |
| Response to treatment     |                        |  |                          |                         |  |                          |
| Adjuvant therapy pCR      | 0.38 0.12–1.20 0.10    |  | 0.17 0.05–0.54 0.003    | 0.58 0.31–1.10 0.10   |  | 0.31 0.16–0.60 0.001    |
| non-pCR                   | 5.01 3.6–6.95 <0.0001  |  | 2.57 1.73–3.81 <0.0001  | 3.64 2.83–4.69 <0.0001 |  | 1.99 1.47–2.69 <0.0001  |

Abbreviations: HR: Hazard ratio; NAT: neoadjuvant chemotherapy; AC: adjuvant chemotherapy; pCR: pathologic complete response.
3.4. Survival analysis of patients with cT3/4 stage disease

There were 256 patients with clinical tumor sizes ≥5 cm, 26.6% of whom received adjuvant therapy, and 188 patients received chemotherapy before surgery. There were no statistically significant differences in the baseline characteristics of both groups. After PSM, 145

Table 3
Clinical characteristic of patients with cT1 and cT2 before or after being matched.

|                       | Before matched | Matched       | P-value | Before matched | Matched       | P-value |
|-----------------------|----------------|---------------|---------|----------------|---------------|---------|
|                       | NAT N = 350    | Adjuvant N = 261 |         | NAT N = 346    | Adjuvant N = 952 |         |
| Age                   |                |               |         |                |               |         |
| ≤35                   | 35(10.0%)      | 223(8.5%)     | 0.15    | 35 (10.1%)     | 76 (8.0%)     | 0.48    |
| ≥65                   | 14(4.0%)       | 168(6.4%)     |         | 14 (4.0%)      | 38 (4.0%)     |         |
| Tumor stage           |                |               |         |                |               |         |
| T1                    | 42(12%)        | 1433(54.8%)   | <0.0001 | 42(12.1%)      | 126 (13.2%)   | 0.60    |
| T2                    | 308(88%)       | 1183(45.2%)   |         | 826(86.8%)     | 304 (87.9%)   |         |
| Nodal status          |                |               |         |                |               |         |
| N0                    | 94(26.9%)      | 1512(57.8%)   | <0.0001 | 94 (27.2%)     | 272 (28.6%)   | 0.62    |
| N+                    | 256(73.1%)     | 1104(42.2%)   |         | 252 (72.8%)    | 680 (71.4%)   |         |
| ER positive           |                |               |         |                |               |         |
| <20%                  | 35(10.0%)      | 210(8.0%)     | 0.04    | 35(10.1%)      | 66(6.9%)      | 0.81    |
| ≥20%                  | 315(90.0%)     | 2388(91.3%)   |         | 311(89.9%)     | 882(92.6%)    | 0.08    |
| Unknown               | 0              | 18(0.7%)      |         | 0              | 4(0.4%)       |         |
| Chemotherapy          |                |               |         |                |               |         |
| Taxane                | 262(74.9%)     | 626(23.9%)    | <0.0001 | 259(74.9%)     | 135(14.2%)    | <0.0001 |
| Anthracyline          | 14(4.0%)       | 31(1.2%)      |         | 14(4.0%)       | 10(1.1%)      |         |
| Taxane and anthracyline | 74(21.1%)   | 1558(59.6%)   |         | 73(21.1%)      | 674(70.8%)    |         |
| Others                | 0              | 113(4.3%)     |         | 0              | 34(3.6%)      |         |
| Radiotherapy          |                |               | <0.0001 |                | <0.0001       |         |
| Yes                   | 242(69.1%)     | 959(36.7%)    |         | 238(68.8%)     | 481(50.5%)    | <0.0001 |
| No                    | 82(23.4%)      | 1482(56.7%)   |         | 82(23.7%)      | 384(40.3%)    |         |
| Unknown               | 26(7.4%)       | 175(6.7%)     |         | 26(7.5%)       | 870(9.1%)     |         |
| Trastuzumab           |                |               | 0.005   |                |               | 0.13    |
| Yes                   | 266(76.0%)     | 1819(69.5%)   |         | 262(75.7%)     | 680(71.4%)    |         |
| No                    | 56(16.0%)      | 620(23.7%)    |         | 56(16.2%)      | 202(21.2%)    |         |
| Unknown               | 28(8.0%)       | 177(6.8%)     |         | 28(8.1%)       | 70(7.4%)      |         |
| Endocrine treatment   |                |               | 0.005   |                |               | 0.301   |
| Yes                   | 129(36.9%)     | 1189(45.5%)   |         | 128(37%)       | 386(40.5%)    |         |
| No                    | 194(55.4%)     | 1289(49.3%)   |         | 191(55.2%)     | 510(53.6%)    |         |
| Unknown               | 27(7.7%)       | 138(5.3%)     |         | 27(7.8%)       | 56(5.9%)      |         |

Fig. 2. Among propensity score matched patients with clinical tumor size smaller than 5 cm at baseline. Kaplan-Meier survival curves for OS (A) and DFS (C) in patients treated with adjuvant therapy (blue) and those treated with NAT (red). Kaplan-Meier survival curves for OS (B) and DFS (D), in patients treated with adjuvant therapy (blue), populations achieving pathologic complete response (pCR) at surgery (green) and those with residual disease at time of surgery (red). NAT = Neoadjuvant therapy.
patients who received NAT were matched with 62 patients who received adjuvant therapy. There were no significant differences between the groups in terms of clinical nodal status, age, ER, PR, and Ki-67 status (Table 6). The pCR rate of these patients after NAT was 42.1% in patients with cT3/4 after PSM. In addition, 74.5% of NAT patients received adjuvant radiotherapy, and the proportion of patients treated with adjuvant therapy was 64.5% ($P = 0.016$).

After PSM, the DFS and OS of patients treated with NAT were similar to those of patients treated with adjuvant therapy (Fig. 4). The 5-year OS was 83.2% in patients treated with NAT and 91.2% in patients treated with adjuvant therapy ($P = 0.25$). Patients who did not achieve pCR had the worst prognosis, with a 5-year OS of 73.8%. There were no significant differences between the OS of the patients who achieved pCR and those treated with adjuvant therapy ($P = 0.26$). After adjusting for the patient’s age, cN, ER, PR, and Ki-67 status, multivariate analysis showed that the DFS of patients who achieved pCR was better than that of patients treated with adjuvant therapy ($HR = 0.29$, $95\% CI = 0.09-0.92$, $P = 0.04$) (Table 7). There were no significant differences among patients with cT3/4 who were treated with different chemotherapy regimens in terms of OS and DFS. For patients treated with taxanes without anthracycline and patients treated with taxanes combined with anthracyclines, there were no significant differences in OS and DFS between the NAT group and the adjuvant therapy group (Supplement Fig 5).

### 4. Discussion

The study retrospectively evaluated the survival outcomes of Chinese patients with HER2-positive breast cancer who were treated with NAT or adjuvant therapy. Based on the large sample size and long follow-up time, the results had high credibility. The reproducibility of trial data in real-world populations is an increasing concern as we investigate new therapies for breast cancer. According to the real-world cohort analysis, we proved that there was no difference in survival outcomes among breast cancer patients who were treated with NAT and those who were treated with adjuvant therapy, and patients who achieved pCR after receiving NAT had superior outcomes compared with patients who were treated with adjuvant therapy. We identified the population of patients...
with HER2-positive breast cancer who were most likely to benefit from neoadjuvant treatment. Patients with cT3/4 or those with positive clinical nodal status were more likely to benefit from NAT. The authors of the Adjuvant Paclitaxel and Trastuzumab (APT) Trial suggested that administering adjuvant paclitaxel and trastuzumab to patients with stage I Her2-positive breast cancer represented a de-escalating therapy that preserved quality of life and achieved excellent outcomes for these patients [14, 15]. Adjuvant Trastuzumab Emtansine Versus Paclitaxel in Combination with Trastuzumab for Stage I HER2-Positive Breast Cancer (ATEMPT) showed that among patients with stage I HER2-positive breast cancer, one year of adjuvant T-DM1 was associated with excellent 3-year invasive disease-free survival (iDFS) compared with paclitaxel plus trastuzumab [16, 17].

The study demonstrates that HER2-positive breast cancer patients had worse survival after treatment with NAT than after treatment with adjuvant therapy. However, these P values failed to be significant after adjusting for the baseline characteristics of the patients. These findings were basically consistent with NSABP B-18, EORTC 10902, and the IBBGS, three large randomized trials that evaluated NAT vs. adjuvant therapy [9, 18, 19]. The results of these trials showed that there was no difference in survival outcomes among breast cancer patients treated with NAT and those treated with adjuvant therapy. Our study proved this finding among HER2-positive breast cancer patients in China. Knowledge of the pathological response to NAT also presents an opportunity for adjuvant therapy and helps to identify high-risk patients for enrollment in novel clinical trials. The study showed that patients who have residual invasive carcinoma after the treatment of HER2-positive breast cancer with NAT have poor prognoses. These patients may benefit from sequential intensive adjuvant chemotherapy. Katherine clinical trials suggested that among patients with HER2-positive early breast cancer who had residual invasive disease after the completion of neoadjuvant therapy, the risk of invasive breast cancer recurrence or death was 50% lower after treatment with adjuvant T-DM1 than after treatment with trastuzumab alone [20]. For patients with cT1-cT2, or cN0not achieving pCR after NAT was an independent predictor of poor prognosis, and sequential intensive adjuvant chemotherapy was necessary for these patients. This may be the potential value of NAT for patients with a low tumor burden.

There are also limitations in our retrospective study of this real-world cohort. We only enrolled patients from a single center, and only 68 patients with a tumor size >5 cm were included, so the population may be slightly underrepresented. Considering that there were fewer
patients with cN2 and cN3 in this study, this study only evaluated patients with clinical nodal negative or positive status, except those who were classified by stage of clinical nodal status. Over 20% of these patients did not receive an anti-HER2 agent as part of NAT. Based on real-world research, some patients failed to receive targeted therapy during 2012–2016 due to economic or other reasons. However, after PSM, there were no significant differences between the NAT group and the adjuvant therapy group in terms of treatment with targeted therapy. Therefore, this limitation did not affect the accuracy of the conclusion. Due to the limitations of retrospective studies, the types of chemotherapy administered to patients who received NAT and those who received adjuvant therapy are different. However, under actual conditions, the

Table 6
Clinical characteristic of patients with cT3/4 before or after being matched.

|                      | Unpaired |                | P-value |                | Paired   |                | P-value |
|----------------------|----------|----------------|---------|----------------|----------|----------------|---------|
|                      | NAT N = 188 | Adjuvant N = 68 |         |                | NAT N = 145 | Adjuvant N = 62 |         |
| Age                  |          |                |         |                |          |                |         |
| ≤35                  | 19(10.1%) | 6(8.8%)        | 0.91    |                | 8 (5.5%) | 3 (4.6%)       | 0.81    |
| 36-64                | 158(84.6%) | 59(66.8%)        |         |                | 136 (93.8%) | 58 (93.5%)        |         |
| ≥65                  | 10(5.3%)  | 3(4.4%)        | 0.12    |                | 1 (0.7%) | 1 (1.6%)       | 0.32    |
| Nodal status         |          |                |         |                |          |                |         |
| N0                   | 47(25%)  | 24(35.3%)       |         |                | 39 (26.9%) | 21 (33.9%)       |         |
| N+                   | 141(75%) | 44(64.7%)       | 0.24    |                | 106 (73.1%) | 41 (66.1%)       | 0.76    |
| ER positive          | 65(34.6%) | 29(42.6%)       | 0.88    |                | 54(37.2%) | 25 (40.3%)       | 0.87    |
| PR positive          | 5(28.2%)  | 18(26.5%)       |         |                | 40(27.6%) | 18(29.0%)       | 0.74    |
| Ki-67                |          |                |         |                |          |                |         |
| <20%                 | 13(6.9%)  | 5(7.4%)        | <0.0001 |                | 7(4.8%)  | 4(6.5%)        | <0.0001 |
| ≥20%                 | 173(92.6%) | 63(92.6%)       |         |                | 138(95.2%) | 58(93.5%)       |         |
| Unknown              | 0        | 1(0.7%)        |         |                | 0        | 4(6.4%)        |         |
| Chemotherapy         |          |                |         |                |          |                |         |
| Taxane               | 145(77.1%) | 14(20.6%)       |         |                | 110(75.9%) | 12(19.4%)       |         |
| Anthracycline        | 2(1.1%)  | 1(1.5%)        | 0.004   |                | 1(0.7%)  | 1(1.6%)        | 0.02    |
| Taxane and anthracycline | 41(21.8%) | 49(72.1%)       |         |                | 34(23.4%) | 46(74.2%)       | 0.19    |
| Others               | 0        | 4(5.9%)        |         |                | 0        | 3(4.8%)        | 0.39    |
| Radiotherapy         |          |                |         |                |          |                |         |
| Yes                  | 137(72.9%) | 42(61.8%)       |         |                | 108(74.5%) | 40(64.5%)       |         |
| No                   | 46(24.5%) | 17(25%)        |         |                | 33(22.8%) | 14(22.6%)       |         |
| Unknown              | 5(2.7%)  | 9(13.2%)       | 0.26    |                | 4(2.8%)  | 8(12.9%)       |         |
| Targeted therapy     |          |                |         |                |          |                |         |
| Yes                  | 158(84%)  | 51(75%)        |         |                | 123 (84.8%) | 46(74.2%)       |         |
| No                   | 23(12.2%) | 13(19.1%)       |         |                | 17(11.7%) | 13(21%)        |         |
| Unknown              | 7(3.7%)  | 4(5.9%)        | 0.23    |                | 5(3.4%)  | 3(4.8%)        |         |
| Endocrine treatment  |          |                |         |                |          |                |         |
| Yes                  | 62(33%)  | 25(36.8%)       |         |                | 48(33.1%) | 23(35.5%)       |         |
| No                   | 122(64.9%) | 39(57.4%)       |         |                | 93(64.1%) | 36(58.1%)       |         |
| Unknown              | 4(2.1%)  | 4(5.9%)        |         |                | 4(2.8%)  | 4(2.8%)        |         |

Fig. 4. Kaplan-Meier survival curves for OS(A,B) and DFS(C,D) among patients with cT3/4 matched.
chemotherapy regimens selected for these patients were determined by multidisciplinary experts and complied with international department standards. For patients treated with neoadjuvant therapy, cytotoxic and targeted drugs are usually administered at the same time at the beginning of treatment to achieve a better tumor-killing effect. For patients treated with adjuvant therapy, considering the substantial cardiac side effects of combination therapy, targeted therapy is often used after anthracycline therapy. This may be one of the possible factors that contributes to the better prognosis of patients who receive neoadjuvant therapy than patients who receive adjuvant therapy. To further confirm these results, multicenter prospective studies are needed.

5. Conclusion

Systemic treatment is essential for patients with HER2-positive breast cancer. In this single-center real-world retrospective study, it was found that neoadjuvant therapy was primarily administered to patients with higher clinical stages. The regimen including anthracycline was mostly used for adjuvant chemotherapy, and the regimen without anthracycline was mainly used for patients treated with NAT. According to a retrospective real-world study, we confirmed the equivalent efficacy of adjuvant therapy and NAT in HER2-positive BC patients.

Ethics approval

This study was approved by the Ethics Committee Review Board of the Fudan University Shanghai Cancer Center (approval number: 1905202-7).

Consent for publication

Not applicable.

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| Variable | OS Univariate analysis | Multivariate analysis | DFS Univariate analysis | Multivariate analysis |
|----------|-----------------------|----------------------|------------------------|----------------------|
|          | HR  | 95% CI | P   | HR  | 95% CI | P   | HR  | 95% CI | P   | HR  | 95% CI | P   |
| Age      |     |        |     |     |        |     |     |        |     |     |        |     |
| ≤35      | 1   | Ref    | –   | –   | –     | –   | 1   | Ref    | –   | –   | –     | –   |
| 36–64    | 1.62| 0.22-11.97 | 0.636 | –   | –   | –   | 2.79| 0.38-20.23 | 0.31 | –   | –   | –   |
| ≥65      | 0   | 0      | 0.985 | –   | –   | –   | 0   | 0      | 0.98 | –   | –   | –   |
| Nodal status |     |        |     |     |        |     |     |        |     |     |        |     |
| N0       | 1   | Ref    | –   | –   | –     | –   | 1   | Ref    | –   | –   | –     | –   |
| N+       | 5.02| 1.19-21.22 | 0.028 | 4.19| 0.98-17.89 | 0.05 | 4.36| 1.56-12.20 | 0.005 | 3.92| 1.39-11.01 | 0.01 |
| ER Status|     |        |     |     |        |     |     |        |     |     |        |     |
| +        | 1   | Ref    | –   | –   | –     | –   | 1   | Ref    | –   | –   | –     | –   |
| -        | 1.52| 0.70-3.28 | 0.29 | –   | –   | –   | 1.01| 0.55-1.84 | 0.99 | –   | –   | –   |
| PR positive |     |        |     |     |        |     |     |        |     |     |        |     |
| +        | 1.03| 0.45-2.38 | 0.94 | –   | –   | –   | 0.80| 0.51-1.58 | 0.52 | –   | –   | –   |
| -        | 1.03| 0.45-2.38 | 0.94 | –   | –   | –   | 0.80| 0.51-1.58 | 0.52 | –   | –   | –   |
| Ki-67    |     |        |     |     |        |     |     |        |     |     |        |     |
| ≥20%     | 1   | Ref    | –   | –   | –     | –   | 1   | Ref    | –   | –   | –     | –   |
| <20%     | 0.58| 0.14-2.46 | 0.46 | –   | –   | –   | 1.19| 0.29-4.93 | 0.81 | –   | –   | –   |
| Timing of chemotherapy |     |        |     |     |        |     |     |        |     |     |        |     |
| Adjuvant therapy |     |        |     |     |        |     |     |        |     |     |        |     |
| 1        | Ref | –   | –   | 1   | Ref    | –   | 1   | Ref    | –   | –   | –     | –   |
| 2        | 1.76| 0.66-4.67 | 0.26 | –   | –   | –   | 1.22| 0.62-2.42 | 0.57 | –   | –   | –   |
| Response to treatment |     |        |     |     |        |     |     |        |     |     |        |     |
| pCR      | 0.39| 0.08-1.99 | 0.26 | 0.37| 0.07-1.91 | 0.23 | 0.33| 0.11-1.04 | 0.06 | 0.29| 0.09-0.92 | 0.04 |
| non-pCR  | 2.81| 1.05-7.52 | 0.04 | 2.66| 0.98-7.17 | 0.05 | 1.94| 0.98-3.88 | 0.06 | 1.76| 0.88-3.56 | 0.11 |

Author contributions

Shuyue Zheng: Conceptualization, investigation, writing–original draft and writing–review, and editing. Lun Li: Help analysis data and draft–review. Ming Chen, Benlong Yang, Jiajian Chen, Guangyu Liu: Help to collect the data. Jiong Wu: Supervise the planning and design of the study; data collection; statistical analysis and data interpretation; have full access to all the data in the study and be responsible for the integrity of the data and the accuracy of the data analysis; and manuscript review, revision, and reporting.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.03.015.

Abbreviations

NAT Neoadjuvant Therapy
pCR Pathological Complete Response
OS Overall Survival
DFS Disease-Free Survival
ER Estrogen Receptor
PR Progesterone Receptor
HER2 Human Epidermal Growth Factor Receptor
IQR Interquartile Range
PSM  Propensity Score Matching
FISH  Fluorescence in Situ Hybridization
FUSCC  Fudan University Shanghai Cancer Center
EFS  Event-Free Survival
CSCO  Chinese Society of Clinical Oncology
AJCC  American Joint Committee on Cancer
HR  Hazard Ratio

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