# Neoadjuvant chemotherapy versus surgery as the initial option for T3 breast cancer (>5 cm): real-world evidence from the Chinese Society of Clinical Oncology Breast Cancer database

**Zhenzhen Liu[1], Meng Lv[2], Jianbin Li[3], Yan Mao[2], Gang Nie[2], Jianguo Zhang[4], Cuizhi Geng[5], Feng Jin[6], Peifen Fu[7], Xiaoming Zha[8], Zhimin Fan[9], Haiqing Zhang[10], Zefei Jiang[3], Haibo Wang[2]**

[1]Department of Breast Cancer, The Fifth Medical Center of PLA General Hospital, Beijing, China; [2]Breast Disease Center, Affiliated Hospital of Qingdao University, Qingdao, China; [3]Department of General Surgery, Second Affiliated Hospital of Harbin Medical University, Harbin, China; [4]Department of Breast Surgery, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China; [5]Department of Breast Cancer Center, Hebei Medical University Fourth Affiliated Hospital and Hebei Provincial Tumor Hospital, Shijiazhuang, China; [6]Department of Breast Surgery, First Affiliated Hospital of China Medical University, Shenyang, China; [7]Breast Disease Center, First Affiliated Hospital of Medicine College of Zhejiang University, Hangzhou, China; [8]Department of Breast Cancer, Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital, Nanjing, China; [9]Department of Breast Surgery, First Hospital of Jilin University, Changchun, China; [10]Department of General Surgery, Dalian Central Hospital, Dalian, China

*Contributions:* (I) Conception and design: Z Jiang, H Wang; (II) Administrative support: Z Liu, H Wang; (III) Provision of study materials or patients: Z Liu, H Wang, J Li, J Zhang, C Geng, F Jin, P Fu, X Zha, Z Fan, H Zhang; (IV) Collection and assembly of data: Z Liu, J Li, G Nie; (V) Data analysis and interpretation: J Li, M Lv, Y Mao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Haibo Wang. Breast Disease Center, Affiliated Hospital of Qingdao University, Haier Road No. 59, Qingdao 266000, China; Email: hbwang66@126.com; Zefei Jiang. The Fifth Medical Center of PLA General Hospital, No. 8 East Street, Fengtai District, Beijing, China. Email: jiangzefei@csco.org.cn.

**Background:** The objectives of the study were to explore the real world treatment of T3 breast cancer (maximum diameter of tumor >5 cm).

**Methods:** We selected T3 breast cases diagnosed from 2011 to 2017 in the Chinese Society of Clinical Oncology (CSCO) breast cancer (BC) database. These cases were categorized into two groups: the neoadjuvant chemotherapy (NAC) group and the non-NAC group. Adjusted hazard ratios for known predictors of event-free survival (EFS) using Kaplan-Meier and Cox proportional hazards regression.

**Results:** The study included 868 patients: for their initial therapeutic strategy, 49.0% (425/868) of patients chose NAC and 51.0% (443/868) chose surgery (non-NAC group). Compared with the non-NAC group, patients in the NAC group were correlated with clinical lymph node positive, hormone receptor (HR) negative, and human epidermal receptor growth factor 2 (HER2) positive. For the non-NAC group, only 87.1% (386/443) of patients were pathologic T3 after surgery, and the overestimation of clinical examination of tumor lesion was 12.9% (57/443). In addition, there was no significant difference in EFS between the NAC group and non-NAC group (HR =0.82, 95% CI: 0.64–1.05). However, for T3 breast cancer patients with positive lymph nodes, and HR-negative and HER2-positive tumors, the NAC group had a better survival rate than the non-NAC group. Cox proportional analysis showed that lymph node negative, HER2-negative status, and neoadjuvant chemotherapy were associated with a longer survival time.

**Conclusions:** For T3 breast cancer patients with positive lymph nodes, and HR-negative and HER2-positive tumors, neoadjuvant chemotherapy should be applied first.

**Keywords:** Breast cancer; T3 stage; neoadjuvant chemotherapy (NAC); surgery; prognosis

## Introduction

The initial purpose of neoadjuvant chemotherapy (NAC) in breast cancer was to downstage locally advanced cancer or to render inoperable cancer operable. Its application was then extended to early breast cancer to enable breast-conserving surgery. Now, it has become widely accepted for use in aggressive subtypes like stage II or III and human epidermal receptor growth factor 2 (HER2)-positive or triple-negative breast cancer, particularly for large tumor lesions (1).

NAC thus provides another therapy option for T3 patients, even though there is a lack of evidence definitively proving initial NAC to be superior to initial surgery. Initial NAC can presumably provide early eradication of large tumor lesions that would lighten the tumor load and decrease the risk of metastatic spread for T3 patients. It might also offer useful information concerning the drug sensitivity of different regimens, helping to guide subsequent therapy selection. Thus, there is urgent need to produce the clinical evidence that would confirm the benefit of initial NAC in breast cancer patients.

Recently, the American Food and Drug Administration (FDA) has considered data from real-world evidence (RWE) and from randomized clinical trial (RCTs) as complementary. The FDA is now working hard to collect data from electronic health records, billing data, and other sources (2). In the last past 2 years, we have been committed to establishing the Chinese Breast Cancer Database which was founded by the Chinese Society of Clinical Oncology of Breast Cancer (CSCO BC). Using this real-world data, we previously explored the difference in trastuzumab use in resource-limited versus resource-abundant regions and its survival benefit on HER2-positive breast cancer patients in China (CSCO BC RWS 15001) (3). For the present study, we used this database to evaluate the real-world treatment of T3 patients and determined whether NAC is better than surgery as an initial option for T3 breast cancer (CSCO BC RWS 17001). We present the following article in accordance with the STROBE reporting checklist. (available at http://dx.doi.org/10.21037/tbcr-20-21).

## Methods

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 and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. This study was approved by the Institutional Review Board of the Affiliated Hospital of Qingdao University. Informed consent was obtained from all individual participants included in the study.

### *Patients and population*

In December 2015, we established the first multicenter database funded by the CSCO BC. As of November 2017, information from more than 17,000 patient cases had been added to the CSCO BC database. These data were collected from more than 11 hospitals in 9 provinces across eastern China. For the current study, eligible cases needed to meet the following criteria: early stage invasive breast cancer (EBC) diagnosed from 2011 to 2017; maximum diameter of tumor larger than 5 centimeters (T3) irrespective to clinical examination; clearly clinical or pathological axillary node staging; NAC or breast cancer surgery received as the initial therapeutic strategy.

For inclusion, patients who received NAC as their initial therapy were required to receive at least two cycles of chemotherapy, while those who underwent breast-conserving surgery or mastectomy could not have also received NAC. Patients with borderline, unknown, or missing information for treatment were excluded (CSCO BC RWS 1701).

### *Outcome measures*

The demographic and clinical characteristics of the two groups (the NAC group *vs.* non-NAC group) were summarized and compared. The primary endpoint of this study was event-free survival (EFS). We calculated EFS as the interval from randomization to the earliest occurrence of disease progression resulting in inoperability, locoregional recurrence (after NAC), distant metastasis, or death from any cause. Information from patients who were alive with no events occurring as of the analysis cutoff date were censored at the last follow-up date. The second endpoint was surgery method, with a focus on the breast-conserving rates of the two groups.

### *Statistical analysis*

In this real world study, we compared the characteristic differences between the two groups using Pearson's test. We also used Kaplan-Meier and Cox proportional
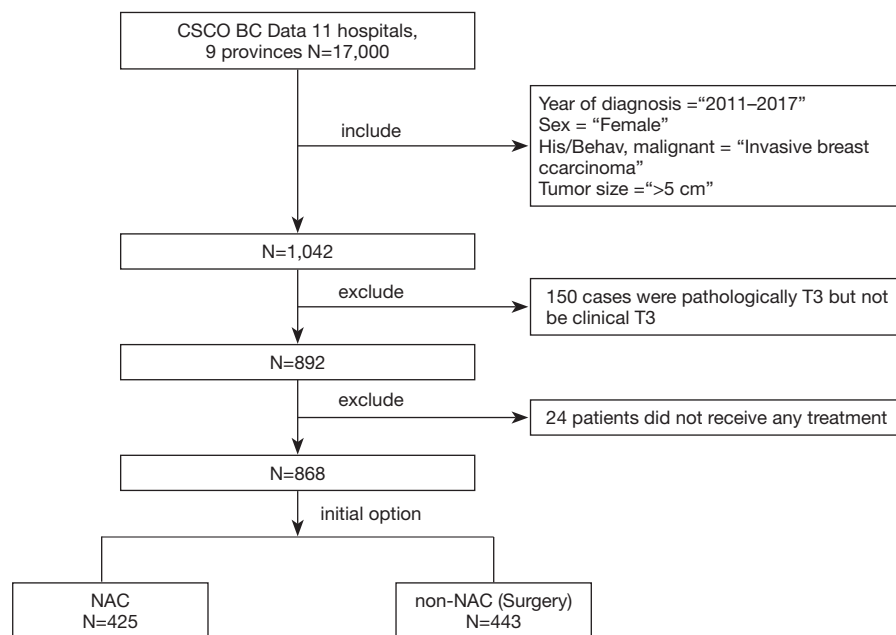
**Figure 1** Cohort selection diagram. Pathologically confirmed invasive breast cancer cases diagnosed between 2011 and 2017 were identified from the CSCO BC database and categorized into the following two groups: a NAC group and a non-NAC group. CSCO, Chinese Society of Clinical Oncology; BC, breast cancer; NAC, neoadjuvant chemotherapy.

hazards regression to estimate hazard ratio (HR) and 95% confidence interval (CI) for the relationship between different initial therapeutic strategies and EFS. P values <0.05 were considered statistically significant; all tests were two-sided. Statistical analysis was carried out using SPSS 20.0.

## Results

### Demographic characteristics

After applying the inclusion and exclusion criteria, data from 868 cases diagnosed as clinical T3 breast cancer were collected from the CSCO BC database (*Figure 1*). *Table 1* shows clinical and demographic characteristics of these patients. Only 49.0% (425/868) of patients chose NAC after diagnosis (NAC group), and the remaining patients (51.0%) chose surgery as their initial therapeutic strategy (non-NAC group). Patients in the NAC group had more clinical positive lymph nodes (82.1% *vs.* 55.1%, P<0.001), more HER2-positive tumors (54.1% *vs.* 44.0%, P<0.05) and hormone receptor (HR)-negative tumors (23.8% *vs.* 16.3%, P<0.05) compared with the non-NAC group. However, Patients in the non-NAC group had more luminal subtype tumors (43.1% *vs.* 33.4%, P<0.05) compared with the NAC

group (*Table 1*). There were no different with triple negative breast cancer in two groups (5.2% *vs.* 5.6%, P>0.05).

### Treatment

There was no difference in surgery category between the two groups. Most patients of both groups chose mastectomy and axillary lymph node dissection (ALND), and fewer than 5% of patients chose breast-conserving surgery. In addition, 168 (39.5%) patients in the NAC group and 343 (77.4%) patients in the non-NAC group underwent adjuvant chemotherapy. Overall, 70 out of 425 patients (16.5%) achieved breast pathologic complete response (pCR) (*Table 2*).

### Overestimation and underestimation of tumor lesion

The accuracy rate between iconography and histopathology was examined, and, to avoid the influence from chemotherapy, only patients in the non-NAC group were included, as they all received surgery first. For these patients, 573 were diagnosed as T3 clinically or pathologically or by both methods. However, 443 of these patients (77.3%) were diagnosed as clinical T3, while 130 patients were diagnosed as pathological T3 but not be

*Transl Breast Cancer Res* 2020;1:16 | http://dx.doi.org/10.21037/tbcr-20-21

**Table 1** Clinical characteristics of two groups

| Variable | NAC, n (%) | Surgery, n (%) | Total, n (%) | P |
|---|---|---|---|---|
| No. of patients | 425 (49.0) | 443 (51.0) | 868 (100) | |
| Age at diagnosis of the primary tumor (years old) | | | | 0.445 |
| ≤45 | 128 (30.1) | 123 (27.8) | 251 (28.9) | |
| >45 | 297 (69.9) | 320 (72.2) | 617 (71.1) | |
| Menopause | | | | 0.590 |
| Premenopause | 161 (37.9) | 160 (36.1) | 321 (37.0) | |
| Postmenopause | 264 (62.1) | 283 (63.9) | 547 (63.0) | |
| Lymph node | | | | 0.000 |
| Negative | 76 (17.8) | 199 (44.9) | 275 (31.7) | |
| Positive | 349 (82.1) | 244 (55.1) | 593 (68.3) | |
| HR status | | | | 0.006 |
| Negative | 101 (23.8) | 72 (16.3) | 173 (19.9) | |
| Positive | 319 (75.1) | 363 (81.9) | 682 (78.6) | |
| Unknown | 5 (1.2) | 8 (1.8) | 13 (1.5) | |
| Her 2 status | | | | 0.007 |
| Negative | 171 (40.2) | 213 (48.1) | 384 (44.2) | |
| Positive | 230 (54.1) | 195 (44.0) | 425 (50.0) | |
| Unknown | 24 (5.7) | 35 (7.9) | 59 (5.8) | |
| Subtype | | | | 0.000 |
| Luminal | 146 (34.4) | 191 (43.1) | 337 (38.8) | |
| Her2+ HR+ | 154 (36.2) | 146 (33.0) | 300 (34.6) | |
| Her2+ HR– | 76 (17.9) | 48 (10.8) | 124 (14.3) | |
| TNBC | 22 (5.2) | 25 (5.6) | 47 (5.4) | |
| Unknown | 27 (6.3) | 33 (7.4) | 60 (6.9) | |

**Table 2** Treatment of two groups

| Variable | NAC, n (%) | Surgery, n (%) | Total, n (%) | P |
|---|---|---|---|---|
| No. of patients | 425 (49.0) | 443 (51.0) | 868 (100.0) | |
| Surgery category | | | | 0.665 |
| Mastectomy | 376 (88.5) | 413 (93.2) | 789 (89.1) | |
| Breast conserving surgery | 14 (3.3) | 18 (4.1) | 32 (3.7) | |
| Unknown | 35 (8.2) | 12 (2.7) | 47 (5.4) | |
| Axillary lymph node surgery | | | | 0.080 |
| SLNB | 105 (24.7) | 89 (2.0) | 194 (22.3) | |
| ALND | 311 (73.2) | 351 (79.2) | 662 (76.3) | |
| Unknown | 9 (2.1) | 3 (0.7) | 12 (1.4) | |
| PCR status | | | | |
| Yes | 70 (16.5) | – | – | |
| No | 336 (79.1) | – | – | |
| Unknown | 19 (4.5) | – | – | |
| Adjuvant chemotherapy | | | | 0.000 |
| Yes | 168 (39.5) | 343 (77.4) | 512 (59.0) | |
| No | 257 (60.5) | 100 (22.6) | 357 (41.0) | |

clinical T3. The underestimation of clinical examination was as high as 22.7% (85/573). Of these 443 patients, only 87.1% (386/443) were pathologic T3 after surgery, and the overestimation of clinical examination was 12.9% (57/443).

### *Survival estimates*

The difference of survival between the two groups was analyzed, with a total of 257 events being recorded among these patients. The NAC group had a median time for EFS of 55 months, while the non-NAC group had a median time of 43 months, with no significance between the two groups (HR =0.82, 95% CI: 0.64–1.05) (*Figure 2A*).

Furthermore, clinical lymph node-negative or HR-positive or HER2-negative patients had a prior survival than the other (*Figure 2B,C,D*).

The EFS of the different subgroups was also analyzed (*Figure 3*). For the positive lymph node group patients, the NAC group had a better survival than the non-NAC group (*Figure 3B*). However, in negative lymph node patients, the difference in EFS was not significant between the NAC and non-NAC group (*Figure 3A*). In addition, in the HR-negative and HER2-positive group, the EFS curve showed an advantage in the NAC group over the non-NAC group (*Figure 3C* and *3F*). However, in negative lymph node patients, the difference in EFS was not significant between the NAC and non-NAC group (*Figure 3D* and *3E*).

Cox proportional models were used to assess the clinicopathological factors related to prognosis (*Table 3*). Lymph node metastasis, HER2 status and neoadjuvant chemotherapy were found to be independent poor prognostic factors of survival in the T3 breast cancer patients. Specifically, lymph node negative, HER2-negative status, and neoadjuvant chemotherapy were associated with a longer survival time.
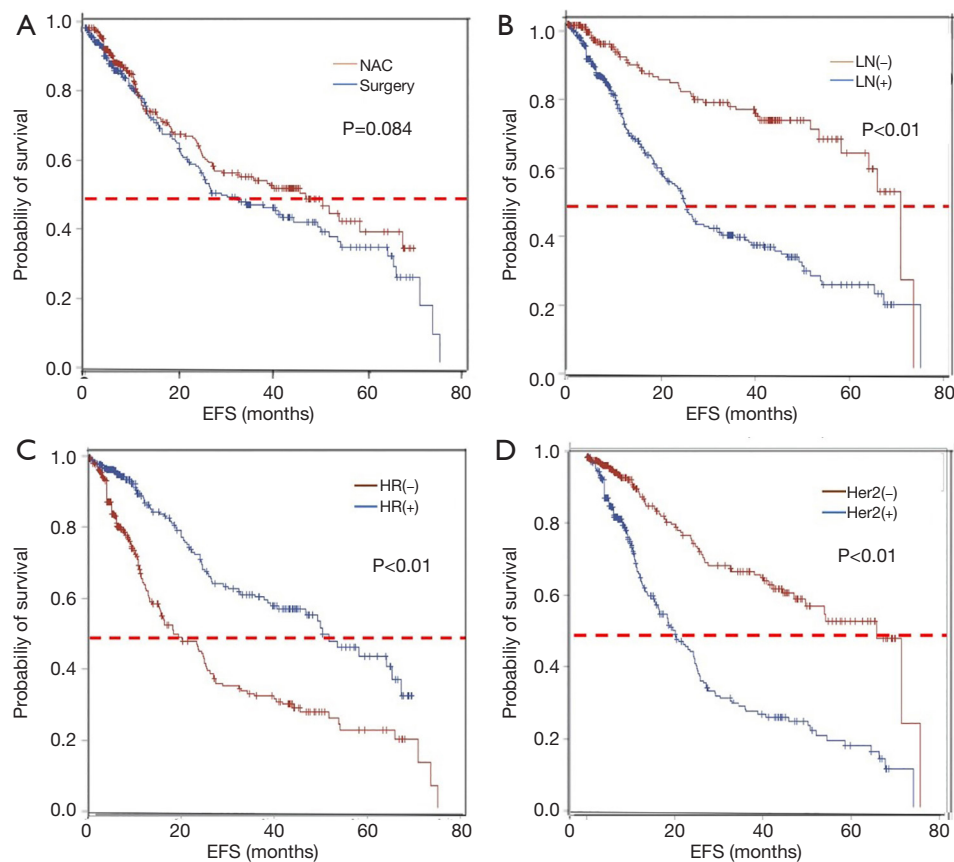
**Figure 2** Survival for T3 patients in the real world. (A) EFS in the NAC and the non-NAC group. (B) EFS in the LN(–) and LN(+) group. (C) EFS in the HR(–) and HR(+) group. (D) EFS in the HER2(–) and HER2(+) group. CI, confidence interval; EFS, event-free survival; LN(–), lymph node negative; LN(+), lymph node positive.

In other words, T3 breast cancer patients with positive lymph nodes and HER2-positive tumors should choose neoadjuvant chemotherapy. Meanwhile, T3 breast cancer patients with negative lymph nodes and HER2-negative tumors should choose either neoadjuvant chemotherapy or surgery as the optimal initial therapy.

## Discussion

Several studies have examined the relationship between large operable or locally T3 breast cancer and survival (4). However, few investigations have compared the survival differences between NAC and non-NAC T3 patients. The present study used RWE and found that T3 patients tended to elect surgery over neoadjuvant chemotherapy as their initial therapy, and, even for those patients who chose neoadjuvant chemotherapy, the major operation was modified radical mastectomy. The inconsistency rate

between imaging examination and histopathologic analysis affected the subsequent therapies. Moreover, patients with aggressive subtypes (lymph node positive, HER2 positive, HR negative) showed inferior outcome in disease-free survival (DFS) compared with their more benign counterparts. Improvements in patients who received neoadjuvant chemotherapy was evidenced by the more aggressive subtypes present in the NAC group.

Many researches have tried to explore whether imaging modalities such as magnetic resonance imaging, sonography, and mammography are as accurate at predicting breast tumor size as histopathologic analysis of resected tumors (5). However, we paid more attention to the impact of medical resources on breast cancer. Although the number of primary health-care professionals has recently increased in China, the regional distribution of doctors and medical equipment is still uneven (6). For example, only a small portion of patients received the full battery of imaging
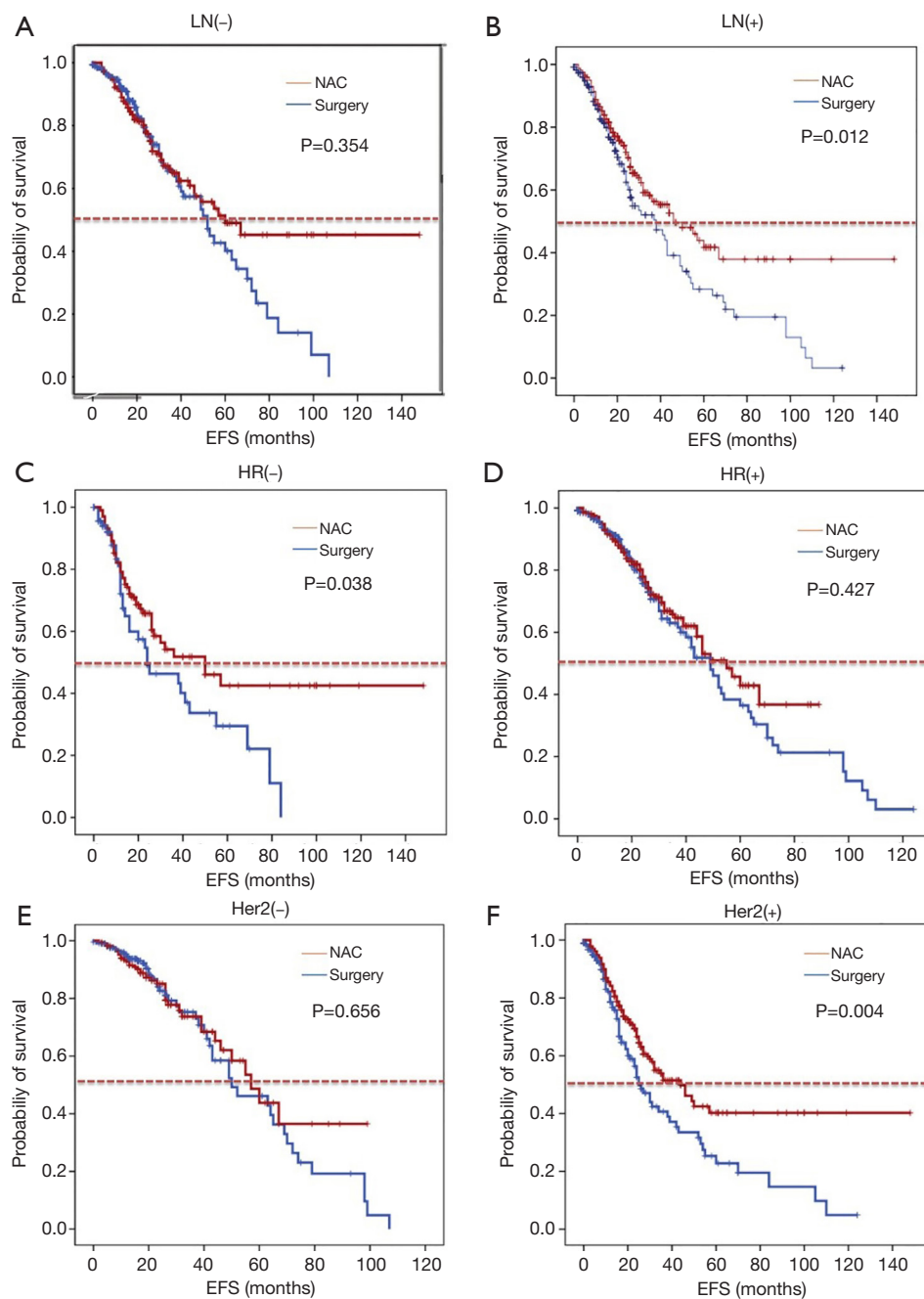
**Figure 3** Survival for T3 patients of different subgroups in the real world. (A,B) EFS of the NAC and non-NAC group in T3 patients with lymph nodes negative [LN(–)] and lymph nodes positive [LN(+)]. (C,D) EFS of the NAC and non-NAC group in T3 patients with HR-negative (HR–) and HR-positive (HR+) tumors. (E,F) EFS of the NAC and non-NAC group in T3 patients with HER2-negative (HER2–) and HER-positive (HER2+) tumors.

examinations for evaluating the dimension of tumor lesions. Most patients underwent biopsy or surgery after a routine ultrasound examination or even a simple physical examination. It is clear that different imaging modalities each have their respective characteristics to be used to their respective strengths, as recommended by the Chinese guidelines (7). The irrational use of imaging contributes to a high proportion of overestimation and underestimation.

**Table 3** Multivariate analysis of EFS in T3 breast cancer cases

| Factor | HR | P | 95% CI |
|---|---|---|---|
| Lymph node | | 0.001 | 0.417–0.791 |
| Negative | 0.575 | | |
| Positive | Reference | | |
| HR | | 0.364 | 0.857–1.525 |
| Negative | 1.143 | | |
| Positive | Reference | | |
| Her 2 status | | 0.000 | 0.420–0.729 |
| Negative | 0.553 | | |
| Positive | Reference | | |
| Neoadjuvant chemotherapy | | 0.002 | 1.168–1.969 |
| No | 1.516 | | |
| Yes | Reference | | |

At odds with the relevant literature, our study found that fewer than 5% of patients chose breast-conserving surgery (8). For those in non-NAC group, the low proportion of breast-conserving surgery was expected due to high burden of tumor lesions. Nevertheless, further discussion is required to understand how NAC leads to the downstaging of the cancer. This downstaging was initially implemented to convert inoperable patients to operable ones and later to increase rates of breast conservation in patients initially considered to be mastectomy-only candidates (9). However, we did not find these kinds of changes in this study. In some cases, this proportion may be appropriate, as patients with fewer economic resources must restrict expenditure in order to continue the expensive and prolonged therapies characteristic of T3 breast cancer treatment (3). Although it has been proven that breast-conserving surgery plus radiotherapy is as effective as mastectomy or sometimes better (10), the additional high price of radiotherapy, aesthetic considerations, and the complexity of breast-conserving technology in China all contribute to the low rate election. Moreover, no rigorous randomized clinical trials (RCTs) have yet been conducted that prove the survival benefit of breast-conserving surgery.

Although the latest guideline of the American Society of Clinical Oncology indicated no sentinel lymph node biopsy (SLNB) should be performed in large or locally advanced invasive breast cancers (11), we found that more than 10% of patients underwent SLNB, with some being clinical lymph node-positive patients. Some trials have explored the feasibility of SLNB after NAC with T0–4, N1–2, and M0 patients, and have found an acceptable false negative rate (9.8%) when combining normal axillary ultrasound with more than two SLNs removed or some other methods (12,13), although this practice is not widely accepted by experts in China. Under such circumstances, radical lymph node dissection is deemed necessary when lymph nodes are clinically positive after NAC. However, when lymph nodes are clinically negative after NAC, although SLNB appears a reasonable compromise between axillary lymph node dissection and no surgery at all, we still believe more clinical trials are needed as there is little evidence for the survival of an SLN-alone method (14).

Neoadjuvant chemotherapy, compared to conventional adjuvant therapy, does not seem to improve the overall survival of patients with breast cancer. Indeed, several RCTs have demonstrated similar outcomes, in terms of DFS and overall survival, between NAC and adjuvant chemotherapy in patients with breast cancer (15). A recent meta-analysis (16) found NAC to be associated with a higher frequency of local recurrence than that from the same chemotherapy started after surgery due to the increased breast-conserving surgery rates. Reassuringly, the increase in local recurrence was not associated with any significant increase in distant recurrence or breast cancer mortality, which indirectly supports a low rate of breast-conserving surgery in the real world. As the RCTs have provided scientific evidence for the safety and efficacy of NAC for T3 breast cancer, we used RWE to investigate the survival benefit of NAC to T3 patients (2). In our study, there was a survival benefit gained from NAC, and the results were comparable to those found in the major randomized controlled trials (17). However, patients receiving NAC were more likely to be lymph node positive with aggressive subtypes (HER2 positive HE-negative) that are the major recurrence risks for patients (18).

From this perspective, NAC does moderately reduce distant recurrence compared with to same chemotherapy given postoperatively. However, across all T3 breast cancer patients, there was no difference in EFS between the NAC group and non-NAC group. We found that NAC could also improve the survival in the T3 breast cancer patients who were lymph node-positive, and had HER2-positive or HR-negative tumors. In multivariate analysis, lymph node metastasis, HER2 status, and neoadjuvant chemotherapy were found to be an independent poor prognostic factors of survival in the T3 breast cancer patients. As the pathological and molecular features of the primary tumor are gaining

importance in the decision-making process, once we find T3 breast cancer patients who are lymph node positive, HER2 positive or HR negative, we can recommend initial neoadjuvant chemotherapy rather than surgery.

There were several limitations in this study. First, we selected data when the CSCO BC database had 17,000 patient cases. However, this database has expanded to include more than 34,000 (as of January 1, 2018). Furthermore, the allure of analyzing existing data may lead to flawed conclusions, and the survival benefit might appear improved if the data pool were to be enlarged. Second, the variable regimens and courses of neoadjuvant or adjuvant therapy were not taken into consideration, which might have obscured the association between NAC and survival if different regimens meaningfully affected long-term outcomes. Third, data on pathologic complete remission was incomplete and is needed for further exploration, while the number of patients in this group was too small to draw any definitive conclusions.

The importance of NAC should be taken seriously. Our next study will involve a randomized clinical trial that compares NAC with adjuvant chemotherapy. In real world study, we will also explore the survival benefit in different molecular subtypes. Ultimately, Neither RCTs nor RWE should be overlooked, and we will combine these two methods to explore the optimal treatment of breast cancer patients.

## Conclusions

For T3 breast cancer patients with positive lymph nodes, and HR-negative and HER2-positive tumors, neoadjuvant chemotherapy should be the initial treatment. Meanwhile, T3 breast cancer patients with negative lymph nodes and HER2-negative tumors should choose neoadjuvant chemotherapy or surgery as the optimal initial therapy.

## Acknowledgments

## Footnote

*Reporting Checklist:* The authors have completed the STROBE Checklist (available at http://dx.doi.org/10.21037/tbcr-20-21

*Data Sharing Statement:* Available at http://dx.doi.org/10.21037/tbcr-20-21

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tbcr-20-21). ZJ serves as an unpaid Editor-in-Chief of *Translational Breast Cancer Research*. JL serves as an unpaid Managing Editor of *Translational Breast Cancer Research*. CG, FJ, ZF, HW serve as the unpaid editorial board members of *Translational Breast Cancer Research* from Mar 2020 to Feb 2022. The other 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 and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. This study was approved by the Institutional Review Board of the Affiliated Hospital of Qingdao University. Informed consent was obtained from all individual participants included in the study.

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