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Original Article

Effects of neoadjuvant chemotherapy combined with breast-conserving surgery on the breast cancer condition and immune and inflammatory indexes of patients with breast cancer

Xiaoxu Li[1], Deba Song[1], Wujie Cao[1], Xiaojian Zhang[1], Mao Li[2]

[1]Thyroid and Breast Surgery, First People's Hospital of Shangqiu, Shangqiu 476100, Henan, China; [2]Thyroid Breast Surgery, Zhuji People's Hospital, Zhuji 311800, Zhejiang, China

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Abstract: Objective: To determine the effects of neoadjuvant chemotherapy combined with breast-conserving surgery (BCS) on the breast cancer (BC) condition and immune and inflammatory indexes of patients with BC. Methods: A total of 114 patients with BC admitted to the First People's Hospital of Shangqiu from March 2018 to March 2020 were retrospectively enrolled in this study. Fifty-four patients who underwent radical mastectomy alone were enrolled into the control group (Con group), and the other 60 patients who received neoadjuvant chemotherapy combined with BCS were assigned to the observation group (Obs group). The two groups were compared in terms of surgical indexes, therapeutic effects, immune indexes including immunoglobulin IgG, IgA, IgM, and inflammatory indexes. Cox regression analysis was conducted to analyze the independent prognostic factors of overall survival (OS) and disease-free survival (DFS). Results: After therapy, the Obs group yielded a significantly higher effective therapy rate than the Con group and experienced notably shorter hospital stay and operation time than the Con group. In addition, the Obs group showed significantly higher levels of IgG, IgA and IgM and significantly lower levels of TNF-α and IL-6 than the Con group after therapy. According to Cox regression analysis, clinical stage and HER2 were independent prognostic factors impacting patients' OS and DFS. Conclusion: Neoadjuvant chemotherapy combined with BCS can substantially alleviate the disease condition, effectively improve the immune ability, and lower the inflammation level of BC patients, without impacting their 2-year OS and DFS.

Keywords: Neoadjuvant chemotherapy, breast-conserving surgery, breast cancer, immune function, inflammation level

Introduction

Breast cancer (BC) is a malignant tumor with high incidence, which predominately attacks females and its incidence is on the rise [1]. According to statistics in 2012, among all cancers, BC ranked the first in the incidence and the second in mortality [2]. In 2020, the global cancer statistics revealed that there were over 2.2 million new cases of BC every year, and over 680,000 deaths from the cancer every year [3]. The onset age of BC tends to be younger, and patients have a higher requirement for the cosmetic effects over the past few years [4].

With the popularization of tumor screening and the improvement of diagnosis, examination and therapy of BC, the surgical methods for BC have progressed considerably [5]. Breast conserving surgery (BCS) has become one crucial surgical choice for BC [6]. Many studies have pointed out that BCS achieved a better cosmetic result in BC patients [7]. Despite the continuous improvement in the tumor screening, many patients still suffer advanced tumors that cannot be treated surgically because they have missed the optimal surgical timing, and those patients can only be given radiotherapy and chemotherapy for symptom alleviation [8]. Neoadjuvant therapy is a systemic chemotherapy for patients before surgery, which can reduce the tumor size and clinical stage and achieve the purpose of adjuvant therapy while meeting patients' requirements [9]. According to early trials of neoadjuvant chemotherapy, the local

recurrence rate and survival rate of patients given neoadjuvant chemotherapy combined with BCS were the same as those of patients given BCS and postoperative adjuvant therapy, so neoadjuvant chemotherapy combined with BCS is a safe choice for patients [10]. Prior research has revealed that for patients with BC, operation will change the immune and inflammatory indexes because of the surgical trauma, and thus impact the postoperative recovery, which may be correlated with the prognosis of patients [11, 12]. However, whether the changes of inflammatory and immune indexes have the same effect on BC patients given neoadjuvant chemotherapy combined with BCS is rarely studied.

With the maturity of neoadjuvant chemotherapy, the complete remission rate and the effective rate of chemotherapy have been improved. Scholars at home and abroad have devoted themselves to the study of breast-conserving surgery on the basis that neoadjuvant chemotherapy reduces the primary tumor and realizes satisfactory breast shape [13]. However, in China, the proportion of patients receiving BCS after neoadjuvant chemotherapy for BC is insufficient, and the therapy scheme of BCS after neoadjuvant chemotherapy is not mature. Its feasibility and safety are still controversial, and further research is required.

Accordingly, this study mainly observed the effects of neoadjuvant chemotherapy combined with BCS on the BC condition and immune and inflammatory indexes of patients with BC to provide guidance for the selection of clinical therapeutic regimen for BC and prognosis observation indexes.

Methods and data

Clinical data

Totally, 114 patients with BC admitted to the First People's Hospital of Shangqiu between March 2018 and March 2020 were retrospectively enrolled in this study. Fifty-four patients who underwent BCS alone were taken as the control group (Con group), and the other 60 patients who received neoadjuvant chemotherapy combined with BCS were assigned to the observation group (Obs group). This study was carried out with approval of the Medical Ethics Committee of the First People's Hospital of Shangqiu (2018(A)012).

Inclusion criteria

Patients meeting the diagnostic guidelines for BC released by the American Joint Committee on Cancer (AJCC) (8th edition, 2017) [14]; patients with single lesion (dimeter of 2-5 cm, without distant metastasis) according to pathological examination and imaging examination; patients without contraindication of BCS; patients who were tolerant to the chemotherapy; and those with complete clinical data.

Exclusion criteria

Patients with heart, liver or kidney dysfunction; patients with mental disorders, psychological disorders or loss of consciousness; patients with other types of malignant tumors; patients with estimated survival time ≤ 3 months; patients with acute infection or endocrine system diseases; patients in pregnancy or lactation; or those with triple negative BC.

Therapeutic regimen

Therapeutic regimen for the Con group: The Con group was given BCS. Surgical methods included quadrant tumor resection, axillary lymph node dissection, or extensive resection of local tumor. If the tumor was located in the upper middle abdomen of the breast, the surgical incision should be parallel to the areola, and an arc incision should be used. If the tumor was located in the lower middle quadrant of the breast, a radial incision should be made. The distance from the tumor to the margin should be 1.5 cm. Routine frozen pathological examination was performed on tissue cut from the upper and lower, inside and outside of the breast to ensure that the cutting edge was negative.

Therapeutic regimen for the Obs group: The Obs group was routinely treated with Taxol (Beijing SL Pharmaceutical Co., Ltd., State Food and Drug Administration (SFDA) approval number: H20066640) plus Epirubicin (Zhejiang Hisun Pharmaceutical Co., Ltd., SFDA approval number: H20041211) (TE; 60 mg/m^2 epirubicin, 150 mg/m^2 paclitaxel, 21 days as a cycle) or Cyclophosphamide (Jilin Jiatai Pharmaceutical Co., Ltd., SFDA approval number: H22024183) plus Epirubicin + Fluorouracil (Shanghai Xudong Haipu Pharmaceutical Co., Ltd., SFDA approval number: H31020593) (CEF; 60 mg/m^2 epirubicin, 600 mg/m^2 cyclo-

phosphamide, 600 mg/m^2 5 murf, 21 days as a cycle). Before chemotherapy, the patients received pre-therapy with dexamethasone (Chongqing Lummy Pharmaceutical Co., Ltd., SFDA approval number: H20052448), and during chemotherapy, acid suppression, gastric protection and antiemetic therapy were supplemented to reduce the occurrence of adverse drug reactions. Patients with low hemogram were supported by colony stimulating factor. One to two weeks after chemotherapy, the patients were examined by imaging, and the risk of operation was evaluated. BCS was carried out under the premise that the conditions of patients were suitable for BCS. The treatment regimen was the same as that in the control group.

Patients were given a total of 6 chemotherapy cycles.

Detection of immune and inflammatory indexes

The peripheral blood was sampled before and after therapy (after chemotherapy), and the serum was acquired centrifugally. Immunoturbidimetry was used to detect the levels of immunoglobulin G (IgG, ml092681), immunoglobulin A (IgA, ml092680) and immunoglobulin M (IgM, ml092683) in the serum. ELISA was adopted to quantify serum levels of tumor necrosis factor-α (TNF-α, ml064303) and interleukin-6 (IL-6, ml058097). All the above kits were offered by Shanghai mlbio ELISA.

Immune index detection

The whole venous blood (2 mL) was collected, placed in the tube containing EDTA anticoagulant and mixed upside down. After numbering, the changes of cluster of differentiation (CD) 8+: CD8, CD4+ and CD3+ were measured by ACEA NovoCyte flow cytometer (Eisen Biosciences).

Follow-up

The 2-year survival of patients was counted by inquiring the outpatient reexamination records and telephone follow-up records.

Outcome measures

Primary observation indexes: The two groups were compared in perioperative indexes (operation time and intraoperative blood loss). The clinical curative effect of the two groups was evaluated after therapy. Complete remission (CR): After the therapy, the tumor lesion disappeared completely and the signs returned to normal; Partial remission (PR): After the therapy, the tumor lesion decreased by over 75%, and the clinical symptoms were obviously alleviated, with basically normal signs; Stable disease (SD): After the therapy, the tumor lesion decreased by over 50% and the symptoms were slightly relieved; Disease progression (PD): After the therapy, the tumor lesions did not shrink or even increased or new lesions appeared, and the symptoms worsened. Total effective rate = CR rate + PR rate. In addition, the levels of serum IgG, IgA, IgM, TNF-α and IL-6, CD4+, CD8+, CD4+/CD8+ were compared between the two groups before and after treatment.

Secondary outcome measures: The clinical data of the two groups were compared. The length of hospital stay of the two groups was observed, and the quality of life (QOL) after therapy was evaluated using the Functional Assessment of Cancer Therapy-Breast (FACT-B) scale [15]. The scale covers functional status, emotional state, social and family condition, and physical condition, with a total of 36 items. A higher score suggests better QOL. Cox regression analysis was performed to analyze the prognostic factors of OS.

Statistical analysis

This study adopted SPSS20.0 software for statistical analysis of collected data, and GraphPad Prism 8 software for visualization of the data. Counting data (5%) were analyzed via the Chi-square test, and presented by X^2. The K-M survival curve was used to draw the overall survival (OS) of patients, and the Log-rank test was used for analysis. Cox regression analysis was performed for analyzing the independent prognostic factors of patients' affecting OS and disease-free survival (DFS). $P < 0.05$ implied a significant difference.

Results

Comparison of clinical data between the two groups

The two groups were not notably different in age, body mass index (BMI), age of menarche,

Table 1. Comparison of baseline data

Group	The control group (n=54)	The observation group (n=60)	x^2 value	*P* value
Age			0.766	0.381
≥ 40 years old	28	36		
< 40 years old	26	24		
BMI			0.039	0.843
≥ 25 (kg/cm^2)	26	30		
< 25 (kg/cm^2)	28	30		
Age of menarche			0.351	0.553
≥ 14 years old	24	30		
< 14 years old	30	30		
Menopause			0.012	0.909
Yes	14	15		
No	40	45		
Clinical stage			4.219	0.121
IIa	12	8		
IIb	34	48		
IIIa	8	4		
Tumor size			1.415	0.234
≥ 3 cm	34	44		
< 3 cm	20	16		
Axillary lymph node positive			1.660	0.197
Yes	45	44		
No	9	16		
ER			0.247	0.618
Positive	29	35		
Negative	25	25		
PR			3.258	0.071
Positive	27	40		
Negative	27	20		
HER-2			0.542	0.461
Positive	18	24		
Negative	36	36		

Note: IBM: Body Mass Index; ER: Estrogen Receptor; PR: Progesterone Receptor; HER2: Human Epidermal Growth Factor Receptor-2.

menopause, clinical stage, tumor size, axillary lymph node positive, estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2), indicating the comparability of the two groups (all P > 0.05, **Table 1**).

Comparison of perioperative indexes between the two groups

The Obs group experienced a notably shorter operation time, less intraoperative blood loss, and a shorter hospital stay than the Con group (all P < 0.001, **Figure 1**).

Comparison of clinical efficacy between the two groups

According to evaluation results of clinical efficacy in the two groups after therapy, the total effective rate of the Obs group was notably higher than that of the Con group (**Table 2**, P < 0.05).

Comparison of changes in inflammation and immune indexes between the two groups before and after the therapy

The changes of serum IgG, IgA, IgM, TNF-α, IL-6, CD4+, CD8+, and CD4+/CD8+ were com-

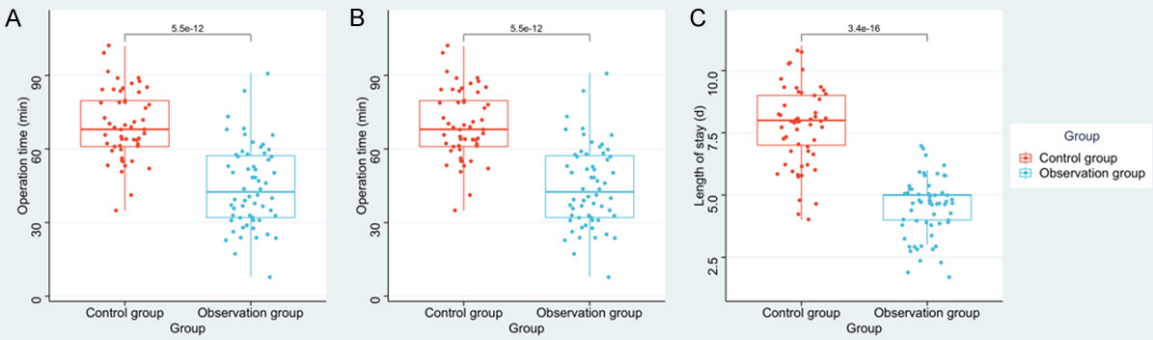

Figure 1. Comparison of operation time, intraoperative blood loss and length of hospital stay between the two groups. A. Comparison of operation time between the two groups. B. Comparison of intraoperative blood loss between the two groups. C. Comparison of length of hospital stay between the two groups.

Table 2. Comparison of efficacy

Group	CR	PR	SD	PD	Total effective rate
Control group (n=54)	15	23	7	9	70.37 (38)
The Observation group (n=60)	25	28	4	3	88.33 (53)
x^2 value					5.694
P-value					0.017

Note: CR: Complete Remission; PR: Partial Remission; SD: Stable Disease; PD: Disease Progression.

pared between the two groups before and after therapy. No notable difference was found in the above-mentioned indexes between the two groups before therapy (all P > 0.05). After the therapy, TNF-α, IL-6 and CD8+ in both groups decreased significantly, while serum IgG, IgA, IgM, CD4+ and CD4+/CD8+ in both groups increased significantly (all P < 0.05). The Obs group showed notably lower TNF-α, IL-6 and CD8+ levels than the Con group (all P < 0.05) but higher levels of serum IgG, IgA, IgM, CD4+ and CD4+/CD8+ than the Con group (P < 0.05, **Figures 2**, **3**).

Comparison of QoL between the two groups before and after the therapy

The patients' QOL was evaluated before and after therapy. Before the therapy, no notable difference was found in physical condition, social and family condition, emotional state and functional status between the Con group and the Obs group (all P > 0.05), while after therapy, the scores of both groups increased notably (all P < 0.05), with significantly better scores in the four dimensions in the Obs group than those in the Con group (all P < 0.05, **Figure 4**).

Analysis of prognostic factors

The 2-year survival of patients was counted. According to the results, nine patients died, showing a mortality rate of 9.21%. Additionally, 15 patients progressed during this period, with a recurrence rate of 13.15%. Then we collected data and analyzed the influencing factors of DFS and OS by Cox regression. According to univariate analysis, clinical stage and HER2 were the factors influencing the patients' OS (**Figure 5A**, P < 0.05), and clinical stage, PR and HER2 were the factors influencing their DFS (**Figure 5B**, P < 0.05). According to multivariate analysis, clinical stage and HER2 were independent prognostic factors impacting patients' OS and DFS (**Figure 6A**, **6B**, P < 0.05). In addition, survival curves revealed that patients at stage II showed higher OS and DFS than those at stage III (**Figure 7A**, **7C**, P < 0.05), and HER2-negative patients showed higher OS and DFS than HER2-positive patients (**Figure 7B**, **7D**, both P < 0.05).

Discussion

Globally, BC is still the malignant tumor with the highest incidence among women, accounting

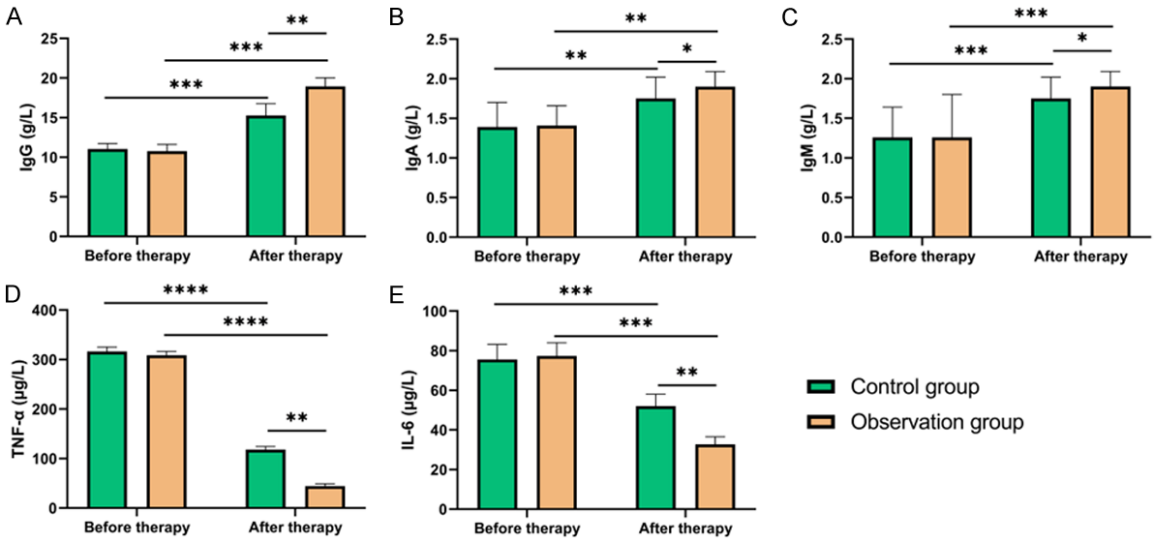

Figure 2. Changes of indexes before and after therapy. A. Changes of serum IgG before and after therapy. B. Changes of serum IgA before and after therapy. C. Changes of serum IgM before and after therapy. D. Changes of serum TNF-α before and after therapy. E. Changes of serum IL-6 before and after therapy. Note: *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001. IgG: Immunoglobulin G; IgA: Immunoglobulin A; IgM: Immunoglobulin M; TNF-α: Tumor Necrosis Factor α; IL-6: Interleukin-6.

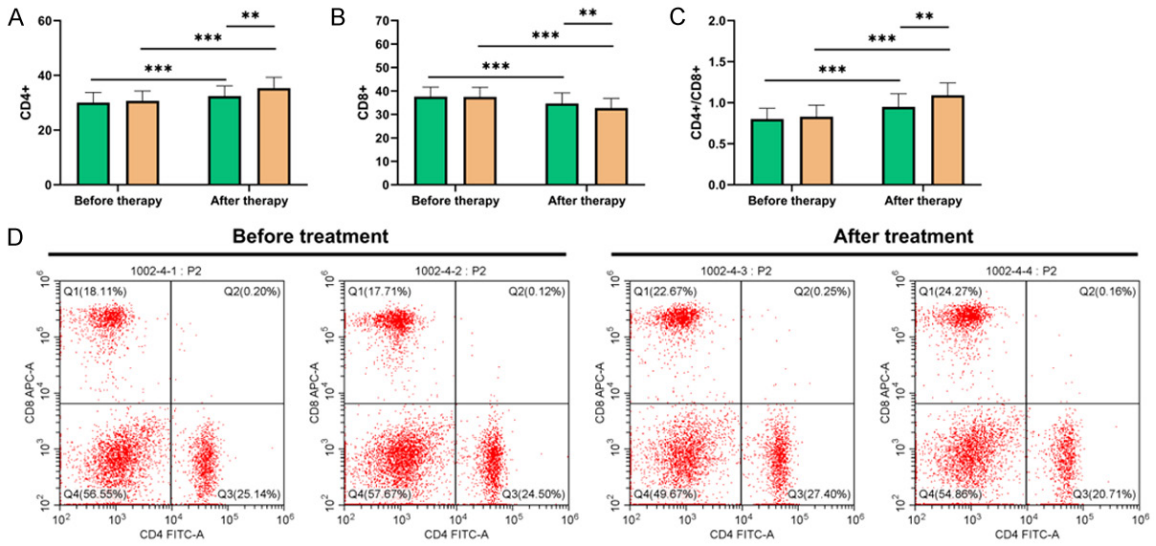

Figure 3. Changes of CD cell percentage before and after treatment. A. Changes of serum CD4+ before and after therapy. B. Changes of serum CD8+ before and after therapy. C. Changes of serum CD4+/CD8+ before and after therapy. D. Original picture of Flow cytometry. Note: CD4+: Cluster of Differentiation 4; CD8+: Cluster of Differentiation 8. **P < 0.01, ***P < 0.001, ****P < 0.0001.

for 30% of all new cases. BC is also one of the cancers with the highest 5-year survival rate [16]. In the past 30 years, the mortality of female BC has decreased by 40%, which is strongly linked to the advent of new drugs, new technologies and early screening [17].

Prior research has revealed that neoadjuvant chemotherapy can substantially increase the proportion of BCS for advanced BC, but there is still controversy about whether the local recurrence rate of patients after BCS is higher than that of patients undergoing radical mastectomy

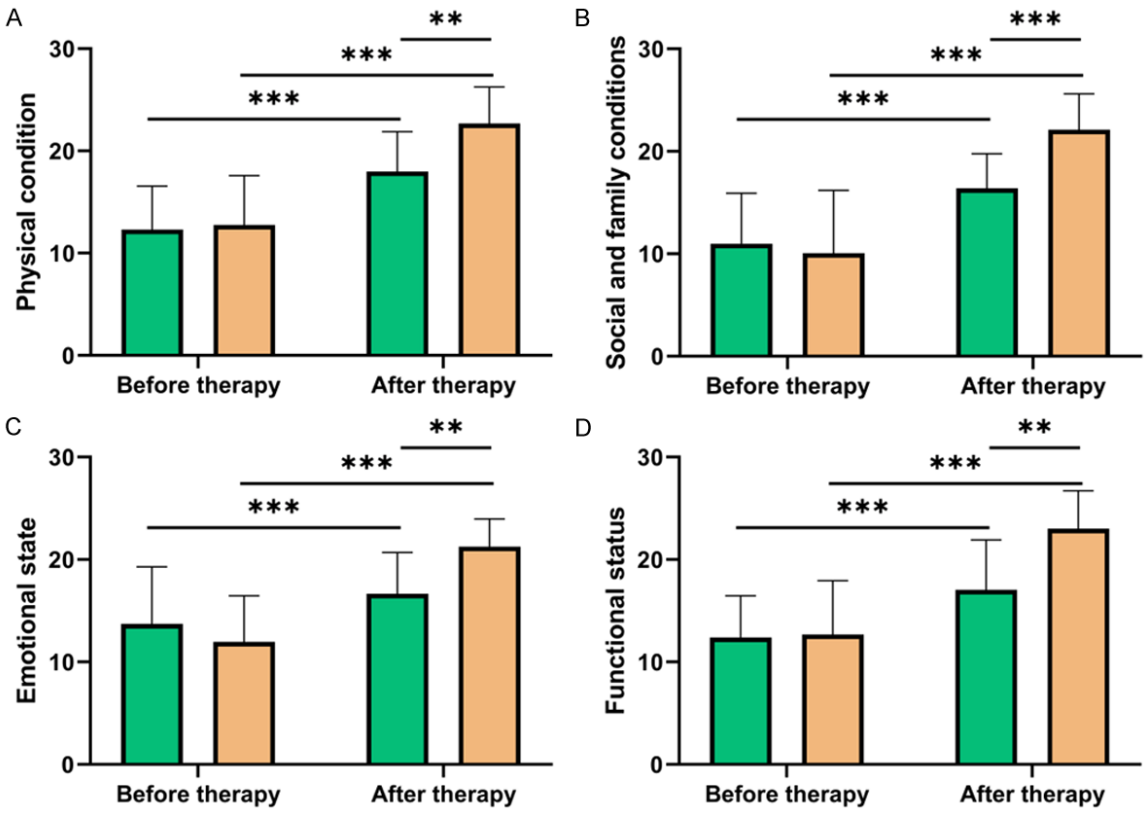

Figure 4. Scores of quality-of-life scale for BC before and after therapy. A. Physical condition score of patients before and after therapy. B. Social and family condition score of patients before and after therapy. C. Emotional state score of patients before and after therapy. D. Functional status score of patients before and after therapy. Note: *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001; BC: Breast Cancer.

[18]. This study analyzed the efficacy of neoadjuvant chemotherapy combined with BCS for the treatment of BC. The results showed that the Obs group experienced less intraoperative blood loss and shorter operation than the Con group, and also experienced notably shorter hospital stay than the Con group. This is mainly because that the early neoadjuvant chemotherapy reduces the tumor volume, which is beneficial to the operation. Moreover, in the present study, the Obs group showed a significantly higher total effective rate than the Con group, which was due to the fact that the tumor development of patients was controlled by neoadjuvant chemotherapy before and after the operation, and the curative effect on patients was thus improved.

Currently, surgery is still the first choice for BC [19]. However, BC surgery greatly impacts patients' immune function and patients usually have low immune functions after it, which results in an increased risk of infection and tumor recurrence. Accordingly, postoperative recovery and improvement of prognosis are of great significance [20]. In this study, we found that the levels of serum IgG, IgA and IgM in the observation group after treatment were higher than those in the control group, while TNF-α and IL-6 levels in the Obs group were lower than those in the control group. It shows that breast conserving surgery has little impact on immune function and inflammatory reaction in the clinical treatment of patients with breast cancer and adenocarcinoma. The main reason is as follows: for patients undergoing modified radical mastectomy, a transverse shuttle-shaped incision or longitudinal shuttle-shaped incision should be selected according to the surgical incision and the location of the tumor; the length of the incision is about 15-20 cm, and the wound is large, so the patients have severe stress reaction and low immune function after surgery, which makes them prone to infection or various complications, resulting in large fluctuations of immune function and inflammatory

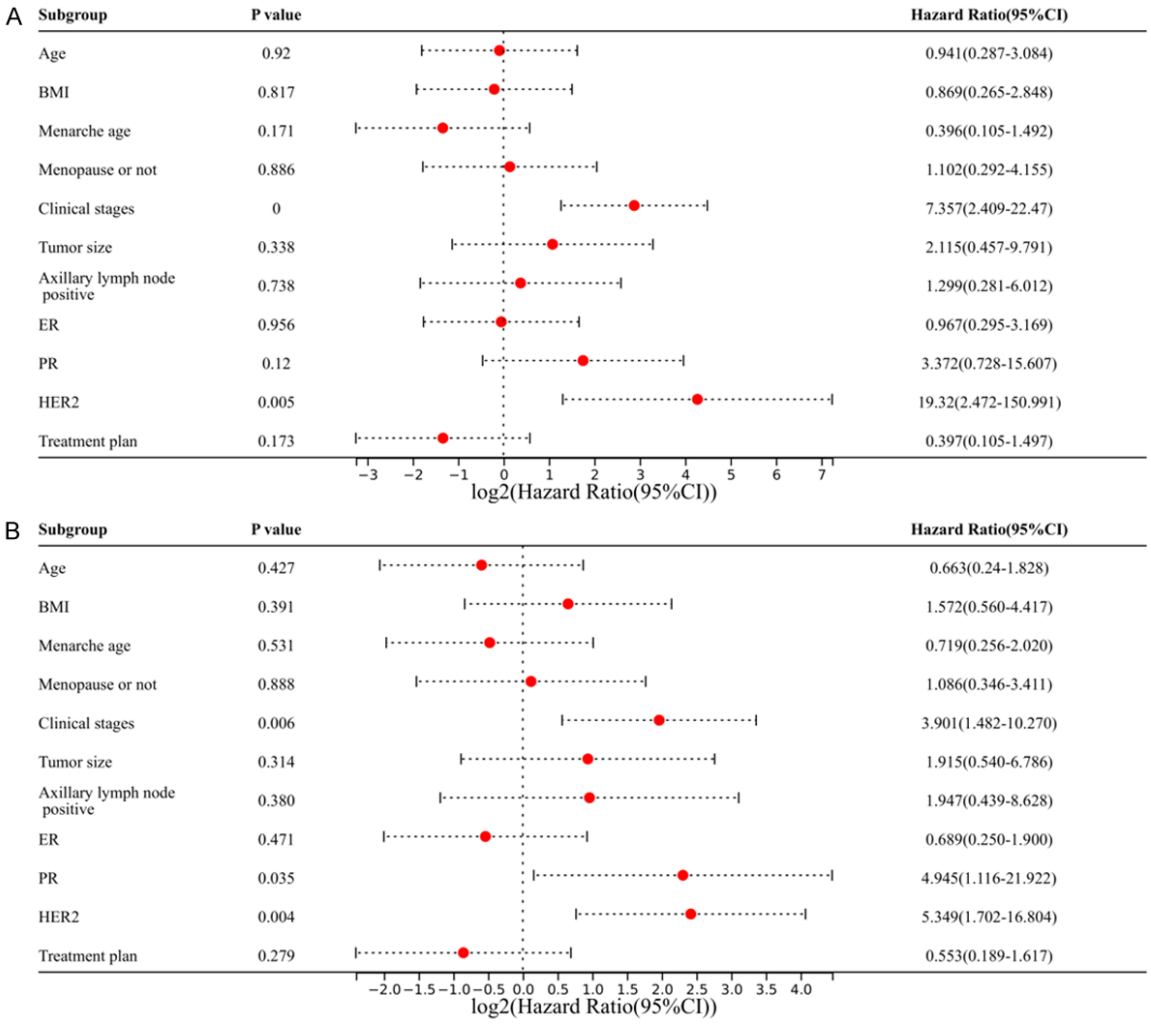

Figure 5. Univariate Cox regression analysis on prognostic factors influencing patients' OS and DFS. A. Univariate Cox regression analysis of prognostic factors influencing patients' OS. B. Univariate Cox regression analysis of prognostic factors influencing patients' DFS. Note: OS: Overall Survival; DFS: Disease-Free Survival; ER: Estrogen Receptor; PR: Progesterone Receptor; HER2: Human Epidermal Growth Factor Receiver-2; BMI: Body Mass Index.

reaction indexes [21]. In our study, the CD4/CD8 ratio of patients increased significantly after the treatment, which indicates that the immune function of patients was improved after the treatment. The reason is that surgical treatment is traumatic, which leads to the decrease of patients' immunity; however, neoadjuvant chemotherapy can kill actively proliferating rectal tumor cells, promote the removal of tumor tissue in later surgery, thereby reducing the tumor load and improving immune function [22]. Moreover, this study also evaluated the QoL of patients before and after the therapy. FACT-B is a famous QoL scale for BC developed in the United States. It is suitable for BC patients at all clinical stages and can be used for both inpatients and outpatients [23]. In the present study, the scores of patients' physical condition, social and family condition, emotional state and functional status all increased significantly after therapy, among which the scores in the Obs group were higher than those in the Con group after therapy, indicating that neoadjuvant chemotherapy combined with BCS could improve the QoL of patients. Research by Shan et al. [24] has revealed that BCS combined with neoadjuvant chemotherapy can improve the QoL of BC patients, which is consistent with our result. The specific reason is that BCS does little harm to breast tissues, and it can also avoid excessive excision of normal tissues, which can effectively maintain the good appearance of

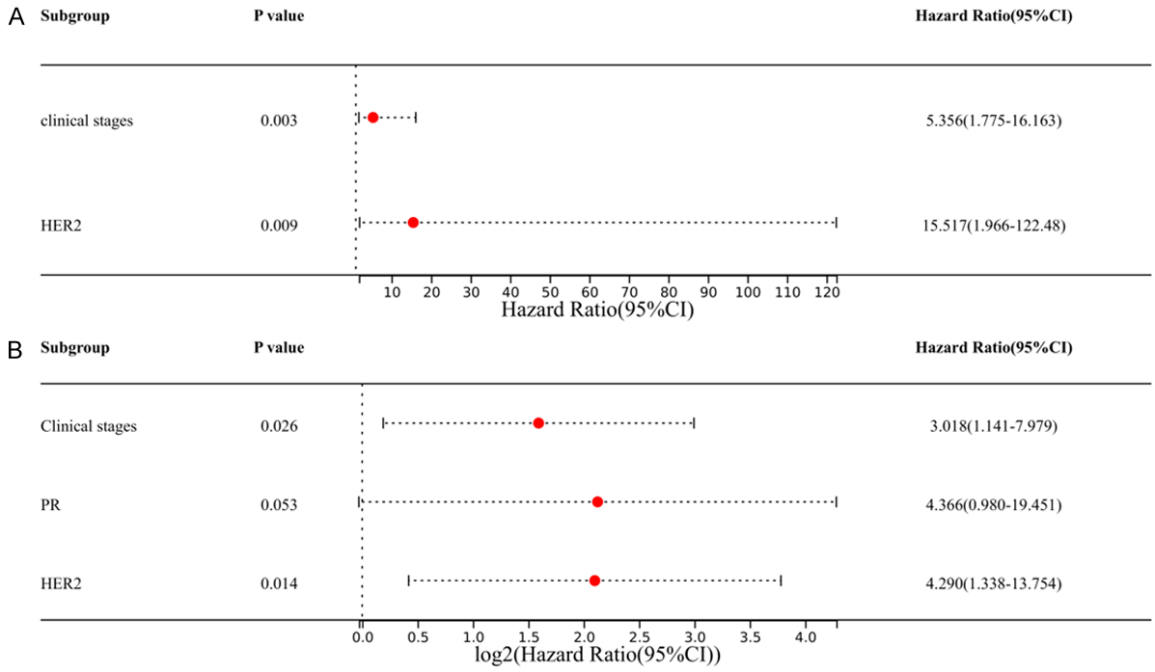

Figure 6. Multivariate Cox regression analysis of prognostic factors influencing patients' OS and DFS. A. Multivariate Cox regression analysis on prognostic factors influencing patients' OS. B. Multivariate Cox regression analysis on prognostic factors influencing patients' DFS. Note: OS: Overall Survival; DFS: Disease-Free Survival; PR: Progesterone Receptor; HER2: Human Epidermal Growth Factor Receiver-2.

patients' breasts, thus improving the QoL of patients.

As compared with total mastectomy, BCS may cause a higher risk of recurrence. For example, a meta-analysis published in the Lancet in 2018 showed that tumors reduced by neoadjuvant chemotherapy may have a higher local recurrence rate after breast-conserving therapy than those that did not receive neoadjuvant chemotherapy [25]. Moreover, the postoperative adjuvant chemotherapy and radiotherapy can greatly reduce the risk of recurrence, and the patients undergoing total mastectomy may not be able to have a radical cure [26]. In the present study, the patients were studied for 2 years. We found that the clinical stage and HER2 positivity were correlated with patients' OS and DFS. An experiment conducted by Loibl et al. [27] has shown that BCS after neoadjuvant chemotherapy is feasible for operable BC patients, and clinical characteristics of the tumor and its sensitivity to neoadjuvant chemotherapy should be measured before formulating the operation plan. According to this study, clinical stage was an independent prognostic factor, and an advanced clinical stage meant worse prognosis. This result is in agreement with the existing research with large sample size. Research by Zhang et al. [28] shows that the lower the expression of HER2, the easier to achieve pathological complete remission after neoadjuvant chemotherapy, and thus the better the prognosis. However, interestingly, in the present study, we have not found that the two therapy methods have any influence on the prognosis of patients, which indicates that the two therapy methods have no obvious influence on the patients' prognosis.

This study has confirmed through analysis that neoadjuvant chemotherapy combined with BCS can improve the clinical efficacy and immune and inflammatory response of patients. However, the study still has some limitations. Due to the retrospective nature, we have collected the 2-year follow-up data of patients, so it is a limitation that we are unable to follow up patients for a longer time. Thus, whether the two therapy methods impact the patients' long-term prognosis needs verification by more samples and a longer follow-up time.

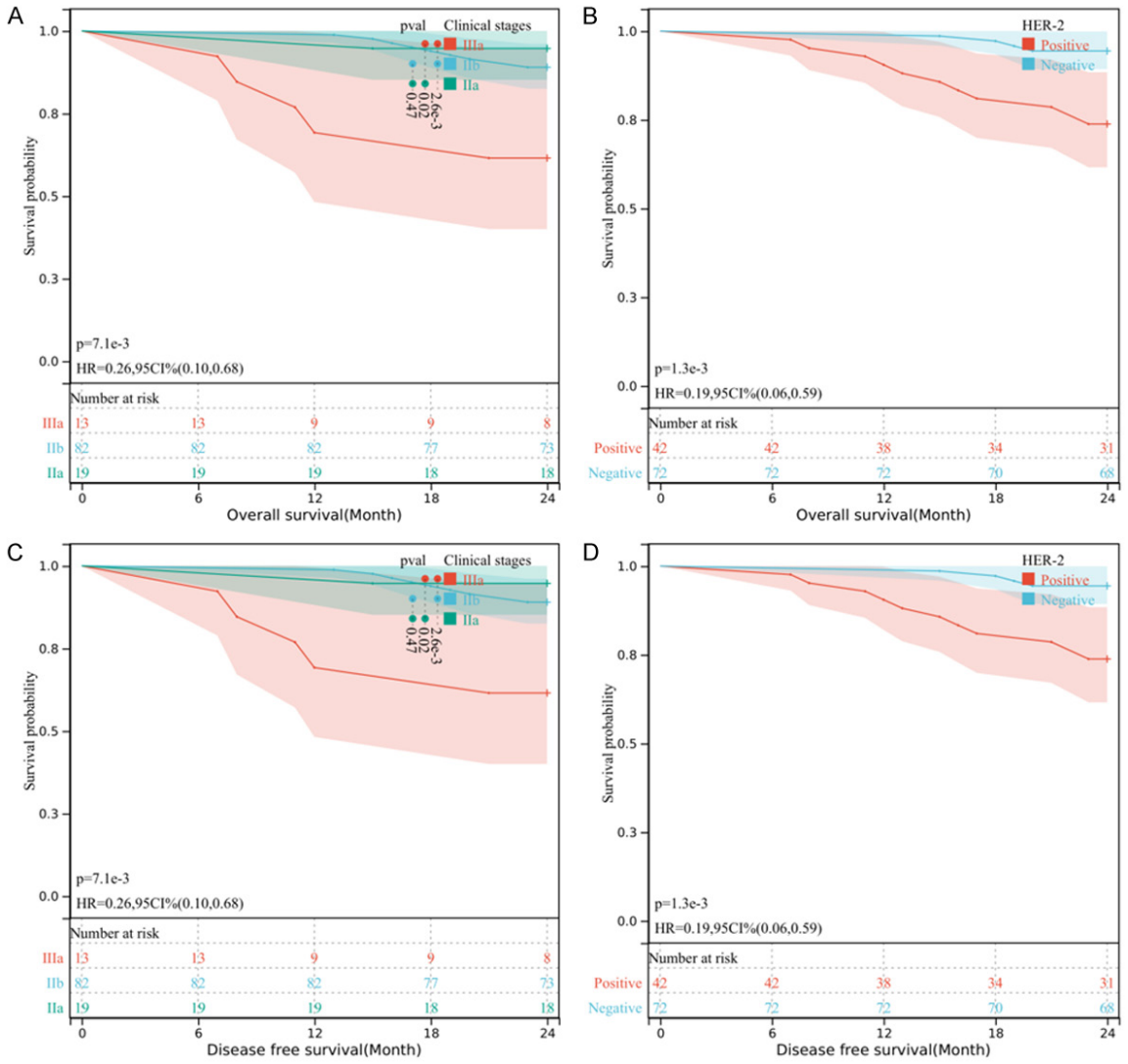

Figure 7. Survival curve of patients with different clinical stage and HER-2 expression. A. OS of patients with different clinical stage. B. OS of patients with different HER2 expression. C. DFS of patient with different clinical stage. D. DFS of patients with different HER2 expression. Note: OS: Overall Survival; DFS: Disease-Free Survival; PR: Progesterone Receptor; HER2: Human Epidermal Growth Factor Receiver-2; HR: Hazard Ratio.

To sum up, neoadjuvant chemotherapy combined with BCS can substantially alleviate the disease condition of BC patients, effectively improve their immune ability and lower the inflammation level of them, without impacting their OS and DFS within 2 years.

Disclosure of conflict of interest

None.

Address correspondence to: Mao Li, Thyroid Breast Surgery, Zhuji People's Hospital, Zhuji 311800, Zhejiang, China. Tel: +86-13758584738; E-mail: limao888888@163.com

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