ORIGINAL RESEARCH

Clinical Efficacy of Neoadjuvant Chemotherapy plus Modified Radical Mastectomy for Stage II-III Breast Cancer Patients and Its Influence on Serum Tumor Markers

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ABSTRACT

Objective • This research aims to assess the clinical efficacy of neoadjuvant chemotherapy (NACT) in combination with modified radical mastectomy (MRM) for stage II-III breast cancer (BC) patients and its impact on serum tumor markers (STMs).

Methods • The study included 119 stage II-III BC patients treated between June 2018 and June 2021. Among them, 55 cases underwent MRM (reference group), while 64 cases received NACT followed by MRM (research group). We compared intraoperative parameters (blood loss, operation time, hospital stay), clinical outcomes, the incidence of postoperative adverse events (AEs), changes in STMs (CA125, CA153, CEA), and one-year postoperative quality of life (QOL).

Results • In comparison to the reference group, the research group exhibited significantly lower intraoperative blood loss, shorter operation times, reduced hospital stays, and higher rates of disease remission. Notably, the research group experienced a lower overall incidence of AEs, including skin flap necrosis, subscalp effusion, infection, and upper limb lymphedema. Postoperatively, all STMs in the research group exhibited statistically significant reductions and were lower than those in the reference group. Additionally, all QOL subscales demonstrated improvements and higher scores in the research group.

Conclusions • NACT followed by MRM represents an effective approach for enhancing surgical outcomes and clinical efficacy in stage II-III BC patients. This combination therapy also reduces the risk of postoperative AEs and leads to favorable changes in STMs and postoperative QOL levels. (*Altern Ther Health Med.* 2024;30(1):260-264).

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INTRODUCTION

In recent decades, the global burden of breast cancer (BC) has become increasingly serious, with the incidence surpassing that of lung cancer to become the world's most commonly diagnosed cancer as of 2021.[1,2] The clinical stage of BC patients at diagnosis is an important factor influencing patients' outcomes. It is reported that the five-year survival rate of BC patients with different stages varies greatly, with that of advanced stage IV patients being less than 30%.[3,4] Early diagnosis through screening programs has a positive impact on reducing the mortality rate of BC.[5] However, the patient's treatment cycle is generally long, leading to an increased risk of immunosuppression and infection, thus adversely affecting the patient's outcome.[6] Thus, finding a treatment with a shorter treatment cycle and better clinical effects is vital.

Surgery is still the best choice for BC treatment today. However, the traditional radical mastectomy involves a large excision area that is detrimental to postoperative recovery.[7] Therefore, the modified radical mastectomy (MRM) came into being, allowing for the preservation of the pectoralis major muscle and improving postoperative aesthetic degree.[8] However, in many cases, BC patients have reached stage II, and III at diagnosis, missing the best treatment opportunity. Given this, some studies have suggested combining neoadjuvant chemotherapy (NACT) with traditional treatment to prevent local recurrence and distant metastasis.[9] NACT was initially only suitable for inoperable locally advanced BC patients but its application scope expanded with the continuous exploration of NACT.[10] In the past clinical practice, using NACT before local treatment of BC can narrow the focus of the lesion, which is more conducive to subsequent surgery.[11] The research of Zhang et al.[12] also suggests that NACT positively affects the subsequent disease control of BC patients.

Despite the potential of neoadjuvant chemotherapy (NACT) to reduce tumor size and positively impact disease

control, there is a notable lack of research focusing specifically on patients with stage II-III breast cancer.

This research aims to investigate the impact of NACT followed by MRM on a series of indicators, including clinical outcomes and serum tumor markers (STMs), in patients with stage II-III breast cancer. By exploring these parameters, we seek to gain a comprehensive understanding of the efficacy and potential benefits of this treatment approach. We aim to provide insights that may help optimize therapeutic strategies for patients in this particular stage of breast cancer.

DATA AND METHODS

Patient information

This was a single-center retrospective analysis. All the enrolled patients met the histopathological diagnosis of BC (clinical staging: II-III) and were unsuitable for breast-conserving therapy after assessing their specific condition, with no mental illness or cognitive dysfunction, nor other abnormalities such as nipple deviation and abnormal discharge. Patients were excluded based on the following criteria: other malignancies or severe organic diseases; pregnant and lactating women; those with preoperative chemoradiotherapy; those with extensive calcification and psammoma bodies of the breast; contraindications to NACT or MRM(e.g severe cardiovascular diseases, severe immunodeficiency and inability to tolerate treatment side effects). Strictly following the above inclusion and exclusion criteria, 119 stage II-III BC patients visited between June 2018 and June 2021 were selected, including 55 cases in the reference group treated with MRM and 64 cases in the research group undergoing NACT followed by MRM. The reference group patients had an age range of (55.53±6.12) years, with clinical stages II and III found in 17 and 38, and the lesion site found on the left side, right side, and both sides in 23, 17, and 15 cases, respectively. The age of the research group was (54.20±8.82) years old, with 25 patients in stage II and 39 patients in stage III, as well as 30 patients with the lesion located on the left side, 15 patients on the right side, and 19 patients on both sides. The two cohorts differed insignificantly in baseline data ($P > .05$), which was clinically comparable.

Treatment methods

The reference group received MRM for BC: for patients with general anesthesia in the supine position, the back of the operative side was raised, and the incision was created 3cm away from the tumor edge according to the tumor position and the shape and size of the breast. After the flap was separated using the electric knife-free flap, the breast and its deep pectoralis major fascia were separated from the bottom to the top until the outer edge of the pectoralis major and the pectoralis major and axillary lymph nodes were thoroughly cleaned. During the operation, attention was paid to avoiding damage to pectoral nerves and blood vessels. After the operation, the wound was cleaned, and negative pressure suction was applied to the armpit and chest wall. Finally, the wound was sutured and bandaged with a chest band. Three to five days after surgery, the chest band was re-wrapped every day, and the subcutaneous and axillary effusion was checked to keep the drainage unobstructed until the drainage tube was removed.

The research group received NACT followed by MRM: dexamethasone was given before chemotherapy to prevent allergy, and ondansetron was administered during and after chemotherapy to prevent gastrointestinal reactions. Cyclophosphamide, epirubicin, and docetaxel were given intravenously on the first day of treatment, with the dosage of 500 mg/m², 80 mg/m², and 75 mg/m², respectively, and intravenous cyclophosphamide (500 mg/m²) was given again on the eighth day of treatment. A total of 6 cycles of 21-day chemotherapy were performed. After that, MRM was performed similarly to the reference group.

Outcome measures

(1) Surgical indicators: the two groups' intraoperative blood loss (IBL), operation time (OT) and hospital stay were observed and compared.

(2) Clinical efficacy: The efficacy was evaluated as follows according to the World Health Organization (WHO) criteria: complete response (CR): the tumor disappeared without new lesions, and the STMs returned to normal and maintained for more than 4 weeks; partial response (PR): the sum of the largest tumor diameters decreased by ≥30% for over 4 weeks; stable disease (SD) was indicated if the condition change was between PR and progressive disease (PD); PD: the sum of the maximum tumor diameters increases by ≥20%, or new lesions appear. The remission rate was the sum of CR rate and PR rate.

(3) Incidence of postoperative adverse events (AEs): we mainly observed and recorded the cases of flap necrosis, subscalp effusion, infection, and upper limb lymphedema and calculated the incidence rate.

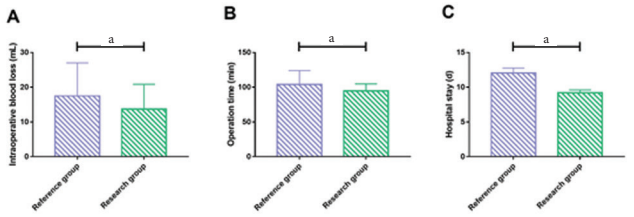
(4) STMs: venous blood (3mL) samples were collected before and 3 days after surgery to quantify carbohydrate antigen 125 (CA125), CA153, and carcinoembryonic antigen (CEA) levels by radioimmunoassay.

(5) Quality of life (QOL): Patients were scored by the Functional Assessment of Cancer Therapy-Breast (FACT-B) before and one year after surgery for QOL assessment from five dimensions: physical, society/family, emotional, functional well-being as well as FACT-B general, with a total score of 0-144. Higher scores corresponded to better QOL.

Statistics and methods

Graphpad Prism 7.0 performed data analyses. The number of cases/percentage (n/%) and the mean±SEM were utilized to represent count data and measurement data, respectively, with the inter-group comparison methods being the χ^2 test and the paired t test, respectively. The significance threshold was $P < .05$.

Figure 1. Influences of two treatment schemes on surgical indexes of stage II-III BC patients. A. The research group had markedly less intraoperative blood loss than the reference group. B. The research group had a markedly shorter operation time than the reference group. C. The research group had markedly shorter hospital stay than the reference group.



[a]represents $P < .05$

Table 1. Impacts of two treatment schemes on clinical efficacy of stage II-III BC patients [n(%)]

Categories	Reference group (n = 55)	Research group (n = 64)	χ^2 value	*P* value
Complete response	12 (21.82)	18 (28.13)	-	-
Partial response	18 (32.73)	29 (45.31)	-	-
Stable disease	17 (30.91)	12 (18.75)	-	-
Progressive disease	8 (14.55)	5 (7.81)	-	-
Remission rate	30 (54.55)	47 (73.44)	4.623	.032

RESULTS

Influences of two therapeutic schemes on surgical indexes of stage II-III BC patients

We analyzed the influence of the two therapeutic schemes on the surgical indexes of stage II-III BC patients by detecting IBL, OT, and hospital stay (Figure 1); the data revealed lower IBL, OT, and hospital stay in the research group as compared to the reference group ($P = .032$).

Impacts of two therapeutic schemes on clinical efficacy of stage II-III BC patients

The remission rates of reference and research groups were 54.55% and 73.44%, respectively, demonstrating higher clinical efficacy in the research group ($P < .05$, Table 1).

Influences of two treatment schemes on the incidence of postoperative AEs in stage II-III BC patients

The overall incidence of postoperative AEs (flap necrosis, subscalp effusion, infection, and upper limb lymphedema) in reference and research groups were 16.36% and 4.69%, respectively, revealing an evidently lower AE rate in the research group ($P = .035$, Table 2).

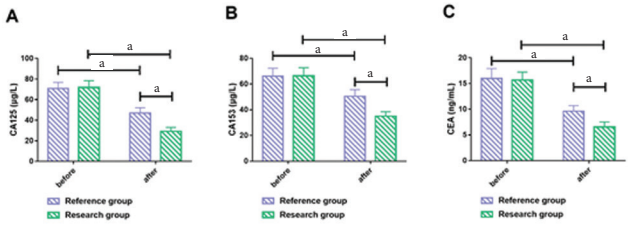
Influences of two therapeutic regimens on STMs in stage II-III BC patients

CA125, CA153, and CEA levels in the two groups were detected to evaluate the effects of the two treatment schemes on STMs in stage II-III BC patients (Figure 2). The three indexes were similar in the two groups before treatment ($P > .05$), but all decreased significantly after treatment ($P < .05$), with lower CA125, CA153, and CEA levels in the research group compared with the reference group ($P < .05$).

Table 2. Influences of two treatment schemes on the incidence of postoperative adverse events in stage II-III BC patients [n(%)]

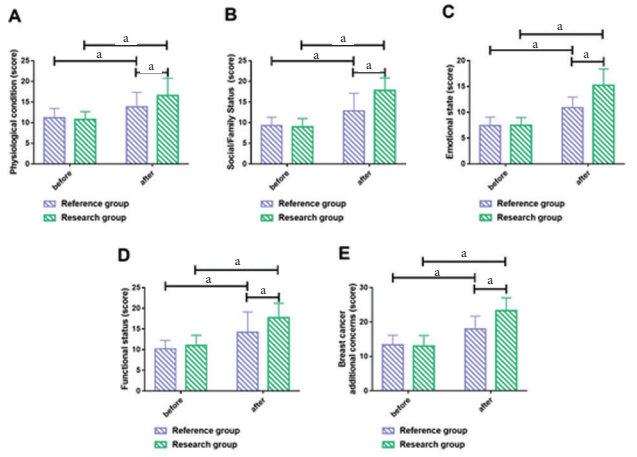
Categories	Reference group (n = 55)	Research group (n = 64)	χ^2 value	*P* value
Flap necrosis	4 (7.27)	0 (0.00)	-	-
Subscalp effusion	3 (5.45)	2 (3.13)	-	-
Infection	1 (1.82)	1 (1.56)	-	-
Upper limb lymphedema	1 (1.82)	0 (0.00)	-	-
Total	9 (16.36)	3 (4.69)	4.448	.035

Figure 2. Influences of two treatment schemes on serum tumor markers in stage II-III BC patients. A. After treatment, the research group had significantly lower CA125 than the reference group. B. The research group had significantly lower CA153 than the reference group after treatment. C. The research group had significantly lower CEA than the reference group after treatment.



[a]represents $P < .05$.

Figure 3. Impacts of two treatment schemes on the quality of stage II-III BC patients. A. The research group had notably higher physiological status scores than the research group after treatment. B. The research group had notably higher social/family status scores than the research group after treatment. C. The research group had notably higher emotional status scores than the research group after treatment. D.The research group had notably higher scores of BC additional concerns than the research group after treatment. E. The research group had notably higher functional status scores than the research group after treatment.



[a]represents $P < .05$

Impacts of two treatment regimens on QOL of stage II-III BC patients

Patients' QOL was tested by the FACT-B scale from the domains of physiological status, social/family status,

emotional status, functional status, and BC additional concerns, with results presented in Figure 3; it showed elevated scores of various domains in the research group after treatment that were markedly higher than the reference group ($P < .05$).

The study results indicate that the intervention group had lower IBL, shorter OT and shorter hospital stay compared to the control group. The intervention group also showed a higher remission rate, fewer adverse reactions, and higher QQL scores compared to the control group.

DISCUSSION

We first analyzed the surgical indexes and found that the IBL, OT and hospital stay were all markedly lower in the research group versus the reference group, indicating that NACT + MRM had better surgical effects on stage I-III BC patients. Lower IBL in the research group suggests better surgical control, potentially leading to reduced risks associated with blood loss during surgery. This can minimize the need for blood transfusions and decrease the chances of complications related to excessive bleeding. Shorter operation time in the research group implies more efficient surgical interventions. Reduced OT can minimize the duration of anesthesia, decrease the risk of surgical site infections, and reduce operative trauma. The shorter hospital stay observed in the research group indicates that patients may experience faster recovery and fewer post-operative complications.This may be attributed to the effective relief of tumor burden and tissue reactive edema of BC patients by NACT, which not only helps to reduce the clinical stage of advanced tumors to a certain extent, but also enhances the surgical effect by narrowing the surgery scope to reduce the surgical difficulty.[13,14] In terms of clinical efficacy, the research group had a significantly remission rate than the reference group (73.44% vs. 54.55%), suggesting higher curative effects of the combined therapy than MRM alone on stage I-III BC patients. The main NACT-related agents used in this study were cyclophosphamide, epirubicin and docetaxel. Of them, cyclophosphamide is an alkylating agent that can exert an anti-tumor role by inhibiting phosphorylation signal transducer and activator of transcription 3 (p-STAT3), which is often used in early adjuvant or neoadjuvant therapy of BC in combination with other anti-tumor drugs.[15] Epirubicin is an anthracycline anticancer drug which can target mitochondria, regulate the expression of apoptosis-related factors or proteins, and mediate the cascade of apoptosis to induce the production of reactive oxygen species (ROS), thus exerting anticancer effects.[16] As the first-line chemotherapy drug for BC, Docetaxel can play an anti-tumor role by targeting BC cells and stem cells and play a more effective therapeutic role based on a nano-drug delivery system.[17] They can interfere with tumor cell growth, induce apoptosis, and inhibit cell division, leading to anti-tumor effects. Additionally, the targeted action of these drugs and the application of nano-drug delivery systems may enhance the specificity and efficacy of treatment while reducing unnecessary drug toxicity and side effects.

In terms of safety, the research group exhibited a notably lower overall incidence of AEs (flap necrosis, subscalp effusion, infection, and upper limb lymphedema) than the reference group (4.69% vs. 16.36%), indicating that the combined intervention can help prevent the occurrence of these AEs to a certain extent. The reason may be that NACT reduces the scope of skin flap resection in stage II-III BC patients and reduces the amount of blood loss and the tension of skin flap, contributing to relatively smaller trauma and less skin flap loss.[18] Douganiotis G et al.[19] also point out that the cyclophosphamide + epirubicin + docetaxel regimen is effective and safe for HER2-positive BC patients. The detection of STMs showed marked reductions in CA125, CA153 and CEA in the research group that were significantly lower than those in the reference group after treatment, suggesting better inhibition of NACT + MRM on STMs in stage II-III BC patients. Tumor markers CA125, CA153, and CEA are indicated to be helpful in reflecting the tumor status, with certain assistance in diagnosing BC patients and predicting the curative effect of NACT.[20] As for patients' QOL, we used the FACT-B scale to analyze and found that the scores of various subscales (physiological status, social/family status, emotional status, functional status, BC additional concerns) elevated markedly after treatment that were higher than the reference group.

However, there are still many limitations of this study that need to be improved. For example, it was a single-center, small-sample retrospective analysis, so there may have been statistical analysis by chance. Second, we did not perform a prognostic follow-up; therefore, it is impossible to assess the prognosis of the two groups of patients.So, it is recommended to conduct larger-scale, multi-center studies with long-term follow-up to validate our findings. According to existing literature and theoretical considerations, the observed differences may have potential implications for long-term patient outcomes in breast cancer. The chemotherapy drugs used in the NACT + MRM treatment approach may decrease tumor volume and burden. A lower tumor burden could be associated with better local lesion control and fewer residual cancer cells, which may reduce the risk of recurrence and potentially lead to improved disease-free survival and overall survival. The chemotherapy drugs employed in this treatment approach may improve treatment efficacy by targeting tumor cells and stem cells. This could aid in eliminating potential residual cancer cells, reducing the risk of local and distant recurrence, thereby positively influencing disease-free survival and overall survival. Lower surgical trauma and postoperative complications, along with shorter hospital stays, may alleviate patients' physical and psychological burden and improve quality of life. Improved postoperative recovery may also allow patients to tolerate subsequent treatments such as radiation therapy and endocrine therapy, further enhancing prognosis. However, these speculations require further research and long-term follow-up data for validation.

Finally, the surgical team's experience is also one of the key factors affecting the final outcome, so we need to

continue to optimize the surgical operation skills of the surgical team in order to provide safer and more secure treatment for patients. In the future, we will conduct a more in-depth and comprehensive experimental analysis to address the above limitations.

CONCLUSION

NACT + MRM is superior to MRM for stage II-III BC, contributing to a reduced incidence of AEs, validly inhibited STMs, and improved QOL, providing an optimized strategy for clinical treatment of stage II-III BC patients. However, further research is needed to validate these speculations and overcome the limitations of this study. This would contribute to a more comprehensive understanding of the impact of the NACT + MRM treatment approach on the long-term prognosis of breast cancer patients and provide a more reliable basis for individualized treatment decisions.

ETHICAL APPROVAL
Not applicable.

CONFLICT OF INTEREST
The author declare no competing interests.

FUNDING STATEMENT
Application of Predictive Model based on Machine Learning Theory in individual accurate diagnosis and treatment of Thoracic tumor and Establishment of Clinical large Database (2019B10039); Ningbo Clinical Medical Research Center for Thoracic Cancer (2021L002); The fourth round of Ningbo Medical key discipline Construction Plan (2022-F03).

CONSENT TO PUBLISH
All authors gave final approval of the version to be published.

AUTHOR CONTRIBUTIONS
Shuixin Yan and Jiadi Li conceived and designed the project, and wrote the paper. Jiafeng Chen and Yuxin Zhou generated the data. Yu Qiu and Yan Chen analyzed the data. Weizhu Wu modified the manuscript. All authors gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

AVAILABILITY OF DATA AND MATERIALS
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ACKNOWLEDGEMENTS
Not applicable.

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