Published online 2022 July 20 **Original Article**

# Efficacy and Safety of Concurrent Chemoradiotherapy with Docetaxel for Locally Advanced Breast Carcinoma after Modified Radical Mastectomy

Juanni Wang[1,*], Chunyan Wei[1], Wei Liu[1], Baofeng Wang[2] and Qiang Han[1]

[1]Department of Obstetrics, The Second Affiliated Hospital of Xi 'an Jiaotong University, Xi 'an, Shaanxi, China
[2]Department of Oncology and Radiotherapy, The Second Affiliated Hospital of Xi 'an Jiaotong University, Xi 'an, Shaanxi, China

*** *Corresponding author:*** Juanni Wang, Department of Obstetrics, The Second Affiliated Hospital of Xi 'an Jiaotong University, Xi 'an, Shaanxi, China. Email: angmanshe54@126.com

**Received** 2022 March 02; **Revised** 2022 April 13; **Accepted** 2022 July 02.

**Abstract**

**Background:** Breast cancer is a common term for a malignant tumor that arises from the epithelial component of the breast. Concurrent chemoradiotherapy's efficacy and safety are controversial, considering the impact on patients' quality of life.
**Objectives:** The aim of this study was investigating the efficacy and safety of concurrent chemoradiotherapy with docetaxel in locally advanced breast cancer who have received a modified radical mastectomy.
**Methods:** A cohort of 110 female patients with locally advanced breast cancer were included in the present study and divided by chemoradiotherapy mode into a concurrent chemoradiotherapy group (n=58) and a sequential chemoradiotherapy group (n=52). Docetaxel was administered concurrently during radiotherapy in the concurrent group, whereas the sequential group underwent adjuvant radiotherapy 1-3 weeks after chemotherapy. Then, the two groups were compared with respect to clinical efficacy, levels of tumor markers across vascular endothelial growth factor (VEGF) and Carcinoembryonic antigen (CEA), adverse reactions, and the 3-year overall survival (OS) rate.
**Results:** The results showed that the mean age, operation, evaluation of Post treatment VEGF (pg / mg) and Post treatment CEA (/g / L), effectiveness of treatment in two sequential and concurrent treatment groups was not significant The results showed that the amount of Prior treatment VGEF (pg / mg) and Post treatment VGEF (pg / mg) in the two groups were statistically significant difference. Which shows the positive effect of this treatment before and after the intervention. Comparison of survival time in the two groups did not show a significant difference.
**Conclusion:** The chemotherapy protocol with a combination of cyclophosphamide, fluorouracil and epirubicin with concurrent docetaxel presented higher efficacy and prolonged the overall survival in locally advanced breast cancer patients who had undergone a radical mastectomy, while it did not significantly increase the toxicity.

*Keywords:* Breast cancer, Concurrent chemoradiotherapy, Docetaxel, Modified radical mastectomy

## 1. Background

Breast cancer is a common term for a malignant tumor that arises from the epithelial component of the breast, with 99% cases in women and only 1% in men. In China, the incidence of breast cancer has been reported to rank first among female malignancies and seriously endangers people's physical and mental health (1). Clinically, radical mastectomy is frequently performed for treating breast cancer, but it fails to appreciably rise the OS rate because the symptoms of the disease are too mild to be confirmed at an early stage and therefore the operation is primarily manipulated for advanced patients (2). Moreover, it provides little improvement in prognosis, whilst subsequent adjuvant chemotherapy can largely lower the risk of local recurrence and distant metastasis (3). Currently, concurrent chemoradiotherapy is given after radical mastectomy to locally advanced breast cancer patients who show postoperative chemoradiotherapy indications, but its efficacy and safety are controversial, considering the impact on patients' quality of life (4,5). Also, traditional sequential modes suffer disadvantages across prolonged radiotherapy cycle, an increased risk of local recurrence, and reported higher incidence of distant metastasis in patients with delayed chemotherapy (6). Sequential chemoradiotherapy with anthracyclines and taxanes, for example, is subject to a long treatment cycle, although being preferred among clinical options to treat high-risk invasive breast cancer (7). Chemotherapy is used in three ways in the treatment of advanced cancers: Induction or neoadjuvant, concurrent and Sequentional. Induction chemotherapy can eliminate latent metastases and thus improve treatment outcomes (8).

## 2. Objectives

With that, the study was designed to compare concurrent chemoradiotherapy using docetaxel with sequential chemoradiotherapy in terms of efficacy and safety on locally advanced breast cancer who had received modified radical mastectomy.

## 3. Methods

Patients with locally advanced breast cancer treated in our hospital from January 2017 to January

2018 were recruited in the study. Allocation of patients to two treatment groups was done based on random allocation (Figure 1). Inclusion criteria: Patients (I) whose symptoms met the diagnostic code of breast cancer in the China Anti-Cancer Association (CACA) Guidelines (9) and Specifications for the Diagnosis of Breast Cancer (2016); (II) who had been diagnosed preoperatively by histopathology or cytology; (III) who were assigned to III-IV clinical stages according to the TNM classification system; (IV) who had undergone radical mastectomy for breast cancer and showed relevant indications; (V) whose Karnofsky performance status (KPS) score > 60; and (VI) who provided complete clinical data were included in the study. Exclusion criteria: Patients were excluded if they (I) were found with distant metastasis via ultrasound imaging or X-ray examination; (II) were in poor physical condition or allergic constitution; (III) had received targeted therapy or endocrine therapy; (IV) presented any other malignant complication; (V) suffered complications of hematopoietic, nervous, digestive and immune systems; (VI) had a prognosis for survival of less than 6 months; (VII) lived with mental illness; (VIII) had got severe dysfunction or disorder of vital organs like heart, liver and kidney; or (IX) were lactating or pregnant women. The research conducted by the Ethics Committee of the Institute met the requirements of relevant laws and ethics, and was discussed at the Hospital Medical Ethics Conference. All subjects had informed consent.

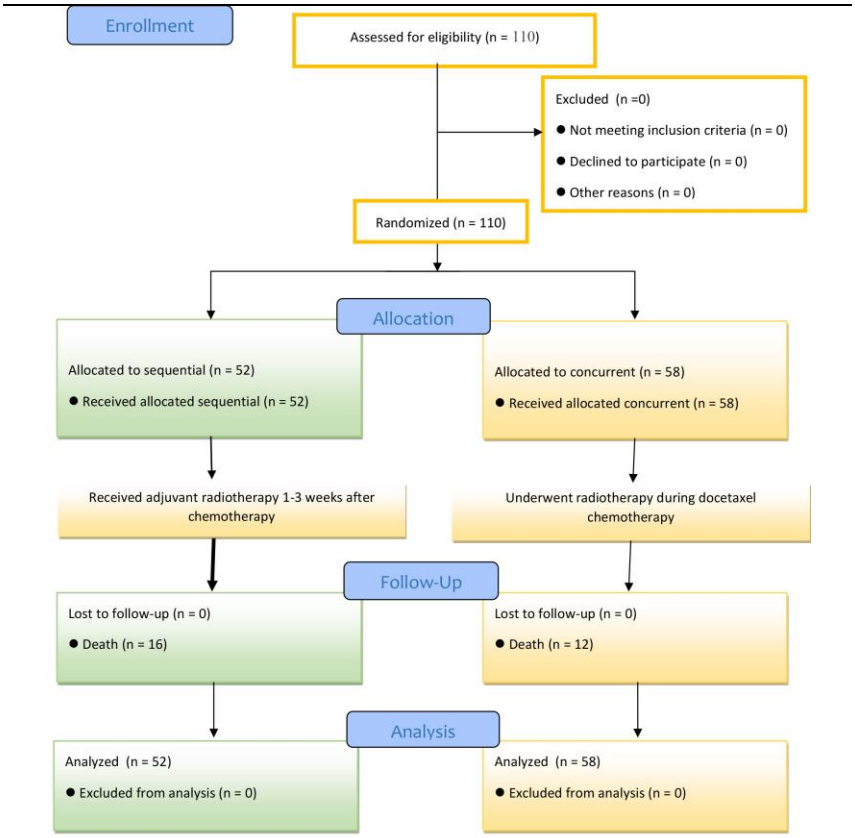


**Figure 1.** Consort Algorithm

Both groups received the chemotherapy protocol by a combination of fluorouracil, epirubicin, and cyclophosphamide (FEC) with docetaxel (T) within 3 weeks after radical mastectomy: Cyclophosphamide, fluorouracil and epirubicin were concurrently administrated via intravenous infusion at the doses of 500 mg/m2, 500 mg/m2, and 100 mg/m2, respectively, on Day 1 of three 28-day circles; After the three circles terminated, docetaxel was given at 100 mg/m2 intravenously on Day 1 of three subsequent 28-day circles. Then the concurrent group underwent radiotherapy during docetaxel chemotherapy via 6MV X-ray intensity-modulated radiation therapy for chest wall with a dose of 50 Gy in 25 fractions over 5 weeks; while the sequential group received adjuvant radiotherapy 1-3 weeks after chemotherapy: the clavicle was irradiated with 6MV X-ray photon beam with a dose of 50 Gy in 25 fractions over 5 weeks. Both were subject to close monitoring of routine blood indexes during radiotherapy and chemotherapy and, if necessary, can be administrated granulocyte colony stimulating factor (G-CSF) to offset chemoradiotherapy-triggered neutropenia, enhance the anti-tumor effect during radiotherapy and ensure that radiotherapy and chemotherapy proceed as scheduled.

The two groups were assessed with regard to clinical efficacy according to the modified Response Evaluation Criteria in Solid Tumors (10): Complete response (CR), Partial response (PR) and Stable disease (SD).

Before and after treatment, 3-5 ml of blood samples were isolated from the peripheral veins of the two groups, and then centrifuged at 3,000 r/min (centrifugal radius = 15 cm) for 15 minutes for serum collection. The collected serum samples were stored at -20°C and subjected to the enzyme-linked immunosorbent assay for vascular endothelial growth factor (VEGF) measurement and the enzyme-luminescence assay for Carcinoembryonic antigen (CEA) detection.

The patients were followed up every 3 months for 3 years by outpatient service, telephone call and visit. The long-term efficacy was evaluated with overall consideration of chief complaints, clinical symptoms and imaging findings with chest X-ray, electrocardiogram, color Doppler ultrasound and blood routine examination at the last follow-up. The 3-year OS rate was compared between the two groups with death or the termination of the 3-year follow-up after discharge as the endpoint of the study.

The adverse reactions of the two groups were evaluated and categorized into grades 0-4 as per the Acute Radiation Morbidity Criteria and Hematologic Toxicity Criteria of the Radiation Therapy Oncology Group (RTOC) (11).

All the data were statistically analyzed using SPSS Statistics V22.0. Of them, the measurement data were expressed by mean ± standard deviation (x ± s) and subjected to grouped comparison with an independent sample T test and intergroup comparison with a paired T test; the counting data were represented in number and rate (%) and compared by $\chi 2$ test between the two groups. The data were plotted into survival curves by the Kaplan-Meier method. A P- value less than 0.05 was considered statistically significant.

## 4. Results

The results of the study showed that out of 110 patients participating in the study, 52 patients are in sequential treatment group and 58 patients are in the treatment group concurrent with radiotherapy and chemotherapy. Demographic variables and clinical characteristics of patients are shown in Table 1.

The mean age of patients in sequential treatment group is 43.7±7.9 years and in concurrent treatment group is 42.8±8.7 years. Also, the average duration of surgery in sequential group therapy is 72.5±8.0 minutes and in concurrent group therapy is 73.4±7.5 minutes. Examination of TNM stage in sequential group therapy showed that 30 people in the third stage and 22 in concurrent group therapy are also in this stage. Examining the location of the tumor in the two treatment groups, the results showed that in the sequential treatment group, 27 patients had tumors on the right side and 25 patients had the tumor site on the left side. In the concurrent treatment group, there are 30 tumors on the right side and 28 tumors on the left side.

The results of treatment (clinical) effectiveness in two groups showed that Stable disease (SD) was observed in 22 patients in sequential and concurrent treatment. Complete Responses (CR) showed that 13 patients in sequential treatment group and 16 patients in concurrent treatment group had this treatment outcome. The results also showed that the result of partial response (PR) treatment was observed in 8 patients in the sequential treatment group and 11 patients in the concurrent treatment group. And progressive disease (PD) was observed in 9 people in both groups.

The results showed that in the sequential group therapy, 46 patients and in the concurrent group therapy 51 patients had no side effects. In sequential treatment group, gastrointestinal complications were observed in 3 patients, leukopenia in 1 patient and thrombocytopenia in 2 patients. In concurrent group therapy, gastrointestinal complications were observed in 1 patient, leukopenia in 4 patients, thrombocytopenia in 1 patient and hepatic and renal complications in one patient.

The final outcome of the disease in patients of the two treatment groups showed that 16 people died in the sequential treatment group and 12 people in the concurrent treatment group. The mean survival time (month) in the sequential treatment group was 25±4.727 and in the concurrent treatment group was 26±5.197.

The results showed that the mean age of individuals in the two treatment groups was not statistically significant (P= 0.553). Also, the operation time in the treatment groups is not statistically significant (P-value= 0.548). Evaluation of Post treatment VEGF (pg / mg) and Post treatment CEA (/g / L) in two sequential and concurrent treatment groups was not significant and shows their ineffectiveness in the treatment groups (P= 0.812 and 0.91). Also, the mean survival time was not significantly different between the two treatment groups (P= 0.293) (Table 2).

The effectiveness of treatment in both groups was also evaluated (Table 3). The results showed that the effectiveness of treatment in the two groups were not statistically significant (P = 0.609).

Table 4 showed that the amount of Prior treatment VEGF (pg / mg) and Post treatment VEGF (pg / mg) in the two groups were statistically significant difference (P<0.001) which shows the positive effect of this treatment before and after the intervention.

Table 5 showed that there was no statistically significant difference between the two treatment

**Table 1.** Demographic characteristics and clinical characteristics of patients participating in the study

| Variable | | Group | |
|---|---|---|---|
| | | Sequential (%)* | Concurrent (%)* |
| **TNM stage** | III | 30 (57.7) | 31 (53.4%) |
| | IV | 22 (423%) | 27 (46.6%) |
| **Tumor location** | Right | 27 (51.9%) | 30 (51.7%) |
| | Left | 25 (48.1%) | 28 (48.3%) |
| **Clinical efficacy** | SD | 22 (42.3%) | 22 (37.9%) |
| | CR | 13 (25%) | 16 (27.6%) |
| | PR | 8 (15.4%) | 11 (19%) |
| | PD | 9 (17.3%) | 9 (15.5%) |
| **Adverse reaction** | Gastro intestinal | 3 (5.8%) | 1 (1.7%) |
| | Leukopenia | 1 (1.9%) | 4 (6.9%) |
| | Thrombocytopenia | 2 (3.8%) | 1 (1.7%) |
| | Liver / kidney injury | 0 | 1 (1.7%) |
| | No | 46 (88.5%) | 51 (87.9%) |
| **State** | Alive | 36 (69.2%) | 46 (79.3%) |
| | Dead | 16 (30.8%) | 12 (20.7%) |
| **Age **** | | 43.788 (7.924) | 42.844 (8.686) |
| **Operation time **** | | 72.538 (8.013) | 73.431 (7.464) |
| **Time **** | | 25 (4.727) | 26 (5.197) |

* F (%)
** Mean (SD)

**Table 2.** Evaluation of clinical features and treatment measures of patients participating in the study

| Variable | Sequential | Concurrent | P-value* | CI: 95% |
|---|---|---|---|---|
| **Age** | 43.788 (7.924) | 42.844 (8.689) | 0.553 | -2.196 – 4.083 |
| **Operation time** | 75.538 (8.013) | 73.431 (7.464) | 0.548 | -3.818 – 2.033 |
| **Post treatment VEGF (pg/mg)** | 112.046 (28.736) | 110.703 (30.167) | 0.812 | - 9.759 – 12.480 |
| **Post treatment CEA (µg/L)** | 4.125 (0.978) | 4.103 (1.015) | 0.91 | 0.355 – 0.398 - |
| **Time** | 26 (5.197) | 25 (4.727) | 0.293 | - 2.875 – 0.875 |

* P-value based on independent sample T test

**Table 3.** Clinical efficacy of treatment measures in two groups

| Group | Clinical efficacy | | | | $X^2$ | df | P-value* |
|---|---|---|---|---|---|---|---|
| | SD | CR | PR | PD | | | |
| **Sequential** | 22 | 13 | 8 | 9 | 0.262 | 3 | 0.609 |
| **Concurrent** | 22 | 16 | 11 | 9 | | | |

* P-value based on chi-square (fisher exact test)

groups in terms of side effects (therapeutic side effects) (P=0.931). This probably indicates that the selected treatment methods in the two treatment groups have the least side effects and this small number of side effects is not statistically significant.

Tumor, nodes, metastasis (TNM) stage system for breast cancer is an internationally accepted system used to determine the stage of the disease. This stage of the disease is used to determine the prognosis and management of treatment. The results regarding the stage variable showed that there was no statistically significant difference between the two groups (P=0.655) (Table 6). Also, no significant difference was observed in the study of the two groups in terms of tumor location (P=0.983) (Table 7).

**Table 4.** The effect VEGF (pg/mg) and CEA (µg/L) before and after intervention in treatment groups

| Group | Prior treatment VEGF (pg/mg) | Post treatment VEGF (pg/mg) | P-value** |
|---|---|---|---|
| **Sequential** | 135* | 115* | 0.001 |
| **Concurrent** | 6.2* | 4.3* | 0.001 |
| | **Prior treatment CEA (µg/L)** | **Post treatment CEA (µg/L)** | |
| **Sequential** | 135* | 115* | 0.001 |
| **Concurrent** | 6.2* | 4.3* | 0.001 |

*MEDIAN
** P-value based on Paired t-test

**Table 5.** Evaluation of adverse reaction of patients participating in the study

| Group | Grade 3-4 adverse reaction | | | | | $X^2$ | df | P-value* |
|---|---|---|---|---|---|---|---|---|
| | Gastro intestinal | Leukopenia | Thrombocytopenia | Liver / kidney injury | No | | | |
| **Sequential** | 46 | 3 | 1 | 2 | 0 | 0.007 | 4 | 0.931 |
| **Concurrent** | 51 | 1 | 4 | 1 | 1 | | | |

* P-value based on chi-square (fisher exact test)

Comparison of survival time in the two groups did not show a significant difference. The treatment methods chosen may not have an effect on increasing patients' survival time (Figure 2).

**Table 6.** Evaluation of TNM stage of patients participating in the study

| Group | TNM stage | | $X^2$ | df | P-value* |
|---|---|---|---|---|---|
| | III | IV | | | |
| **Sequential** | 30 | 22 | 0.2 | 1 | 0.655 |
| **Concurrent** | 31 | 27 | | | |

*P-value based on chi-square

**Table 7.** Evaluation of Tumor location of patients participating in the study

| Group | Tumor location | | $X^2$ | df | P-value* |
|---|---|---|---|---|---|
| | Right | Left | | | |
| **Sequential** | 27 | 25 | 0.125 | 1 | 0.983 |
| **Concurrent** | 30 | 28 | | | |

*P-value based on chi-square

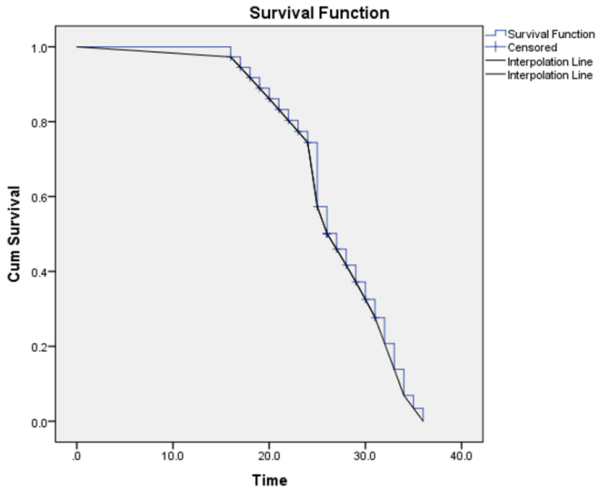


**Figure 2.** Comparison of survival time in the two groups

## 5. Discussion

The study was designed to compare concurrent chemo radiotherapy using docetaxel with sequential chemo radiotherapy in terms of efficacy and safety on locally advanced breast cancer who had received modified radical mastectomy. The results showed that the mean age, operation, evaluation of Post treatment VEGF (pg/mg) and Post treatment CEA (/g / L), effectiveness of treatment in two sequential and concurrent treatment groups was not significant The results showed that the amount of Prior treatment VGEF (pg/mg) and Post treatment VGEF (pg/mg) in the two groups were statistically significant difference. Which shows the positive effect of this treatment before and after the intervention. The results showed that there was no statistically significant difference between the two treatment groups in terms of side effects. Comparison of survival time in the two groups did not show a significant difference. The treatment methods chosen may not have an effect on increasing patients' survival time.

The mean age of patients in sequential treatment group is 43.733±7.924 years and in concurrent treatment group is 42.844±8.686 years.

The results showed that the mean age in the consecutive group therapy was 43 years and in the simultaneous group therapy was 42 years while in the study of Brackstone et al. (2011) the mean age of the two in the chemotherapy group was 51 years and in the radiotherapy group was 49 years, which showed a higher mean age than the present study (12). Also in the study by Li, L, et al (2018) on breast cancer patients, the mean age of patients was higher than the mean age of the present study however, there was no significant difference between the two treatment groups in terms of mean age (13), which is also consistent with the results of the present study. The mean duration of surgery in the two treatment groups was 72 and 73 minutes while this time was obtained in the study of et al Haixia Zhao (2015) in two groups of 43 and 58 minutes (14), which is higher than the average duration of surgery in the present study.

TNM classification is a system for classifying

malignancies. It is used primarily in solid tumors (masses of abnormal cells that lack cysts and fluid areas) and can be used to aid in the prognosis of cancer. A standard classification system improves communication between providers and enables better information sharing and research among populations. The system is based on the evaluation of tumors, regional lymph nodes and distant metastases. Examination of TNM stage in consecutive group therapy showed that 30 patient in the third stage and 22 patient in the simultaneous group therapy are in this stage and considering that most patients are in these stages, which is consistent with the results of other studies in which most patients are in these stages (15). This lack of difference in TNM stage is also consistent with the study of Lu, Y et al (2017) who were not significantly different in TNM stage (16).

Examination of the location of the tumor on which side it is located showed that the tumors are scattered on both the right and left sides. There is no significant difference between the two treatment groups in terms of tumor location, which is consistent with the results of other studies (17,18).

Clinical effectiveness is a measure of the success of a treatment in achieving a goal. Most patients in the two treatment groups showed clinical response to Stable disease (SD) and Complete responses (CR), which is consistent with the results of the study Malgorzata K Tuxen et al (2014) (19). The effectiveness of therapeutic measures performed in the two treatment groups did not show a statistically significant difference that is consistent with the results of other studies (20,21).

Any therapeutic action or intervention may have unpleasant side effects for the patient. Gastrointestinal complications and leukopenia were the most common complications observed in the two groups of patients and these complications did not show a significant difference between the two groups. In the study et al. (2011) H. Wildiers, the two complications observed in most patients was gastrointestinal complications and leukopenia, which is consistent with the results of the present study (22).

Vascular Endothelial Growth Factor (VEGF) (pg/mg) is one of the most important antagonistic regulators that the association between increased growth factor expression and tumor progression has been reported in several cancers, including breast cancer. The results of this study showed that the expression of genes due to intervention in both sequential treatment group and concurrent treatment group showed a significant decrease that is consistent with the results of other studies (23,24). CEA (Carcinoembryonic Antigen) levels should be increased in both benign and malignant diseases. CEA levels are low or normal in patients who are in the early stages of the disease and have a small tumor. Patients with progressive tumors or metastases are likely to have higher CEA levels. Therefore, this test is useful for determining the effectiveness of treatment measures. The results of the present study showed that interventional measures were associated with CEA levels and the results of various studies have shown that therapeutic interventions can be useful in reducing CEA levels (25,26).

Finally, the comparison of survival time between the two groups did not show a significant difference, which could indicate that the chosen treatment methods may not have an effect on increasing the survival time of patients. While the mean survival time in other studies in different treatment groups showed a significant difference (27,28).

### *5.1. Limitation*

The follow-up time of the participants in the study seems to be longer than this time to reveal the effect of treatment measures and interventions in increasing the average survival time.

## 6. Conclusion

To sum up, concurrent chemoradiotherapy with docetaxel presented high clinical efficacy and prolonged the survival cycle, though not significantly, in locally advanced breast cancer patients who received modified radical mastectomy, while it did not significantly increase the toxicity.

## Acknowledgments

None.

## Footnotes

**Conflicts of Interest:** The authors have no financial conflicts of interest to disclose.
**Ethical Certification:** The research conducted by the Ethics Committee of the Institute met the requirements of relevant laws and ethics, and was discussed at The Second Affiliated Hospital of Xi 'an Jiaotong University Medical Ethics Conference. All subjects had informed consent.
**Fund Support:** Effect and neuroimmune mechanism of intestinal micro flora transplantation in the treatment of preeclampsia (2020SF-046).

## References

1. Zhang X, Ju S, Wang X, Cong H. Advances in liquid biopsy using circulating tumor cells and circulating cell-free tumor DNA for detection and monitoring of breast cancer. *Clin Exp Med*. 2019;**19**(3):271-9. doi: 10.1007/s10238-019-00563-w. [PubMed: 31190187]
2. Sambyal V, Guleria K, Kapahi M, Manjari M, Sudan M, Uppal MS, et al. Association of VEGF haplotypes with breast cancer risk in North-West Indians. *BMC Med Genomics*. 2021;**14**(1):1-9. doi: 10.1186/s12920-021-01060-4. [PubMed: 34429108]
3. Adams J, Carder PJ, Downey S, Forbes MA, MacLennan K, Allgar V, et al. Vascular endothelial growth factor (VEGF) in breast cancer: comparison of plasma, serum, and tissue VEGF and

microvessel density and effects of tamoxifen. *Cancer Res*. 2000;**60**(11):2898-905. [PubMed: 10850435]
4. Zheng C, Yu ZG. Clinical practice guidelines for pre-operative evaluation of breast cancer: Chinese Society of Breast Surgery (CSBrS) practice guidelines 2021. *Chin Med J (Engl)*. 2021;**134**(18):2147-9. doi: 10.1097/CM9.0000000000001520. [PubMed: 34039864]
5. Ditsch N, Untch M, Kolberg Liedtke C, Jackisch C, Krug D, Friedrich M, et al. AGO recommendations for the diagnosis and treatment of patients with locally advanced and metastatic breast cancer: update 2020. *Breast Care*. 2020;**15**(3):294-309. doi: 10.1159/000508736. [PubMed: 32774225]
6. Kawaguchi R, Furukawa N, Kobayashi H, Asakawa L. Posttreatment cut-off levels of squamous cell carcinoma antigen as a prognostic factor in patients with locally advanced cervical cancer treated with radiotherapy. *J Gynecol Oncol*. 2013;**24**(4):313-20. doi: 10.3802/jgo.2013.24.4.313. [PubMed: 24167666]
7. Zheng R, Han S, Duan C, Chen K, You Z, Jia J, et al. Role of taxane and anthracycline combination regimens in the management of advanced breast cancer: a meta-analysis of randomized trials. *Medicine*. 2015;**94**(17):1-10. doi: 10.1097/MD.0000000000000803. [PubMed: 25929935]
8. Ferrari D, Ghi MG, Franzese C, Codeca C, Gau M, Fayette J. The slippery role of induction chemotherapy in head and neck cancer: myth and reality. *Front Oncol*. 2020;**10**:1-12. doi: 10.3389/fonc.2020.00007. [PubMed: 32038985]
9. Society of gastric cancer of china anti-cancer. CACA guidelines for holistic integrative management of gastric cancer. Holistic Integrative Oncology. 2022;**1**(1):1-45. doi: 10.1007/s44178-022-00004-x.
10. Armato SG 3rd, Nowak AK. Revised modified response evaluation criteria in solid tumors for assessment of response in malignant pleural mesothelioma (Version 1.1). *J Thorac Oncol*. 2018;**13**(7):1012-21. doi: 10.1016/j.jtho.2018.04.034. [PubMed: 29753121]
11. Cox JD, Stetz J, Pajak TF, Toxicity criteria of the radiation therapy oncology group (RTOG) and the european organization for research and treatment of cancer (EORTC). *Int J Radiat Oncol Biol Phys*. 1995;**31**(5):1341-6. doi: 10.1016/0360-3016(95)00060-C. [PubMed: 7713792]
12. Brackstone M, Palma D, Tuck AB, Scott L, Potvin K, Vandenberg T, et al. Concurrent neoadjuvant chemotherapy and radiation therapy in locally advanced breast cancer. *Int J Radiat Oncol Biol Phys*. 2017;**99**(4):769-76. doi: 10.1016/j.ijrobp.2017.06.005. [PubMed: 28870785]
13. Li L, Yang Y, Li W, Zhao X, He J, Mei S, et al. Latissimus dorsi myocutaneous flap repair is effective after neoadjuvant chemotherapy for locally advanced breast cancer. *World J Surg Oncol*. 2022;**20**(1):1-10. doi: 10.1186/s12957-022-02598-y. [PubMed: 35477520]
14. Zhao H, Zhang J, Lu Y, Jin J. Neoadjuvant chemotherapy in combination with surgery in the treatment of local advanced breast cancer. *Pak J Med Sci*. 2019;**35**(5):1402-7. doi: 10.12669/pjms.35.5.310. [PubMed: 31489015]
15. McCarthy N, Boyle F, Bull J, Leong E, Simpson A, Kannourakis G, et al. Neoadjuvant chemotherapy with sequential anthracycline-docetaxel with gemcitabine for large operable or locally advanced breast cancer: ANZ 0502 (NeoGem). *Breast*. 2014;**23**(2):142-51. doi: 10.1016/j.breast.2013.12.001. [PubMed: 24393617]
16. Lu Y, Huang H, Yang H, Chen D. Randomized controlled trial of late-course concurrent versus sequential chemoradiotherapy after mastectomy and axillary surgery in locally advanced breast cancer. *Medicine (Baltimore)*. 2017;**96**(41):1-6. doi: 10.1097/MD.0000000000008252. [PubMed: 29019894]
17. Daryiush M, Gholizadeh Pasha A, Hajjan K, Sum SH, Pourghasem M, Jahantigh R. Comparison of modified radical mastectomy with breast conservative therapy and radiotherapy in patients with breast cancer. *J Babol Univ Medical Sci*. 2012;**14**(5):36-41.
18. Nirhale DS, Sooraj R, Rawat A. Role of neoadjuvant chemotherapy in downstaging locally advanced breast carcinoma, selection of surgical procedure and its outcome. *Int Surg*. 2020;**7**(2):526. doi: 10.18203/2349-2902.isj20200309
19. Tuxen MK, Cold S, Tange UB, Balslev E, Nielsen DL. Phase II study of neoadjuvant pegylated liposomal doxorubicin and cyclophosphamide ± trastuzumab followed by docetaxel in locally advanced breast cancer. *Acta Oncol*. 2014;**53**(10):1440-5. doi: 10.3109/0284186X.2014.921727. Epub 2014 Jul 3. [PubMed: 24991893]
20. Montagna E, Bagnardi V, Rotmensz N, Viale G, Pruneri G, Veronesi P, et al. Pathological complete response after preoperative systemic therapy and outcome: relevance of clinical and biologic baseline features. *Breast Cancer Res Treat*. 2010;**124**(3):689-99. doi: 10.1007/s10549-010-1027-4. [PubMed: 20625816]
21. Won HS, Kim YS, Kim JS, Chang ED, Na SJ, Whang IY, et al. Clinical outcome and predictive factors for docetaxel and epirubicin neoadjuvant chemotherapy of locally advanced breast cancer. *Korean J Intern Med*. 2020;**35**(6):1489-96. doi: 10.3904/kjim.2019.031. [PubMed: 32069523]
22. Wildiers H, Neven P, Christiaens MR, Squifflet P, Amant F, Weltens C, et al. Neoadjuvant capecitabine and docetaxel (plus trastuzumab): an effective non-anthracycline-based chemotherapy regimen for patients with locally advanced breast cancer. *Ann Oncol*. 2011;**22**(3):588-94. doi: 10.1093/annonc/mdq406. [PubMed: 20709813]
23. Sadeghi M, Hojati Z, Ghaedi K, To assay the relation between the vascular endothelial growth factor expression and breast cancer tumor formation. *J Arak Uni Med Sci*. 2014;**17**(8):27-34.
24. Saravani R, Sargazi S, Rabbani M, Saravani R. Evaluation of VEGF gene expression levels and induction of apoptosis in crocin-treated MCF-7 breast cancer cells. *JSSU*. 2019;**26**(10):845-56. doi: 10.18502/ssu.v26i10.474.
25. Molina R, Auge JM, Farrus B, Zanon G, Pahisa J, Munoz M, et al. Prospective evaluation of carcinoembryonic antigen (CEA) and carbohydrate antigen 15.3 (CA 15.3) in patients with primary locoregional breast cancer. *Clin Chem*. 2010;**56**(7):1148-57. doi: 10.1373/clinchem.2009.135566. Epub 2010 May 14. [PubMed: 20472825]
26. Svobodova S, Kucera R, Fiala O, Karlikova M, Narsanska A, Zednikova I, et al. CEA, CA 15-3, and TPS as prognostic factors in the follow-up monitoring of patients after radical surgery for breast cancer. *Anticancer Res*. 2018;**38**(1):465-9. doi: 10.21873/anticanres.12245. [PubMed: 29277810]
27. Carrara GFA, Scapulatempo Neto C, Abrahao Machado LF, Brentani MM, Nunes JS, Folgueira MA, et al. Breast-conserving surgery in locally advanced breast cancer submitted to neoadjuvant chemotherapy. Safety and effectiveness based on ipsilateral breast tumor recurrence and long-term follow-up. *Clinics (Sao Paulo)*. 2017;**72**(3):134-42. doi: 10.6061/clinics/2017(03)02. [PubMed: 28355358]
28. Houssami N, Macaskill P, Marinovich ML, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. *Ann Surg Oncol*. 2014;**21**(3):717-30. doi: 10.1245/s10434-014-3480-5. Epub 2014 Jan 29. [PubMed: 24473640]