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Original Article

Comparative analysis between multimodalities for refractory locoregional recurrent breast cancer

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Abstract: Objective: To evaluate the clinical efficacy and safety of two multimodal therapies upon the locally recurrent breast cancer patients who had undergone surgical resection, aiming to provide more evidence for clinical intervention. Methods: In this randomized control study, 106 eligible breast cancer patients who had chest wall recurrence following surgical intervention were recruited and randomly divided into the experimental group (chemotherapy followed by surgery) and the control group (surgery followed by chemotherapy). After corresponding combined therapeutic regime, the progression-free survival (PFS), overall survival (OS) and quality of life (QoL) were quantitatively assessed and statistically compared between two groups. The therapeutic safety and patients' tolerance were also evaluated. Results: In the experimental group, the mean PFS was calculated as (49.80±14.42) months, and (18.57±4.76) months in the control group. The median PFS in the chemotherapy group was (34.00±27.56) months, significantly longer compared with (13.00±1.25) months in the surgery group. The mean OS was (65.00±11.70) months resembled (61.03±6.79) months in the control group. The median OS in the chemotherapy group was (50.00±39.90) months, similar to (51.00±4.44) months in the control group. Conclusion: Therapeutic regime of chemotherapy followed by surgery yields similar even higher clinical efficacy compared with the conventional surgery-based therapy, which provides novel option for treatment of breast cancer with local chest wall recurrence.

Keywords: Multimodal therapy, breast cancer, recurrence, overall survival, progression-free survival

Introduction

In recent years, the prevalence of breast cancer is the leading malignant tumor in the female globally. Postoperative topical recurrence of breast cancer refers to chest wall and/or lymph node recurrence with a recurrence rate ranging from 10% to 30%. The percentage of chest wall recurrence is the highest among all recurrent sites, which plays a pivotal role in the postoperative survival rate of breast cancer patients. According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™ Breast Cancer [1] and ESMO International Consensus Guidelines for Topical Recurrent Breast Cancer [2], topically recurrent lesion should be treated with complete resection or radiotherapy as the de novotumor.

According to the National consensus in China on diagnosis and treatment of breast cancer and NCCN guidelines, combined therapy of surgery followed by systemic chemotherapy and adjuvant management is recommended for breast cancer patients with chest wall recurrence after surgery. However, there is no consensus on the standard treatment of chest wall recurrence of breast cancer. Some researchers emphasize topical treatment and ignore the importance of systemic chemotherapy [3], others recommend systemic chemotherapy followed by surgery for large recurrent lesions. A majority of published data have supported that comprehensive treatment yields more clinical benefits compared with topical therapy alone [4]. Systemic therapeutic regime should be implemented based upon the degree of tumor invasion, medical history of systemic auxiliary therapy, concurrent diseases and patients' willingness, *etc*. [5]. Endocrinotherapy is recommended as the standard treatment for patients with positive hormone receptor. For HER-2 positive patients without a medical history of trastuzumab treatment or heart disease contraindications, trastuzumab therapy is highly recommended. At present, tumor resection followed

Table 1. Comparison of baseline data between the experimental and control groups

Parameter	Experimental group (n=56)	Control group (n=50)	χ^2 value	*P* value
Age (year, $\bar{x}\pm s$)	48.00±11.41	49.14±8.72	-0.294	0.771
Maximal tumor size (cm, $\bar{x}\pm s$)	3.23±1.68	3.18±1.40	0.088	0.930
Maximal size of recurrent tumor (cm, $\bar{x}\pm s$)	2.32±1.56	2.54±1.47	-0.364	0.719
Clinical staging (n, %)				
Stage I	9 (15.4)	8 (14.3)	0.054	0.973
Stage II	26 (46.2)	21 (42.9)		
Stage III	21 (38.5)	21 (42.9)		
ER (n, %)				
Positive	34 (61.5)	36 (71.4)	-	0.695
Negative	22 (38.5)	14 (28.6)		
PR (n, %)				
Positive	30 (53.8)	32 (64.3)	-	0.704
Negative	26 (46.2)	18 (35.7)		
HER2 (n, %)				
Positive	17 (30.8)	18 (35.7)	-	1.000
Negative	39 (69.2)	32 (64.3)		
KI67 (n, %)				
Positive	26 (46.2)	26 (51.0)	-	1.000
Negative	30 (53.8)	24 (49.0)		

by radiotherapy is widely adopted by oncologists. However, whether radiotherapy followed by surgery is applicable remains elusive. The selection of therapeutic plan depends upon the characteristics of potential systemic recurrence of malignant tumors. The goal of the therapy is to eliminate the recurrent lesions and reduce the potential risk of localrecurrence. If the local and systemic recurrent lesions can be fully controlled, surgery or radiotherapy should be selected to eliminate the remnant topical lesions [6]. If the topical tumors are resected by surgery or radiotherapy, the opportunity of systemic therapeutic regime will be missed. Subsequent treatment is blind and invalid without evaluation standard. In this study, all eligible breast cancer patients who had chest wall recurrence following surgical intervention received chemotherapy followed by surgery, or surgery followed by chemotherapy. The progression-free survival (PFS) and overall survival (OS) were statistically compared to evaluate the clinical efficacy and safety of each therapeutic regime.

Materials and methods

Inclusion criteria

A total of 106 female patients, aged 18 to 75 years, histologically diagnosed with breast cancer, histologically confirmed with chest wall recurrence with a number ranging from 1 to 3 recurrent lesions which were resectable; Those initially diagnosed with stage I-III breast cancer and underwent modified radical operation combined with postoperative systemic adjuvant therapies including chemotherapy, radiotherapy, target treatment and endocrinotherapy. According to the RECIST criterion, at least one lesion which was measurable was considered as the target lesion. ECOG scoring: 0 or 1; Estimated survival time ≥3 months. This study was designed as a singlecenter random and control investigation. All patients were randomly divided into the experimental (chemotherapy followed by surgery) and control groups (surgery followed by chemotherapy).

Baseline data

Written informed consents were obtained from all participants prior to this study. All study procedures were in accordance with the ethics committee of our hospital. Baseline data including age, tumor size, clinical staging, positive rates of ER, PR, HER2 and KI67 between two groups were illustrated in **Table 1** in details. No statistical significance was observed in terms of all baseline characteristics between the experimental and control groups, suggesting all parameters were matched between two groups.

Therapeutic scheme

The patients eligible for this study were tolerant with the surgery combined with chemotherapy or radiotherapy. Subsequent endocrine treatment was implemented according to the clinical indications. Those presenting with disease progression, non-tolerant toxic reaction and those chose to discontinue were excluded from subsequent research. One cycle of chemotherapy endured for 3 weeks. Completion of surgery and radiotherapy was regarded as 1 cycle of treatment. All patients were randomly assigned into the experimental group and control group. In the experimental group, the patients firstly received 4 to 6 cycles of chemotherapy. At 2 weeks after the chemotherapy, they further underwent extended resection of chest wall tumors and subsequently received radiotherapy targeting the chest wall at postoperative 2 weeks. In the control group, the enrolled patients initially underwent extended resection of chest wall tumors. At postoperative 2 weeks, they subsequently were treated with 4-6 cycles of chemotherapy. At 2 weeks following the chemotherapy, they subsequently received radiotherapy of the chest wall.

Follow-up

After corresponding treatment, the patients positive for HER2 further received 1-year target therapy. Those positive for hormone receptor were subject to endocrine treatment for 5 years. Subsequent follow-up was conducted until the presence of disease progression, non-tolerant toxic reaction or the patients chose to drop out of the experiment. Progression-free survival (PFS) and overall survival (OS) were regarded as the endpoint events.

Evaluation methods

Evaluation criterion for tumor remission: During the period of chemotherapy, the tumor remission was assessed every 2 cycles of treatment. In addition, it was evaluated by surgery and radiotherapy. If the patients withdrew from the experiment due to other causes, such as adverse events and management malfunction, tumor remission was further evaluated every 8 weeks until the incidence of disease progression or use of novel anti-tumor therapy. PFS evaluation: after the completion of treatment, PFS was evaluated every 12 weeks during subsequent follow-up via telephone or visiting until the presence of disease progression or death. OS evaluation: after the completion of treatment, OS was evaluated every 12 weeks during subsequent follow-up via telephone or visiting until the death OR loss to follow-up. The observation period of follow-up endured until December 31, 2015. The quality of life of patients was assessed by EORTC QLQ-C30 questionnaire. The type and severity of adverse events were recorded to evaluate the therapeutic safety using NCI-CTC AE 4.0.

Statistical analysis

SPSS17.0 statistical software was utilized for data analysis. Measurement data were expressed as mean ± standard deviation (SD). Enumeration data were expressed as rate and percentage. Data analysis was performed using *t*-test, analysis of variance, *chi*-square test and rank-sum test. A *P* value of less than 0.05 was considered as statistical significance. PFS distribution between the experimental control groups was analyzed using Kaplan-Meier survival analysis. The HR and 95% CI of PFS were assessed using Cox regression analysis. OS distribution between two groups was evaluated using Kaplan-Meier survival analysis. The HR and 95% CI of OS were assessed using Cox regression analysis. Adverse events were analyzed using descriptive statistical method. The frequency and percentage of adverse events, and the relationship between abnormal results and experimental medication were statistically described. The incidence of adverse events between the experimental and control groups was analysed by Fisher's exact test.

Results

Baseline data

A total of 106 patients were divided into the experimental (chemotherapy followed by surgery, n=56) and control groups (surgery followed by chemotherapy group, n=50). The mean age in the chemotherapy group was (48.00 ±11.40) years and (49.14±8.72) years in the surgery group (*P*=0.771). The maximal diameter of the recurrent tumour was measured as (3.23±1.68) cm in the chemotherapy group, and (3.18±1.40) cm in the surgery group (*P*= 0.930). The clinical staging outcomes did not significantly differ between two groups. No significant difference was observed in terms of the positive rates of ER, PR, HER2 and KI67 between two groups (all *P*>0.05), as illustrated in **Table 1**.

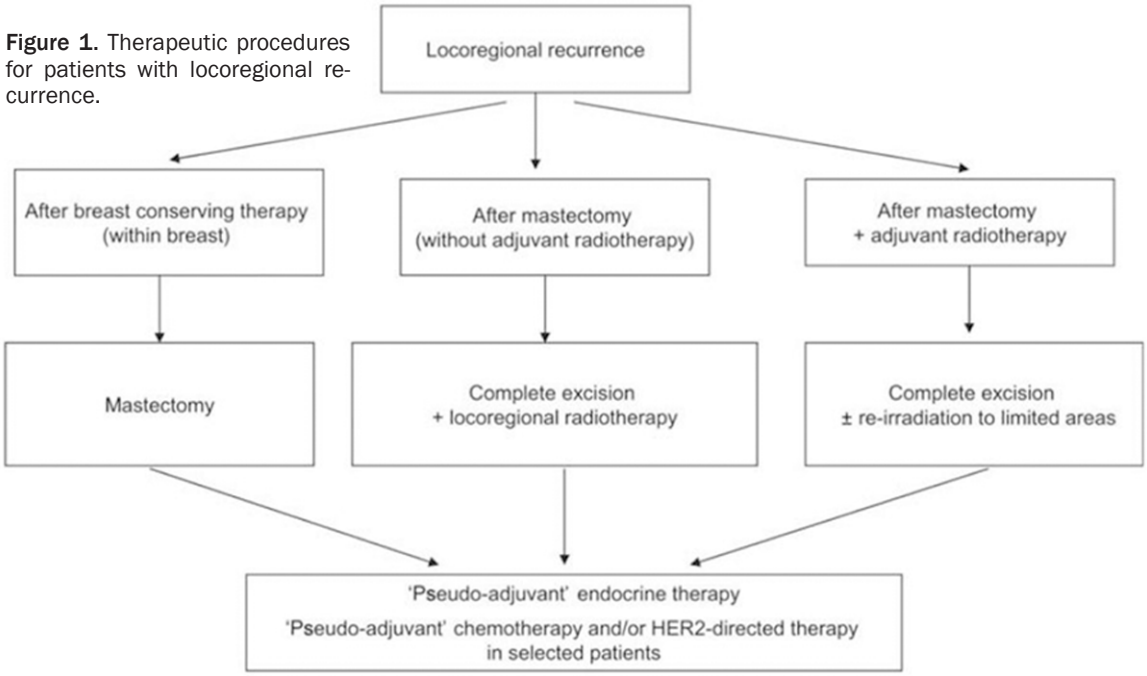

Figure 1. Therapeutic procedures for patients with locoregional recurrence.

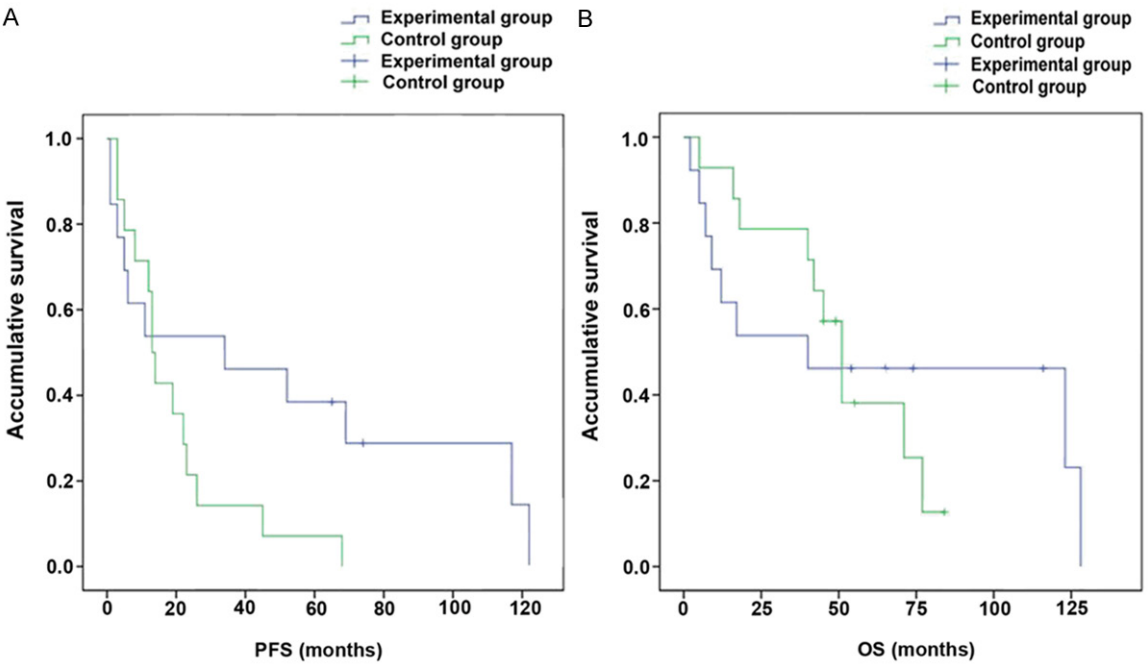

Figure 2. Comparison of PFS and OS between the experimental and control groups.

Locoreginal recurrence

Whenever possible, isolated locoregional recurrence should be treated with a curative intent, as illustrated in **Figure 1**. If feasible, complete excision of recurrent tumor is highly recommended. In patients previously treated by breast-conserving surgery, a mastectomy should be performed. In patients not previously irradiated, full-dose radiotherapy to chest wall and regional lymph node areas should be delivered. In those previously irradiated, re-irradiation to limited areas of the chest wall may be applied, taking into consideration the duration of radia-

tion-free period, intensity of existing late radiation effects and the risk of additional local-regional relapse. Inoperable patients can, if feasible, undergo radical radiotherapy to chest wall and regional lymph node areas with boost to macroscopic disease sites. However, in these patients, primary systemic therapy to decrease the size of the tumor and render it operable is preferred.

Comparison of PFS between two groups

In the experimental group, the mean PFS was calculated as (49.80±14.42) months, and (18.57±4.76) months in the control group. The median PFS in the chemotherapy group was (34.00±27.56) months, significantly longer compared with (13.00±1.25) months in the surgery group (χ^2=3.167; *P*=0.045), as revealed in **Figure 2A**.

Comparison of OS between two groups

In the chemotherapy followed by surgery group, the mean OS was calculated as (65.00±11.70) months, and (61.03±6.79) months in the surgery group with no statistical significance. The median OS in the chemotherapy group was (50.00±39.90) months, almost equal to (51.00 ±4.44) months in the surgery group (χ^2=0.084; *P*=0.773), as described in **Figure 2B**.

Discussion

The chest wall recurrence of breast cancer is defined as the recurrence of breast cancer in the affected breast and/or chest wall following surgery and/or radiotherapy [7-9]. Topical recurrence refers to the breast cancer recurs in the lymph node, armpit andsubclavicular region. Isolated local-regional recurrence (ILRR) is defined as cancer recurrence without metastasis of other sites. In this study, all enrolled patients were diagnosed with ILRR. The 5-year incidence of topical recurrence of breast cancer is reported to be between 6% and 23% following mastectomy, and approximately 6% following breast-conserving surgery and radiotherapy. Treatment of local recurrence in a previously irradiated postmastectomy breast cancer patient remains a clinically challenging problem [10]. Therapeutic options include resection, systemic therapy or additional radiation. Despite these approaches some patients develop progressing local cutaneous recurrence [11]. Local tumour control, regardless of any distant metastases, is important since the presence of an uncontrolled cutaneous recurrence may be highly distressing for the patient. Previous studies have demonstrated that young age, hereditary predisposition, extensive intraductal component, vascular invasion, positive incisional margin, positive lesion and insufficient systemic treatment are the risk factors of the topical recurrence of breast cancer following breast-conserving surgery [12]. Whether molecular typing is a prognosis factor for topical recurrence of breast cancer is widely debated. The 5-year survival of breast cancer patients with positive Luminal A, Luminal B and HER-2 and base type was 0.8%, 1.5%, 8.4% and 7.1%, respectively. Multi-variate analysis found that positive HER-2 and base type breast cancer acted as the independent high risk factors of topically recurrent breast carcinoma. Few prospective studies have been conducted. Optimization of clinical therapy and application of systemic treatment are urgently required. In this investigation.

According to the National consensus in China on diagnosis and treatment of breast cancer and NCCN guidelines, combined therapy of surgery followed by systemic chemotherapy and adjuvant management is recommended for breast cancer patients with chest wall recurrence after surgery. However, there is no consensus on the standard treatment of chest wall recurrence of breast cancer. Some researchers emphasize topical treatment and ignore the importance of systemic chemotherapy [13-15], others recommend systemic chemotherapy followed by surgery for large recurrent lesions. A majority of published data have supported that comprehensive treatment yields more clinical benefits compared with topical therapy alone [16]. Systemic therapeutic regime should be implemented based upon the degree of tumor invasion, medical history of systemic auxiliary therapy, concurrent diseases and patients' willingness, *etc*. Endocrinotherapy is recommended as the standard treatment for patients with positive hormone receptor [17]. For HER-2 positive patients without a medical history of trastuzumab treatment or heart disease contraindications, trastuzumab therapy is highly recommended. At present, tumor resection followed by radiotherapy is widely adopted by oncologists. However, whether radiotherapy followed by surgery is applicable remains elusive. The

selection of therapeutic plan depends upon the characteristics of potential local recurrence of malignant tumors. The goal of the therapy is to eliminate the recurrent lesions and reduce the potential risk of systemic metastasis. If the local and systemic recurrent lesions can be fully controlled, surgery or radiotherapy should be selected to eliminate the remnant topical lesions. If the topical tumors are resected by surgery or radiotherapy, the opportunity of systemic therapeutic regime will be missed. Subsequent treatment is blind and invalid without evaluation standard. The objective of treatment of chest wall recurrent breast cancer is to significantly control the severity of topical diseases and decrease or delay the incidence of distal recurrence. Active and rational strategies are urgently required including surgical resection, radio- and chemo-therapy, *etc*.

Conclusion

Application of systemic chemotherapy followed by surgical intervention resembles the neoadjuvant chemotherapy, which is capable of minimizing the toxic responses induced by long-term chemotherapy. Moreover, timely replacement of effective medications should be implemented to reduce the tumor size, enhance surgical efficacy and reduce the risk of recurrence, which eventually prolongs the PFS.

Disclosure of conflict of interest

None.

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