The Effect of Neoadjuvant Chemotherapy on ER, PR and HER-2 Expression in Breast Cancer

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Abstract

Objective: Through comparativing the change of the ER, PR and HER-2 expression in tumor tissue before and after neoadjuvant chemotherapy (NAC) in locally advanced breast cancer patient, to discuss whether there is influence for NACon ER, PR, HER-2 expression for breast cancer. Also, the relationship of ER, PR, HER-2 and chemosensitivity is also discussed. **Methods:** The expressions of ER, PR and HER2 in paraffin sections of breast cancer tissues from 51 patients before and after NAC were detected by immunohistochemical method. The assessment for the relationships between ER, PR, HER-2 and the efficiently of NAC is done. **Results:** For the 51 peoples, there is no statistical significance for change of ER, PR and HER-2 expression before and after NAC (P > 0.05). There is statistical significance for the differences of chemotherapeutic effectiverate between ER negative and ER positive, PR negative and PR positive, HER2 over-expressed group and HER2 non over-expressed group (P < 0.05). Pathological complete response (pCR) was related to molecular classification and the number of chemotherapy cycles. There is statistically significant or prognisis difference about hormone receptor, HER2 over-expressed and three-negative breast cancer (P < 0.05). **Conclusion:** NAC maybe could not change the expression of ER and PR, and HER2 for breast cancer patients. The patients with HER-2 over-expressed are not sensitive to chemotherapy, and the patients with ER or PR negative get more benefits from chemotherapy. The breast cancer patients who could obtain pCR could get better prognosis after NAC.

Keywords

Breastcancer, Neoadjuvant Chemotherapy, ER, PR, HER-2

1. Introduction

Breast cancer is a malignant tumor with a high incidence, accounting for 7% -

10% of patients with malignant tumors [1]. Breast cancer is the second most common malignant tumor in women. According to the statistics, the quality of breast cancer patients in China has accounted for 12.2% of worldwide breast cancer patients. The number of infected people can reach more than 160,000 per year and it is the second common malignant tumor for women, the deaths can reach more than 40,000, accounting for 9.6% in the world [2]. It is the sixth leading cause of death common malignant tumors among women, and its incidence is still increasing year by year. It is estimated that by 2030, the number of persons infected breast cancer will reach 2.64 million cases worldwide and the death toll will be reached 1.7 million [3]. The pathological features, biological characteristics and prognosis of breast cancer are closely related to the expression of ER、PR and HER-2 in system. Although surgical treatment is still the first choice for the treatment of breast cancer, the importance of adjuvant chemotherapy is getting more and more attention.

Neoadjuvant Chemotherapy (NAC) refers to use of systemic cytotoxic drugs for person who is already diagnosed malignancy before surgery or before radiotherapy. Neoadjuvant chemotherapy has been clinically carried out since the 1970s and it is an important treatment. Although NAC does not improve disease-free survival (DFS) and overall survival (OS), it can significantly increase the chance of surgery in patients with locally advanced breast cancer [4]. NAC is a clinically widely used trend. For patients with locally advanced breast cancer, it is generally the preferred treatment.

In this experiment, we examined the expression of ER, PR and HER2 in tumor tissues before and after neoadjuvant chemotherapy in 51 patients with locally advanced breast cancer, and compared them to understand the effect of NAC on these factors and the efficacy of neoadjuvant chemotherapy. And the survival of different types of breast cancer patients was evaluated.

2. Data Collection

2.1. Experimental Object

51 patients who were diagnosed (In core needle penetration pathology department) as breast cancer and received neoadjuvant chemotherapy by the First People's Hospital of Jingzhou City from 2010 to 2013. All selected person are women (Age: 28 - 65 years old). Median age is 48.8 years old, no other treatment was done before neoadjuvant chemotherapy. All patients have completed the entire treatment plan, tumor diameter ≥ 4 cm (measured by clinical physical examination two-path measurement combined with color Doppler ultrasound measurements to obtain primary breast cancer Size values), all patients had no distant metastasis.

2.2. Neoadjuvant Chemotherapy

The chemotherapy cycle of all cases is 2 cycles at least, the anthracycline combined with purple shirts mainly are mainly used. Chemotherapy regimens in-

cludes TEC, EC-T, FEC-T, and NP regimens, as follows: TEC regimen: DOC (Docetaxel) 75 mg/m², EPI (Epirubicin) 100 mg/m², CTX (Cyclophosphamide) 500 mg/m²d₁. EC-Tregimen: EPI 100 mg/m², CTX 600 mg/m²d₁, sequential administration of DOC 100 mg/m²d₁ after 4 cycles. FEC-Tprotocol: 5-FU500 mg/m², EPI 100 mg/m², DOC 100 mg/m²d₁, sequential administration of DOC 100 mg/m²d₁ after 3 cycles. NP regimen: NVB (Vinorelbine) 25 mg/m²d₁, d₈, DDP (Cis-platinum complexes) 75 mg/m² d₁, all are 3 week plan. Before the next cycle of chemotherapy, the changes in tumor size were assessed by measurement and mammography to assess the efficacy of chemotherapy. In the third cycle, patients who were evaluated as ineffective before chemotherapy were changed to their chemotherapy regimen to re-enter the evaluation procedure or to change the treatment plan for surgery.

2.3. Experimental Methods

Immunohistochemistry was used to detect ER, PR and HER-2 in breast cancer tissues before and after neoadjuvant chemotherapy.ER, PR and HER2 antibodies were purchased from Ventana, USA. The film was read by a professional pathology chief physician through an optical microscope, and the results were judged based on the percentage of positive cells. According to the results of HE staining, the tumor tissue is distinguished from the normal breast tissue, and the cancer nest is distinguished from the cancerous periphery. The evaluation criteria for ER and PR: 1) ≥50% of infiltrating cancer cells were labeled with nuclear staining (+++); 2) 20% - 50% of infiltrating cancer cells were labeled with nuclear staining (++); 3) 1% - 20% of invasive cancer cells are labeled with nuclear staining (+); 4) labeled negative if not stained. The recommended criteria "Herceptin Test" was used for determining HER-2 results.ER, PR, and HER2 are changed from +++ to − - ++, ++ to + - −, and + to − are determined to be down-regulated. Otherwise, it shall be determined to up-regulated.

2.4. Efficacy Evaluation

The efficacy of chemotherapy was measured by the change of the size of the primary breast cancer. The size of the primary breast cancer was measured by clinical examination and combined with the color ultrasound measurement. According to the solid tumor efficacy evaluation criteria established by "WHO", the efficacy of breast cancer chemotherapy was evaluated.

2.5. Follow-Up Visit

From the start of treatment to March 31, 2016, the median follow-up time was 45 months. All patients were followed up by telephone or outpatient visit and the DFS and OS data were obtained.

3. Statistical Methods

All data were processed by statistical software SPSS19.0. The correlation between

ER, PR and HER2 and neoadjuvant chemotherapy and their changes before and after neoadjuvant chemotherapy were inspected by the calibration X^2 and use Kaplan-Meier to analyze the survival of breast cancer. $P < 0.05$ was considered statistically significant.

4. Results

4.1. More Information about Sociodemographic and Clinical Characteristics of the Participants Should Be Showed in Table 1

See Table 1.

Table 1. Sociodemographic and clinical characteristics of the participants (n = 51).

Clinical characteristics		n
Age (years)	≥50	25
	<50	26
Menopausal	No	22
	Yes	29
Paracentesis type	Invasive duct carcinoma	38
	Invasive small-leaf cancer	3
	Myeloid cancer	1
TNM periodization	IIb	14
	IIIa	32
	IIIb	4
	IIIc	1
ER	−	16
	+	7
	++	8
	+++	20
PR	−	20
	+	15
	++	19
	+++	7
HER-2	0	23
	+	8
	++	10
	+++	10
Chemotherapy programme	EC	41
	EC-T	4
	TEC	4
	NP	2
Preoperative chemotherapy	≤3	23
	>3	28
Molecular typing of breast cancer	Luminal subtype	34
	Her-2 over-expression subtype	9
	Triple Negative subtype	8

4.2. Relationship between Expression of ER, PR, HER2 and Curative Effect of Chemotherapy

Clinical assessment of curative effect after 2 - 6 cycles of neoadjuvant chemotherapy: 15 patients with PR (partial response), 17 patients with CR (complete remission), 9 patients with SD (stable disease), and 1 patient with disease progression, with a total effective rate of 80.3%. The pCR (pathologic complete response) was 9 cases. Statistical analysis showed that the difference in the effective rate between the negative and positive groups of ER, PR, HER2 was statistically significant (P < 0.05), ER, PR and HER2 negative breast cancer were more sensitive to neoadjuvant chemotherapy (details should be showed in Table 2).

4.3. Analysis of Influencing Factors of Pathological Complete Response Rate

Among the 51 patients, breast cancer patients with positive hormone receptors had lower pCR rates. Age, menstrual status, pathological type of tumor, clinical stage, hormone receptor status, HER2 expression status, and chemotherapy regimen were not significantly associated with neoadjuvant chemotherapy for pathological complete remission (P > 0.05), while the number of neoadjuvant chemotherapy cycles and the molecular typing status was significantly correlated with pathological complete remission (P < 0.05) (details should be showed in Table 3).

4.4. Changes in Tumor Biological Factors before and after Neoadjuvant Chemotherapy

Among the 51 patients, 9 patients have achieved pathological remission, and no cancer tissue was detected after chemotherapy. In the other 42 cases with cancer tissue detection, ER, PR, and HER-2 showed some changes after chemotherapy. However, these changes were not statistically significant (p > 0.05) (details should be showed in Table 4 and Figure 1).

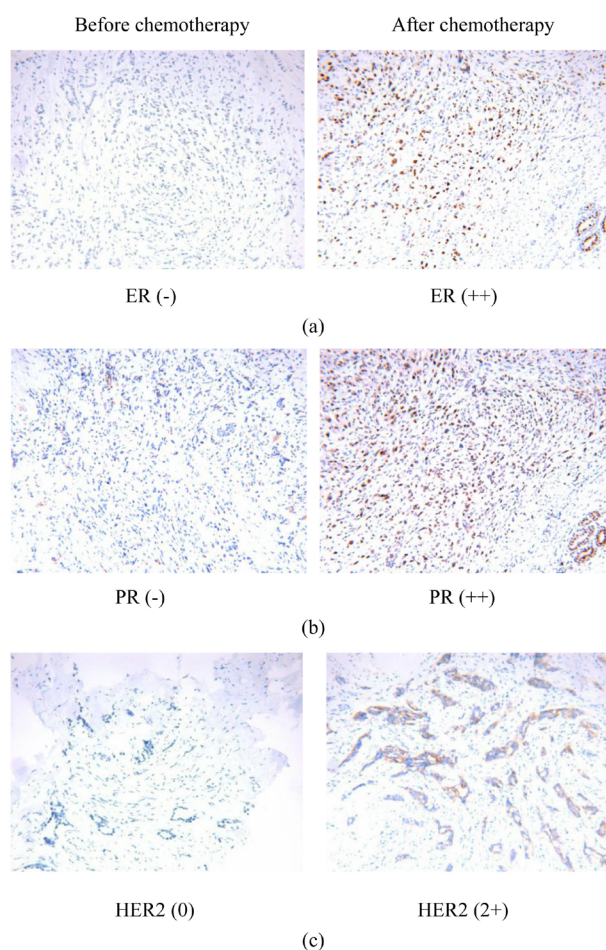## 4.5. Influence Factors for Survival Prognosis

The follow-up time of all cases was from 12 months to 55 months. The median follow-up time was 45 months. The DFS and OS for hormone receptor type were

Table 2. The relationship between the changes of ER, PR, HER2 and the efficacy of NAC (n = 51).

		pCR	CR + PR	SD + PD	x^2	P
ER	_	6	22	2	7.753	0.021
	+	3	10	8		
PR	_	7	11	3	6.105	0.047
	+	2	21	7		
HER2	+++	1	9	7	8.441	0.015
	Ohter	8	23	3		
Total		9	32	10	51	

Table 3. The correlation for pathological complete response and each factor (n = 51).

P	pCR		non-pCR		P
	n	Percentage	n	Percentage	
Age (years)					
≥50	5	9.8	20	39.1	0.187
<50	4	7.8	22	43.1	
Menopausa					
No	3	5.9	19	37.3	0.420
Yes	6	11.8	23	45.1	
Paracentesis type					
Invasiveduct carcinoma	8	15.8	30	58.8	
Invasive small-leaf cancer	0	0	2	3.9	0.736
Myeloid cancer	1	1.9	0	0	
TNM periodization					
IIb	2	3.9	12	23.5	
IIIa	7	13.7	25	49	0.834
IIIb	0	0	3	5.9	
IIIc	0	0	1	1.9	
ER					
Negative	6	11.8	10	19.6	0.920
Positive	3	5.9	31	60.8	
PR					
Negative	7	13.7	13	25.5	0.818
Positive	2	3.9	29	56.9	
Her-2					
Negative	8	15.7	33	64.7	0.501
Positive	1	2	9	17.6	
Chemotherapy programme					
TEC	9	17.6	32	62.2	
EC-T	0	0	4	7.8	0.666
FEC-T	0	0	4	7.8	
NP	0	0	2	3.9	
Preoperative chemotherap					
≤3	4	5.9	19	54.9	0.002
>3	5	11.8	23	27.5	
Molecular typing					
Luminal subtype	2	3.9	32	62.2	
Her2 over-expression	4	7.8	5	9.8	0.007
Triple Negative subtype	5	5.8	5	9.8	

Before chemotherapy   After chemotherapy

ER (-)   ER (++)

(a)

PR (-)   PR (++)

(b)

HER2 (0)   HER2 (2+)

(c)

Figure 1. (a): The ER expression change before and after NAC (×200); (b): The PR expression change before and after NAC (×200); (c): The HER-2 expression change before and after NAC (×200).

**Table 4.** The compare about ER, PR, HER2 change before and after neoadjuvant chemotherapy.

|	ER		PR		Her2	
	(−)	(+)	(−)	(+)	(−)	(+)
Before chenotherapy	11	31	12	30	31	11
After chemotherapy	13	29	13	29	28	14
x2	0.2	33	0.0	57	0.5	13
P	0.6	29	0.8	11	0.4	74

significantly higher than HER-2 type and triple negative type ($P < 0.05$). There is statistic significance (see **Figure 2** and **Figure 3** about details). The DFS of the pCR and non-pCR groups were 88.9% and 47.6%, respectively, $P = 0.005$; the OS of the pCR and non-pCR groups were 100% and 71.4%, respectively, $P = 0.041$. After neoadjuvant chemotherapy, the breast cancer patient who has received pCR had significantly longer DFS and OS than patients who did not receive pCR (see **Figure 4** and **Figure 5**).
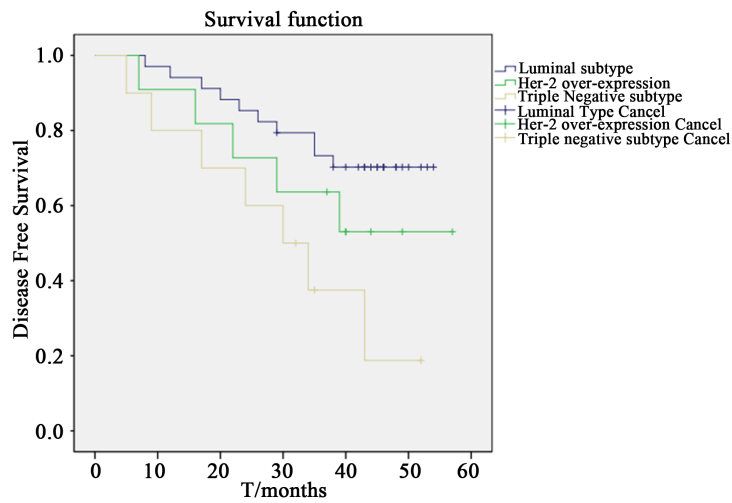
Figure 2. The Kaplan-Meier analysis for disease free survival about different molecular subtype of breast cancer (P = 0.02).
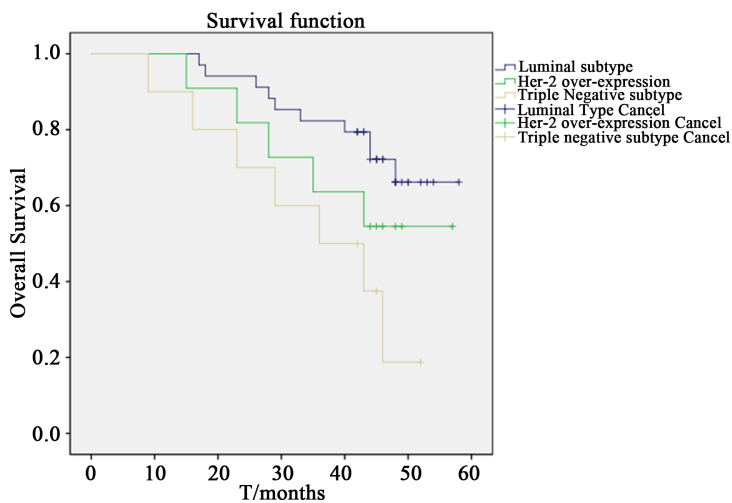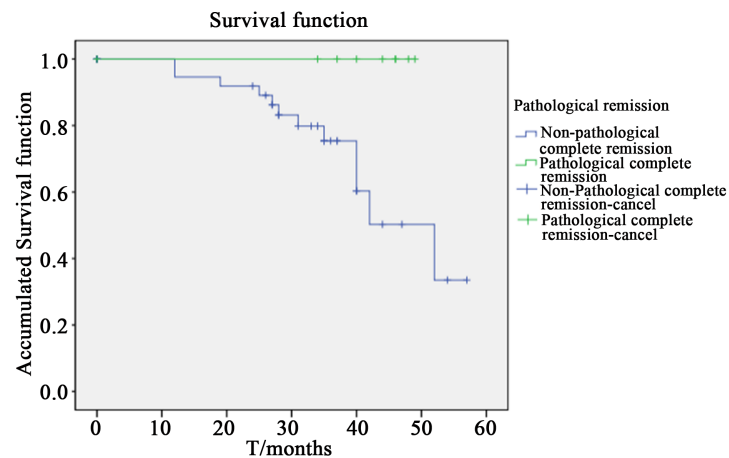

Figure 3. The Kaplan-Meier analysis for overall survival about different molecular subtype of breast cancer (P = 0.03).
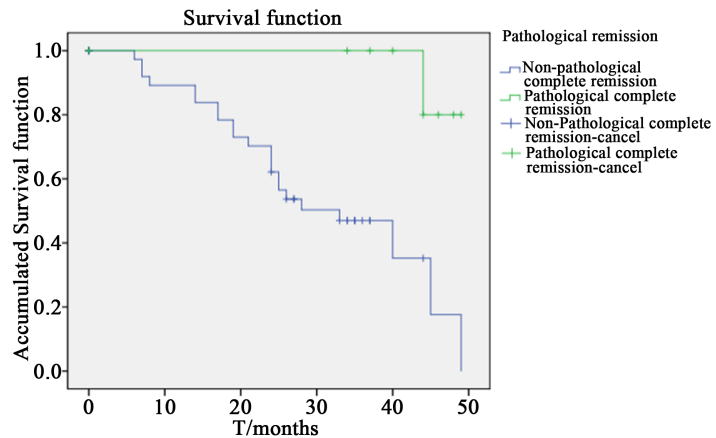
Figure 4. The Kaplan-Meier analysis for disease free survival about pCR and non-pCR of breast cancer (P = 0.005).

Figure 5. The Kaplan-Meier analysis for overall survival about pCR and non-pCR of breast cancer (P = 0.041).

5. Discussion

Neo-adjuvant chemotherapy (NAC) can reduce tumor burden, reduce tumor volume, reduce tumor stage, increase patient's chance of surgery, and increase breast-conserving rate by eliminating tumor cells. At the same time, we could also obtain information on the response of the tumor to the treatment through tumor size change and pathological change, it will be a great help for developing a treatment plan [5] [6] in next step, then avoid the blindness of postoperative chemotherapy, improve the quality of life for patients. Because of its advantage in lowering the stage for primary tumor, NAC has become a standard treatment for patients with late-stage breast cancer [7] [8] [9].

Clinically, according to the expression of ER, PR, HER2 and Ki67, breast cancer is divided into: 1) Luminal type A; 2) Luminal type B; 3) HER-2 overexpression type; 4) three-negative type [10]. It is well-known that ER and PR positive normally mean that patients are more sensitive to endocrine therapy. A retrospective analysis has reported that ER and PR in breast cancer predict patients' sensitivity to chemotherapy and can help assess prognosis [11] [12]. By studying thousands of patients with locally advanced breast cancer and lymph node metastasis, Berry found that ER-negative breast cancer patients benefited more from chemotherapy [13] than ER-positive breast cancer patients. Compared with ER-positive breast cancer, NSABP B27 clinical trials showed ER-negative breast cancer has a higher pCR (16.7% vs. 6.8%) [14]. Some clinical trials in China have reached the same conclusion [15] [16], and no different opinions have been reported in the literature. This study also concluded that hormone receptor-negative patients have better chemotherapy results, which may be because ER-negative tumors have better replication capacity than ER-positive tumors, so ER-negative tumors are more sensitive to chemotherapy than ER-positive tumors, and this sensitivity maybe also increases as tumor expansion increases. The overexpression of HER2 predicts that the tumor has a strong invasive ability, and the tumor has a high possibility of malignancy, it is prone to

recurrence and has a poor prognosis [17]. There are few studies on the correlation between HER2 expression and chemotherapy efficacy, and most of these studies have no significant correlation between HER2 overexpression and chemotherapy case response rate [18]. In this study, the effective rate in the HER2 expression group was 58.8%, and the effective rate in the non-overexpression group was 91.1%. The difference between the two groups was statistically significant, indicating that HER2 overexpressing patients are more susceptible to drug resistance and less sensitive to chemotherapy. For patients with HER2-strong positives, the combination of the targeted therapy Herceptin and neoadjuvant chemotherapy can significantly improve the case remission rate of breast cancer, so the Herceptin shall be used for HER2-positive patients at the same time.

Whether Chemotherapy could change the expression status and level of these factors such as er, pr and HER2 or not, there is no unified conclusion till now. Previous studies have shown that NAC could change the status of hormone receptor [19]-[24] and HER2 [21] [23] [24] [25] [26], but some studies have reached the opposite conclusion [27] [28] [29] [30]. This study reminds that chemotherapy could change the status of hormone receptors and her2, but it is mainly about increase and decrease of expression, the qty of changing from positive to negative or changing from negative to positive is less, there is no statistical significance, and the change have no correlation with chemotherapy regimen Choose.

This study shows that hormone receptors and HER2-negative patients have better efficacy and benefit more from chemotherapy, so it could be used as an indicator to predict whether breast cancer is sensitive to neoadjuvant chemotherapy or not. The status of hormone receptors may be changed after neoadjuvant chemotherapy, but there is no statistically significant about that the change could affect the change of treatment. Patients with pCR obtained by neoadjuvant chemotherapy have significantly better DFS and OS than those without pCR, it means patients with pCR have a better prognosis, so the molecular typing of breast cancer and pCR could be as a independent prognostic factors for chemotherapy of breast cancer.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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