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Original Article

Prognostic value of hormone receptor status conversion following neoadjuvant chemotherapy in a series of operable breast cancer patients

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Abstract: Background: To investigate the prognostic value of hormone receptor (HR) status conversion after neoadjuvant chemotherapy (NAC) in patients with primary breast cancer. Methods: 267 stage II-III breast cancer patients treated with NAC who had residual disease in the breast after NAC were retrospectively studied. The patients were divided into four groups based on the HR status: Group A, patients with HR-positive both before and after NAC; Group B, patients with HR status positive-to-negative change; Group C, patients with HR status negative-to-positive change; Group D, patients with HR-negative both before and after NAC. Patients with positive HR status (regardless of before or after NAC) were treated with adjuvant endocrine therapy, and a survival analysis was performed. Results: In total, 15.7% of patients had HR status change after NAC. progression-free survival (PFS) in Group A was similar to that in Group C (hazard ratio, 1.16; $P = 0.652$), but that in Group B was significantly lesser than that in Group A (hazard ratio, 6.88; $P = 0.001$), and that in Group C was significantly longer than that in Group D (hazard ratio, 6.88; $P = 0.001$). A similar pattern of results was obtained for overall survival (OS). Conclusions: The switch of HR status after NAC is remarkable for breast cancer. An HR switch may identify patients who would benefit from adjuvant endocrine therapy and impact the long-term outcome.

Keywords: Breast cancer, neoadjuvant chemotherapy, hormone receptor, changes

Introduction

Breast cancer is the most common malignancy found in women worldwide, with a relatively high incidence of 20% of all malignancies [1]. Neoadjuvant chemotherapy (NAC) has been a relatively standard treatment for locally advanced and initially inoperable breast cancer. This strategy allows patients to undergo breast-conserving surgery and provides information on the efficacy of chemotherapy [2].

Before the initiation of NAC, core-needle biopsy (CNB) is usually performed to establish the histological diagnosis. NAC for breast cancer is evolving and subsequent adjuvant systemic treatment is mainly based on the presence of the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) statuses on the core needle biopsy. Breast cancer is a composite, and immunohistochemistry allows the definition of three main subgroups with different therapeutic responses and different outcomes, including luminal tumors, HER2-positive and triple-negative subtype [3]. The effect of NAC varies according to the intrinsic subtype of tumors. Patients with HER2-overexpressed and triple-negative breast cancer have better responses and higher pathologic complete response (pCR) rates to NAC [4]. On the other hand, HR-positive breast cancer is widely known as a subtype with favorable prognosis despite lower sensitivity to chemotherapy. Adjuvant endocrine therapy is indicated in all patients with a positive hormone receptor (HR) status, which is defined as ER positive and/or PR positive. Several retrospective breast cancer studies have suggested that NAC significantly altered estrogen receptor (ER) or progesterone receptor (PR) status [5-9], however, it is not well known whether these receptors change after NAC, requiring a change in

further adjuvant systemic treatment, and whether an HR switch may identify patients who would benefit from adjuvant endocrine therapy and impact the long-term outcome. The current study was therefore conducted with the objective of evaluating the frequency and impact of change in the HR status on the long-term outcomes in the breast cancer patients receiving NAC.

Materials and methods

Patients

We selected 296 female patients with primary breast carcinoma treated with both NAC and surgery, which were diagnosed from 2008 to 2013 by needle core biopsy at Guangxi University Affiliated Tumor Hospital (China). A complete history of patient characteristics, clinical and imaging examinations (e.g., bilateral mammography, breast ultrasound, or MRI), and the pathologic assessments of morphologic and biologic features were collated. Patients with metastatic diseases before surgery, bilateral breast cancer and inflammatory breast cancer were not included in this study. Patients without both surgical pathology reports for pre- and post-neoadjuvant chemotherapy and tumors without complete hormone receptor expression profiles corresponding pre- and post-neoadjuvant chemotherapy were excluded. The clinical stages of the patients ranged from cT2N0M0 to cT3dN3M0. The patients were classified into four groups on the basis of the HR status of their lesions before and after NAC: Group A, 135 patients with lesions that were HR-positive both before and after NAC; Group B, 28 patients with lesions showing HR status positive-to-negative change; Group C, 14 patients with lesions showing HR status negative-to-positive change; Group D, 90 patients with lesions that were HR-negative both before and after NAC. The mean age at the time of diagnosis of breast cancer was almost the same in the four groups. Patients with positive HR status (regardless of before or after NAC) were treated with adjuvant endocrine therapy following chemotherapy.

Treatment

NAC was assigned to each patient according to their risk on the basis of clinical parameters, also in accordance with the recommendation by the St. Gallen International Expert Consensus at the time. The NAC regimens included FEC (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2, every 3 weeks), AC (doxorubicin 50 mg/m^2, and cyclophosphamide 500 mg/m^2, every 3 weeks) followed by T (docetaxel 75 mg/m^2 every 3 weeks) each for 4 cycles, AT (doxorubicin 50 mg/m^2, docetaxel 75 mg/m^2 every 3 weeks) and TEC (docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks). Chemotherapy was administered for a median of 4 cycles (range 2-6 cycles) before surgery. All the patients underwent mastectomy plus axillary lymph node dissection within 4 weeks after NAC at Guangxi University Affiliated Tumor Hospital. Additional courses of adjuvant chemotherapy, including anthracycline-based and/or taxane-based regimens, were administered after operation to complete a total of 6-8 courses of adjuvant chemotherapy according to their risk on the basis of clinical parameters and pathologic evaluations after surgery. Radiotherapy was applied after the completion of adjuvant chemotherapy. All of the patients with HR-positive tumors before NAC or HR-positive residual tumors after NAC received standard endocrine therapy for 5 years (tamoxifen for premenopausal patients, aromatase inhibitor for postmenopausal patients or sequential tamoxifen and aromatase inhibitor).

Evaluation of NAC response

The clinical response to NAC was evaluated by physical and imaging examinations according to RECIST. No clinical evidence of tumor in the breast and axillary lymph nodes was defined as a complete response (CR). Reduction in the greatest tumor diameter exceeded 30% was graded as a partial response (PR). Tumor reduction less than 30% or an increase up to 20% in the greatest diameter was considered as a stable disease (SD). Tumors that increase of more than 20% in the greatest diameter or appearance of new disease were considered as a progressive disease (PD). The achievement of pathologic complete response (pCR) on postoperative specimens was defined as the absence of invasive residuals in breast or nodes.

Clinical outcome assessment

All patients were followed-up until the date of death or when censored at the latest date

Table 1. Patient and baseline tumor characteristics

Characteristic	N (%)
Age, ≤45 years	152 (56.9)
Menopausal status	
Premenopausal	163 (61.0)
Postmenopausal	104 (39.0)
Stage	
2	113 (42.3)
3	154 (57.7)
Tumor size (cm)	
≤2.0	49 (18.4)
>2.0	118 (81.6)
Clinical nodal status	
Negative	73 (27.3)
Positive	194 (72.7)
Nuclear grade	
1	22 (8.2)
2	65 (24.4)
3	180 (67.4)
HR status	
Negative	104 (39.0)
Positive (>1%)	163 (61.0)
HER2 status	
Positive	129 (48.3)
Negative	138 (51.7)
Ki-67 index	
≤14%	58 (21.7)
>14%	209 (78.3)
Histology	
Invasive ductal carcinoma	254 (95.1)
Others	13 (4.9)
NAC regimens	
FEC	107 (40.1)
TEC	72 (27.0)
AT	30 (11.2)
AC followed by T	58 (21.7)
Clinical response	
CR	38 (14.2)
PR	197 (73.8)
SD/PD	32 (12.0)

NAC, neoadjuvant chemotherapy; HR, hormone receptor; HER-2, human epidermal receptor; FEC, 5-fluorouracil + epirubicin + cyclophosphamide; TEC, docetaxel + epirubicin + cyclophosphamide; AT, doxorubicin + docetaxel; AC followed by T, doxorubicin + cyclophosphamide followed by docetaxel; CR, complete response; PR, partial response; SD/PD, stable disease or progression of disease.

(December 30th 2013). The median duration of follow-up for all of the patients in this study was 42 months. Overall survival was defined as the time from the date of operation to death or when censored at the latest date if patients were still alive. DFS was defined as the length of time from the date of operation to events such as local relapse or distant metastases, the occurrence of a new primary tumor, or death without evidence of cancer.

Table 2. Estrogen receptor and progesterone receptor statuses in cases pre- and post-neoadjuvant chemotherapy

(ER, PR) pre-NAC	(ER, PR) post-NAC (n)			
	(+, +)	(+, -)	(-, +)	(-, -)
(+, +)	43	8	11	3
(+, -)	9	27	6	10
(-, +)	9	7	15	15
(-, -)	3	8	3	90

NAC, neoadjuvant chemotherapy; ER, estrogen receptor; PR, progesterone receptor. n, numbers of patients.

Immunohistochemical analysis

ER, PR, HER-2 status and Ki-67 index were evaluated before and after NAC by immunohistochemistry (IHC). All immunohistochemical analyses were carried out in a single reference laboratory and evaluated by light microscopy blindly and independently by two pathologists. The cutoff value for ER positivity and PR positivity was 1% positive tumor cells with nuclear staining. HR positivity was defined as positivity for ER and/or PR. HER2 protein overexpression was defined as with 3+ complete membrane staining. Ki-67 positivity was scored as the percentage of nuclear stained cells greater than 14% (at least 500) in each case. Antibodies, dilutions and suppliers were as follows: ER (M7047, clone 1D5, 1: 100 dilution, Dako), PR (M3569, clone PgR636, 1: 100 dilution, Dako), Ki-67 (MIB1, 1: 100 dilution; Dako); HER-2 (polyclonal, 1: 100 dilution; Dako, Carpenteria, CA, USA).

Statistical analysis

Analyses were conducted using SPSS v16.0 (SPSS Inc., Chicago, IL). The relationship between HR alterations and other characteristics was evaluated using Chi-square or Fisher's exact test. Univariate and multivariate analyses to determine independent prognostic factors were performed by the Cox proportional model. Variables with a $P < 0.05$ were accepted for the

Table 3. Correlation between patients' characteristics, pre-neoadjuvant chemotherapy and HR conversion

Characteristic	Group A (HR+→HR+) (n = 135)	Group B (HR+→HR-) (n = 28)	Group C (HR-→HR+) (n = 14)	Group D (HR-→HR-) (n = 90)	*P* value*
Age					NS
≤45 years	77	16	9	50	
>45 years	58	12	5	40	
Menopausal status					NS
Premenopausal	81	18	9	55	
Postmenopausal	54	10	5	35	
Stage					NS
2	62	8	5	38	
3	73	20	9	52	
Tumor size (cm)					0.018
≤2.0	18	21	1	9	
>2.0	117	7	13	81	
Clinical nodal status					NS
Negative	40	4	4	25	
Positive	95	24	10	65	
Nuclear grade					0.003
1	11	3	0	8	
2	35	2	1	27	
3	89	23	13	55	
HER2 status					NS
Positive	57	21	8	43	
Negative	78	7	6	47	
Ki-67 index					NS
≤14%	25	8	5	20	
>14%	110	20	9	70	
NAC regimens					NS
FEC	57	16	7	28	
TEC	26	8	5	30	
AT	17	1	0	12	
AC followed by T	35	3	2	20	
Clinical response					NS
CR	12	2	7	17	
PR	98	22	7	70	
SD/PD	25	4	0	3	

*The significance of differences in variables between the patients with and without HR conversion was evaluated. NS, not significant; NAC, neoadjuvant chemotherapy; HR, hormone receptor; HER-2, human epidermal receptor; FEC, 5-fluorouracil + epirubicin + cyclophosphamide; TEC, docetaxel + epirubicin+ cyclophosphamide; AT, doxorubicin + docetaxel; AC followed by T, doxorubicin + cyclophosphamide followed by docetaxel; CR, complete response; PR, partial response; SD/PD, stable disease or progression of disease.

multivariate model. Kaplan-Meier and the log-rank test were employed to evaluate the distribution of DFS and OS. All *P* values reported in this analysis were two sided, and a *P* value of less than 0.05 was considered significant.

Results

Patient characteristics

Table 1 summarizes the characteristics of patients in this study. Overall, among the 296 NAC-administered patients, pCR was achieved in 9.8% of patients (29/296). Complete responders were excluded from this study because a retest of biomarkers in surgery specimens was not possible. The median age of the remaining 267 non-pCR patients was 46 years (range 22-73 years), and 61.0% of these patients were premenopausal. The distribution of these patients in the four groups was as follows: Group A, 135 (45.0%) patients; Group B, 28 (15.8%) patients; Group C, 14 (6.5%) patients and Group D, 90 (32.7%) patients.

All patients underwent 2-6 cycles of NAC using a chemotherapy regimen of FEC (40.1%), TEC (27.0%), AT (11.2%), or AC followed by T (21.7%). All patients whose lesions showed positive HR status regardless of pre- or post-NAC had been treated with endocrine therapy. None of the HER2-positive patients were administered trastuzumab during neoadjuvant or adjuvant chemotherapy in this study.

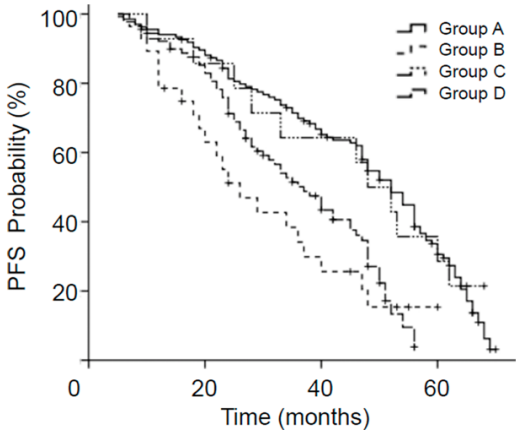

Figure 1. Kaplan-Meier curves of progression-free survival (PFS) in four groups. Crosslet "+" indicate censored data points. Log-rank test was significant for PFS (P = 0.026).

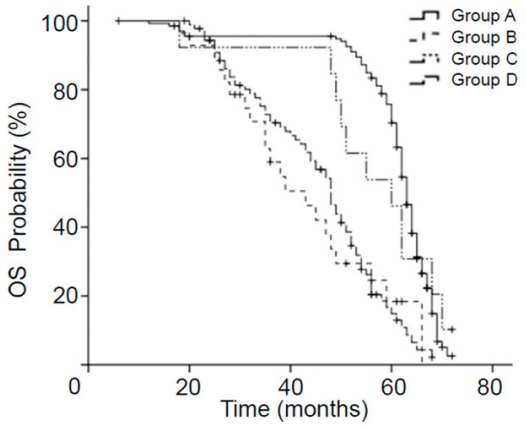

Figure 2. Kaplan-Meier curves of overall survival (OS) in four groups. Crosslet "+" indicate censored data points. Log-rank test was significant for OS (P = 0.014).

Change in HR status

The ER, PR status was retested by using IHC of the operation specimens in 267 patients with residual invasive carcinoma. The pre- and post-NAC ER and PR status are shown in **Table 2**. The HR status changed from positive to negative in 17.2% (28 of 163) of patients, meanwhile the HR status changed from negative to positive in 13.5% (14 of 104) of patients. The changes in the ER or PR status were observed not only in cases with borderline positive (grades 1-2) staining but also in those with strongly positive (grades 3-5) staining.

Relationship between HR conversion and clinical variables

A correlation in HR conversion and other variables, including age, menopausal status, tumor size, node status, HER-2 status, Ki-67 index, and nuclear grade, were performed to investigate the differences in the clinical characteristics and biomarkers for predicting HR conversion after NAC. As showed in **Table 3**, the patients with or without HR conversion did not differ by age, menopausal status, node status, tumor size, NAC regimens or cycles, and clinical response. Conversions of HR-positive to HR-negative were more frequently observed in HER-2-positive patients compared to HER-2 negative (P = 0.023). However, no significant differences in HER2 levels were detected in patients with HR-negative tumors changed to HR-positive. HR conversions was also observed more frequently in poorly differentiate tumors (grade 3, P = 0.038). Besides, a relatively high proportion of high Ki-67 indexes were observed in tumors with HR alteration compared to tumors in which HR status remained negative (62% vs. 34%, P = 0.016).

HR alteration and patient outcomes

The median duration of follow-up was 42 months. **Figures 1** and **2** shows the Kaplan-Meier curves for PFS and OS in the four groups, respectively. The differences among the curves were statistically significant as determined by the log rank test (P = 0.026 and P = 0.014). The 3-year DFS rates in Groups A, B, C, and D were 68.9, 32.1, 64.3, and 43.3%, respectively; meanwhile, the 4-year OS rates in Groups A, B, C, and D were 94.1, 32.1, 92.9, and 48.9%, respectively. The PFS of Groups A and C was similar (hazard ratio, 0.83; 95% CI, 0.36-2.17, P = 0.484), whereas that of Group B was significantly shorter than that of Group A (hazard ratio, 0.39; 95% CI, 0.16-0.92, P = 0.024), and that in Group C was significantly longer than that in Group D (hazard ratio, 0.58; 95% CI, 0.22-1.43, P = 0.046). The OS analysis was similar with the PFS, except that there was no significant difference between group C and group D (P = 0.452). We evaluated the clinical variables at baseline predicting for PFS using logistic regression analyses (**Table 4**). Age (P = 0.021), tumor size (P = 0.006), nuclear grade (P = 0.037), pre-NAC node metastasis (P = 0.035),

Table 4. Univariate and multivariate logistic regression models of baseline characteristics predictive of PFS

Characteristic	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age (y): >45 vs. ≤45	2.13	1.01-4.53	0.021	3.05	1.03-6.39	0.043
Menopause: pre vs. post	1.54	0.65-3.12	0.208			
Tumor size (cm): >2.0 vs. ≤2.0	2.34	1.18-5.32	0.006	2.64	1.02-5.66	0.026
Nuclear grade: G2-3 vs. G1	1.87	0.76-3.65	0.037	1.66	0.81-4.22	0.204
pre-NAC axillary lymph node: Positive vs. negative	1.86	0.83-3.29	0.035	1.62	0.65-4.18	0.203
pre-NAC HER2 status: Positive vs. negative	1.02	0.54-2.27	0.813			
pre-NAC Ki-67 labeling index (%): >14 vs. ≤14	1.35	0.61-2.83	0.439			
post-NAC axillary lymph node: Positive vs. negative	2.85	1.12-5.26	0.018	3.52	1.07-6.25	0.037
post-NAC HER2 status: Positive vs. negative	2.21	0.93-4.87	0.023	3.02	1.10-6.03	0.008
post-NAC Ki-67 labeling index (%): >14 vs. ≤14	2.64	1.20-5.24	0.003	2.86	1.09-5.21	0.012
Clinical response: SD/PD vs. PR/CR	4.35	1.18-10.86	0.001	6.12	1.24-13.66	0.001
group A vs. group B	0.48	0.22-0.97	0.003	0.39	0.16-0.92	0.024
group A vs. group C	0.83	0.36-2.17	0.484			
group B vs. group C	1.02	0.48-2.45	0.436			
group C vs. group D	0.55	0.28-1.46	0.039	0.58	0.22-1.43	0.046

NAC, neoadjuvant chemotherapy; HR, hormone receptor; HER-2, human epidermal receptor; CR, complete response; PR, partial response; SD/PD, stable disease or progression of disease.

Table 5. Univariate and multivariate logistic regression models of baseline characteristics predictive of OS

Characteristic	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age (y): >45 vs. ≤45	1.63	0.76-2.83	0.221			
Menopause: pre vs. post	1.66	0.72-3.48	0.214			
Tumor size (cm): >2.0 vs. ≤2.0	3.87	1.05-9.33	0.002	2.58	1.14-10.18	0.013
Nuclear grade: G2-3 vs. G1	2.14	0.86-5.64	0.029	1.84	0.71-6.32	0.486
pre-NAC axillary lymph node: Positive vs. negative	1.78	0.66-4.21	0.048	1.86	0.83-3.29	0.335
pre-NAC HER2 status: Positive vs. negative	1.22	0.49-3.66	0.353			
pre-NAC Ki67 labeling index (%): >14 vs. ≤14	1.11	0.33-4.82	0.814			
post-NAC axillary lymph node: Positive vs. negative	3.62	1.24-7.52	0.004	3.94	1.06-5.72	0.037
post-NAC HER2 status: Positive vs. negative	2.57	1.03-6.17	0.033	2.07	0.77-4.62	0.208
post-NAC Ki-67 labeling index (%): >14 vs. <14	2.87	1.08-7.66	0.026	1.69	0.59-4.96	0.314
Clinical response: SD/PD vs. PR/CR	3.22	1.12-12.48	0.016	2.59	1.21-10.46	0.054
group A vs. group B	0.31	0.18-0.82	0.006	0.55	0.26-1.04	0.033
group A vs. group C	0.86	0.25-1.84	0.234			
group B vs. group C	1.22	0.55-2.58	0.162			
group C vs. group D	0.42	0.24-1.33	0.022	0.66	0.31-1.65	0.452

NAC, neoadjuvant chemotherapy; HR, hormone receptor; HER-2, human epidermal receptor; CR, complete response; PR, partial response; SD/PD, stable disease or progression of disease.

post-NAC node metastasis (P = 0.018), post-NAC HER2 status (P = 0.023), post-NAC Ki67 labeling index (P = 0.003) and clinical response (P = 0.001) were identified as independent predictive factors for PFS in univariate analysis. In multivariate analysis, Age (P = 0.043), tumor size (P = 0.026), post-NAC node metastasis (P = 0.037), post-NAC HER2 status (P = 0.008), post-NAC Ki67 labeling index (P = 0.012) and clinical response (P = 0.001) remained significant and HR expression was marginally significant (P = 0.051).

Next, we investigated the differences in the variables for predicting OS. Tumor size (P = 0.002), nuclear grade (P = 0.029), pre-NAC

node metastasis (P = 0.048), post-NAC node metastasis (P = 0.004), post-NAC HER2 status (P = 0.033), post-NAC Ki67 labeling index (P = 0.026) and clinical response (P = 0.016) were identified as independent predictive factors for OS in univariate analysis. Tumor size (P = 0.013) and post-NAC node metastasis (P = 0.037) were identified by the stepwise selection method in the multivariate Cox regression model as the variables affecting the OS, as show in **Table 5**.

Discussion

Neoadjuvant systemic treatment is increasingly used for breast cancer and there is a trend for tailored therapies currently based on the presence of ER, PR and HER2-receptor in the tumor. The discordance in ER, PR and HER-2 between CNB and excision specimens has been reported in the neoadjuvant setting, but these results have not been consistent. A change in HR or HER2 status would have important therapeutic, prognostic and financial consequences for both patients and health care providers. With the growing use of NAC, it is important to know whether these therapies modulate these markers and the possible consequences for subsequent adjuvant systemic therapy. Two reviews [10, 11] summarized published data and concluded that NAC seems able to change ER and PR receptors expression and status, but HER2 amplification appears to be more stable. Our present study focuses on the effect of NAC on HR changes and the long-term outcomes and impact of adjuvant endocrine therapy in patients with HR status conversion after NAC.

In our study, 267 patients were retrospective analysis, the ER and PR status changes were observed in 21.3% and 20.2% of the patients included, respectively. The overall frequency of patients with HR status conversion was 15.7%, among them, 17.2% of HR-positive tumors changed to HR negative, while 13.5% of HR-negative tumors changed to HR positive. These results are similar to previous studies [12, 13]. Interestingly, the incidence of HR-positive tumors changed to HR negative was more frequently observed in HER-2-positive tumors than HER-2-negative tumors. Besides, HR status conversion was observed more frequently in tumors that with a poorly differentiated. A relatively high proportion of high Ki-67 indexes were observed in tumors with HR alteration compared to tumors in which HR status remained negative. Other clinicopathological features, such as age, menopausal status axillary node status and tumor size were not associated with HR conversions significantly. Except for random changes that due to heterogeneity, laboratory procedures or observer variability, the possible mechanisms for a change in receptor status or expression in breast cancer cells caused by chemotherapy are complicated. Chemotherapy might directly or indirectly change the biology of tumor cells; one explanation is that, targeting chemosensitive tumor cells with chemotherapeutic agents may leaves insensitive tumor cells with different biology behind in the residual disease. In addition, change in receptor status and biology may as a survival mechanism of tumor cells, leading to resistance of a specific therapy. Moreover, as the expression of ER, PR and HER2 are highly dependent on each other, modulating one receptor with NAC can change the expression of other receptors as well [14]. Although the exact mechanism of HR conversion is not clear, most investigators believe that chemotherapy may have an effect on HR status.

Little is known about the predictive or prognostic value of a changed receptor status. A few studies have demonstrated the correlations between HR conversion and treatment response, but discordant conclusions were drawn. Chen et al. [15] have reported that patients with a HR positive to negative switch benefit less from endocrine therapy compared to patients whose HR status remains stable. In contrast, Tacca et al. [16] and Hirata et al. [8] observed that no significant difference in PFS and OS rates between endocrine therapy-administered patients with HR-negative switch lesions and those of endocrine therapy-administered patients with lesions that were HR-positive both before and after NAC, but they demonstrated that a positive switch of the HR-status could be an indicator for a better outcome. In the present study, the survival analyses show that a positive switch of the HR-status was significantly correlated with better PFS and OS in patients that were treated with adjuvant endocrine therapy compared to those with negative-HR status remains stable who were not. Furthermore, patients with negative switch of HR-status may benefit less from endocrine therapy compared to patients whose HR status remains positive, for both PFS and OS. However,

the PFS and the OS of endocrine therapy administered patients with a positive switch of HR status were similar to those with lesions that were HR-positive status both before and after NAC. These findings indicate that a positive switch of the HR status could be an indicator for a better outcome, while a negative switch seemed to be associated with a worse prognosis, and it is necessary to determine the HR status of the lesions both before and after NAC and to administer endocrine therapy to patients with HR status conversion.

The strengths of our study were as follow: in concordance with published data, we did find significant changes in IHC expression of ER, PR in breast cancer with neoadjuvant chemotherapy; more importantly, we also demonstrated that HR status conversion was observed more frequently in tumors with positive HER2 status, poorly differentiated and a relatively high proportion of Ki-67 indexes; another important finding in our study was that the PFS and OS for patients whose tumors changed from HR positivity to negativity with chemotherapy may be worse than that of patients whose tumors remained positive after chemotherapy, while that tumors changed from HR negativity to positivity may be better than that remained positive.

Limitations of our study should be highlighted. First, this is a retrospective study; some uncontrollable factors may affect the prognosis of the patients. Secondly, the existence of tumor heterogeneity has led to concerns that core biopsies may not be representative of the tumor tissue as a whole as they are often restricted to the superficial aspects of the tumor.

In conclusion, NAC seems able to change ER and PR receptors expression and status. The HR-negative switch can lead to a poor outcome regardless of adjuvant endocrine therapy, and the HR-positive switch appears to be significantly correlated with better outcome. Until more comparable studies are done, retesting of the hormone receptors should be considered in certain situations to optimize adjuvant systemic therapy, and adjuvant endocrine therapy appears to be suitable for patients with positive-HR status at least once, that is, either before or after NAC. Moreover, further research is warranted to understand the relationship between NAC and hormonal pathways and explore strategies to manipulate it for therapeutic benefit.

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Disclosure of conflict of interest

None.

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