Study characteristics affecting the responses to neoadjuvant chemotherapy and the prognosis of patients with bilateral breast cancer: A retrospective analysis

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Abstract

Background Bilateral breast cancer (BBC) is defined as breast cancer diagnosed in both breasts in the same patient. Neoadjuvant chemotherapy (NAC) is a well-established approach to evaluate the tumor response to chemotherapeutic agents. The consensus is that different responses in characteristics after NAC can affect prognosis in unilateral breast cancer (UBC), but little is known about the responses of the BBC to NAC. This analysis explored the characteristics that can affect the prognosis of patients with BBC.

Methods The characteristics of patients diagnosed with BBC (n = 126) was collected and the immunohistochemistry staining was used to detect expression levels of estrogen receptor (ER), progesterone receptor (PR), Ki67, and HER2. A statistical analysis of the differences was performed to identify the factors that affect survival times in all patients with BBC.

Results A logistic regression indicated that the status of sentinel and axillary lymph node, expression of PR of the right breast tumor, and molecular subtype of the right breast tumor might relate to survival times. Tumor size, status of axillary lymph node, clinical stage, tumor type, histological grade, and molecular subtype of the left breast tumor might have a more profound effect on the survival time than the right breast tumor in the synchronous breast cancer (SBBC) patients. A multivariate analysis of overall survival times in patients with metachronous breast cancer (MBBC) showed that age was the only factor affecting survival time. After NAC treatment in SBBC patients, the Kaplan-Meier survival estimate showed that a decrease in tumor size, clinical stage, Ki67 and P53 levels were positive for a prolonged life span. However, a decrease in ER, PR, and HER2 were negative for prolonged life span. Changes in tumor type and molecular subtype also influenced the survival time.

Conclusion Characteristic changes in the left breast tumor were significant factors affecting survival times in patients with SBBC. After NAC treatment, changes in tumor size, Ki67, P53, ER, PR, and HER2 might affect the prognosis of patients with SBBC. For MBBC, only age was a factor affecting survival time. These findings provide clinical insight for the treatment of patients with BBC.

Background

Bilateral breast cancer (BBC) is a rare type of breast cancer (BC), for which the incidence rate is reported to be from 1%-11.8% of all cases of BC [1, 2]. The mortality of BBC, especially synchronous bilateral breast cancer (SBBC), is significantly higher than that of unilateral breast cancer (UBC) [3, 4]. With the increase in the number of patients with BC, numerous patients will be diagnosed with this distinct form of BC with inferior prognosis.

Neoadjuvant chemotherapy (NAC) is a well-established approach to treat large or locally advanced breast cancer [5-7] and could be used to evaluate the tumor response to chemotherapeutic agents at the same time [8, 9]. The consensus is that different responses in tumor size, biomarkers, or tumor type after NAC can affect prognosis in UBC [10-13]. Controversially, *Mattea Reinisch* et al reported that patients with BBC had a lower pathologic complete response (PCR) rate and a lower disease-free survival (DFS) than those with UBC [14]. They did not concentrate on changes in biomarkers or tumor type. However, *Mathias Kvist Mejdahl* et al found that a higher predictive cumulative mortality rate was described in the tumor of left

breast than that in the right side of the breast in SBBC [15]. Thus, it is valuable to further explore and verify whether this phenomenon is caused by biomarkers or tumor type between both sides or whether it has the same result in metachronous bilateral breast cancer (MBBC).

Because of the low incidence, BBC usually is ignored or excluded in many clinical research studies. Little is known about the responses of the BBC to NAC, especially in the biomarkers and tumor type and the difference of prognosis. Here, we analyzed changes in some biomarkers and tumor types after NAC. We also identified some important factors that could affect the survival time of patients with SBBC. These results may provide novel insights into the therapeutic strategies of clinical treatment for patients with SBBC.

Methods

Patients

All patients diagnosed with BBC in the First Affiliated Hospital of Chongqing Medical University between January 2012 and November 2018 were recruited. The exclusion criteria were patients' age <18 years, missing data for tumors in both sides of breasts, previous other malignant tumors, determination of metastatic cancer from the contralateral side of earlier BC, lack of surgical treatment, or cancer of non-breast parenchyma origin. The diagnostic criteria of primary BBC followed the *Chaudary* et al standard [16]:

1. Contralateral tumor contains in situ cancer components.
2. Different histopathology is evident on tumor in both side breasts.
3. tumor cells in the second breast differentiated relatively well.
4. Evidence of no tumor recurrence and metastasis on the first side of the lesion.
5. If the bilateral pathology is the same, the fourth case should be met.
6. BBC is combined with other indicators, such as tumor location (external upper quadrant), tumor growth site imaging evidence (in breast tissue), growth pattern (invasive growth), and assisted diagnosis.

SBBC and MBBC usually are defined according to the length of the diagnosis time of tumors in both breasts. This classification cannot specify the exact time interval, which ranges from one month to five years, according to other studies [17, 18]. In our study, we used a cut-off time interval of one year to distinguish between the two types of BBC. The regime of NAC treatment that patients with SBBC received was docetaxel, epirubicin, and cyclophosphamide and all treatment strategies were carried out in accordance with the guidelines of Chinese society of clinical oncology 2012.v1. All experimental protocols were approved by Department of Endocrine and Breast Surgery, The First Affiliated Hospital of Chongqing Medical University.

Immunohistochemistry

The tissue sections of the core needle biopsies taken before NAC and the resection of surgery were evaluated by the pathology department of Chongqing Medical University. The staining intensity in the immunohistochemistry was recorded in terms of percentage for estrogen receptor (ER), progesterone receptor (PR), Ki67, and P53. Samples were defined as ER (+) or PR (+) with at least 1% of nuclei stained, and four grades were classified according to percentages ranging from 0–95%: grade 1 0%, grade 2 1–30%, grade 3 31–60%, and grade 4 61–95%. HER2 status was recorded as grades: – or + was negative, 2+ was doubtful, which required fluorescence in situ hybridization (FISH): positive grades showed a more than 2.2-fold increase, and 3+ was positive.

Follow-up

The followed up was carried out by telephone and records of examination in our hospital. If all the common contact was lost, survival state was confirmed by checking for the patient's identification in the police system. The mean follow-up time of all patients was 75 months (median: 55 months, range: 3-386 months).

Statistical analysis

Because of missing data for tumor in one side of breast in MBBC, significant statistical differences could be seen between SBBC and MBBC. To eliminate this bias, according to the results from statistical research [19], the frequency of the indicator was used as an alternative of the missing data. To compare variables between groups, after normality test (Kolmogorov-Smirnov), chi-square testing was used to compare qualitative variables and performed multivariate analysis using Cox regression analysis. To draw the survival rate curve in patients with SBBC receiving NAC, the Kaplan-Meier method was applied. The log-rank test was used to determine the difference between survival curves and considered *p*-values less than 0.05 to be statistically significant. Statistical analyses used the SPSS software version 23.

Results

Baseline characteristics

In the First Affiliated Hospital of Chongqing Medical University between January 2012 and November 2018, 6,453 patients were diagnosed with BC. A total of 126 patients diagnosed as BBC were recruited and 59 patients were diagnosed as SBBC, of which 16 patients received NAC treatment, and 67 patients were diagnosed as MBBC. Figure 1 shows the flow chart of reasons for exclusion. The disease characteristics of SBBC and MBBC are shown in Table 1. Because of missing data on one side of MBBC, significant statistical differences could be seen between SBBC and MBBC. Thus, to eliminate this bias, and according to the result of statistical research, we used the frequency of the indicator instead of the missing data (original data is provided in Supplementary table 1). It is clear in the table 1 that patients with SBBC more often had an early clinical stage (stage I and II at diagnosis) on the right side (*P* = 0.007), low histological grade on the left side (*P* = 0.021), and higher HER2 expression on the left side (*P* = 0.017) than patients with MBBC. A significantly higher expression of hormone receptor (HR) was evident in

patients with SBBC compared with patients with MBBC. This led to the conclusion that more luminal subtypes, especially luminal A, are found in patients with SBBC, and more triple-negative subtypes are found in patients with MBBC. Considering the time interval of the two sides and drug resistance, patients with MBBC usually received two regimens of chemotherapy.

Survival state in all patients and separately in patients with SBBC and MBBC

At the end of follow-up, 101 patients had survived. The differences in the patients and disease characteristics between the survival and non-survival groups are given in Table 2. Interestingly, some obvious differences were identified in these two groups. For the survival group, statistically different characteristics included a smaller tumor size (left $P = 0.074$; right $P = 0.022$), negative sentinel lymph node (left $P = 0.000$; right $P = 0.000$) of both sides, an earlier clinical stage at diagnosis (left $P = 0.038$; right $P = 0.028$), and lower expressions of ER (left $P = 0.037$; right $P = 0.079$) and PR (left $P = 0.059$; right $P = 0.047$). On the contrary, in the non-survival group, higher expression of ER and PR, larger tumor size, and positive sentinel lymph nodes and axillary lymph nodes could be seen. These data showed that higher expression of ER and PR, larger tumor size, and positive sentinel lymph nodes and axillary lymph nodes were associated with survival.

The logistic regression of all characteristics indicated that sentinel lymph node (left odds ratio [OR] = 12.102; 95% confidence interval [CI]: 2.24–65.31; $P = 0.004$; right OR = 22.969; 95% CI: 4.39–120.16; $P = 0.000$), axillary lymph node (left OR = 2.916; 95% CI: 1.16–7.32; $P = 0.023$; right OR = 15.671; 95% CI: 3.32–74.01; $P = 0.001$), PR of right (OR = 2.361; 95% CI: 1.08–5.17; $P = 0.032$) and molecular subtype of the right side (OR = 4.932; 95% CI: 1.71–14.23; $P = 0.003$) might relate to the survival state (Table 3). The analysis and results above were for all the patients with BBC.

Furthermore, the Cox survival analysis of all characteristics in SBBC showed that the statistically different characteristics were concentrated on the left side tumor of the breast (Table 4). The left-side characteristics, including tumor size (HR = 2.941; 95% CI: 1.41–6.15; $P = 0.004$), axillary lymph node (HR = 2.222; 95% CI: 0.95–5.18; $P = 0.064$), clinical stage (HR = 1.566; 95% CI: 1.06–2.31; $P = 0.023$), tumor type (HR = 3.815; 95% CI: 1.62–8.99; $P = 0.002$), histological grade (HR = 1.881; 95% CI: 1.14–3.11; $P = 0.014$), and molecular subtype (HR = 1.952; 95% CI: 1.19–3.20; $P = 0.008$), all influenced survival. This result indicated that the tumor in the left side of breast might have a more profound effect on survival state than the right side. To exclude whether differences in the characteristics of the two sides contributed to this result, the characteristics between the two sides were compared, but identified no difference (Table 5). The multivariate analysis of overall survival time of patients with SBBC showed that the only factor that affected survival was left-side tumor type (HR = 4.532; 95% CI: 1.77–11.61; $P = 0.002$; Supplementary table 2). The Cox survival analysis of all characteristics for patients with MBBC showed that the only factors involved in survival were age (HR = 0.105; 95% CI: 0.013–0.819; $P = 0.032$) and Ki67 of the right side (HR = 2.186; 95% CI: 1.04–4.60; $P = 0.040$). A multivariate analysis of patients with

MBBC, however, showed that age (HR = 0.101; 95% CI: 0.01–0.79; P = 0.029) was the only characteristic that affected survival time (Supplementary table 3 and 4).

Changes of characteristics after NAC in SBBC

In patients with SBBC, 16 received NAC treatment, and only 10 patients survived during the follow-up time. Because changes in the characteristics of the tumor after NAC predict a different prognosis in patients with UBC [10-13], characteristics through core needle biopsy and surgical tissue section were collected (Supplementary table 5 and 6). The changes in characteristics were compared before and after NAC between the survival group and non-survival group (Table 6) and also recorded the response to NAC (Table 7). However, no statistical difference was found.

The Kaplan-Meier survival estimate was used to analyze changes in factors affecting prognosis in patients with SBBC who received NAC. Results showed that a decrease in tumor size (survival time left and right: 53.50 ± 10.35 , P = 0.887), clinical stage (survival time left: 72.33 ± 10.65 , P = 0.159, survival time right: 54.20 ± 11.42 , P = 0.918), Ki67 (survival time left: 51.57 ± 9.22 , P = 0.530, survival time right: 57.25 ± 12.21 , P = 0.924), and P53 (due to the limited number of patients, the conclusions can only be draw for survival time of the right in the SPSS software; the survival time of right: 59.14 ± 7.27 , P = 0.079) may indicate a prolonged life span. In contrast, however, a decrease in ER (survival time left: 34.40 ± 11.91 , P = 0.215, survival time right: 41.33 ± 10.76 , P = 0.888), PR (survival time left: 34.75 ± 10.35 , P = 0.561, survival time right: 43.71 ± 10.17 , P = 0.961), and HER2 (due to the limited number of patients, the conclusions can only be draw for survival time of the right in the SPSS software; survival time of right: 39.50 ± 7.1375 , P = 0.518) may indicate a shortened life span (Table 8). It is also reminded that changes in tumor type and molecular subtype might influence survival time. Although the life span differed between groups that showed a decrease or no decrease in all characteristics of tumor in both side breasts, this difference did not reach the traditional statistically significant level.

According to patient response to NAC treatment and RECIST 1.1(response evaluation criteria in solid tumors), we classified PCR, CCR(clinical complete response), and PR(partial response) as the response group, and SD(stable disease) and PD(progressive disease) as the non-response group. The Kaplan-Meier survival estimate showed that the life span of the response group (left and right: life time = 57.27 ± 10.58 ; 95% CI: 36.54–78.01) was longer than the life span of the non-response group (left and right: life time = 25.50 ± 6.75 ; 95% CI: 12.27–38.73); however, this difference did not reach the traditional statistically significant level (P = 0.518; Table 9). The factors affecting survival also indicated differences in the cumulative survival time between these two groups (Figure 2).

Discussion

In our study, we found that some patients with SBBC had different responses to NAC in the tumor in two sides of breasts, but whether this phenomenon affected prognosis is uncertain. No specific guidelines or

consensus about follow-up treatment are available. This study was conducted to summarize the clinical characteristics and prognosis of BBC in China and focused on patients with SBBC who received NAC. This study verified the characteristics and prognosis of BBC in China and provided clinical data to explore follow-up treatment plans for patients with BBC.

The incidence of BBC in our study was 2.51% of all patients with BC. Of the total, 64 were diagnosed with SBBC (the incidence was 0.99%) and 98 were diagnosed with MBBC (the incidence was 1.52%). The results were similar to data reported by Glenda Quan et al [2] and Ying Xing et al [20].

The comparison of SBBC and MBBC indicated that a significantly higher expression of ER and PR was seen in patients with SBBC compared with patients with MBBC (Table 1). This result showed that SBBC tumors relied more on hormone levels. BC growth on both sides of breasts at the same time may be related to the expression level of hormones *in vivo*. This finding may provide support for investigating a follow-up treatment strategy for patients with SBBC. Some studies have reported that survival times were significantly higher in patients with MBBC compared with patients with SBBC [21]. We also found that patients with SBBC more often had early clinical stage at diagnosis of the right side of the breast, and low histological grade of the left side breast, but higher HER2 expression of the left side breast than patients with MBBC. The reasons for these differences and whether they influence prognosis or treatment strategy require further exploration.

The univariate analysis of survival times showed that the survival group had an earlier clinical stage in both sides of the tumor compared with the non-survival group, and a higher expression level of ER and PR was seen in the survival group (Table 2). The multivariate analysis showed that the sentinel lymph node and axillary lymph node influenced survival time (Table 3). In our study, the clinical stage of the lymph node status and positive expression of HR were the most important factors affecting survival time in patients with BBC (Table 2).

The Cox survival analysis of all characteristics in patients with SBBC showed that different characteristics concentrated on the tumor in the left side of breast. This result indicated that tumor in the left side breast might have a more profound effect on the survival state than those in the right side of breast (Table 4). When comparing the characteristics of both sides, we did not find any difference (Table 5). The multivariate analysis of overall survival in patients with SBBC showed that only tumor type in the left side breast had an impact on survival (Supplementary table 2). This result may explain the outcomes reported by *Mathias Kvist Mejdahl* et al that the impact of a right and left tumor on greater mortality was different and that the left side had a higher predictive cumulative mortality rate [15]. In our study, however, other differences were not found in the factors between the left and the right tumor of the breasts. Other factors may exist that we have not considered, in particular a distinction between the left and right breast, which influenced the prognosis of patients with SBBC, such as differences in the physiology and anatomy of the lymphatic system in the chest area. As for patients with MBBC, three factors (including age, left sentinel lymph node, and right Ki67) had a significant influence on overall survival (Table 1).

We compared changes in tumor characteristics before and after NAC between the survival group and non-survival group in patients with SBBC (Table 6). The Kaplan-Meier survival estimate showed that a decrease in tumor size, clinical stage, Ki67, and P53 may prolong life span, but a decrease of ER, PR, and HER2 may shorten life span (Table 8). We also found that changes in tumor type and molecular subtype may influence life span. Although life span differed between the decrease and no-decrease group, the difference did not reach the traditional statistically significant level. This result showed that these characteristic changes, especially in both sides of the breast in patients with SBBC, may have an impact on survival time. However, because of the limited number of patients with this rare type of cancer, we could not draw a definitive conclusion. If the number of patients expands, we believe we could obtain a clinically significant conclusion. Because of the particularity of SBBC, in our next study, we will set a better self-control, for instance, the tumor in two sides breasts have the same clinical stage, but different molecular subtype, to explore whether differences in response to NAC treatment in both sides of the tumor would have an impact on survival times. This result may guide the treatment plan for patients with this rare type of BBC.

Conclusions

Different factors affect the prognosis of two kinds of patients with BBC. Left-side tumors affected the survival times of patients with SBBC, and three factors, including age, left-side sentinel lymph node, and right-side Ki67 expression level, had significant influences on the survival time of patients with MBBC. After NAC treatment, tumor size, Ki67, P53, ER, PR, and HER2 were factors that contributed to the prognosis of patients with BSSC. These findings may provide clinical ideas for the treatment of patients with SBBC.

Abbreviations

BC, breast cancer; BBC, bilateral breast cancer; SBBC, synchronous breast cancer; MBBC, metachronous breast cancer; NAC, neoadjuvant chemotherapy; UBC, unilateral breast cancer; HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor; PCR, pathologic complete response; CCR, clinical complete response; PR, partial response; SD, stable disease; PD, progressive disease; DFS, disease-free survival; FISH, fluorescence in situ hybridization; OR, odds ratio; CI, confidence interval.

Declarations

Ethics approval and consent to participate

This study was approved by ethics committee of The First Affiliated Hospital of Chongqing Medical University. Written informed consent was obtained for each participant according to ethics committee guidelines.

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Competing Interests

All authors declare that they have no conflict of interest.

Authors' contributions

ZRT, YHW, and LY designed and carried out experiments; LC analyzed experimental results; YZZ and CQ assisted with analyzing data and developing analysis tools.; ZRT wrote the manuscript. all authors have read and approved the manuscript.

Availability of data and materials

The datasets used or analyzed in this study are available from the corresponding author on reasonable request.

Consent for publication

Not Applicable.

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Tables

Table 1. Patients and disease characteristics of SBBC and MBBC.

	SBBC	MBBC	P-value
N(%)	N(%)		
Total	59	67	
Age(year)			0.530
≤50	42(71.2%)	51(76.1%)	
≥50	17(28.8%)	16(23.9%)	
Menopausal status			0.466
postmenopausal	21(35.6%)	29(43.3%)	
premenopausal	38(64.4%)	38(56.7%)	
Tumor size(left)			0.955
0-20mm	33(55.9%)	36(53.7%)	
21-50mm	23(39.0%)	28(41.8%)	
>50mm	3(5.1%)	3(4.5%)	
Tumor size(right)			0.200
0-20mm	38(64.4%)	40(59.7%)	
21-50mm	17(28.8%)	26(38.8%)	
>50mm	4(6.8%)	1(1.5%)	
Clinical stage(left)			0.164
0	6(10.3%)	3(4.5%)	
I	21(35.6%)	18(26.9%)	
II	22(37.3%)	39(58.2%)	
III	9(15.3%)	7(10.4%)	
IV	0(0.0%)	0(0.0%)	
Clinical stage(right)			0.007
0	3(5.1%)	3(4.5%)	
I	24(40.7%)	11(16.4%)	
II	18(30.5%)	40(59.7%)	
III	12(20.3%)	12(17.9%)	
IV	2(3.4%)	1(1.5%)	
Tumor type(left)			0.767
ductal	21(35.6%)	23(34.3%)	
lobular	34(57.6%)	37(55.2%)	
other	4(6.8%)	7(10.4%)	
Tumor type(right)			0.816
ductal	22(37.3%)	23(34.3%)	
lobular	32(54.2%)	40(59.7%)	
other	5(8.5%)	4(6.0%)	
Histological grade(left)			0.021
DCIS	8(13.6%)	5(7.5%)	
I	2(3.4%)	0(0.0%)	
II	41(69.5%)	60(89.6%)	
III	8(13.6%)	2(3.0%)	
Histological grade(right)			0.170
DCIS	5(8.5%)	4(6.0%)	
I	2(3.4%)	0(0.0%)	
II	43(72.9%)	58(86.6%)	
III	9(15.3%)	5(7.5%)	
Sentinel lymph node(left)			0.496
negative	21(36.2%)	19(28.4%)	
positive	2(3.4%)	5(7.5%)	
undone	36(61.0%)	43(64.2%)	

Sentinel lymph node(right)		0.111
negative	19(32.2%)	15(22.4%)
positive	9(15.3%)	5(7.5%)
undone	31(52.5%)	47(70.1%)
Axillary lymph node(left)		0.212
negative	18(30.5%)	21(31.3%)
positive	16(27.1%)	10(14.9%)
undone	25(42.4%)	36(53.7%)
Axillary lymph node(right)		0.398
negative	18(30.5%)	16(23.9%)
positive	22(37.3%)	33(49.3%)
undone	19(32.2%)	18(26.9%)
ER(left)		0.002
1	18(30.5%)	40(59.7%)
2	4(6.8%)	7(10.4%)
3	9(15.3%)	6(9.0%)
4	28(47.5%)	14(20.9%)
ER(right)		0.022
1	18(30.5%)	37(55.2%)
2	3(5.1%)	5(7.5%)
3	12(20.3%)	6(9.0%)
4	26(44.1%)	19(28.4%)
PR(left)		0.000
1	23(39.0%)	50(74.6%)
2	8(13.6%)	12(17.9%)
3	12(20.3%)	2(3.0%)
4	16(27.1%)	3(4.5%)
PR(right)		0.009
1	22(37.3%)	45(67.2%)
2	15(25.4%)	7(10.4%)
3	10(16.9%)	7(10.4%)
4	12(20.3%)	8(11.9%)
HER2(left)		0.017
-	12(20.3%)	14(20.9%)
+	18(30.5%)	36(53.7%)
++	17(28.8%)	13(19.4%)
+++	12(20.3%)	4(6.0%)
HER2(right)		0.313
-	11(18.6%)	8(11.9%)
+	15(25.4%)	22(32.8%)
++	24(40.7%)	32(47.8%)
+++	9(15.3%)	5(7.5%)
Ki 67(left)		0.271
1	1(1.7%)	2(3.0%)
2	51(86.4%)	54(80.6%)
3	5(8.5%)	11(16.4%)
4	2(3.4%)	0(0.0%)
Ki 67(right)		0.177
1	1(1.7%)	1(1.5%)
2	51(86.4%)	49(73.1%)
3	7(11.9%)	15(22.4%)

4	0(0.0%)	2(3.0%)	
P53(left)			0.120
1	20(33.9%)	36(53.7%)	
2	25(42.4%)	17(25.4%)	
3	5(8.5%)	4(6.0%)	
4	9(15.3%)	10(14.9%)	
P53(right)			0.299
1	21(35.6%)	18(26.9%)	
2	25(42.4%)	33(49.3%)	
3	8(13.6%)	5(7.5%)	
4	5(8.5%)	11(16.4%)	
Molecular subtype(left)			0.047
luminal A	18(30.5%)	8(11.9%)	
luminal B	25(42.4%)	33(49.3%)	
HER2 positive	6(10.2%)	6(9.0%)	
Triple negative	10(16.9%)	20(29.9%)	
Molecular subtype(right)			0.157
luminal A	20(33.9%)	11(16.4%)	
luminal B	22(37.3%)	33(49.3%)	
HER2 positive	8(13.6%)	11(16.4%)	
Triple negative	9(15.3%)	12(17.9%)	
Surgery			0.917
modified radical mastectomy	51(86.4%)	59(88.1%)	
radical mastectomy	6(10.2%)	5(7.5%)	
breast conserving surgery	2(3.4%)	3(4.5%)	
Chemotherapy			0.000
TEC	37(62.7%)	13(19.4%)	
EC followed by T	12(20.3%)	13(19.4%)	
NP	1(1.7%)	8(11.9%)	
2 or more regimens	0(0.0%)	29(43.3%)	
undone	9(15.3%)	4(6.0%)	
Endocrine therapy			0.177
yes	46(78.0%)	45(67.2%)	
no	13(22%)	22(32.8%)	
Radiotherapy			0.010
yes	28(47.5%)	17(25.4%)	
no	31(52.5%)	50(74.6%)	

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor; DCIS, ductal carcinoma in situ; TEC, epirubicin, docetaxel, and cyclophosphamide; NP, navelbine and cisplatin.

Table 2. Patients and disease characteristics of survival status for all patients.

	Survival	Not survival	P-value
Total	101	25	
Age(year)			0.228
≤50	73(72.3%)	21(84.0%)	
≥50	28(27.7%)	4(16.0%)	
Menopausal status			0.674
postmenopausal	41(40.6%)	9(36.0%)	
premenopausal	60(59.4%)	16(64.0%)	
Tumor size(left)			0.074
0-20mm	60(59.4%)	9(36.0%)	
21-50mm	36(35.6%)	15(60.0%)	
>50mm	5(5.0%)	1(4.0%)	
Tumor size(right)			0.022
0-20mm	67(66.3%)	11(44.0%)	
21-50mm	32(31.7%)	11(44.0%)	
>50mm	2(2.0%)	3(12.0%)	
Clinical stage(left)			0.038
0	8(7.9%)	1(4.0%)	
I	36(35.6%)	3(12.0%)	
II	47(46.5%)	15(60.0%)	
III	10(9.9%)	6(24.0%)	
IV	0(0.0%)	0(0.0%)	
Clinical stage(right)			0.028
0	6(5.9%)	0(0.0%)	
I	32(31.7%)	3(12.0%)	
II	46(45.5%)	12(48.0%)	
III	16(15.8%)	8(32.0%)	
IV	1(1.0%)	0(0.0%)	
Tumor type(left)			0.751
ductal	35(34.7%)	9(36.0%)	
lobular	58(57.4%)	13(52.0%)	
other	8(7.9%)	3(12.0%)	
Tumor type(right)			0.884
ductal	37(36.6%)	8(32.0%)	
lobular	57(56.4%)	15(60.0%)	
other	7(6.9%)	2(8.0%)	
Histological grade(left)			0.552
DCIS	12(11.9%)	1(4.0%)	
I	2(2.0%)	0(0.0%)	
II	80(79.2%)	21(84.0%)	
III	7(6.9%)	3(12.0%)	
Histological grade(right)			0.336
DCIS	9(8.9%)	0(0.0%)	
I	2(2.0%)	21(84.0%)	
II	80(79.2%)	4(16.0%)	
III	10(9.9%)	0(0.0%)	
Sentinel lymph node(left)			0.000
negative	39(38.6%)	1(4.0%)	
positive	7(6.9%)	0(0.0%)	
undone	55(54.5%)	24(96.0%)	
Sentinel lymph node(right)			0.000

negative	33(32.7%)	1(4.0%)	
positive	14(13.9%)	0(0.0%)	
undone	54(53.5%)	24(96.0%)	
Axillary lymph node(left)			0.071
negative	36(35.6%)	3(12.0%)	
positive	19(18.8%)	7(28.0%)	
undone	46(45.5%)	15(60.0%)	
Axillary lymph node(right)			0.057
negative	32(31.7%)	2(8.0%)	
positive	41(40.6%)	14(56.0%)	
undone	28(27.7%)	9(36.0%)	
ER(left)			0.037
1	41(40.6%)	17(68.0%)	
2	9(8.9%)	2(8.0%)	
3	12(11.9%)	3(12.0%)	
4	39(38.6%)	3(12.0%)	
ER(right)			0.079
1	40(39.6%)	15(60.0%)	
2	7(6.9%)	1(4.0%)	
3	13(12.9%)	5(20.0%)	
4	41(40.6%)	4(16.0%)	
PR(left)			0.059
1	53(52.5%)	20(80.0%)	
2	18(17.8%)	2(8.0%)	
3	14(13.9%)	0(0.0%)	
4	16(15.8%)	3(12.0%)	
PR(right)			0.047
1	49(48.5%)	18(72.0%)	
2	21(20.8%)	1(4.0%)	
3	16(15.8%)	1(4.0%)	
4	15(14.9%)	5(20.0%)	
HER2(left)			0.701
-	20(19.8%)	6(24.0%)	
+	43(42.6%)	11(44.0%)	
++	26(25.7%)	4(16.0%)	
+++	12(11.9%)	4(16.0%)	
HER2(right)			0.408
-	16(15.8%)	3(12.0%)	
+	29(28.7%)	8(32.0%)	
++	47(46.5%)	9(36.0%)	
+++	9(8.9%)	5(20.0%)	
Ki 67(left)			0.191
1	1(1.0%)	2(8.0%)	
2	84(83.2%)	21(84.0%)	
3	14(13.9%)	2(8.0%)	
4	2(2.0%)	0(0.0%)	
Ki 67(right)			0.094
1	2(2.0%)	0(0.0%)	
2	84(83.2%)	16(64.0%)	
3	14(13.9%)	8(32.0%)	
4	1(1.0%)	1(4.0%)	

P53(left)			0.094
1	41(40.6%)	15(60.0%)	
2	36(35.6%)	6(24.0%)	
3	6(5.9%)	3(12.0%)	
4	18(17.8%)	1(4.0%)	
P53(right)			0.627
1	29(28.7%)	10(40.0%)	
2	49(48.5%)	9(36.0%)	
3	10(9.9%)	3(12.0%)	
4	13(12.9%)	3(12.0%)	
Molecular subtype(left)			0.175
Luminal A	24(23.8%)	2(8.0%)	
Luminal B	47(46.5%)	11(44.0%)	
HER2 positive	8(7.9%)	4(16.0%)	
Triple negative	22(21.8%)	8(32.0%)	
Molecular subtype(right)			0.007
Luminal A	28(27.7%)	3(12.0%)	
Luminal B	47(46.5%)	8(32.0%)	
HER2 positive	15(14.9%)	4(16.0%)	
Triple negative	11(10.9%)	10(40.0%)	
Surgery			0.313
modified radical mastectomy	90(89.1%)	20(80.0%)	
radical mastectomy	7(6.9%)	4(16.0%)	
breast conserving surgery	4(4.0%)	1(4.0%)	
Chemotherapy			0.187
TEC	43(42.6%)	7(28.0%)	
EC followed by T	22(21.8%)	3(12.0%)	
NP	7(6.9%)	2(8.0%)	
2 or more regimens	19(18.8%)	10(40.0%)	
undone	10(9.9%)	3(12.0%)	
Endocrine therapy			0.003
yes	79(78.2%)	12(48.0%)	
no	22(21.8%)	13(53.0%)	
Radiotherapy			0.152
yes	33(32.7%)	12(48.0%)	
no	68(67.3%)	13(53.0%)	

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor; DCIS, ductal carcinoma in situ; TEC, epirubicin, docetaxel, and cyclophosphamide; NP, navelbine and cisplatin.

Table 3. Multivariate analysis of survival status for all patients.

Variable	OR	P-value	95% CI
Sentinel lymph node(left)	12.102	0.004	2.24-65.31
Sentinel lymph node(right)	22.969	0.000	4.39-120.16
Axillary lymph node(left)	2.916	0.023	1.16-7.32
Axillary lymph node(right)	15.671	0.001	3.32-74.01
PR(right)	2.361	0.032	1.08-5.17
Molecular subtype(right)	4.932	0.003	1.71-14.23

OR, odds ratio; CI, confidence interval.

Table 4. Univariate analysis of overall survival in SBBC.

Variable	P-value	HR	95% CI
Age	0.567	1.488	0.38-5.79
Menopausal status	0.733	1.266	0.33-4.90
Tumor size(left)	0.004	2.941	1.41-6.15
Tumor size(right)	0.053	2.233	0.99-5.04
Clinical stage(left)	0.023	1.566	1.06-2.31
Clinical stage(right)	0.125	1.457	0.90-2.36
Tumor type(left)	0.002	3.815	1.62-8.99
Tumor type(right)	0.072	2.496	0.923-6.75
Histological grade(left)	0.014	1.881	1.14-3.11
Histological grade(right)	0.290	1.349	0.78-2.35
Sentinel lymph node(left)	0.180	7.310	0.39-134.24
Sentinel lymph node(right)	0.162	12.200	0.37-405.32
Axillary lymph node(left)	0.064	2.222	0.95-5.18
Axillary lymph node(right)	0.186	1.755	0.76-4.04
ER(left)	0.185	0.725	0.45-1.17
ER(right)	0.392	0.813	0.51-1.31
PR(left)	0.091	0.591	0.32-1.09
PR(right)	0.648	0.870	0.48-1.58
HER2(left)	0.273	1.413	0.76-2.62
HER2(right)	0.233	1.560	0.75-3.26
Ki67 (left)	0.615	0.611	0.09-4.16
Ki67 (right)	0.354	2.078	0.44-9.74
P53(left)	0.219	0.612	0.28-1.34
P53(right)	0.365	0.698	0.32-1.52
Molecular subtype(left)	0.008	1.952	1.19-3.20
Molecular subtype(right)	0.068	1.662	0.96-2.87
Surgery	0.007	3.149	1.36-7.27
Chemotherapy	0.509	1.137	0.77-1.67
Endocrine therapy	0.043	3.600	1.04-12.45
Radiotherapy	0.186	0.400	0.10-1.56

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor; HR, hazard ratio; CI, confidence interval.

Table 5. The differences between characteristics of two sides.

	Left(N)	Right(N)	P-value
Tumor size			0.521
0-20mm	33	38	
21-50mm	23	17	
>50mm	3	4	
Clinical stage			0.418
0	6	3	
I	21	24	
II	23	18	
III	9	12	
IV	0	2	
Histological grade			0.905
DCIS	8	5	
I	2	2	
II	41	43	
III	8	9	
Tumor type			0.921
ductal	21	22	
lobular	34	32	
other	4	5	
Sentinel lymph node			0.085
negative	21	19	
positive	2	9	
undone	36	31	
Axillary lymph node			0.414
negative	18	18	
positive	16	22	
undone	25	19	
ER			0.900
1	18	18	
2	4	3	
3	9	12	
4	28	26	
PR			0.406
1	23	22	
2	8	15	
3	12	10	
4	16	12	
HER2			0.781
-	12	11	
+	16	15	
++	19	24	
+++	12	9	
Ki 67			0.658
1	1	1	
2	51	51	
3	5	7	
4	2	0	
P53			0.602
1	20	21	
2	25	25	

3	5	8
4	9	5
Molecular subtype		0.888
Luminal A	18	20
Luminal B	25	22
HER2 positive	6	8
Triple negative	10	9

N: number. DCIS: ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor.

Table 6. The changes of disease characteristics before and after neoadjuvant chemotherapy.

	Survival	Not survival	P-value
	N(%)	N(%)	
Total	10	6	
Tumor size(left)			1.000
decrease	8(80.0%)	5(83.3%)	
increase	1(10.0%)	0(0.0%)	
stable	1(10.0%)	1(16.7%)	
Tumor size(right)			1.000
decrease	8(80.0%)	5(83.3%)	
increase	1(10.0%)	0(0.0%)	
stable	1(10.0%)	1(16.7%)	
Clinical stage(left)			0.145
decrease	6(60.0%)	1(16.7%)	
increase	0(0.0%)	0(0.0%)	
stable	4(40.0%)	5(83.3%)	
Clinical stage(right)			1.000
decrease	6(60.0%)	4(66.7%)	
increase	0(0.0%)	0(0.0%)	
stable	4(40.0%)	2(33.3%)	
Tumor type(left)			0.588
change	4(40.0%)	1(16.7%)	
stable	6(60.0%)	5(83.3%)	
Tumor type(right)			1.000
change	2(20.0%)	1(16.7%)	
stable	8(80.0%)	5(83.3%)	
ER(left)			0.803
decrease	3(30.0%)	3(50.0%)	
increase	2(20.0%)	1(16.7%)	
stable	5(50.0%)	2(33.3%)	
ER(right)			0.275
decrease	5(50.0%)	3(50.0%)	
increase	3(30.0%)	0(0.0%)	
stable	2(20.0%)	3(50.0%)	
PR(left)			0.790
decrease	6(60.0%)	2(33.3%)	
increase	1(10.0%)	1(16.7%)	
stable	3(30.0%)	3(50.0%)	
PR(right)			1.000
decrease	5(50.0%)	3(50.0%)	
increase	1(10.0%)	0(0.0%)	
stable	4(40.0%)	3(50.0%)	
HER2(left)			0.588
decrease	4(40.0%)	1(16.7%)	
increase	0(0.0%)	0(0.0%)	
stable	6(60.0%)	5(83.3%)	
HER2(right)			1.000
decrease	3(30.0%)	2(33.3%)	
increase	1(10.0%)	0(0.0%)	
stable	6(60.0%)	4(66.7%)	
Ki 67(left)			0.180
decrease	6(60.0%)	1(16.7%)	

increase	4(40.0%)	4(66.7%)	
stable	0(0.0%)	1(16.7%)	
Ki 67(right)			0.554
decrease	6(60.0%)	3(50.0%)	
increase	4(40.0%)	2(33.3%)	
stable	0(0.0%)	1(16.7%)	
P53(left)			0.257
decrease	3(30.0%)	0(0.0%)	
increase	5(50.0%)	3(50.0%)	
stable	2(20.0%)	3(50.0%)	
P53(right)			0.070
decrease	7(70.0%)	1(16.7%)	
increase	2(20.0%)	2(33.3%)	
stable	1(10.0%)	3(50.0%)	
Molecular subtype(left)			0.607
change	3(30.0%)	3(50.0%)	
stable	7(70.0%)	3(50.0%)	
Molecular subtype(right)			0.145
change	6(60.0%)	1(16.7%)	
stable	4(40.0%)	5(83.3%)	

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor.

Table 7. Response to NAC in SBBC.

	left	right	P-value
Response to NAC			0.809
PCR	1(6.3%)	2(12.5%)	
CCR	0(0.0%)	1(6.3%)	
PR	11(68.7%)	8(50.0%)	
SD	3(18.7%)	4(25.0%)	
PD	1(6.3%)	1(6.3%)	

PCR, pathologic complete response; CCR, clinical complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 8. Kaplan-Meier survival estimate for SBBC received NAC.

	time[month]	95%CI	P value
Change in tumor size(left)			0.887
decrease	53.50±10.35	33.22-73.78	
no decrease	30.00±7.35	15.60-44.40	
Change in tumor size(right)			0.887
decrease	53.50±10.35	33.22-73.78	
no decrease	30.00±7.35	15.60-44.40	
Change in clinical stage(left)			0.159
decrease	72.33±10.65	51.46-93.21	
no decrease	25.75±4.58	16.77-34.73	
Change in clinical stage(right)			0.918
decrease	54.20±11.42	31.82-76.58	
no decrease	28.20±5.92	16.61-39.79	
Change in tumor type(left)			0.604
change	66.50±15.16	36.80-96.21	
no change	40.00±7.27	25.76-54.24	
Change in tumor type(right)			0.887
change	60.00±19.60	21.59-98.41	
no change	44.01±7.78	28.81-59.31	
Change in ER(left)			0.215
decrease	34.40±11.91	11.06-57.74	
no decrease	61.60±10.72	40.60-82.61	
Change in ER(right)			0.888
decrease	41.33±10.76	20.24-62.42	
no decrease	57.00±12.32	32.85-81.16	
Change in PR(left)			0.561
decrease	34.75±10.35	12.46-55.04	
no decrease	54.86±12.80	29.78-79.94	
Change in PR(right)			0.961
decrease	43.71±10.17	23.79-63.64	
no decrease	48.75±12.08	25.08-72.42	
Change in HER2(left)			0.153
decrease	-	-	
no decrease	-	-	
Change in HER2(right)			0.518
decrease	39.50±13.75	12.55-66.45	
no decrease	57.27±10.58	36.54-78.01	
Change in Ki 67(left)			0.530
decrease	51.57±9.22	33.50-69.65	
no decrease	49.50±12.27	25.46-73.54	
Change in Ki 67(right)			0.924
decrease	57.25±12.21	33.32-81.18	
no decrease	39.32±8.48	22.70-55.95	
Change in P53(left)			0.384
decrease	-	-	
no decrease	-	-	
Change in P53(right)			0.079
decrease	59.14±7.27	44.89-73.40	
no decrease	38.25±12.23	14.28-62.22	
Change in molecular subtype (left)			0.636
change	39.50±13.75	12.55-66.45	

no change	55.82±11.15	33.95-77.68
Change in molecular subtype (right)		0.124
change	69.00±12.99	43.54-94.46
no change	33.11±7.72	17.98-48.25

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor.

Table 9. Respond to NAC.

	time[month]	95%CI	Log Rank P value
Respond to NAC (left)			0.518
respond	57.27±10.58	36.54-78.01	
no respond	25.50±6.75	12.27-38.73	
Respond to NAC (right)			0.518
respond	57.27±10.58	36.54-78.01	
no respond	25.50±6.75	12.27-38.73	

CI confidence interval.

Figures

Figure 1

The flow chart of reasons for exclusion.

Figure 2

The cumulative survival time between response group and no-response group in SBBC patients received NAC.

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