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 Mejdalh 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
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,
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(%)              |---|---|---|
| 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    | 4    |
|---|------|------|
|   | 9(15.3%) | 6(9.0%) |
|   | 28(47.5%) | 14(20.9%) |

**ER(right)**

|   | 1     | 2     |
|---|-------|-------|
|   | 18(30.5%) | 37(55.2%) |
|   | 3(5.1%)  | 5(7.5%)  |
|   | 12(20.3%) | 6(9.0%)  |
|   | 26(44.1%) | 19(28.4%) |

**PR(left)**

|   | 1     | 2     |
|---|-------|-------|
|   | 23(39.0%) | 50(74.6%) |
|   | 8(13.6%)  | 12(17.9%) |
|   | 12(20.3%) | 2(3.0%)  |
|   | 16(27.1%) | 3(4.5%)  |

**PR(right)**

|   | 1     | 2     |
|---|-------|-------|
|   | 22(37.3%) | 45(67.2%) |
|   | 15(25.4%) | 7(10.4%)  |
|   | 10(16.9%) | 7(10.4%)  |
|   | 12(20.3%) | 8(11.9%)  |

**HER2(left)**

|   |   |   |
|---|---|---|
|   | -   | +   |
|   | 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)**

|   |   |   |
|---|---|---|
|   | -   | +   |
|   | 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)**

|   |   |   |
|---|---|---|
|   | 1   | 2   |
|   | 1(1.7%) | 2(3.0%) |
|   | 51(86.4%) | 54(80.6%) |
|   | 5(8.5%)  | 11(16.4%) |
|   | 2(3.4%)  | 0(0.0%)  |

**Ki 67(right)**

|   |   |   |
|---|---|---|
|   | 1   | 2   |
|   | 1(1.7%) | 1(1.5%) |
|   | 51(86.4%) | 49(73.1%) |
|   | 7(11.9%) | 15(22.4%) |
|   | 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%)     |         |
|                         | Left          | Right         | p-value |
|-------------------------|---------------|---------------|---------|
| **Tumor type**          |               |               |         |
| ductal                  | 35 (34.7%)    | 37 (36.6%)    | 0.751   |
| lobular                 | 58 (57.4%)    | 57 (56.4%)    |         |
| other                   | 8 (7.9%)      | 7 (6.9%)      |         |
| **Histological grade**  |               |               |         |
| DCIS                    | 12 (11.9%)    | 9 (8.9%)      | 0.552   |
| I                       | 2 (2.0%)      | 2 (2.0%)      |         |
| II                      | 80 (79.2%)    | 80 (79.2%)    |         |
| III                     | 7 (6.9%)      | 10 (9.9%)     |         |
| **Sentinel lymph node** |               |               |         |
| negative                | 39 (38.6%)    | 33 (32.7%)    | 0.000   |
| positive                | 7 (6.9%)      | 14 (13.9%)    |         |
| undone                  | 55 (54.5%)    | 54 (53.5%)    |         |
| **Axillary lymph node** |               |               |         |
| negative                | 36 (35.6%)    | 32 (31.7%)    | 0.071   |
| positive                | 19 (18.8%)    | 41 (40.6%)    |         |
| undone                  | 46 (45.5%)    | 28 (27.7%)    |         |
| **ER**                  |               |               |         |
| 1                       | 41 (40.6%)    | 41 (40.6%)    | 0.037   |
| 2                       | 9 (8.9%)      | 11 (10.9%)    |         |
|    |       |       |       |
|----|-------|-------|-------|
|    | 3     | 4     |       |
|    | 12(11.9%) | 3(12.0%) |
|    | 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 |
|                | Values | Percentages |
|----------------|--------|-------------|
| 1              | 41     | 40.6%       |
| 2              | 36     | 35.6%       |
| 3              | 6      | 5.9%        |
| 4              | 18     | 17.8%       |
| P53 (right)    |        | 0.627       |
| 1              | 29     | 28.7%       |
| 2              | 49     | 48.5%       |
| 3              | 10     | 9.9%        |
| 4              | 13     | 12.9%       |
| Molecular subtype (left) |        | 0.175       |
| Luminal A      | 24     | 23.8%       |
| Luminal B      | 47     | 46.5%       |
| HER2 positive  | 8      | 7.9%        |
| Triple negative| 22     | 21.8%       |
| Molecular subtype (right) |        | 0.007       |
| Luminal A      | 28     | 27.7%       |
| Luminal B      | 47     | 46.5%       |
| HER2 positive  | 15     | 14.9%       |
| Triple negative| 11     | 10.9%       |
| Surgery        |        | 0.313       |
| modified radical mastectomy | 90 | 89.1%       |
| radical mastectomy       | 7    | 6.9%        |
| breast conserving surgery | 4  | 4.0%        |
| Chemotherapy    |        | 0.187       |
| TEC             | 43     | 42.6%       |
| EC followed by T | 22  | 21.8%       |
| NP              | 7      | 6.9%        |
| 2 or more regimens | 19 | 18.8%       |
| undone          | 10     | 9.9%        |
| Endocrine therapy|      | 0.003       |
| yes             | 79     | 78.2%       |
| no              | 22     | 21.8%       |
| Radiotherapy    |        | 0.152       |
| yes             | 33     | 32.7%       |
| no              | 68     | 67.3%       |

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2
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       |         |
| HER2 | 16 | 12 | 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%)     |         |
| Variable                  | Left          | Right         | p-value |
|---------------------------|---------------|---------------|---------|
| Clinical stage (left)     |               |               | 0.145   |
| increase                  | 1 (10.0%)     | 0 (0.0%)      |         |
| stable                    | 1 (10.0%)     | 1 (16.7%)     |         |
| 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   |
|                  | Left                  | Right                  |
|------------------|-----------------------|------------------------|
| decrease         | 3(30.0%)              | 6(60.0%)               |
| increase         | 1(10.0%)              | 4(40.0%)               |
| stable           | 6(60.0%)              | 4(66.7%)               |
| Ki 67 (left)     |                       |                        |
| decrease         | 6(60.0%)              | 7(70.0%)               |
| increase         | 4(40.0%)              | 2(20.0%)               |
| stable           | 2(20.0%)              | 3(50.0%)               |
| Ki 67 (right)    |                       |                        |
| decrease         | 6(60.0%)              | 6(60.0%)               |
| increase         | 4(40.0%)              | 4(66.7%)               |
| stable           | 0(0.0%)               | 1(16.7%)               |
| P53 (left)       |                       |                        |
| decrease         | 3(30.0%)              | 7(70.0%)               |
| increase         | 5(50.0%)              | 3(50.0%)               |
| stable           | 2(20.0%)              | 3(50.0%)               |
| P53 (right)      |                       |                        |
| decrease         | 1(10.0%)              | 1(16.7%)               |
| increase         | 2(20.0%)              | 2(33.3%)               |
| stable           | 3(50.0%)              | 3(50.0%)               |
| Molecular subtype (left) |       |                        |
| change           | 3(30.0%)              | 6(60.0%)               |
| stable           | 7(70.0%)              | 4(40.0%)               |
| Molecular subtype (right) |        |                        |
| 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 Mean ± SD | Range            |
|----------------------|--------------------|------------------|
|                      | 41.33±10.76        | 20.24-62.42      |
| No decrease          | 57.00±12.32        | 32.85-81.16      |
| Change in PR (left)  | 0.561              |                  |
|                      | 34.75±10.35        | 12.46-55.04      |
| No decrease          | 54.86±12.80        | 29.78-79.94      |
| Change in PR (right) | 0.961              |                  |
|                      | 43.71±10.17        | 23.79-63.64      |
| No decrease          | 48.75±12.08        | 25.08-72.42      |
| Change in HER2 (left)| 0.153              |                  |
|                      | -                  | -                |
| No decrease          | -                  | -                |
| Change in HER2 (right)| 0.518             |                  |
|                      | 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              |                  |
|                      | 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             |                  |
|                      | 57.25±12.21        | 33.32-81.18      |
| No decrease          | 39.32±8.48         | 22.70-55.95      |
| Change in P53 (left) | 0.384              |                  |
|                      | -                  | -                |
| No decrease          | -                  | -                |
| Change in P53 (right)| 0.079              |                  |
|                      | 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 |                  |
|                      | 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          |                  |
|                      | 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 | 95%CI    | Log Rank P value |
|----------------------|------|----------|------------------|
| Respond to NAC (left)|      |          |                  |
| respond              | 57.27±10.58 | 36.54-78.01 | 0.518            |
| no respond           | 25.50±6.75  | 12.27-38.73 |                  |
| Respond to NAC (right)|     |          |                  |
| respond              | 57.27±10.58 | 36.54-78.01 | 0.518            |
| no respond           | 25.50±6.75  | 12.27-38.73 |                  |

CI confidence interval.

**Figures**
Patients diagnosed as breast cancer in the First Affiliated Hospital of Chongqing Medical University between January 2012 and November 2018: N=6453

Exclusions: Total: 6287
- Patients diagnosed with unilateral breast cancer N=6255
- Patients age <18 years N=32

Patients diagnosed as bilateral breast cancer: N=166

Exclusions: Total: 40
- Missing the data of both side tumor N=37
- A metastatic cancer from the contralateral side of earlier BC N=1
- Not receiving surgical treatment N=1
- Abandon treatment N=1

Patients diagnosed as SBBC included in analysis: N=59
Patients diagnosed as MBBC included in analysis: N=67

Figure 1

The flow chart of reasons for exclusion.
The cumulative survival time between response group and no-response group in SBBC patients received NAC.

Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.

- Supplementary table 6.docx
- Supplementary table 1.docx
- Supplementary table 3.docx
- Supplementary table 2.docx
- Supplementary table 4.docx
- Supplementary table 5.docx