Clinical characteristics and clinicopathological correlations of bilateral breast cancer in China: A multicenter study from Chinese Society of Breast Surgery (CSBrS-006)

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Abstract

Objective: To investigate the clinical characteristics and clinicopathological correlations of bilateral breast cancer (BBC) in China.

Methods: Data of 440 patients diagnosed with BBC in 2018 were collected from 33 centers of the Chinese Society of Breast Surgery. Demographic characteristics, bilateral tumor characteristics, and comprehensive treatment data were obtained. Correlations between the clinicopathological characteristics of bilateral tumors were analyzed.

Results: The proportion of BBC was 0.22%−3.08%. A total of 33 (7.5%) patients had a family history of malignant tumors, 304 (69.1%) patients had synchronous BBC. Only 1 (0.2%) patient was male. More than half of all patients received concurrent or asynchronous endocrine/chemotherapy, 32.5% of all human epidermal growth factor receptor 2 (HER2)-positive patients received HER2-targeted therapy, and approximately 21.6% of all patients received radiotherapy. The most common pathological cancer type was invasive ductal cancer (>60%). Approximately 70% of all patients had bilateral hormone receptor (HR)-positive tumors and presented with a single breast mass. Significant correlations were found with pathological type, histological grade, locations of tumor, molecular subtype, Ki-67 index, tumor site and size of bilateral tumors. Results of the subgroup analysis showed more clinicopathological characteristics when synchronous BBC was compared with metachronous BBC.

Conclusions: In China, the clinicopathological characteristics of bilateral tumors showed significant correlations, and more significant clinicopathological correlations were observed when synchronous BBC was compared with metachronous BBC.

Keywords: Adjuvant therapy; bilateral breast cancer; clinicopathological correlation; demographic characteristics

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Introduction

Bilateral breast cancer (BBC) is classified as either synchronous BBC, diagnosed simultaneously in both breasts in the same patient, or metachronous BBC, diagnosed within a time interval after the first breast cancer diagnosis (1). Different time intervals have been used to define BBC. According to the Surveillance, Epidemiology, and End Results (SEER) database in the United States, the
incidence of BBC increased significantly from 2.6% in 1975 to 7.5% in 2014 (1,2). There are no evidence-based guidelines for the management of BBC, and little is known about the optimal treatment regimen. Hence, it is urgent to investigate the clinicopathological factors that should be considered when making therapeutic decisions.

To the best of our knowledge, no multicenter study on BBC has been conducted in China. Therefore, we aimed to analyze the clinical characteristics and clinicopathological correlations of BBC in China.

Materials and methods

Patients and clinicopathological data

We retrospectively collected data of 440 patients suffering from BBC who were diagnosed in 33 centers (members of the Chinese Society of Breast Surgery) between January 2018 and December 2018. The demographic characteristics, bilateral tumor characteristics, pathological information, and comprehensive treatment data of all patients were collected using a uniform electronic questionnaire designed by the Chinese Society of Breast Surgery. In our study, we defined synchronous BBC as a tumor diagnosed within one year of the first tumor diagnosis, and defined metachronous BBC as a tumor diagnosed more than one year of the first tumor diagnosis.

Patients with a pathologically confirmed diagnosis of BBC were included in the study, while patients with a secondary malignant breast tumor were excluded. The patients’ demographic characteristics including age and sex, family history of breast cancer, body mass index (BMI), and breast cancer susceptibility genes1/2 (BRCA1/2) and Oncotype DX status were collected. Pathological information such as histological type, malignancy grade, location of breast tumor, TNM stage, estrogen/progesterone receptor, and human epidermal growth factor receptor-2 (HER2) status were collected from the patients’ pathologic reports. Treatment data such as surgery information and comprehensive treatment data were collected from the patients’ medical files.

This study was approved by the Ethics Committee of Shengjing Hospital of China Medical University (No. 2019PS466K). The requirement for informed consent was waived as this was a retrospective study. This study conforms to the provisions of the Declaration of Helsinki (as revised in Edinburgh 2000).

Results

Basic characteristics of patients with BBC

In our study, a total of 440 patients were diagnosed with BBC. The proportion of BBC was 0.22% to 3.08%. The distribution of patients with BBC among the different districts in China is shown in Table 1. The proportion was highest in Northeast China (1.96%, 133/6,798) and lowest in North China (0.94%, 90/9,566). The median age of the patients was 55 (range, 21–91) years (Table 2). Thirty-three (7.5%) patients had a family history of malignant tumors. A total of 304 (69.1%) patients had synchronous bilateral cancer and 94 (21.4%) patients had metachronous bilateral cancer. The rate of genetic screening was very low, 15 (3.4%) patients were screened of BRCA1/2, while 3 (0.7%) patients were screened for Oncotype DX. Only 1 (0.2%) patient with BBC was male (Table 2).

Clinicopathological characteristics of BBC patients

Different types of breast surgery were performed among the patients with BBC (Supplementary Table S1). The most common form of surgery was the modified radical double mastectomy (47.5%, 209/440), and 100 (22.7%) patients underwent bilateral/unilateral mastectomy ± contralateral breast-conserving surgery. Postoperative complications

Table 1 Proportion of bilateral breast cancer in different districts

| Districts          | % (n/N)   |
|--------------------|-----------|
| Northeast China    | 1.96 (133/6,798) |
| South China        | 1.72 (231/1,341)  |
| East China         | 1.70 (109/6,400)  |
| Northwest China    | 1.08 (24/2,213)   |
| Central China      | 1.03 (34/3,306)   |
| Southwest China    | 0.98 (49/4,985)   |
| North China        | 0.94 (80/9,566)   |

Statistical analysis

Statistical analyses were performed using Prism 8 (GraphPad Software Inc., La Jolla, CA, USA). Associations between left or right tumor and clinical or pathological variables of patients with BBC were determined using Chi-square ($\chi^2$) or Fisher’s exact test. Spearman’s correlation coefficient was used to test correlations. All the statistical tests used were two-tailed. A P-value <0.05 was considered statistically significant.
were very rare; only 5 (1.1%) patients had postoperative lymphedema, and 2 (0.5%) patients had postoperative wound infections (Supplementary Table S1). The adjuvant therapy information of the patients with BBC was similar to that of the patients with unilateral breast cancer. More than half of all patients received concurrent or asynchronous endocrine/chemotherapy, 32.5% of all HER2-positive patients received HER2-targeted therapy, and approximately 21.6% of all patients received radiotherapy (Supplementary Table S2). Invasive ductal cancer was the most common pathological cancer type (>60%), followed by ductal carcinoma in situ; this was similar in the patients with unilateral breast cancer. The malignancy grade and the distribution of the four molecular subtypes (HER2+, triple-negative breast cancer, HR+ and HR+/HER2+) among the patients with BBC was similar to that among the patients with the unilateral breast cancer. Approximately 70% of all patients had bilateral HR+ tumors and presented with a single breast mass (Table 3).

**Clinicopathological correlations of BBC**

We analyzed the clinicopathological correlations with histological type, malignancy grade, tumor location, molecular subtype, Ki-67 index, tumor site and tumor size. All these variables showed significant correlations (Table 4). Results of the subgroup analyses of the main characteristics are presented in Supplementary Table S3. More significant clinicopathological correlations were observed when synchronous BBC was compared with metachronous BBC (Table 5). Only tumor location (P=0.011, r=0.333), molecular subtype (P=0.001, r=0.448), and Ki-67 index (P=0.027, r=0.346) showed significant clinicopathological correlations in metachronous BBC (Table 5). Together, results of the subgroup analysis showed more clinicopathological characteristics when synchronous BBC was compared with metachronous BBC.

**Discussion**

In this study, we investigated the clinicopathological characteristics of BBC in China. Based on the results of the subgroup analysis, we found significant BBC clinicopathological correlations with pathological type, histological grade, tumor location, molecular subtype, Ki-67 index, tumor site, and size of bilateral tumors. More significant clinicopathological correlations were observed when synchronous BBC was compared with metachronous BBC.

Nichol et al. reported that 1.32% (207/15,704) of breast cancer cases diagnosed in British Columbia between 1989 and 2000 were BBCs (3). Several meta analyses (4,5) and studies (6,7) observed that the incidence of BBC comprised 2%–11% of all breast cancers. According to the SEER database, the proportion of BBC significantly increased from 2.6% in 1975 to 7.5% in 2014 (1,2). In our study, a proportion of 0.22%–3.08% in 33 different centers was observed. A very low rate of genetic screening was observed; 3.4% (15/440) for BRCA1/2 and 0.7% (3/440) for Oncotype DX.

The clinicopathological characteristics of BBC are still
Table 3 Clinicopathological characteristics of patients with bilateral breast cancer

| Clinicopathological characteristics | n (%) | P  |
|-------------------------------------|-------|----|
| **Histological type**               |       |    |
| DCIS                               | 70 (15.9) | 90 (20.5) | 0.0524 |
| LCIS                               | 0 (0) | 4 (0.9) |
| IDC                                | 287 (65.2) | 276 (62.7) |
| ILC                                | 11 (2.5) | 6 (1.4) |
| Other                              | 30 (6.8) | 35 (8.0) |
| NA                                 | 42 (9.5) | 29 (6.6) |
| **Malignancy grade**               |       |    |
| I                                  | 28 (6.4) | 31 (7.0) | 0.7355 |
| II                                 | 178 (40.5) | 167 (38.0) |
| III                                | 77 (17.5) | 73 (16.6) |
| Carcinoma in situ                  | 41 (9.3) | 53 (12.0) |
| Other                              | 55 (12.5) | 49 (11.1) |
| NA                                 | 61 (13.9) | 67 (15.2) |
| **Tumor location**                 |       |    |
| Upper inner                        | 64 (14.5) | 48 (10.9) | 0.5052 |
| Low inner                          | 32 (7.3) | 27 (6.1) |
| Upper lateral                      | 151 (34.3) | 170 (38.6) |
| Low lateral                        | 37 (8.4) | 33 (7.5) |
| Nipple deep                        | 32 (7.3) | 36 (8.2) |
| NA                                 | 124 (28.2) | 126 (28.6) |
| **TNM stage**                      |       |    |
| 0                                  | 47 (10.7) | 63 (14.3) | 0.1417 |
| I                                  | 126 (28.6) | 139 (31.6) |
| II                                 | 136 (30.9) | 119 (27.0) |
| III                                | 35 (8.0) | 39 (8.9) |
| IV                                 | 13 (3.0) | 5 (1.1) |
| NA                                 | 83 (18.9) | 75 (17.0) |
| **Molecular subtype**              |       |    |
| HR+                                | 249 (56.6) | 253 (57.5) | 0.2568 |
| HR+/HER2+                          | 57 (13.0) | 67 (15.2) |
| HER2+                              | 23 (5.2) | 22 (5.0) |
| TNBC                               | 47 (10.7) | 29 (6.6) |
| NA                                 | 64 (14.5) | 69 (15.7) |
| **Tumor site**                     |       |    |
| Single                             | 291 (66.1) | 307 (69.8) | 0.6980 |
| Multiple                           | 35 (8.0) | 31 (7.0) |
| Multicenter                        | 15 (3.4) | 12 (2.7) |
| NA                                 | 99 (22.5) | 90 (20.5) |

DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; NA, not applicable; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

Table 4 Clinicopathological correlations of bilateral breast cancer

|                         | Left vs. Right | r (95% CI) | P       |
|-------------------------|----------------|------------|---------|
| **Histological type**   |                |            | <0.001  |
| (n=371)                 |                |            |         |
| Malignancy grade        |                |            | <0.001  |
| (n=328)                 |                |            |         |
| Tumor location          |                |            | <0.001  |
| (n=309)                 |                |            |         |
| Molecular subtype       |                |            | <0.001  |
| (n=326)                 |                |            |         |
| Ki-67 index             |                |            | <0.001  |
| (n=307)                 |                |            |         |
| Tumor site              |                |            | 0.001   |
| (n=309)                 |                |            |         |
| Tumor size              |                |            | <0.001  |
| (n=321)                 |                |            |         |

95% CI, 95% confidence interval.

In China, the proportion of BBC ranged from 0.22%–3.08% in different centers. The clinicopathological characteristics of bilateral tumors with pathological type, histological grade, tumor location, molecular subtype, Ki-67 index, tumor site and size of bilateral tumors. However, for metachronous BBC, some systemic treatments and the primary tumor type may influence the clinicopathological characteristics of contralateral tumors. Li et al. (15) and Song et al. (16) defined the origin and evolution of BBC in several Chinese women using whole exome sequencing and cancer genome analysis. Further studies will provide more mechanistic insights into the progression of BBC. Additional follow-up will be necessary to determine whether there is an effect of clinicopathological factors on disease-free and overall survival. The main limitation of this study was its retrospective nature.

**Conclusions**

In China, the proportion of BBC ranged from 0.22%–3.08% in different centers. The clinicopathological characteristics of bilateral tumors showed significant correlations, and more significant clinicopathological correlations were observed when synchronous BBC was compared with metachronous BBC. Further studies are needed to confirm the clinicopathological correlations of BBC in China.

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**Footnote**

Conflicts of Interest: The authors have no conflicts of interest to declare.

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| Table 5 Clinicopathological correlations of synchronous and metachronous bilateral breast cancer |
|----------------------------------|------------------|------------------|
|                                   | Simultaneous     | Metachronous     |
|                                   | Left vs. Right   |                  |
|                                   | r (95% CI)       | P                |
| Histological type (n=272)         | 0.245 (0.126–0.356) | <0.001           |
| Malignancy grade (n=244)          | 0.486 (0.380–0.579) | <0.001           |
| Tumor location (n=244)            | 0.015 (0.004–0.141) | 0.072            |
| Molecular subtype (n=235)         | 0.421 (0.310–0.524) | <0.001           |
| Ki-67 index (n=229)               | 0.224 (0.094–0.347) | 0.001            |
| Tumor site (n=259)                | 0.184 (0.060–0.302) | 0.003            |
| Tumor size (n=243)                | 0.322 (0.201–0.434) | <0.001           |
|                                   | 0.167 (0.101–0.412) | 0.209            |
|                                   | 0.236 (0.048–0.484) | 0.093            |
|                                   | 0.333 (0.074–0.550) | 0.011            |
|                                   | 0.448 (0.188–0.649) | 0.001            |
|                                   | 0.346 (0.034–0.597) | 0.027            |
|                                   | 0.182 (0.035–0.464) | 0.244            |
|                                   | −0.182 (−0.468–0.138) | 0.249            |

95% CI, 95% confidence interval.
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### Table S1 Surgery information of patients with bilateral breast cancer

| Surgery information | n (%) |
|---------------------|-------|
| **Operation type**  |       |
| Modified radical double mastectomy | 209 (47.5) |
| Bilateral breast-conserving surgery | 32 (7.3) |
| Unilateral modified radical mastectomy + unilateral breast-conserving surgery | 20 (4.5) |
| Unilateral breast reconstruction | 6 (1.4) |
| Bilateral breast reconstruction | 23 (5.2) |
| Other (bilateral/unilateral mastectomy ± contralateral breast-conserving surgery) | 100 (22.7) |
| NA | 50 (11.4) |
| **Sentinel lymph node biopsy** |       |
| Sentinel lymph node biopsy of synchronous carcinoma |     |
| Negative | 153 (34.8) |
| Positive | 73 (16.6) |
| Without this procedure | 75 (17.0) |
| Sentinel lymph node biopsy of metachronous carcinoma |     |
| Negative | 31 (7.0) |
| Positive | 17 (3.9) |
| Without this procedure | 11 (2.5) |
| NA | 80 (18.2) |
| **Status of axillary lymph node** |       |
| Bilateral sentinel lymph node biopsy | 145 (33.0) |
| Bilateral axillary lymph node dissection | 90 (20.5) |
| Left sentinel lymph node biopsy + right axillary lymph node dissection | 37 (8.4) |
| Left axillary lymph node dissection + right sentinel lymph node biopsy | 57 (13.0) |
| Other | 61 (13.9) |
| NA | 50 (11.4) |
| **Postoperative complications** |       |
| Upper limb lymphedema | 5 (1.1) |
| Incision infection | 2 (0.5) |
| No | 361 (82.0) |
| NA | 72 (16.4) |

NA, not applicable.
| Adjuvant therapy information | n (%   ) |
|------------------------------|---------|
| Endocrine therapy            |         |
| No                           | 86 (19.5) |
| TAM of synchronous carcinoma | 96 (21.8) |
| TAM of metachronous carcinoma| 21 (4.8)  |
| AI of synchronous carcinoma  | 95 (21.6) |
| AI of metachronous carcinoma | 26 (5.9)  |
| Other                        | 11 (2.5)  |
| NA                           | 105 (23.9) |
| Chemotherapy                 |         |
| No                           | 96 (21.8) |
| Neoadjuvant chemotherapy of synchronous carcinoma | 72 (16.4) |
| Neoadjuvant chemotherapy of metachronous carcinoma | 5 (1.1)  |
| Adjuvant chemotherapy of synchronous carcinoma | 132 (30.0) |
| Adjuvant chemotherapy of metachronous carcinoma | 46 (10.5) |
| NA                           | 89 (20.2) |
| Radiotherapy                 |         |
| No                           | 208 (47.3) |
| Radiotherapy of synchronous carcinoma | 69 (15.7) |
| Radiotherapy of metachronous carcinoma | 26 (5.9)  |
| NA                           | 137 (31.1) |
| Targeted therapy- HER2-positive |         |
| No                           | 32 (40.0) |
| Targeted therapy of synchronous carcinoma | 21 (26.3) |
| Targeted therapy of metachronous carcinoma | 5 (6.3)  |
| NA                           | 22 (27.5) |

TAM, tamoxifen; AI, aromatase inhibitor; NA, not applicable.
| Cinicopathological features | Synchronous | Metachronous | P   |
|----------------------------|-------------|-------------|-----|
|                            | Left        | Right       |     |
|                            | 0.0442      | NA          |     |
| **Histological type**      | 0.0442      | 0.0651      |     |
| DCIS                       | 51 (16.8)   | 67 (22.0)   | 10 (10.6) |
| LCIS                       | 0 (0)       | 4 (1.3)     | 0 (0) |
| IDC                        | 203 (66.8)  | 192 (63.2)  | 53 (56.4) |
| ILC                        | 9 (3.0)     | 2 (0.7)     | 2 (2.1) |
| Other                      | 26 (8.5)    | 22 (7.2)    | 3 (3.2) |
| NA                         | 15 (4.9)    | 17 (5.6)    | 26 (27.7) |
| **Malignancy grade**       | 0.2908      | 0.9464      |     |
| I                          | 21 (6.9)    | 25 (8.2)    | 4 (4.2) |
| II                         | 135 (44.4)  | 124 (40.8)  | 27 (28.7) |
| III                        | 49 (16.1)   | 38 (12.5)   | 17 (18.1) |
| Carcinoma in situ          | 33 (10.9)   | 47 (15.5)   | 8 (8.5) |
| Other                      | 34 (11.2)   | 29 (9.5)    | 9 (9.6) |
| NA                         | 32 (10.5)   | 41 (13.5)   | 29 (30.9) |
| **Tumor location**         | 0.4986      | <0.0001     |     |
| Upper inner                | 58 (19.1)   | 47 (15.5)   | 9 (9.6) |
| Low inner                  | 26 (8.6)    | 22 (7.2)    | 63 (67.0) |
| Upper lateral              | 132 (43.4)  | 148 (48.7)  | 0 (0) |
| Low lateral                | 36 (11.8)   | 27 (8.9)    | 0 (0) |
| Nipple deep                | 15 (4.9)    | 19 (6.3)    | 0 (0) |
| NA                         | 37 (12.2)   | 41 (13.5)   | 22 (23.4) |
| **TNM stage**              | 0.0698      | 0.7178      |     |
| 0                          | 32 (10.5)   | 48 (15.8)   | 9 (9.6) |
| I                          | 90 (29.6)   | 103 (33.9)  | 16 (17.0) |
| II                         | 102 (33.6)  | 83 (27.3)   | 24 (25.5) |
| III                        | 26 (8.6)    | 30 (9.9)    | 7 (7.4) |
| IV                         | 11 (3.6)    | 4 (1.3)     | 1 (1.1) |
| NA                         | 43 (14.1)   | 36 (11.8)   | 37 (39.4) |
| **Molecular subtype**      | 0.2403      | 0.9464      |     |
| HR+                        | 178 (58.6)  | 182 (59.9)  | 37 (39.4) |
| HR+/HER2+                  | 35 (11.5)   | 45 (14.8)   | 15 (16.0) |
| HER2+                      | 15 (4.9)    | 13 (4.3)    | 8 (8.5) |
| TNBC                       | 36 (11.8)   | 21 (6.9)    | 10 (10.6) |
| NA                         | 40 (13.2)   | 43 (14.1)   | 24 (25.5) |
| **Tumor site**             | 0.5703      | 0.6254      |     |
| Single                     | 230 (75.7)  | 244 (80.3)  | 56 (59.6) |
| Multiple                   | 29 (9.5)    | 22 (7.2)    | 4 (4.3) |
| Multicenter                | 14 (4.6)    | 11 (3.6)    | 1 (1.1) |
| NA                         | 31 (10.2)   | 27 (8.9)    | 33 (35.1) |

DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HR, hormone receptor; HER2+, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; NA, not applicable.