Original Article

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).

Statistical analysis

Statistical analyses were performed using Prism 8 (GraphPad Software Inc., LaJolla, CA, USA). Associations between left or right tumor and clinical or pathological variables of patients with BBC were determined using Chi-square (χ^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.

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 (23/1,341)
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 (90/9,566)

Table 2 Basic characteristics of patients with bilateral breast cancer

Basic information	n (%)
Age (year)	
<55	220 (50.0)
≥55	212 (48.2)
NA	8 (1.8)
Gender	
Female	419 (99.8)
Male	1 (0.2)
Family history	
Yes	33 (7.5)
No	407 (92.5)
BMI (kg/m^2)	
<24	228 (51.8)
24≤BMI<28	142 (32.3)
≥28	51 (11.6)
NA	19 (4.3)
BRCA1/2 screening	
Yes	15 (3.4)
No	405 (92.1)
NA	20 (4.5)
Oncotype DX	
Yes	3 (0.7)
No	417 (99.3)
NA	20 (4.5)
Time	
Simultaneous	304 (69.1)
Metachronous	94 (21.4)
NA	42 (9.5)

NA, not applicable; BMI, body mass index; *BRCA1/2*, breast cancer susceptibility genes1/2.

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
	Left	Right	
Histological type			0.0524
DCIS	70 (15.9)	90 (20.5)	
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			0.7355
I	28 (6.4)	31 (7.0)	
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			0.5052
Upper inner	64 (14.5)	48 (10.9)	
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			0.1417
0	47 (10.7)	63 (14.3)	
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			0.2568
HR+	249 (56.6)	253 (57.5)	
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			0.6980
Single	291 (66.1)	307 (69.8)	
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 (n=371)	0.259 (0.159–0.355)	<0.001
Malignancy grade (n=328)	0.452 (0.359–0.537)	<0.001
Tumor location (n=309)	0.210 (0.098–0.318)	<0.001
Molecular subtype (n=326)	0.477 (0.386–0.559)	<0.001
Ki-67 index (n=307)	0.283 (0.173–0.386)	<0.001
Tumor site (n=309)	0.192 (0.079–0.300)	0.001
Tumor size (n=321)	0.250 (0.141–0.353)	<0.001

95% CI, 95% confidence interval.

unclear, and their influence on prognosis is controversial (8-14). In this study, we found significant clinicopathological correlations 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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Table 5 Clinicopathological correlations of synchronous and metachronous bilateral breast cancer

Left *vs.* Right	Simultaneous		Left *vs.* Right	Metachronous	
	r (95% CI)	P		*r* (95% CI)	P
Histological type (n=272)	0.245 (0.126–0.356)	<0.001	Histologal type (n=59)	0.167 (–0.101–0.412)	0.209
Malignancy grade (n=244)	0.486 (0.380–0.579)	<0.001	Malignancy grade (n=52)	0.236 (–0.048–0.484)	0.093
Tumor location (n=244)	0.115 (–0.014–0.241)	0.072	Tumor location (n=58)	0.333 (0.074–0.550)	0.011
Molecular subtype (n=235)	0.421 (0.310–0.524)	<0.001	Molecular subtype (n=51)	0.448 (0.188–0.649)	0.001
Ki-67 index (n=229)	0.224 (0.094–0.347)	0.001	Ki-67 index (n=41)	0.346 (0.034–0.597)	0.027
Tumor site (n=259)	0.184 (0.060–0.302)	0.003	Tumor site (n=43)	0.182 (–0.135–0.464)	0.244
Tumor size (n=243)	0.322 (0.201–0.434)	<0.001	Tumor size (n=42)	–0.182 (–0.468–0.138)	0.249

95% CI, 95% confidence interval.

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Footnote

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

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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 procudure	75 (17.0)
Sentinel lymph node biopsy of metachronous carcinoma	
Negative	31 (7.0)
Positive	17 (3.9)
Without this procudure	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.

Table S2 Adjuvant therapy information of patients with bilateral breast cancer

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.

Table S3 Cinicopathological features of simultaneous and metachronous bilateral breast cancer

Cinicopathological features	Synchronous		P	Metachronous		P
	Left	Right		Left	Right	
Histological type			0.0442			NA
DCIS	51 (16.8)	67 (22.0)		10 (10.6)	7 (7.4)	
LCIS	0 (0)	4 (1.3)		0 (0)	0 (0)	
IDC	203 (66.8)	192 (63.2)		53 (56.4)	60 (63.8)	
ILC	9 (3.0)	2 (0.7)		2 (2.1)	3 (3.2)	
Other	26 (8.5)	22 (7.2)		3 (3.2)	13 (13.8)	
NA	15 (4.9)	17 (5.6)		26 (27.7)	11 (11.7)	
Malignancy grade			0.2908			0.0651
I	21 (6.9)	25 (8.2)		4 (4.2)	1 (1.1)	
II	135 (44.4)	124 (40.8)		27 (28.7)	28 (29.8)	
III	49 (16.1)	38 (12.5)		17 (18.1)	25 (26.6)	
Carcinoma *in situ*	33 (10.9)	47 (15.5)		8 (8.5)	6 (6.4)	
Other	34 (11.2)	29 (9.5)		9 (9.6)	18 (19.1)	
NA	32 (10.5)	41 (13.5)		29 (30.9)	16 (17.0)	
Tumor location			0.4986			<0.0001
Upper inner	58 (19.1)	47 (15.5)		9 (9.6)	3 (3.2)	
Low inner	26 (8.6)	22 (7.2)		63 (67.0)	5 (5.3)	
Upper lateral	132 (43.4)	148 (48.7)		0 (0)	42 (44.7)	
Low lateral	36 (11.8)	27 (8.9)		0 (0)	7 (7.4)	
Nipple deep	15 (4.9)	19 (6.3)		0 (0)	20 (21.3)	
NA	37 (12.2)	41 (13.5)		22 (23.4)	17 (18.1)	
TNM stage			0.0698			0.7178
0	32 (10.5)	48 (15.8)		9 (9.6)	4 (4.2)	
I	90 (29.6)	103 (33.9)		16 (17.0)	22 (23.4)	
II	102 (33.6)	83 (27.3)		24 (25.5)	24 (25.5)	
III	26 (8.6)	30 (9.9)		7 (7.4)	7 (7.4)	
IV	11 (3.6)	4 (1.3)		1 (1.1)	1 (1.1)	
NA	43 (14.1)	36 (11.8)		37 (39.4)	36 (38.4)	
Molecular subtype			0.2403			0.9464
HR+	178 (58.6)	182 (59.9)		37 (39.4)	40 (42.6)	
HR+/HER2+	35 (11.5)	45 (14.8)		15 (16.0)	14 (14.9)	
HER2+	15 (4.9)	13 (4.3)		8 (8.5)	9 (9.6)	
TNBC	36 (11.8)	21 (6.9)		10 (10.6)	7 (7.4)	
NA	40 (13.2)	43 (14.1)		24 (25.5)	24 (25.5)	
Tumor site			0.5703			0.6254
Single	230 (75.7)	244 (80.3)		56 (59.6)	57 (60.6)	
Multiple	29 (9.5)	22 (7.2)		4 (4.3)	8 (8.5)	
Multicenter	14 (4.6)	11 (3.6)		1 (1.1)	1 (1.1)	
NA	31 (10.2)	27 (8.9)		33 (35.1)	28 (29.8)	

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.