



Breast-conserving therapy is safe both within *BRCA1/2* mutation carriers and noncarriers with breast cancer in the Chinese population

Xin Huang¹, Xiu-Yu Cai², Jia-Qi Liu³, Wen-Wen Hao⁴, Yi-Dong Zhou¹, Xiang Wang³, Ying Xu¹, Chang Chen¹, Yan Lin¹, Chang-Jun Wang¹, Yu Song¹, Qiang Sun¹

¹Departments of Breast Surgery, Peking Union Medical College Hospital, Xicheng District, Beijing, China; ²Department of VIP Region, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China; ³Department of Breast Surgical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; ⁴Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China

Contributions: (I) Conception and design: Q Sun, X Huang; (II) Administrative support: Q Sun; (III) Provision of study materials or patients: X Huang, XY Cai, JQ Liu, YD Zhou; (IV) Collection and assembly of data: X Huang, JQ Liu, XY Cai, YD Zhou, X Wang, CJ Wang; (V) Data analysis and interpretation: X Huang, Y Xu, C Chen, Y Lin, Y Song; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Qiang Sun, MD. Department of Breast Surgery, Peking Union Medical College Hospital, No. 41, Damucang Road, Xicheng District, Beijing 100032, China. Email: sunqiang104095@163.com.

Background: *BRCA1/2* mutation is associated with a high risk of breast cancer, which may preclude breast cancer patients with *BRCA1/2* mutation from breast-conserving therapy (BCT) [breast-conserving surgery (BCS), followed by radiotherapy, BCT]. It is debatable whether BCT could be a rational choice for Chinese breast cancer patients with a *BRCA1/2* mutation.

Methods: The study comprised a cohort of women with invasive breast cancer either receiving BCT or mastectomy following the criteria for the germline *BRCA1/2* mutation test. Germline DNA for *BRCA1/2* testing was derived from blood samples. Survival analyses were performed. The correlations were analyzed between survival and distinct types of surgery. To compare the survival between different surgical management, Kaplan-Meier univariate analysis and multivariate Cox regression was used.

Results: In *BRCA1/2* mutation carriers (N=176) and noncarriers (N=293), 25% and 27.3% of the patients received BCT, respectively (P=0.675). Patients receiving mastectomy (without radiotherapy or followed by radiotherapy) have larger tumor size (P<0.05 both in *BRCA1/2* mutation carriers and noncarriers), prognostically worse tumor characteristics including significantly more advanced TNM stage (P=0.017 and P<0.0001 respectively) and more positive lymph nodes (P=0.008 and P<0.0001, respectively) both in *BRCA1/2* mutation carriers and noncarriers. Still, more often received systemic therapy has also been observed. After adjustment for clinical-pathological characteristics and systemic treatment, patients who received BCT had a similar breast cancer disease-free survival compared with patients who received mastectomy, both in *BRCA1/2* mutation carriers and noncarriers [HR_{*BRCA1/2*} =1.17, confidence interval (CI): 0.57–2.39, P=0.68; HR_{noncarriers} =0.91, CI: 0.47–1.77, P=0.79, respectively). The recurrence free survival after BCT did not differ from mastectomy in *BRCA1/2* mutation carriers [BCT, 5-year cumulative recurrence-free survival (RFS) =0.95, CI: 0.89–1.00; mastectomy, 5-year cumulative RFS =0.93, CI: 0.85–1.00], even better for BCT in noncarriers (BCT, 5-year cumulative RFS =0.67, CI: 0.42–0.89; mastectomy, 5-year cumulative RFS =0.83, CI: 0.71–0.95).

Conclusions: Thus, BCT may be a safe and rational choice for Chinese female breast cancer patients with a *BRCA1/2* mutation. However, tumor size, the TNM stage, the number of positive lymph nodes, might be taken into consideration when choosing surgical management.

Keywords: Breast-conserving therapy (BCT); mastectomy; BRCA1/2 mutation; breast cancer; prognosis

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Introduction

Breast cancer is the most frequently diagnosed life-threatening form of cancer in women and the leading cause of cancer deaths among women (1). The integration of genomics into the care of oncology patients has led to an increasing population of patients with breast cancer identified with germline mutations in breast cancer susceptibility genes, requiring physicians to integrate this information into treatment decision making (2). *BRCA*-associated breast cancer is the most common type in hereditary breast cancer, which can differ from sporadic breast cancer both in screening and prevention. However, it is still subject to debate on whether surgical management is also different. Breast-conserving therapy (BCT), breast-conserving surgery (BCS) followed by radiotherapy, is now widely accepted in China for breast cancer patients with unknown gene mutation status. However, BCT remains a relative contraindication to patients with breast cancer with a known or suspected genetic predisposition due to concerns about an increased risk of ipsilateral disease, breast recurrence or contralateral breast cancer, as reported in the National Comprehensive Cancer Network guidelines version 2.2020 (3,4). Even the Society of Surgical Oncology Guideline (2) still moderately recommended BCT to those patients meeting the eligibility. Although long-term follow-up data of the early trials have shown that BCT is associated with a higher rate of local recurrence, no differences in survival were found compared with mastectomy (5-8). Also, the risk of local recurrence has decreased in recent years (9-11).

A genetic test is not as common in China as in western countries. Chinese breast cancer patients with unknown *BRCA* mutation status have received standard surgical management if eligible, including BCS and mastectomy. Among them, those with *BRCA1/2* mutation indeed have received BCS, followed by radiotherapy. Thus, whether BCT is a safe and rational choice for breast cancer patients carrying a mutation in the *BRCA1* or *BRCA2* gene is still unknown.

Observational studies have reported these findings.

However, study populations are mainly white patients (3,12). For example, Nilsson *et al.* (12) compared local recurrence (LR) rates and survival between *BRCA1/2* mutation carriers treated with BCT and those treated with mastectomy. In this cohort study, *BRCA1/2* carriers treated with BCT versus mastectomy had a higher risk of LR as first recurrence, although many of the LRs in the BCT group were likely new primary breast cancers. Significant differences were still non found in death resulting from breast cancer, distant recurrence, or overall survival (OS) between the BCT group and the mastectomy group. van den Broek *et al.* (13) studied the effects of BCT versus mastectomy both in *BRCA1/2* mutation carriers compared with noncarriers. In both noncarriers and *BRCA1* mutation carriers, patients treated with BCT had similar OS compared with patients treated with mastectomy. However those two studies just involved in White race. As the lifetime risk of breast cancer for a *BRCA* mutation carrier is with variability based on population studied (14-16), the results can not be applied into Chinese population directly. Cao *et al.* (17) reported that in Chinese patients with breast cancer who received BCT, there was no statistically significant difference in ipsilateral breast tumor recurrence between *BRCA1/2* carriers and noncarriers. However, survival was still not included directly comparing BCT (BCS followed by radiotherapy) with mastectomy (without radiotherapy or followed by radiotherapy) in *BRCA1/2* mutation carriers. In addition, for the general breast cancer population, these studies (6,7) did not stratify on *BRCA1/2* mutation status.

This study aims to compare the prognostic impact of the two different types of surgery both in *BRCA1/2* mutation carriers and noncarriers with breast cancer, BCT (BCS followed by radiotherapy) and mastectomy. The results will yield more direct and convincing conclusions that BCT is a safe choice for the surgical management of Chinese female patients with breast cancer and *BRCA1/2* mutations. Thus, finding *BRCA1/2* mutation status is unnecessary for the choice of surgical management.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/ggs-20-531>).

Methods

Ethics

All the procedures performed in this study involving human participants were conducted following the ethical standards of the institutional and national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Peking Union Medical College Hospital (No. ZS 1655), and written informed consent was obtained from all participants.

Study design and participants

Eligible for a genetic test of *BRCA1/2* mutation status, a total of 490 Chinese women with primary invasive breast cancer treated with either BCT or mastectomy were recruited from three centers, Peking Union Medical College Hospital, Sun Yat-sen University Cancer Center and Cancer Hospital of Chinese Academy of Medical Sciences, between January 2016 and April 2020. All the patients have been confirmed *BRCA1/2* mutation status. Patients with a diagnosis of ovarian cancer, except for patients with no ovarian cancer recurrences and ≥ 10 years elapsed after ovarian cancer diagnosis before breast cancer, were excluded.

At last, stratifying on *BRCA1/2* mutation status, the *BRCA1/2* mutation carriers and noncarriers were analyzed on clinical pathological characteristics, breast cancer disease-free survival, recurrence-free survival (RFS) and breast cancer-specific survival comparing BCT with mastectomy (without radiotherapy or followed by radiotherapy). Current analyses are for follow-up information through April 30, 2020. The TNM stage was classified according to the American Joint Committee on Cancer 8th edition.

BRCA1/2 mutation testing

The inclusion criteria for the genetic test of *BRCA1/2* mutation included: (I) triple-negative breast cancer (TNBC) (diagnosed at an age ≤ 60 years); (II) breast cancer diagnosed at an age ≤ 45 years; (III) breast cancer diagnosed at any age with at least one close blood relative with a family history including breast cancer, ovarian carcinoma, male breast cancer, prostate cancer, or pancreatic cancer; and (IV) two primary breast cancer primaries including bilateral (contralateral) disease or ≥ 2 separate ipsilateral primary tumors diagnosed either synchronously or asynchronously.

Screening for *BRCA1/2* mutations was performed by analyzing genomic DNA extracted from the patients' peripheral blood and capturing targeted sequences followed by high-throughput sequencing. Quality control of the raw data was performed, followed by removing duplicated reads. Clean data were aligned to the hg19 reference genome using variants obtained by GATK 4.0. Further, the ExAC filtered the variants, the 1,000 Genome project. The filtered variants included untranslated region variants, intronic variants, splicing variants, and exotic variants. All harmful mutations were confirmed by Sanger sequencing in duplicate. Pathogenic mutations and pathogenic mutations are defined as mutations that lead to a truncated protein or that have previously been reported as disease-associated.

Statistical analysis

Breast cancer cases were allocated to groups according to the most extensive surgery they received for the primary breast cancer: BCT (BCS followed by radiotherapy) and mastectomy (without or followed by radiotherapy). All analyses were performed in the subgroups of *BRCA1/2* mutation carriers and noncarriers.

The endpoints for treatment comparisons are breast cancer disease-free survival, RFS, and breast cancer-specific survival. The times to these endpoints were calculated from the date of surgery. The events included in our analysis of breast cancer disease-free survival were the first recurrence of disease at a local, regional, or distant site, and the diagnosis of contralateral breast cancer. The events for RFS was the first recurrence of disease at a local and regional site. All the deaths in our cohort were related to breast cancer, which was breast cancer-specific survival. For women with bilateral breast cancer, we were unable to distinguish death or distant recurrence due to the first primary breast cancer from death or distant recurrence due to the second primary breast cancer.

Clinicopathological characteristics were evaluated for an association with the type of surgery within these subgroups, using the Pearson Chi-square test or the Mann-Whitney U test.

Subgroup survival curves were generated via the Kaplan-Meier method to explore the effects of the different types of surgery on survival for *BRCA1/2* mutation carriers and noncarriers. Kaplan-Meier univariate analyses and multivariate Cox regressions were used. Factors at or close to a $P < 0.05$ in the univariate analysis, together with some critical clinical confounders (13,17), were used to perform

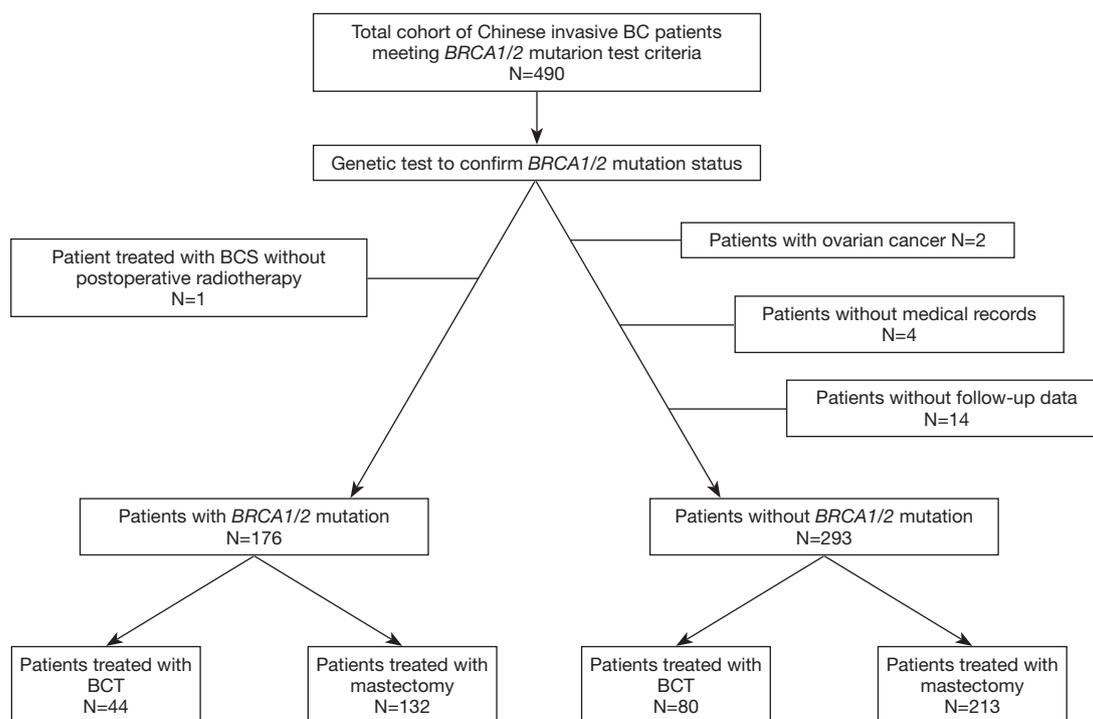


Figure 1 Flow diagram of the patients in the study and analyses.

the multivariate Cox regression to compare survival between different types of surgery both in *BRCA1/2* mutation carriers and noncarriers. Factors included for the multivariable analysis were age at diagnosis (≤ 35 , 36–45, and >45 years), tumor size (≤ 2 , 2–5, and >5 cm), TNM stage (0 or I stage, II stage and III stages), estrogen receptor (ER) status (positive/negative), and systemic treatment for the first breast cancer. That is, chemotherapy (no/yes), endocrine therapy (yes/no) and radiotherapy (no/yes) (12).

All statistical analyses were done with SAS version 9.4 (Cary, NC, USA). All statistical tests were two-sided, and a probability level with a random difference of $P < 0.05$ was considered statistically significant.

Results

Four hundred and ninety breast cancer patients either treated with BCT or mastectomy had been confirmed *BRCA1/2* mutation status. Among them, two patients were excluded with a diagnosis of ovarian cancer; one patient was excluded as treated with BCS without postoperative radiotherapy; another four patients were excluded without entire medical records and the other fourteen subjects were lost to follow-up. At last, stratifying on *BRCA1/2* mutation

status, 176 *BRCA1/2* mutation carriers and 293 noncarriers were analyzed (Figure 1). Associations between the distinct types of surgery with clinicopathological characteristics within *BRCA1/2* mutation carriers ($N=176$, Table 1) and noncarriers ($N=293$, Table 2) were summarized. The rate of BCT was nearly the same within *BRCA1/2* mutation carriers (25%, 44/176) and noncarriers (27.3%, 80/293, $P=0.675$). Patients treated with BCT appeared to be younger in noncarriers ($P < 0.05$); however, there was no statistical significance within *BRCA1/2* carriers ($P=0.29$). The patients who received mastectomy more often had larger tumor size ($P < 0.05$ in *BRCA1/2* mutation carriers and $P=0.002$ in noncarriers), more positive nodes ($P=0.008$ and $P < 0.0001$ respectively) and displayed significantly more advanced TNM stages ($P=0.017$ and $P < 0.0001$, respectively) both in *BRCA1/2* mutation carriers and noncarriers. However, the patients treated with mastectomy received systemic endocrine therapy more often compared with those receiving BCT ($P < 0.05$) within carriers. While the patients treated with mastectomy received systemic chemotherapy more often ($P=0.027$) within noncarriers. Follow-up and events during follow-up are also summarized in Tables 1 and 2 among *BRCA1/2* mutation carriers and noncarriers.

There are no significant differences in breast cancer

Table 1 Association of the types of surgery with clinicopathological characteristics, treatment, and follow-up data, within BRCA1/2 mutation carriers (N=176)

| Clinicopathological characteristics | Breast-conserving therapy (%) (N=44) | Mastectomy (combined) (%) (N=132) | Total (N=176) | P |
|-------------------------------------|--------------------------------------|-----------------------------------|---------------|-------|
| Age (y) | | | | 0.29 |
| <35 | 18 (40.91) | 40 (30.30) | 58 (32.95) | |
| 36–45 | 20 (45.45) | 62 (46.97) | 82 (46.59) | |
| >45 | 6 (13.64) | 30 (22.73) | 36 (20.45) | |
| Tumor size (cm) | | | | <0.05 |
| ≤2 | 26 (59.09) | 60 (45.45) | 86 (48.86) | |
| 2–5 | 17 (38.64) | 67 (50.76) | 84 (47.73) | |
| >5 | 1 (2.27) | 5 (3.79) | 6 (3.41) | |
| Histological type | | | | 0.84 |
| IDC | 2 (4.55) | 7 (5.30) | 9 (5.11) | |
| Other | 42 (95.45) | 125 (94.70) | 167 (94.89) | |
| Histological grade | | | | 0.54 |
| Low grade | 1 (2.27) | 1 (0.76) | 2 (1.14) | |
| Medium grade | 18 (40.91) | 54 (40.91) | 72 (40.91) | |
| High grade | 23 (52.27) | 63 (47.73) | 86 (48.86) | |
| Unknown | 2 (4.55) | 14 (10.61) | 16 (9.09) | |
| Number of positive LNs | | | | 0.008 |
| 0 | 31 (70.45) | 59 (44.70) | 90 (51.14) | |
| 1–3 | 10 (22.73) | 36 (27.27) | 46 (26.14) | |
| 4–9 | 3 (6.82) | 22 (16.67) | 25 (14.20) | |
| >9 | 0 (0.00) | 15 (11.36) | 15 (8.52) | |
| TNM stage | | | | 0.017 |
| 0 or I | 24 (54.55) | 46 (34.85) | 70 (39.77) | |
| II | 15 (34.09) | 45 (34.09) | 60 (34.09) | |
| III | 5 (11.36) | 41 (31.06) | 46 (26.14) | |
| ER status | | | | 0.06 |
| Positive | 18 (40.91) | 76 (57.58) | 94 (53.41) | |
| Negative | 26 (59.09) | 56 (42.42) | 82 (46.59) | |
| HER-2 status | | | | 0.40 |
| Negative | 43 (97.73) | 125 (94.70) | 168 (95.45) | |
| Positive | 1 (2.27) | 7 (5.30) | 8 (4.55) | |
| Postoperative radiotherapy | | | | |
| No | 0 | 70 (53.03) | 75 (42.61) | |
| Yes | 44 (100.00) | 62 (46.97) | 101 (57.39) | |
| (Neo)adjuvant chemotherapy | | | | 0.84 |
| No | 3 (6.82) | 6 (4.55) | 9 (5.11) | |
| Yes | 41 (93.18) | 126 (95.45) | 167 (94.89) | |

Table 1 (continued)

Table 1 (continued)

| Clinicopathological characteristics | Breast-conserving therapy (%) (N=44) | Mastectomy (combined) (%) (N=132) | Total (N=176) | P |
|--|--------------------------------------|-----------------------------------|---------------|-------|
| Anthracycline or taxane included only | 13 (29.55) | 26 (19.70) | 39 (22.16) | |
| Platinum included | 3 (6.82) | 12 (9.09) | 15 (8.52) | |
| Combined anthracycline and txane | 25 (56.82) | 88 (66.67) | 113 (64.20) | |
| Endocrine therapy | | | | <0.05 |
| Yes | 18 (40.91) | 77 (58.33) | 95 (53.98) | |
| No | 26 (59.09) | 55 (41.67) | 81 (46.02) | |
| Follow-up information | | | | |
| Median follow-up, SD | 60.52±50.68 | 57.33±45.36 | 58.13±46.62 | 0.70 |
| Event of interest: death | 2 (4.55) | 5 (3.79) | 7 (3.98) | 0.82 |
| Follow-up information for breast cancer patients with information on recurrence and breast cancer-specific death | | | | |
| Median follow-up, SD | 50.98±42.34 | 47.4±35.97 | 48.3±37.57 | 0.59 |
| Event of interest: death due to breast cancer | 15 (34.09) | 37 (28.03) | 52 (29.55) | 0.45 |
| Median follow-up, SD | 57.48±47.13 | 54.88±42.49 | 55.53±43.57 | 0.73 |
| Event of interest: recurrence | 4 (9.09) | 4 (3.03) | 8 (4.55) | 0.10 |
| Events of interest during follow-up | | | | |
| Metastasis | 7 (15.91) | 23 (17.42) | 30 (17.05) | 0.82 |
| First local recurrence | 3 (6.82) | 3 (2.27) | 6 (3.41) | 0.15 |
| First regional recurrence | 1 (2.27) | 2 (1.52) | 3 (1.70) | 0.74 |

P values were derived from the Pearson Chi-square test for categorical variables and the Mann-Whitney U test for median values.

Table 2 Association of the types of surgery with clinicopathological characteristics, treatment, and follow-up data, within noncarriers (N=293)

| Clinicopathological characteristics | Breast-conserving therapy (%) (N=80) | Mastectomy (combined) (%) (N=213) | Total (N=293) | P |
|-------------------------------------|--------------------------------------|-----------------------------------|---------------|-------|
| Age | | | | <0.05 |
| <35 | 29 (36.25) | 48 (22.54) | 77 (26.28) | |
| 36–45 | 23 (28.75) | 46 (21.60) | 69 (23.55) | |
| >45 | 28 (35.00) | 119 (55.87) | 147 (50.17) | |
| Tumor size (cm) | | | | 0.002 |
| ≤2 | 44 (55.00) | 84 (39.44) | 128 (43.69) | |
| 2–5 | 36 (45.00) | 106 (49.77) | 142 (48.46) | |
| >5 | 0 (0.00) | 23 (10.80) | 23 (7.85) | |
| Histological type | | | | 0.96 |
| IDC | 73 (91.25) | 194 (91.08) | 267 (91.13) | |
| Other | 7 (8.75) | 19 (8.92) | 26 (8.87) | |

Table 2 (continued)

Table 2 (continued)

| Clinicopathological characteristics | Breast-conserving therapy (%) (N=80) | Mastectomy (combined) (%) (N=213) | Total (N=293) | P |
|--|--------------------------------------|-----------------------------------|---------------|---------|
| Number of positive LNs | | | | <0.0001 |
| 0 | 62 (77.50) | 80 (37.56) | 142 (48.46) | |
| 1–3 | 10 (12.50) | 42 (19.72) | 52 (17.75) | |
| 4–9 | 3 (3.75) | 48 (22.54) | 51 (17.41) | |
| >9 | 5 (6.25) | 43 (20.19) | 48 (16.38) | |
| TNM stage | | | | <0.0001 |
| 0 or I | 39 (48.75) | 35 (16.43) | 74 (25.26) | |
| II | 33 (41.25) | 87 (40.85) | 120 (40.96) | |
| III | 8 (10.00) | 91 (42.72) | 99 (33.79) | |
| ER status | | | | 0.76 |
| Positive | 27 (33.75) | 76 (35.68) | 103 (35.15) | |
| Negative | 53 (66.25) | 137 (64.32) | 190 (64.85) | |
| HER-2 status | | | | 0.62 |
| Negative | 76 (95.00) | 199 (93.43) | 275 (93.86) | |
| Positive | 4 (5.00) | 14 (6.57) | 18 (6.14) | |
| Postoperative radiotherapy | | | | |
| No | 0 | 98 (46.01) | 99 (33.79) | |
| Yes | 80 (100.00) | 115 (53.99) | 194 (66.21) | |
| (Neo)adjuvant chemotherapy | | | | 0.027 |
| No | 14 (17.50) | 18 (8.45) | 32 (10.92) | |
| Yes | 66 (82.50) | 195 (91.55) | 261 (89.08) | |
| Endocrine therapy | | | | 0.45 |
| Yes | 23 (28.75) | 71 (33.33) | 94 (32.08) | |
| No | 57 (71.25) | 142 (66.67) | 199 (67.92) | |
| Follow-up information | | | | |
| Median follow-up, SD | 31.79±19.18 | 31.7±15.63 | 31.73±16.64 | 0.97 |
| Event of interest: death | 5 (6.25) | 28 (13.15) | 33 (11.26) | 0.10 |
| Follow-up information for breast cancer patients with information on recurrence and breast cancer-specific death | | | | |
| Median follow-up, SD | 27.21±15.26 | 27.71±14.47 | 27.58±14.66 | 0.79 |
| Event of interest: death due to breast cancer | 5 (6.25) | 28 (13.15) | 33 (11.26) | 0.10 |
| Median follow-up, SD | 28.6±14.68 | 30.28±14.73 | 29.82±14.71 | 0.38 |
| Event of interest: recurrence | 10 (12.50) | 17 (7.98) | 27 (9.22) | 0.23 |

P values were derived from the Pearson Chi-square test for categorical variables and the Mann-Whitney U test for median values.

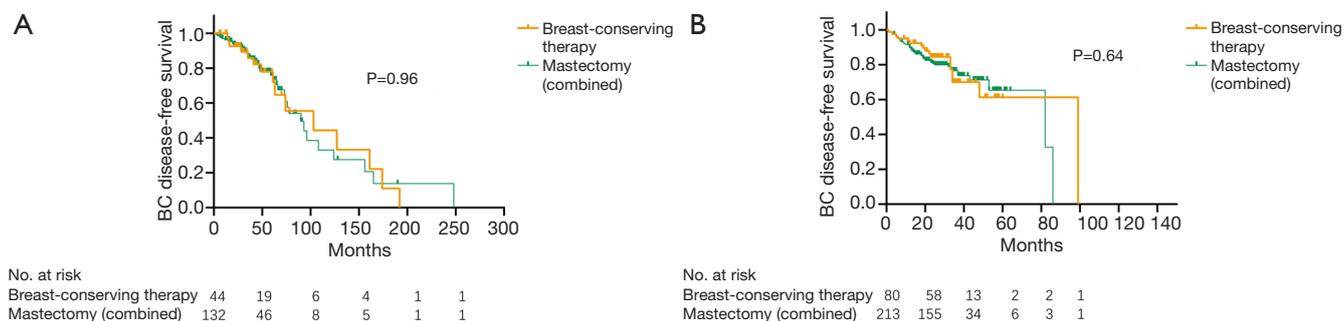


Figure 2 Cumulative Breast cancer disease-free survival for patients stratified by the type of surgery for *BRCA1/2* mutation, N=176 (A), and noncarriers, N=293 (B). Breast-conserving therapy indicates breast-conserving surgery followed by radiotherapy; Mastectomy (combined) indicates mastectomy (without radiotherapy or followed by radiotherapy); BC indicates breast cancer.

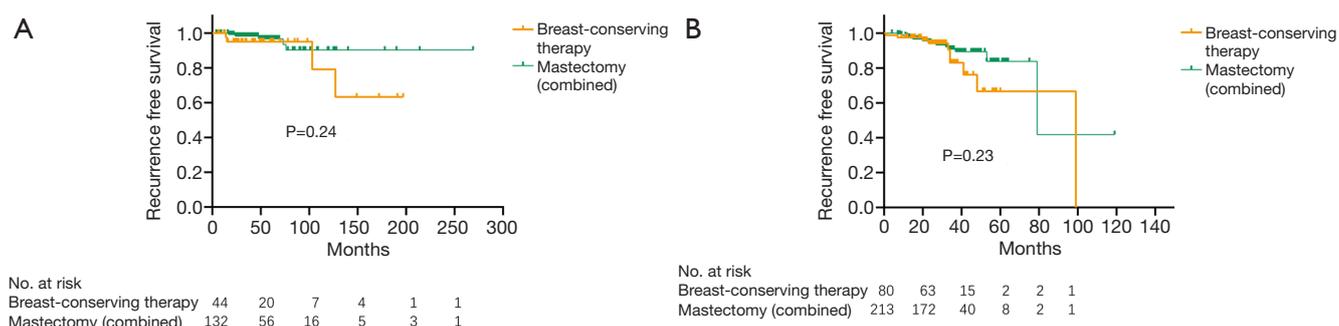


Figure 3 Cumulative recurrence-free survival for patients stratified by the type of surgery for *BRCA1/2* mutation, N=176 (A), and noncarriers, N=293 (B). Breast-conserving therapy indicates breast-conserving surgery followed by radiotherapy; Mastectomy (combined) indicates mastectomy (without radiotherapy or followed by radiotherapy); BC indicates breast cancer.

disease-free survival, RFS and breast cancer-specific survival compared BCT to mastectomy, (without radiotherapy or followed by radiotherapy) both within *BRCA1/2* mutation carriers and noncarriers (breast cancer disease-free survival, $P=0.96$ and $P=0.64$, *Figure 2*; RFS, $P=0.24$ and $P=0.23$, *Figure 3*; breast cancer-specific survival, $P=0.87$ and $P=0.13$, *Figure 4*, respectively).

Within both *BRCA1/2* mutation carriers and noncarriers, unadjusted breast cancer disease-free survival was comparable for patients receiving BCT to those receiving mastectomy (without radiotherapy or followed by radiotherapy) [$HR_{BRCA1/2} = 1.02$, confidence interval (CI) = 0.55–1.87, $P=0.96$; $HR_{noncarriers} = 0.88$, CI: 0.50–1.54, $P=0.65$]. After adjustment for clinicopathological characteristics and treatment, it was still similar ($HR_{BRCA1/2} = 1.17$, CI: 0.57–2.39, $P=0.68$; $HR_{noncarriers} = 0.91$, CI: 0.47–1.77, $P=0.79$, *Table 3*).

Within *BRCA1/2* mutation carriers, the results for breast

cancer-specific survival were in line with those for breast cancer disease-free survival (*Table 4*). Likewise, HRs for breast cancer-specific survival is still nonsignificant higher both in unadjusted and adjustment for clinicopathological characteristics and

Treatment ($HR_{BRCA1/2} = 1.15$, CI: 0.22–5.94, $P=0.87$; $HR_{BRCA1/2} = 1.53$, CI: 0.25–9.17, $P=0.64$, respectively, *Table 4*) within *BRCA1/2* carriers. Interestingly, it appears patients receiving BCT have a nonsignificantly better survival (lower HR) than the patients receiving mastectomy (without radiotherapy or followed by radiotherapy) within noncarriers both in unadjustment and adjustment ($HR_{noncarriers} = 0.49$, CI: 0.19–1.26, $P=0.14$; $HR_{noncarriers} = 0.53$, CI: 1.17–1.69, $P=0.28$, respectively).

The results for RFS are summarized in *Table 5*. In noncarriers, the higher risk was observed for patients treated with BCT (5-year cumulative survival, RFS = 0.67, CI: 0.42–0.89). However, in *BRCA1/2* mutation carriers,

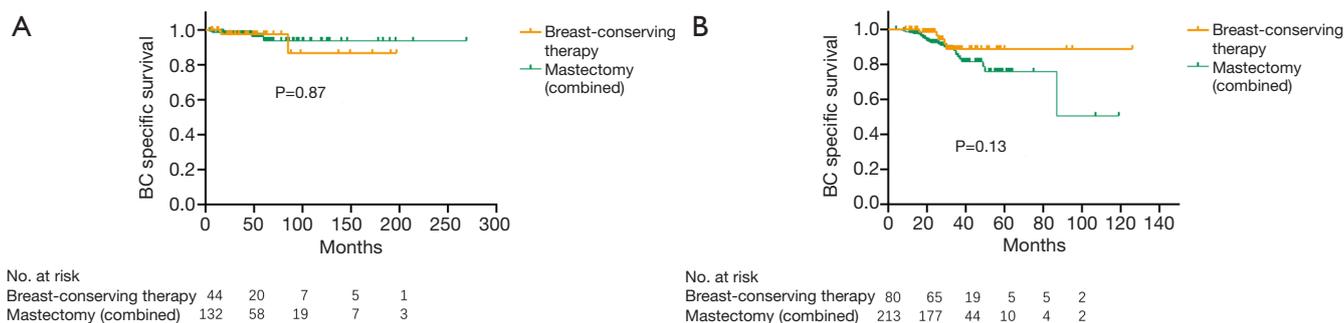


Figure 4 Breast cancer specific survival for patients stratified by the type of surgery for *BRCA1/2* mutation, N=176 (A), and noncarriers, N = 293 (B). Breast-conserving therapy indicates breast-conserving surgery followed by radiotherapy; Mastectomy (combined) indicates mastectomy (without radiotherapy or followed by radiotherapy); BC indicates breast cancer.

Table 3 Hazard ratios for breast cancer disease-free survival by the type of surgery, within *BRCA1/2* mutation carriers and noncarriers (N=469)

| <i>BRCA1/2</i> mutation status | Type of surgery | *HR (95% CI) | P | †HR (95% CI) | P | ‡HR (95% CI) | P | *HR (95% CI) | P |
|--------------------------------|---------------------------|------------------|------|------------------|------|------------------|------|------------------|------|
| <i>BRCA1/2</i> | Mastectomy (combined) | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| | Breast-conserving therapy | 1.02 (0.55–1.87) | 0.96 | 1.25 (0.60–2.57) | 0.55 | 1.17 (0.57–2.39) | 0.68 | 1.73 (0.72–4.16) | 0.22 |
| Noncarriers | Mastectomy (combined) | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| | Breast-conserving therapy | 0.88 (0.50–1.54) | 0.65 | 0.92 (0.47–1.79) | 0.81 | 0.91 (0.47–1.77) | 0.79 | 1.03 (0.44–2.40) | 0.95 |

*HR unadjusted hazard ratio. †HR hazard ratio adjusted for age, size, stage, and ER. ‡HR additionally adjusted for chemotherapy and endocrine therapy. *HR additional adjustment for postoperative radiotherapy. CI, confidence interval; HR, hazard ratio; combined, without radiotherapy or followed by radiotherapy.

Table 4 Hazard ratios for breast cancer-specific survival by the type of surgery, within *BRCA1/2* mutation carriers and noncarriers (N=469)

| <i>BRCA1/2</i> mutation status | Type of surgery | *HR (95% CI) | P | †HR (95% CI) | P | ‡HR (95% CI) | P |
|--------------------------------|---------------------------|------------------|------|------------------|------|------------------|------|
| <i>BRCA1/2</i> | Mastectomy (combined) | 1.00 | | 1.00 | | 1.00 | |
| | Breast-conserving therapy | 1.15 (0.22–5.94) | 0.87 | 1.44 (0.22–9.44) | 0.70 | 1.53 (0.25–9.17) | 0.64 |
| Noncarriers | Mastectomy (combined) | 1.00 | | 1.00 | | 1.00 | |
| | Breast-conserving therapy | 0.49 (0.19–1.26) | 0.14 | 0.48 (0.15–1.53) | 0.48 | 0.53 (0.17–1.69) | 0.28 |

*HR unadjusted hazard ratio. †HR hazard ratio adjusted for age, size, stage, and ER. ‡HR additionally adjusted for chemotherapy and endocrine therapy. CI, confidence interval; HR, hazard ratio; combined, without radiotherapy or followed by radiotherapy.

Table 5 Recurrence free survival, of patients by the type of surgery, within *BRCA1/2* mutation carriers and noncarriers (N=469)

| <i>BRCA1/2</i> mutation status | Type of surgery | No. | No. events | Person-years | Events/1,000 person-years | 5-y cum survival | CI |
|--------------------------------|---------------------------|-----|------------|--------------|---------------------------|------------------|-----------|
| <i>BRCA1/2</i> | | | | | | | |
| | Mastectomy (combined) | 132 | 5 | 7,174 | 7 | 0.93 | 0.85–1.00 |
| | Breast-conserving therapy | 44 | 4 | 2,529 | 16 | 0.95 | 0.89–1.00 |
| Noncarriers | | | | | | | |
| | Mastectomy (combined) | 213 | 17 | 6,540 | 26 | 0.83 | 0.71–0.95 |
| | Breast-conserving therapy | 80 | 10 | 2,288 | 44 | 0.67 | 0.42–0.89 |

5-y cum survival, 5-year cumulative recurrence-free survival; Breast-conserving therapy, combined, without radiotherapy or followed by radiotherapy. CI, 95% confidence interval; Events/10,000 person-years, number of events per 10,000 person-years; No. events, number of events during follow-up; No., number of patients at the start of follow-up; Person-years, the sum of person-years of follow-up.

the risk was nearly equal between BCT and mastectomy (BCT, 5-year cumulative survival, RFS =0.95, CI: 0.89–1.00; mastectomy, 5-year cumulative RFS =0.93, CI: 0.85–1.00).

Discussion

In this study, we showed that the prognostic impact of different types of surgery given for the first primary breast cancer on breast cancer disease-free survival, as well as breast cancer-specific survival, is similar within both *BRCA1/2* mutation carriers and noncarriers. Furthermore, RFS is also similar between *BRCA1/2* mutation carriers and noncarriers. Our study is the first to evaluate the effect of BCT and mastectomy directly both in *BRCA1/2* mutation carriers and noncarriers in the Chinese population. Furthermore, after nearly a decade of practice, the optimal local therapy for women with *BRCA*-associated breast cancer remains controversial (4). Many studies have focused on the white population with much less focus on the Chinese population. BCS has become the standard local therapy for sporadic breast cancer; although it results in increased LR, the survival is equivalent (5). Currently, Chinese patients with breast cancer tend to be younger (18). Thus, many patients request BCT because it has a much lower impact on their life and psychological status compared with mastectomy. Conserving the breasts of patients can have many positive effects on their lives. The result is the same as in the White race reported by van den Broek *et al.* (13), which showed *BRCA1* mutation carriers and noncarriers who received BCT had similar survival as those who received mastectomy. Two other previous studies (12,19) also directly compared the types of surgery between *BRCA1/2* mutation carriers and found

no differences in the overall and breast cancer-specific survival rates for carriers treated with BCT compared with mastectomy. In our study, within noncarriers, even patients treated with BCT seem to have a nonsignificant better breast cancer disease-free survival and breast cancer-specific survival compared to *BRCA1/2* mutation carriers, which still reminds us of those patients without *BRCA1/2* mutation that might be more suitable to receive BCT.

Although local recurrence risk was estimated to increase in the BCT group (5,6,19), more and more studies reported there was no increased recurrence for *BRCA1/2* mutation carriers (20,21), this was following the result of our studies. Two studies were reporting an unadjusted worse survival for *BRCA1/2* mutation carriers (22–24), and another two studies did not find a survival difference (24,25). As we showed, 5-year cumulative RFS was similar, comparing BCT to mastectomy. The reason that why recurrence risk decreased in recent years may be due to the improvement of breast-conservation and radiotherapy technology. Furthermore, even if an increase in recurrence risk, it still could not result in a loss of survival; additionally, the literature shows patients who undergo BCT have better survival than patients who undergo mastectomy (26). Current Dutch guidelines recommend BCT as a more suitable management option for early invasive breast cancer compared with mastectomy (27).

We observed a suggestion for a slightly better, though nonsignificant, breast cancer-specific survival for BCT than mastectomy in noncarriers, even when adjusting for clinical-pathological characteristics and systemic treatment. The same results were also reported in the general breast cancer population ever before (28–30). As the breast remained in the patients who received BCT, the

risk of ipsilateral and contralateral breast cancer increased. Therefore, better survival could not be observed in the BCT group compared to the mastectomy group within *BRCA1/2* mutation carriers.

Guidelines recommend some contradictions for BCT, including tumor size and specific tumor and patient characteristics. For example, active connective tissue disease involving the skin was considered a relative contradiction (3).

Our results also showed that patients who received mastectomy had prognostically worse tumor characteristics, including larger tumor size, more advanced TNM stages and more positive lymph nodes. However, survival was still equal between different surgical management groups. Systemic therapy played an important role. As we showed, patients treated with mastectomy received endocrine therapy more often within carriers and chemotherapy more often within non-carriers which was also observed by van den Broek *et al.* (13). In accordance with the guidelines, tumor size was still the most important factor to be considered for BCT. In addition to that, TNM stage and the status of lymph node were still needed to be considered. Actually those factors in consideration for *BRCA1/2* carriers were consistent with sporadic breast cancer patients. Before genetic testing, all patients received the standard systemic treatment, including chemotherapy and radiotherapy, according to the indication for sporadic breast cancer.

Although substantial amounts of data are available for patients in our cohort, insufficient adjustment of our risk estimates may have occurred due to different characteristics of our treatment subgroups (Tables 1,2). BCS, followed by radiotherapy, is well known as the standard management compared with mastectomy for sporadic breast cancer (31). All patients in this study received radiotherapy after BCS, which accounts for the significant difference in whether radiotherapy was administered to patients in either group (BCT and mastectomy).

Due to the equal survival between different surgical managements within both *BRCA1/2* mutation carriers and noncarriers, BCT may be a safe and reasonable surgical option for patients with breast cancer with *BRCA* mutations. Also, a genetic test is unnecessary to select either BCT or mastectomy. Thus, even *BRCA1/2* mutation status has not been confirmed before surgery, no need to be nervous. Confirmation of *BRCA1/2* mutation status may be more critical to screening and indication for PARP-inhibitors for advanced breast cancer (32).

Although our cohort has stratified on *BRCA1/2* mutation status and compared prognostic impact directly on BCT

compared to mastectomy, follow-up was still not enough. Except for that, insufficient stratification on *BRCA1* and *BRCA2* mutation type, more precise conclusions cannot be conducted. Due to the low rate of BCT in both *BRCA1/2* mutation carriers (25%) and noncarriers (27.35%), survival analysis cannot be conducted with the ratio 1 to 1. Therefore, bias may be introduced to some degree. Moreover, only female patients were included in this study. Thus, the results and conclusions may only be proper for female patients with breast cancer with *BRCA1/2* mutations.

Conclusions

In summary, by comparing the survival between BCT and mastectomy among Chinese breast cancer both within *BRCA1/2* mutation carriers and noncarriers, our results confirm BCT is a safe surgical treatment to offer to *BRCA1/2* mutation carriers for the Chinese population. Because all the patients received BCS followed by radiotherapy, adjuvant radiotherapy is necessary after BCS. Due to differences in clinicopathological characteristics between the two groups, tumor size, TNM stage and number of positive lymph nodes should be considered when selecting surgical management for Chinese female patients with breast cancer with *BRCA1/2* germline mutations.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All the procedures performed in this study involving human participants were conducted following the ethical standards of the institutional and national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Peking Union Medical College Hospital (No. ZS 1655), and written informed consent was obtained from all participants.

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