Original Article

Clinical features, prognosis, and influencing factors of contralateral prophylactic mastectomy in 58 patients with breast cancer

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Background: The past two decades have witnessed the increasing application of contralateral prophylactic mastectomy (CPM) for women with breast cancer in the western countries. Over 30% of young patients choose to underwent CPM up to 2015. However, the adoption rate of CPM has not shown a remarkably increasing in Asian countries. In China, only a few centers have introduced CPM, and no relevant literature has been published. In this study, we look forward to identify the clinical features and prognostic factors of women who underwent CPM in our hospital, to inform decision-making processes for both doctors and patients.

Methods: The clinical data of 58 eligible patients were retrospectively analyzed. Intergroup comparisons were based on independent samples *t*-test and chi square test. The 5-year disease-free survival (DFS) and overall survival (OS) were obtained by using life tables, and factors affecting the survivals were analyzed by using the Kaplan-Meier method.

Results: The mean age of these women was 40.14±11.17 years, with 30 patients (51.7%) being ≤40 years; 13 patients (22.4%) had a family history of breast cancer; and 49 (69.0%) had known risk factors for breast cancer. The median follow-up period was 66.77 months, the 5-year OS was 89% and the 5-year DFS was 74%. The average age of onset was 41.53 (±10.964) in the disease-free survival group and 34.18 (±10.4) years in the recurrence/metastasis group, and *t*-test revealed a significant difference in the average age between these two groups (P=0.049). Chi-square test showed that the disease progression rate significantly differed among the different age subgroups and among subjects with different body mass index (BMI) (all P≤0.05). Moreover, surgical procedure, family history of breast cancer, and some other factors showed no significant correlation with disease progression (all P>0.05). Kaplan-Meier survival analysis and log rank test further confirmed the above findings.

Conclusions: The majority of patients who choose CPM are young and with known risk factors for breast cancer. Part of the young patients (≤40 years of age) are at a higher risk of disease progression.

Keywords: Breast cancer; contralateral prophylactic mastectomy; subcutaneous nipple-areola-complex-sparing mastectomy; breast reconstruction; survival analysis

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Introduction

Contralateral prophylactic mastectomy (CPM) has been shown to reduce the risk for developing contralateral breast cancer (CBC). It has become particularly popular among female breast cancer patients in the United States and some European countries, where the clinical application of CPM has increased annually (1). In 2015, over 20% of women with breast cancer in the United States chose to undergo CPM, and up to 30% of breast cancer patients younger than 40 years old had undergone CPM (2). In contrast, few centers in Asian countries have introduced CPM. For instance, only a small number of centers in China have performed CPM in a limited number of patients, and, to our knowledge, no relevant article from China has been published. This probably effected by the social culture, medical insurance, or the medical environment of these countries. Since 2007, the General Surgery Department of the First Medical Center of the People's Liberation Army (PLA) General Hospital has performed CPM for about 100 patients with unilateral breast cancer who had a strong desire to receive CPM. In the current study, we retrospectively analyzed the clinical data of these patients, with a view to investigate the characteristics and prognosis of patients who choose CPM, identify prognostic factors, and thus provide relevant evidence for evidence-based medicine in China.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-7780).

Methods

Subjects

This study was conducted on female breast cancer patients who received CPM at the First Medical Center of the PLA General Hospital from January 2007 to December 2017. This is a retrospective nonrandom and self control experimental study. The patients inclusion criteria were as follows: (I) females; (II) with pathologically confirmed unilateral breast cancer; (III) receiving surgical treatment in PLA General Hospital from January 1, 2007 to December 31, 2017; (IV) with preoperative imaging examination showing unilateral breast malignant lesion, while no suspicious malignant lesions in the contralateral breast [i.e., lesions on imaging was the Breast Imaging Reporting and Data System (BI-RADS): category 1–3]; (V) receiving bilateral mastectomy; (VI) with complete clinical data; and (VII) with complete follow-up records. They were excluded when the survival data was incomplete.

The study was approved by the Ethics Committee of PLA General Hospital (the approval number: S2020-451-01). All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

Retrieval of clinical data and follow-up data

By accessing the Hospital Information System (HIS) of the Big Data Center of the PLA General Hospital, we obtained the demographic data and the information on surgery, pathology, postoperative multidisciplinary treatment, and outcomes.

The follow-up data included information on survival status (e.g., local recurrence, and/or distant metastasis, or death). In particular, the location and time-of-onset of recurrence/metastasis and the date of death were recorded. Telephone follow-up was performed by a dedicated staff member. The follow-up data were managed by Excel software.

Surgical methods and subsequent treatments

Two major mastectomy procedures including nipple-sparing mastectomy (NSM) and simple mastectomy (SM) were adopted. The same procedure was applied during mastectomy on the affected side and for CPM.

According to different clinical statuses, two-step methods, in which saline breast implants were implanted in during the first operation, followed by the replacement with permanent silicone prosthesis after adjuvant chemotherapy and/or radiotherapy; or one-step method, in which silicon implants were directly placed in, were applied.

The treatment of axillary lymph nodes was performed as follows. In principle, sentinel lymph node biopsy (SLNB) was performed in patients without suspicious signs at either physical examination or imaging; if one or more metastatic lymph nodes were detected during SLNB, axillary lymph node dissection (ALND) was performed. SLNB was performed via the mastectomy incision or a newly created incision.

The pathological staging was based on the *American Joint Committee on Cancer (AJCC) Cancer Staging Manual* 2017 edition (3). Neoadjuvant chemotherapy, adjuvant chemotherapy, radiotherapy, and endocrine therapy

Table 1 Demographic data and clinicopathological of the subjects

	Frequency	Percentage (%)
Age		
≤40 years	30	51.7
>40 years	28	48.3
Body mass index (kg/m^2)		
<18.5	4	6.9
18.5–24.0	35	60.3
>24.0	19	32.8
Mastectomy method		
NSM	36	62.1
SM	22	37.9
Management of axillary lymph nodes		
SLNB	30	51.7
ALND	28	48.3
Breast reconstruction		
None	35	60.3
Yes	23	39.7
Family history		
None	45	77.6
Yes	13	22.4
Pathologic stage		
0	17	29.3
1	31	53.4
2	6	10.3
3	4	6.9
Total	58	100

NSM, nipple-sparing mastectomy; SM, simple mastectomy; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

were implemented in accordance with the National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology released in the year of the tumor diagnosis.

Statistical analysis

The statistical analysis was completed in SPSS 26.0 software package. The independent-samples *t*-test was used to compare the differences in continuous variables between a progressive disease (PD) (including local recurrence or distant metastasis) group and a non-PD group. The comparisons of categorical variables were based on chi-square test. The 5-year disease-free survival (DFS) and overall survival (OS) were obtained by using life tables, and factors affecting the survivals were analyzed by using the Kaplan-Meier method. We use various methods and multi-factor analysis to address potential sources of bias. P values below 0.05 were considered statistically significant.

Results

Demographic characteristics

Accordingly, a total of 58 eligible patients entered our analysis. The subjects had a mean age of 40.14±11.17 years (median: 40.50 years; range: 21–69 years). The average BMI was 22.12 (±3.21) kg/m^2, and the average maximum tumor diameter was 2.23 (±1.99) cm. Some patients had the following high-risk factors for breast cancer: (I) a history of ovarian cancer (2/58, 3.4%) or other malignant tumor (1/58, 1.7%); (II) breast cancer diagnosed when ≤40 years old (30/58, 51.7%); and/or (III) a family history of breast cancer (13/58, 22.4%) or other malignant tumors (19/58, 32.8%). The patients without survival data were excluded.

Clinicopathology characteristics

SM was performed in 22 cases (37.9%) and NSM in 36 cases (62.1%). Twenty-three patients (39.7%) who underwent NSM followed by immediate or delayed implants-based breast reconstruction. ALND was performed in 28 cases (48.3%) and SLNB in 30 cases (51.7%) (*Table 1*).

The pathological types of breast tumors on the affected side included non-specific invasive breast cancer (n=44, 75.9%), special types of breast cancer (n=4, 6.9%), and intraductal carcinoma (n=10, 17.2%). Immunohistochemical findings included positive estrogen and progesterone receptor (ER/PR) in 43 cases (74.1%), positive human epidermal growth factor receptor-2 (HER-2) in 15 cases (25.9%), and triple-negative breast cancer in 6 cases (10.3%). Two patients (3.4%) underwent tumor resection biopsy in other hospitals before they received CPM, so they did not receive immunohistochemical testing in this hospital.

Pathological findings of the contralateral breasts included intraductal carcinoma (n=1, 1.7%), invasive

Table 2 Results of the t test on continuous variables between the PD group and non-PD group

PD/non-PD groups	Mean	Standard deviation	95% confidence interval		P value
			Lower limit	Upper limit	
Age					
PD group	34.2	10.5	27.1	41.2	0.049*
Non-PD group	41.5	11.0	38.3	44.8	
Body mass index (kg/m^2)					
PD group	21.0	4.2	18.2	23.8	0.201
Non-PD group	22.4	2.9	21.5	23.2	
Maximum tumor diameter					
PD group	2.8	3.5	0.4	5.1	0.376
Non-PD group	1.8	1.6	1.3	2.3	

*, P<0.05. PD, progressive disease.

lobular carcinoma (n=1, 1.7%), intraductal papilloma (n=10, 17.2%), atypical ductal hyperplasia (n=2, 3.4%), fibroadenoma (n=12, 20.7%), sclerosing adenopathy/apocrine metaplasia/dilated breast duct (n=2, 3.4%), changes after Amazingel injection for breast augmentation (n=2, 3.4%), and simple adenopathy (n=24, 41.4%), etc.

PD and survivals

The median follow-up period was 66.77 months, during which the 5-year OS was 89% and the 5-year DFS was 74%. PD (including local recurrence, distant metastasis, and/or death) was noted in 11 patients (18.97%), among whom 5 patients (8.6%) developed simple local recurrence (including chest wall and/or axillary lymph node metastases), 5 patients (8.6%) had simple distant metastasis, and 1 patient (1.7%) suffered from both local recurrence and distant metastasis. Four patients with distant metastasis died from breast cancer, yielding an overall mortality rate of 6.9%. As of the follow-up date, no asynchronous contralateral breast cancer was noted.

Results of statistical analyses

The average age of them was 34.18 (±10.486) years in the PD group and 41.53 (±10.964) years in the non-PD group, which was a significant difference (P=0.049). The mean age of patients was 40.78 (±10.729) years in the survival group and 31.5 (±15.155) years in the death group, which was not a significant difference (P>0.05). BMI and maximum tumor diameter were not significantly different between the PD group and non-PD group (both P>0.05) (*Table 2*).

The chi-square test showed that PD significantly differed between the ≤40-year-old group and the >40-year-old group and among groups with different BMI values (all P≤0.05); however, PD showed no significant difference between the different surgery groups, among patients with different tumor types, or among patients with different receptor phenotypes. However, some chi-square test results may be invalid due to the small sample size (*Table 3*).

Log-rank (Mantel-Cox) test showed that DFS significantly differed between the ≤40-year-old group and the >40-year-old group (P=0.041), whereas the difference in OS was not statistically significant (P=0.411) (*Figure 1A,B*); meanwhile, DFS significantly differed among the three BMI strata (<18.5, 18.5–24.0, and >24 kg/m^2) (P=0.021), although the survival curves overlapped (*Figure 1C*).

Discussion

Breast cancer–specific mortality increases in patients with contralateral breast cancer (CBC) diagnosed before the age of 70 (4). A population-based analysis showed the overall risk for CBC in 10 to 15 years after primary diagnosis was 4.4%; in another study, the 10-year cumulative risk for CBC was 9.8% and 23.8% for BRCA1/2 carriers and non-carriers, respectively (5,6). CPM significantly reduced the risk for CBC in patients with a family history of unilateral breast cancer and improved breast cancer–specific survival (7). More women with breast cancer in the United States have

Table 3 Results of the chi-square test on categorical variables between the PD group and non-PD group

Factors(categorical variables)	Non-PD group		PD group		Total		P value
	Count	Line N %	Count	Line N %	Count	Line N %	
Age							
≤40 years	21	70	9	30	30	100	0.026*
>40 years	26	92.9	2	7.1	28	100	
Body mass index							
<18.5	1	25	3	75	4	100	0.012*[bc]
18.5–24.0	30	85.7	5	14.3	35	100	
>24.0	16	84.2	3	15.8	19	100	
Surgical procedures							
NSM	28	77.8	8	22.2	36	100	0.507
SM	19	86.4	3	13.6	22	100	
Management of axillary lymph nodes							
SLNB	25	83.3	5	16.7	30	100	0.744
ALND	22	78.6	6	21.4	28	100	
Breast reconstruction							
No	31	88.6	4	11.4	35	100	0.093
Yes	16	69.6	7	30.4	23	100	
Family history							
None	34	75.6	11	24.4	45	100	0.055
Yes	13	100	0	0	13	100	
Tumor type							
Non-special types of invasive breast cancer	9	90	1	10	10	100	0.394[bc]
Special types of invasive breast cancer	34	77.3	10	22.7	44	100	
In situ breast cancer	4	100	0	0	4	100	
Total	47	81%	11	19%	58	100	

*, using a 0.05 level of significance. [b], in this subtable, more than 20% of the expected counts are lower than 5; the results of the chi-square test may be invalid; [c], in this subtable, all individual expected counts are lower than 1; the results of the chi-square test may be invalid. PD, progressive disease; NSM, nipple-sparing mastectomyc; SM, simple mastectomy; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

elected to undergo CPM, especially those patients younger than 40 years old. CPM adoption rates in young breast cancer patients grew from 3.7% in 1998 to 38.7% in 2014, although this dropped slightly to 32.7% in 2015 (2).

In the present study, we retrospectively analyzed the clinical data of breast cancer patients who underwent CPM in PLA General Hospital between 2007 and 2017, with the aim of investigating the clinical characteristics and prognosis of these patients, identifying the prognostic factors, and thus informing future clinical practices in China. Our findings indicated that patients in this cohort were relatively young in age; patients younger than 40 years tended to have poor DFS; and the type of mastectomy procedure, mode of lymph node management, and breast

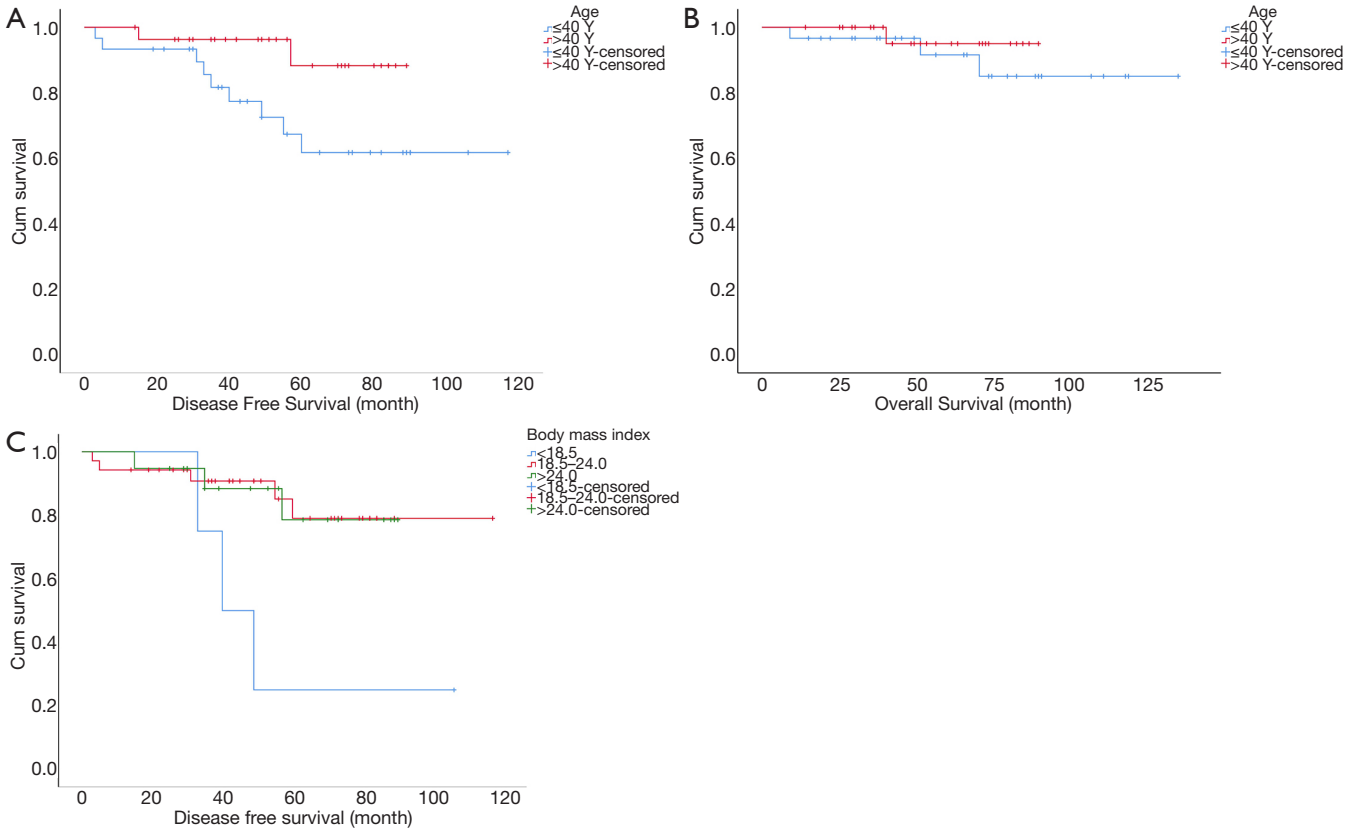

Figure 1 Kaplan-Meier curve of different age group and body mass index (BMI) groups. (A) Disease free survival of different age groups; (B) overall survival of different age groups; (C) disease free survival of different BMI groups.

reconstruction status, were not significantly correlated with DFS. Furthermore, two patients (3.45%) were found to have an occult malignancy in the contralateral breast. We could not, however, determine whether BMI is correlated with prognosis, and this issue warrants further investigation.

The median age at the time of BC diagnosis in our current cohort was earlier than that in conventional breast cancer patients. The proportion of women diagnosed with breast cancer before the age of 40 ranges from 5% to 7% among all breast cancer patients in developed countries and is about 20% in less developed countries (such as in Middle Eastern, African, and Asian countries) (8). In our current study, more than half of the patients were older than 40 years old, yielding an age composition of the population similar to that in the United States, suggesting that younger age is a key factor influencing CPM adoption (2). Most patients chose CPM with an attempt to improve their survival. Patients with greater awareness of tumor risk have an intense fear of the disease and are willing to choose the more invasive CPM instead of breast-conserving surgery, with an attempt to lower the incidence of CBC and improve survival (9). However, some young patients, especially the women with macromastia, will choose a bilateral mastectomy combined with breast reconstruction to obtain symmetry.

Young patients under the age of 40 in our cohort had increased risks of recurrence/metastasis, which was consistent with reports in the literature (2). This mostly because young patients tend to present at later stages and with more aggressive, larger tumors (10). The rate of PD reached 30% in the ≤40-year-old group but was only 7.1% in the >40-year-old group, which was a significant difference; meanwhile, OS was not significantly different between these two groups. Young patients under 40 years may achieve longer OS, although their DFS is suboptimal. Careful preoperative evaluation of the patient's prognosis and the future CBC risk can help doctors and patients make reasonable treatment decisions. For some patients, postponing CPM may also be a good option.

There was no significant correlation between the surgical

method and the prognosis in our current cohort. Although the PD rate was higher in the NSM group (22.2%) than in the SM group (13.6%), the chi-square test showed no significant difference in DFS between these two groups. As a mainstay in subcutaneous gland resection, NSM can be performed in combination with immediate breast reconstruction with implants to restore the shape and appearance of breasts to an extreme, for its reserving of nipple-areola, and rebuild confidence of patients. So NSM will be accepted more easily by patients than SM, and will get higher degree of satisfaction. The safety of NSM for tumors has been well recognized in appropriately selected patients (11). Bilateral NSM was performed in 58.3% of patients in our current cohort, and the rate of local breast cancer recurrence at the retained nipple-areola complex was 8.3% (n=3), which was higher than that (2.38%) reported in the literature (12). Therefore, to reduce the local recurrence rate after NSM, adequate preoperative assessment by breast MRI, mammography, and other imaging means is particularly important before a plan for NSM is made; also, intraoperative pathological examination of the glands behind NAC is required. If necessary, intraoperative or postoperative adjuvant radiotherapy may be performed to reduce the local recurrence rate following NSM.

In this group, postoperative pathological examination of the specimens confirmed occult malignancy in the contralateral breast in two cases. Occult malignant tumor cannot be detected easily by imaging. If not CPM and complete sample of the breast tissue, these two cases would certainly develop CBC in the future. Moreover, no contralateral breast cancer was noted during follow-up. Studies that have evaluated CBC risk estimate it to be approximately 0.5% annually on average (11), which shows that longer survival is associated with higher risk for CBC, and therefore the benefits of CPM may be more significant. Based on an annual increase rate of 0.5%, the 5-year CBC incidence is expected to be 2.5%, and the discovery of two cases of occult breast cancer in our current cohort fits this probability.

In addition to this, most patients in our cohort had varying degrees of risk factors for breast cancer. Among them, no patient with a family history of breast cancer experienced disease progression, suggesting that family history of breast cancer does not increase the risk of PD. Therefore, patients at high risk for breast cancer, for instance, who are with family history, or history of thoracic radiation therapy, or with benign lesions need to be biopsy, and meanwhile who are still at an early stage and with a good prognosis are more likely to benefit from CPM, but this assertion needs to be further confirmed in studies with longer follow-up periods. In our current study, 75% of patients with a BMI of <18.5 kg/m^2 experienced PD; however, the results of the chi-square test could have been invalid as the values in some cells were lower than 5. Again, studies with larger samples are needed to validate our findings. This research is a retrospective analysis in single center, so there must be a certain degree of selective bias in the results, so we need to verify them through a multicenter clinical experiment in the future.

Conclusions

The majority of patients who choose CPM are those with high-risk factors for breast cancer, for instance who are with family history, or history of thoracic radiation therapy, or with benign lesions need to be biopsy, and younger patients. Patients aged 40 years and younger have a higher rate of PD. Patients at high risk for contralateral breast cancer, and meanwhile, who are still at an early stage and with a good prognosis are more likely to benefit from CPM. NSM combined with breast reconstruction is preferred in appropriately selected patients to ensure surgical safety and achieve better cosmetic results.

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Footnote

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Ethial 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. This study was approved by the Ethics Committee of PLA General Hospital (The approval number: S2020-451-01). Individual consent for this retrospective analysis was waived. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

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