Original Article
Predictors for contralateral prophylactic mastectomy in breast cancer patients

Yun Fu[1,3*], Zhigang Zhuang[3*], Michelle Dewing[1], Sophia Apple[2], Helena Chang[1]

[1]Department of Surgery, Revlon/UCLA Breast Center, David Geffen School of Medicine, University of California of Los Angeles, Los Angeles, United States; [2]Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States; [3]Department of Breast Surgery, Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, Shanghai, China. *Co-first authors.

Abstract: Background: In recent years, radical breast cancer surgery has been largely replaced by breast conservation treatment, due to early diagnosis and more effective adjuvant treatment. While breast conservation is mostly preferred, the trend of bilateral mastectomy has risen in the United States. The aim of this study is to determine factors influencing patients' choice for having contralateral prophylactic mastectomy (CPM). Methods: This is a retrospective study of 373 patients diagnosed with primary invasive breast cancer who were treated by bilateral or unilateral mastectomy (BM or UM) at the Revlon/UCLA Breast Center between Jan. 2002 and Dec. 2010. In the BM group, only those with unilateral breast cancer who chose CPM were included in the analysis. Results: When compared with the UM group, the following factors were found to be associated with BM: younger age, pre-menopausal, a family history of breast/ovarian cancer, BRCA mutation, more breast biopsies, history of breast augmentation, having MRI study within 6 months before the surgery, more likely to have reconstruction and sentinel lymph node biopsy (SLNB) and fewer had neoadjuvant/adjuvant chemotherapy/radiation. When patients with bilateral breast cancer were excluded, multivariate logistic regression analysis indicated younger patients with negative nodes, SLNB as the only nodal surgery and positive family history were significant factors predicting CPM and immediate reconstruction using tissue expanders or implants. Conclusion: Younger age, lower TN stage, requiring only SLNB and high risk family history predict contralateral prophylactic mastectomy. Tissue expander/implant-based reconstructions were more frequently chosen by patients with BM.

Keywords: Breast cancer, bilateral mastectomy, BRCA mutation, contralateral prophylactic mastectomy, predictors

Introduction

Breast cancer surgery has gone through a tremendous shift from radical mastectomy to conservative surgeries because of earlier diagnosis and successful adjuvant systemic treatment and radiation [1]. However, a noticeable trend is observed towards a markedly increased use of bilateral mastectomy at the turn of the century in the United States with many choosing contralateral prophylactic mastectomy [2, 3]. Speculations including better understanding of the genetics, more frequent use of breast MRI studies and improved surgical approaches have been suggested to be responsible for this trend. The availability of immediate reconstructive surgeries with skin and/or nipple sparing options might make contralateral prophylactic

mastectomy more acceptable to women even in the absence of high-risk genetic mutation. The exact reasons for choosing bilateral mastectomy surgery in patients with unilateral breast cancer are not clear. The aim of this study was to evaluate factors influencing the choice of bilateral mastectomy with or without immediate reconstruction.

Materials and methods

Study cohort

This was an Institutional Review Board approved retrospective study including patients with non-metastatic invasive breast cancer who had undergone mastectomy at Revlon/UCLA Breast Center between January 2002 and December
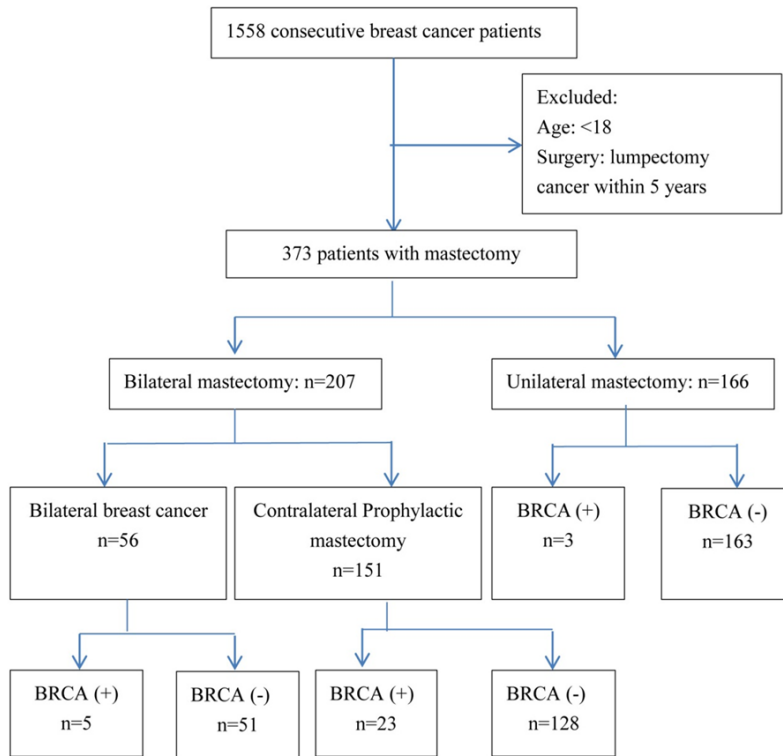
Figure 1. Flow chart of study enrollment.

2010. Of the 1558 breast cancer patients treated, 373 patients underwent mastectomy. Patients with any cancer diagnosed within five years, choosing lumpectomy as surgery treatment, or 18 years of age or younger were excluded from analysis (**Figure 1**). Data collected include: patients' demographics, clinical data, and types of treatment. Demographic and clinical data collected included age, race, menopausal status, Body Mass Index (BMI); number of previous breast biopsies; BRCA1 or BRCA2 mutation; family history of breast cancer or ovarian cancer; breast MRI study within six months of mastectomy; consultation for reconstruction and type of reconstruction and detailed histopathology characteristics of the index breast cancer. Patient treatment data such as laterality of mastectomy, type of lymph node surgery, radiation, adjuvant chemotherapy and endocrine therapy were also included for analysis.

Pathological examination of primary tumor

Standard pathological examination of the primary tumor included; histologic type, size, lymph/vascular invasion (LVI), tumor grade, estrogen receptor (ER), progesterone receptor (PR), HER-2/neu status and Ki-67 index. Each tumor was staged according to the 7th edition of the breast cancer staging of AJCC [4].

Breast cancers with positive ER or PR staining in ≥1% of examined cancer cells were considered as ER or PR positive tumors, respectively. HER-2 status determined by FISH gene amplification test with an R/G ratio ≥2.0 was considered amplified. A Ki-67 index ≥15% of examined cancer cells was considered 'high' and an index <15% was considered 'low'. Modified Bloom Richardson score (MBRS) was used to grade the degree of tubule formation, nuclear pleomorphism and mitosis of tumor cells and was classified into grade 1 if a score of 3-5/9, grade 2 if a score of 6-7/9, and grade 3 if a score of 8-9/9.

Postsurgical treatment and follow-up

Adjuvant treatments were prescribed based on the primary tumor characteristics and stage of the disease as suggested by the NCCN guidelines [5]. The reported time of follow-up began from the date of each patient's first cancer surgery and until March 2014. Postoperative follow-ups included annual mammographies, clinical examinations and other appropriate studies. Some patients had incomplete follow-up.

Statistics

Continuous patient characteristics were tabulated using medians and ranges and compared with the Wilcoxon rank sum test. We compared the differences in categorical variables and proportions between various groups of patients using the Pearson Chi square test. Backward stepwise logistic regression analysis was performed to evaluate factors affecting the risk of bilateral mastectomy. The results were presented as odds ratio (OR) with 95% Confidence

Table 1. Differences of clinical and histopathological characteristics of breast cancer patients between bilateral mastectomy and unilateral mastectomy groups from 2002 to 2010 (n=373)

Characteristics	Bilateral mastectomy	Unilateral mastectomy	P value
N	207	166	
Median age (Range)	50 (24-82)	55 (21-81)	<0.001*
Race			0.203
White	160 (77.3%)	111 (66.9%)	
Black	10 (4.8%)	7 (4.2%)	
Hispanic/Latino	8 (3.9%)	10 (6.0%)	
Asian/Pacific Islander	24 (11.6%)	34 (20.5%)	
American Indian/Alaskan Native	2 (1.0%)	1 (0.6%)	
Others	3 (1.4%)	3 (1.8%)	
Menstruation			<0.001*
Pre-menopausal	109 (52.7%)	59 (35.5%)	
Post-menopausal	98 (47.3%)	107 (64.5%)	
Family history			
Breast cancer	118 (57.0%)	49 (29.5%)	<0.001*
Ovarian cancer	21 (10.1%)	7 (4.2%)	0.046*
Both	17 (8.2%)	4 (2.4%)	
BRCA test			
Positive	28 (13.5%)	2 (1.2%)	<0.001*
Negative	179 (86.5%)	164 (98.8%)	
BMI index			0.415
<18.5	7 (3.4%)	5 (3.0%)	
18.5-24.9	102 (49.3%)	71 (42.8%)	
25-29.9	55 (26.6%)	45 (27.1%)	
30-34.9	17 (8.2%)	23 (13.9%)	
≥35	15 (7.2%)	9 (5.4%)	
Unknown	11 (5.3%)	13 (7.8%)	
Multiple breast biopsies			0.005*
≤3	181 (87.4%)	159 (95.8%)	
>3	26 (12.6%)	7 (4.2%)	
History of breast augmentation			0.005*
Yes	15 (7.2%)	2 (1.2%)	
No	192 (92.8%)	164 (98.8%)	
MRI within 6 months before the surgery			0.041*
Yes	61 (29.5%)	33 (19.9%)	
No	146 (70.5%)	133 (80.1%)	
Histopathological characteristics			
Tumor stage			<0.001*
T1	106 (51.2%)	32 (19.3%)	
T2	67 (32.4%)	72 (43.4%)	
T3	25 (12.1%)	51 (30.7%)	
T4	6 (2.9%)	10 (6.0%)	
Tx	3 (1.4%)	1 (0.6%)	
Lymph node stage			<0.001*
N0	113 (54.6%)	9 (5.4%)	
N1	63 (30.4%)	99 (59.6%)	

Interval (95% CI). The area under the receiver operating characteristic curve (c-statistics) to evaluate the sensitivity and specificity of the logistic model with the value greater than 0.9 indicating the reliability of the logistic regression model.

All statistical analysis was performed using SPSS 17.0 software. Significance was set at the 0.05 level for all tests and regressions.

Results

Patient comparison between bilateral mastectomy and unilateral mastectomy

We analyzed a total of 373 breast cancer patients diagnosed between 2002 and 2010 who received mastectomy at Revlon/UCLA Breast Center. The median follow-up was 52 months. The patients were divided into two groups: bilateral mastectomy (BM) group (55.5%) and the unilateral mastectomy (UM) group (44.5%). Among the 207 patients with BM (**Figure 1**), 56 (27.1%) had bilateral breast cancer, of which 20 had synchronous breast cancer. Thus 151 (72.9%) patients underwent a contralateral prophylactic mastectomy. In the bilateral breast cancer group, 5 patients (8.9%) had BRCA1 mutation and none had BRCA2 mutation. In patients who underwent contralateral prophylactic mastectomy, 15 (9.7%) had BRCA1 mutation, 10 (6.5%) had

N2	20 (9.7%)	34 (20.5%)	
N3	4 (1.9%)	22 (13.3%)	
Nx	7 (3.4%)	2 (1.2%)	
Histological grade			0.007*
I (MBRS 3-5/9)	59 (28.5%)	24 (14.5%)	
II (MBRS 6-7/9)	89 (43.0%)	75 (45.2%)	
III (MBRS 8-9/9)	56 (27.1%)	64 (38.6%)	
Not provided	3 (1.4%)	3 (1.8%)	
Hormone receptor			
ER (+)	169 (81.6%)	128 (77.1%)	0.302
			0.089
PR (+)	134 (64.7%)	93 (56.0%)	
HER-2 (+)	28 (13.5%)	34 (20.5%)	0.093
Ki67			0.055
High (≥15%)	98 (47.3%)	99 (59.6%)	
Low (<15%)	97 (46.9%)	58 (34.9%)	
Not provided	12 (5.8%)	9 (5.4%)	
LVI			<0.001*
Yes	50 (24.2%)	83 (50.0%)	
No	157 (75.8%)	83 (50.0%)	
AJCC stage			<0.001*
0	1 (0.5%)	0	
I	81 (39.1%)	5 (3.0%)	
II	81 (39.1%)	68 (41.0%)	
III	44 (21.3%)	93 (56.0%)	
Subtypes			0.164
TNBC	32 (15.5%)	20 (12.0%)	
HER-2(+)	28 (13.5%)	34 (20.5%)	
HR (+) & HER-2(-)	147 (71.0%)	112 (67.5%)	

BMI: body mass index; MRI: magnetic resonance imaging; SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; ER: estrogen receptor; PR: progesterone receptor; MBRS: Modified Bloom Richardson score; LVI: lymph vessel invasion; TNBC: triple negative breast cancer. *P Value <0.05.

BRCA2 mutation and of these, 2 had both BRCA1 and BRCA2 mutations. Among the 166 patients with UM, only 3 patients (1.8%) had BRCA mutations and of whom, one had both BRCA1 and BRCA2 mutations.

Table 1 summarized the patients' characteristics who had either UM or BM for breast cancer. We found the following factors were associated with the BM group: younger age (P<0.001), premenopause (P<0.001), having a family history of breast cancer (P<0.001) or ovarian cancer (P=0.046), BRCA mutations (P<0.001), and more breast biopsies (P=0.005). In the BM group, more patients also had a history of breast augmentation (P=0.005), and had a

breast MRI study within 6 months before the surgery (P=0.041).

When tumor characteristics were compared, patients in the BM group were more likely to have smaller tumor (P<0.001), lower nodal staging (P<0.001), lower histological grade (P=0.007) and fewer LVI (P<0.001). The hormone receptor and HER-2 expression were similar between the two groups. When neo-adjuvant chemotherapy was excluded, the significant associations with the BM group remained unchanged (Appendix Table 1).

When treatment was compared between the two groups, more patients in the BM group chose immediate reconstruction (P<0.001) using tissue expander/ implant approach (P< 0.001) and had sentinel lymph node biopsy (P< 0.001). Fewer patients in the BM group had adjuvant or neoadjuvant chemotherapy (P=0.004, P=0.002, respectively), or received radiation (P<0.001, Table 2).

Effect of surgeons on the decision of BM vs UM

We also analyzed a possible influence of the surgeon on the incidence of bilateral mastectomy. We found that there was no significant difference among the 5 surgeons (P= 0.396; Figure 2A) and 5 plastic surgeons (P=0.076; Figure 2B) in choosing UM or BM. Our finding suggested that the doctor's influence was unlikely to be a driving force behind the trend of having contralateral prophylactic mastectomy.

Table 2. Differences of breast cancer treatment in patients with bilateral and unilateral mastectomy between 2002 and 2010 (n=373)

Characteristics	Bilateral mastectomy	Unilateral mastectomy	P value
N	207	166	
Chemotherapy			0.004*
Yes	126 (60.9%)	125 (75.3%)	
No	81 (39.1%)	41 (24.7%)	
Neo-adjuvant chemotherapy	28 (13.5%)	44 (26.5%)	0.002*
Radiation			<0.001*
Yes	71 (34.3%)	90 (54.2%)	
No	111 (53.6%)	44 (26.5%)	
Unknown	25 (12.1%)	32 (19.3%)	
Endocrine therapy			0.448
Yes	83 (40.1%)	73 (44.0%)	
No	70 (33.8%)	46 (27.7%)	
Unknown	54 (26.1%)	47 (28.3%)	
Lymph node surgery			<0.001*
SLNB	96 (46.4%)	18 (10.8%)	
ALND	104 (50.2%)	147 (88.6%)	
None	7 (3.4%)	1 (0.6%)	
Reconstruction surgery			<0.001*
Yes	157 (75.8%)	91 (54.8%)	
No	50 (24.2%)	75 (45.2%)	
Type of reconstruction			<0.001*
Tissue expanders/implants	103 (49.8%)	21 (12.7%)	
Flaps	54 (26.1%)	70 (42.2%)	
Both flaps and implants	7 (3.4%)	1 (0.6%)	

SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; *P value<0.05.

Comparison of types of reconstruction-tissue expander/implant vs autologous flap approaches

The methods of reconstruction used by different plastic surgeons were compared. More plastic surgeons preferred tissue expanders/implants over autologous flaps. The ratio between the two choices among the plastic surgeons ranged 0.52-1.58 (*P*=0.037), (**Figure 2C**).

Predictors of contralateral prophylactic mastectomy in breast cancer patients

Since most patients with bilateral breast cancer may choose BM for their cancer treatment, we excluded 56 patients with either synchronous or metachronous breast cancer. Of the remaining 317 patients with unilateral breast

cancer, we wish to identify factors that may influence patient's decision on selecting the type of mastectomy. Using a logistic regression, we found that patients' age, pathological lymph node status, type of nodal surgery, BRCA mutation and family history had significant correlation with choosing BM. In the multivariate analysis, patients of younger age (*P*<0.001, OR 942, 95% CI 0.912~0.973), with negative node (*P*<0.001, OR 0.072, 95% CI 0.030~0.174), having sentinel lymph node biopsy as the only nodal surgery (*P*=0.003, OR 0.274, 95% CI 0.116~0.646) and having high risk family history (*P*<0.001, OR 4.042, 95% CI 2.082~7.847) were more likely to choose bilateral mastectomy. Tissue expanders or implants were more frequently used than autologous flaps for reconstruction after bilateral mastectomy (*P*< 0.001, OR 4.952, 95% CI 2.125~ 11.537, **Table 3**). C-statistics of the model was 0.911 with 95% CI 0.879~0.943, *P*<0.001 which confirmed the reliability of the logistic regression model (**Appendix Figure 1**).

Comparison of patient characteristics between women with and without immediate reconstruction after mastectomy

Of the 373 patients with either bilateral or unilateral mastectomy, 247 patients (66.2%) underwent immediate breast reconstruction and 126 patients (33.8%) did not. When compared with the non-reconstruction group (**Table 4**), patient's characteristics such as younger age (*P*<0.001), pre-menopausal status (*P*<0.001), white race (*P*=0.004), BRCA mutations (*P*=0.004), and bilateral mastectomy were associated with having immediate breast reconstruction (*P*<0.001). Pathologically, patients with a lower clinical and pathological stage of tumor and lymph node (*P*<0.01) with a lower index of Ki-67 expression (*P*=0.021) were more likely to choose immediate reconstruction.

Among the 126 patients who did not have immediate breast reconstruction, 75.6% did not have a consultation with a plastic surgeon
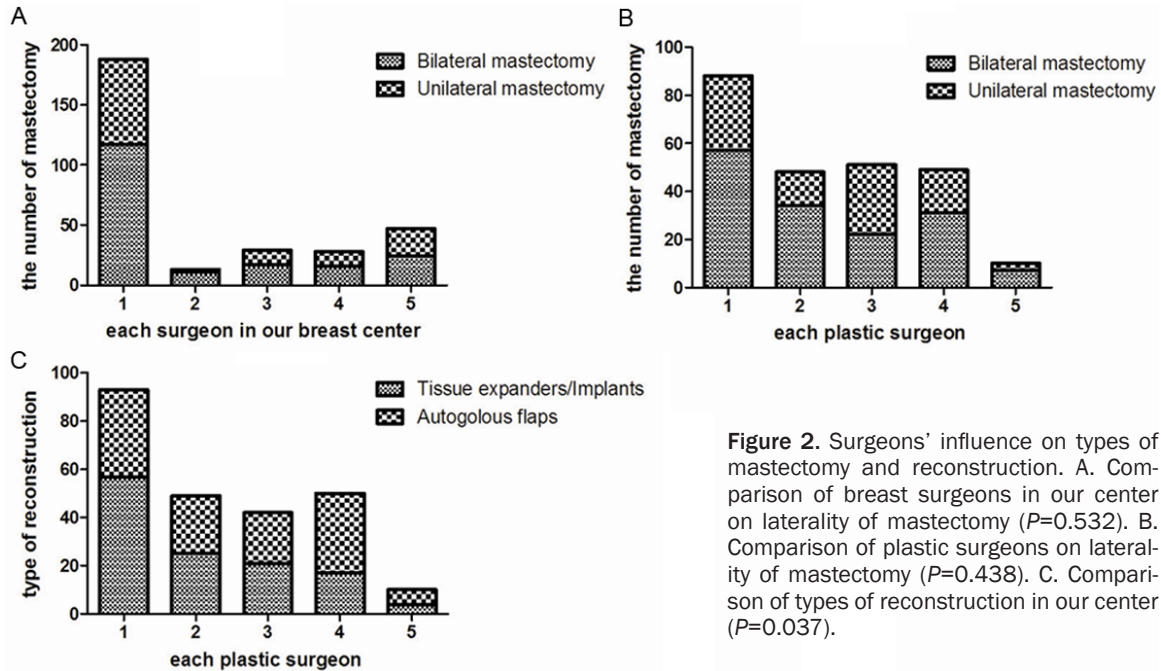
Figure 2. Surgeons' influence on types of mastectomy and reconstruction. A. Comparison of breast surgeons in our center on laterality of mastectomy (*P*=0.532). B. Comparison of plastic surgeons on laterality of mastectomy (*P*=0.438). C. Comparison of types of reconstruction in our center (*P*=0.037).

before their surgery. Of the cases with a clear documentation of the reasons for not having immediate breast reconstruction, 7.94% were recommended to have delayed reconstruction; 0.79% had insurance issue; 19.84% were patient's preference who chose to focus on treatments only; 7.15% had advanced breast cancer; 1.58% were heavy smokers and 3.17% had comorbidity such as significant diabetes, cardiac-pulmonary disease, or elderly age. Unfortunately, no clear reason was provided in the 57.94% of patients who did not have immediate reconstruction (**Appendix Figure 2**).

It is clear that patients who did not see a plastic surgeon before surgery would not receive immediate reconstruction. We then analyzed the differences in ethnicity, disease characteristics and surgeries in patients without reconstruction who either had or did not have a pre-operative consultation with plastic surgeon. We found that patients of younger age (*P*<0.001), premenopausal (*P*=0.004) and having clinically smaller tumor (*P*=0.019) were more likely to be referred to a plastic surgeon (**Appendix Table 2**).

Discussion

In the United States, the rates of contralateral prophylactic mastectomy in patients who are undergoing therapeutic mastectomy have increased significantly in recent years. A review of the Surveillance, Epidemiology and End Results (SEER) database showed contralateral prophylactic mastectomy rates increased from 4.2% in 1998 to 11.0% in 2003 among all patients with surgically treated invasive breast cancer [6]. A similar trend has also been observed in patients with DCIS [2]. McLaughlin et al. reviewed the New York State Cancer Registry and reported that the incidence of contralateral prophylactic mastectomy in women with breast cancer was more than doubled between 1995 and 2005 [7]. King TA et al [8] reported that the rate of contralateral prophylactic mastectomy at Memorial Sloan-Kettering Cancer Center was 13.8%, during the period of 1997-2005, increasing from 6.7% in 1997 to 24.2% in 2005.

Although there have been no prospective studies evaluating the decision-making process that has led to this increase, several recent advances in breast cancer care may play roles in this shift. The development and availability of genetic testing, the increased use of magnetic resonance imaging (MRI) for pre-surgical planning and improved surgical techniques for bilateral mastectomy and reconstruction may contribute to this trend.

BRCA gene mutations have been shown to play an important role in breast cancer development. Women with the BRCA mutation have a

Table 3. Logistic regression analysis of factors associated with bilateral mastectomy in patients with unilateral breast cancer

Characteristics	Univariate (Unadjusted)		Multivariate (Adjusted)	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (per year)	0.941 (0.909, 0.074)	0.001*	0.942 (0.912, 0.973)	<0.001*
Menstruation				
pre-menopausal	1.000			
post-menopausal	0.833 (0.282, 2.427)	0.737		
BMI				
<25	1.000			
≥25	1.648 (0.811, 3.348)	0.167		
Clinical tumor stage				
T<5 cm	1.000			
T≥5 cm	0.690 (0.234, 2.032)	0.500		
Pathological tumor stage				
T<5 cm	1.000			
T≥5 cm	0,925 (0.394, 2.169)	0.875		
Pathological lymph node status				
Negative	1.000		1.000	
Positive	0.071 (0.029, 0.175)	<0.001*	0.072 (0.030, 0.174)	<0.001*
Histological grade				
MBRS≤5	1.000			
MBRS≥6	0.607 (0.253, 1.455)	0.263		
LVI				
No	1.000			
Yes	0.755 (0.359, 1.585)	0.457		
ER status				
Negative	1.000			
Positive	0.805 (0.344, 1.879)	0.615		
PR status				
Negative	1.000			
Positive	1.406 (0.553, 3.576)	0.475		
HER-2 expression				
Negative	1.000			
Positive	1.592 (0.654, 3.879)	0.306		
Ki-67 index				
Low	1.000			
High	0.738 (0.334, 1.634)	0.454		
Multiple biopsy				
No	1.000			
Yes	2.418 (0.553, 10.575)	0.241		
History of augmentation				
No	1.000			
Yes	6.347 (0.984, 40.936)	0.052		
Nodal surgery				
SLNB	1.000		1.000	
ALND	0.276 (0.115, 0.663)	0.004*	0.274 (0.116, 0.646)	0.003*
MRI within 6 months before the surgery				
No	1.000			
Yes	1.549 (0.699, 3.432)	0.281		

BRCA mutation				
No	1.000			
Yes	4.508 (0.837, 24.275)	0.080		
Family history				
No	1.000		1.000	
Yes	3.439 (1.726, 6.854)	<0.001*	4.042 (2.082, 7.847)	<0.001*
Reconstruction				
No	1.000			
Yes	<0.001	0.999		
Type of reconstruction				
None	1.000	<0.001*	1.000	<0.001*
Tissue expanders/implants	4.323 (1.794, 10.416)	0.001*	4.952 (2.125, 11.539)	<0.001*
Autologous flaps	0.739 (0.315, 1.732)	0.486	0.746 (0.329, 1.691)	0.482
Both	1.152 (0.043, 31.052)	0.933	1.522 (0.067, 34.809)	0.792
Neo-adjuvant chemotherapy				
No	1.000			
Yes	0.453 (0.193, 1.062)	0.069		

MBRS: Modified Bloom Richardson score; LVI: lymphatic vessel invasion; ER: Estrogen receptor; PR: Progesterone receptor; OR: odds ratio; 95% CI: 95% confidence interval; *P value less than 0.05.

56% to 87% lifetime risk of developing breast cancer [9], and once diagnosed with breast cancer, they also have a higher risk for developing a second primary breast cancer either in the contralateral breast or in the same breast after lumpectomy [10]. Studies showed that prophylactic mastectomy can decrease the risk of future breast cancer by 90-97% [11]. Nearly 50% of patients with BRCA mutation undergo mastectomy to treat ipsilateral breast cancer and prophylactic mastectomy for the uninvolved breast in the United States [10]. In our study, 89% of patients with BRCA1 and/or BRCA2 mutations had BM for treating unilateral breast cancers. The NCCN Guidelines and Preventive Service Task Force Recommendations suggest that prophylactic mastectomy should be part of the discussion among patients who test positive for BRCA mutation or have a strong family history of breast cancer [12]. Women who test negative for BRCA mutation typically do not choose contralateral prophylactic mastectomy, however, some may still elect to have contralateral prophylactic mastectomy. Howard-McNattesal reported 37% of BRCA-negative patients at their institution chose contralateral prophylactic mastectomy [12]. Our study showed that 83.4% of patients who underwent contralateral prophylactic mastectomy did not have a known BRCA mutation.

Studies also suggested that availability of MRI in recent years to women with newly diagnosed breast cancer and women with significantly elevated breast cancer risk might also contribute to the trend of choosing bilateral mastectomy. A prospective study reported that fewer incidences of advanced breast cancer were detected in women with BRCA mutation with annual MRI than without screening MRI [13]. Breast MRI has been recommended by the American Cancer Society as a part of the surveillance for women with BRCA mutations [14]. When the impact of MRI on mastectomy was studied, many found a positive association between the two. Katipamula et al [15] demonstrated a 50% increased use of breast MRI with a simultaneous rise of mastectomy in their institution. Miller et al [16] reported mastectomy was more frequently performed in women who received breast MRI for preoperative planning of breast cancer surgery than those who did not. Our study is consistent with the finding of Sobrero et al [17] that preoperative MRI was associated with an increased rate of contralateral prophylactic mastectomy.

In many institutions, breast reconstruction is considered part of the routine preoperative discussion for women who choose mastectomy. Timely access to plastic surgeon, option of immediate reconstruction with various types of reconstruction tailored for each woman make mastectomy a much more acceptable choice to patients [18-20]. Dragun et al reported a rate of 8.4% contralateral prophylactic mastectomy

Table 4. Differences of clinical-pathological characteristics and treatments of breast cancer patients between reconstruction and non-reconstruction groups after mastectomy from 2002 to 2010 (n=373)

Characteristics	Reconstruction	Non-reconstruction	P value
N	247	126	
Median age (Range)	48 (21-75)	60.5 (30-82)	<0.001*
Race			0.004*
White	194 (78.5%)	76 (60.3%)	
Black	11 (4.5%)	6 (4.8%)	
Hispanic/Latino	10 (4.0%)	8 (6.3%)	
Asian/Pacific Islander	28 (11.3%)	30 (23.8%)	
American Indian/Alaskan Native	2 (0.8%)	1 (0.8%)	
Others	2 (0.8%)	5 (4.0%)	
Menstruation			<0.001*
Pre-menopausal	143 (57.9%)	25 (19.8%)	
Post-menopausal	104 (42.1%)	101 (80.2%)	
Family history			
Breast cancer	112 (45.3%)	55 (43.7%)	0.826
Ovarian cancer	21 (8.2%)	7 (5.6%)	0.410
Both	15 (6.1%)	5 (4.0%)	
BRCA test			0.004
Positive	27 (10.9%)	3 (2.4%)	
Negative	220 (89.1%)	0	
BMI index			0.150
<18.5	7 (2.8%)	6 (4.8%)	
18.5-24.9	124 (50.2%)	49 (38.9%)	
25-29.9	62 (25.1%)	30 (23.8%)	
30-34.9	29 (11.7%)	19 (15.1%)	
≥35	11 (4.5%)	12 (9.5%)	
Unknown	14 (5.7%)	10 (7.9%)	
Multiple breast biopsies			0.350
≤3	221 (89.5%)	117 (92.9%)	
>3	26 (10.5%)	9 (7.1%)	
History of breast augmentation			0.440
Yes	13 (5.3%)	4 (3.2%)	
No	234 (94.7%)	122 (96.8%)	
Breast surgery			<0.001*
Bilateral mastectomy	157 (63.6%)	50 (39.7%)	
Unilateral mastectomy	90 (36.4%)	76 (60.3%)	
Lymph node surgery			0.126
SLNB	84 (34.0%)	30 (23.8%)	
ALND	157 (63.6%)	93 (73.8%)	
None	6 (2.4%)	3 (2.4%)	
MRI within 6 months before the surgery			0.530
Yes	65 (26.3%)	29 (23.0%)	
No	182 (73.7%)	97 (77.0%)	
Neo-adjuvant chemotherapy	48 (19.4%)	24 (19.0%)	1.000
Clinical tumor stage			0.009*
T1	109 (44.1%)	36 (28.6%)	

between 1995 and 2003 which increased to 36% in the more recent period between 2004 and 2008 [21]. Jagsi et al [22] reported that immediate reconstruction increased from 46% in 1998 to 63% in 2007 (P<0.001), with an increased use of implants and decreased use of autologous flaps over time (P<0.001). In the same study, they also reported that patients with bilateral mastectomy more frequently received reconstruction (odd ratio=2.3; P<0.001). In current reports, 55.5% of patients had bilateral mastectomy if patients with bilateral breast cancer were included, and 49% if only those with unilateral breast cancer cases were included. The immediate reconstruction rate was 63.5% in our patients and was similar to the reported national trend.

In our study, we found more patients in the BM group had BRCA-1 or BRCA-2 mutation, MRI study within six months of the surgery and chose tissue expanders/implants for their reconstruction. While we cannot conclusively link them to the decision of having bilateral mastectomy, they are likely to affect the type of breast cancer surgery chosen. In the logistic regression analysis, we found that family history of breast or ovarian cancer was significant in predicting bilateral mastectomy.

Using the logistic regression analysis, younger

T2	96 (38.9%)	53 (42.1%)	
T3	30 (12.1%)	25 (19.8%)	
T4	7 (2.8%)	10 (7.9%)	
Tx	5 (2.0%)	2 (1.6%)	
Clinical lymph node status			0.006*
Positive	46 (18.6%)	40 (31.7%)	
Negative	201 (81.4%)	86 (68.3%)	
Pathological tumor stage			0.001*
T1	110 (44.5%)	28 (22.2%)	
T2	84 (34.0%)	55 (43.7%)	
T3	42 (17.0%)	34 (27.0%)	
T4	9 (3.6%)	7 (5.6%)	
Tx	2 (0.8%)	2 (1.6%)	
Pathological lymph node stage			<0.001*
N0	95 (38.5%)	27 (21.4%)	
N1	109 (44.1%)	53 (42.1%)	
N2	27 (10.0%)	27 (21.4%)	
N3	12 (4.9%)	14 (11.1%)	
Nx	4 (1.6%)	5 (4.0%)	
Histological grade			0.615
I (MBRS 3-5/9)	60 (24.3%)	23 (18.3%)	
II (MBRS 6-7/9)	105 (42.5%)	59 (46.8%)	
III (MBRS 8-9/9)	78 (31.6%)	42 (33.3%)	
Not provided	4 (1.6%)	2 (1.6%)	
Hormone receptor			
ER (+)	201 (81.4%)	96 (76.2%)	0.277
PR (+)	156 (63.2%)	71 (56.3%)	0.218
HER-2 (+)	35 (14.2%)	27 (21.4%)	0.079
Ki67			0.021*
High (≥15%)	120 (50.6%)	94 (64.4%)	
Low (<15%)	105 (44.3%)	44 (30.1%)	
Not provided	12 (5.1%)	8 (5.5%)	
LVI			0.205
Yes	79 (32.0%)	49 (38.9%)	
No	168 (68.0%)	77 (61.1%)	
Radiation			0.091
Yes	100 (40.5%)	60 (47.6%)	
No	98 (39.7%)	52 (41.3%)	
Unknown	49 (19.8%)	14 (11.1%)	
Plastic surgery consultation			<0.001*
Yes	247 (100.0%)	31 (24.6%)	
No	0	95 (75.4%)	

BMI: body mass index; MRI: magnetic resonance imaging; SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; ER: estrogen receptor; PR: progesterone receptor; MBRS: Modified Bloom Richardson score; LVI: lymph vessel invasion. *P value <0.05.

node biopsy only were more likely to choose bilateral mastectomy. In contrast, women with more advanced stage of disease seemed to be less interested in prophylactic surgery for the non-involved breast.

We also evaluated reasons that may influence patients not considering immediate reconstruction. We found that older patients with more advanced clinical tumor stage were less likely to consult a plastic surgeon. Factors such as obesity, smoking, significant comorbidity and insurance issues may also contribute to the decision of not having immediate reconstruction.

The improved surgical techniques for both mastectomy and reconstruction providing more cosmetically appealing results and less invasive options may also underline the increased popularity of bilateral mastectomy in recent years.

Our study provides a thorough analysis of factors affecting patient's decision for electing bilateral mastectomy and immediate reconstruction and sheds light into understanding the reasons for choosing contralateral prophylactic mastectomy. More studies are needed to understand the impact of bilateral mastectomy on patients' disease free and overall survival, immediate and long term effects of the added surgery, and the perceived body image after their chosen surgery.

patients were more likely to choose bilateral mastectomy which was consistent with other reports [8, 23, 24]. Furthermore, patients with lower nodal staging, requiring sentinel lymph

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Helena Chang, 200 UCLA Medical Plaza, Suite B265-1 (B2 Level), Peter Morton Medical Building, Los Angeles, CA 90095-7028. Tel: (310) 267-0499; Fax: (310) 267-0520; E-mail: hchang@mednet.ucla.edu

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Appendix Table 1. Histopathological characteristics of breast cancer patients with mastectomy between 2002 and 2010 (excluded patients having neo-adjuvant chemotherapy)

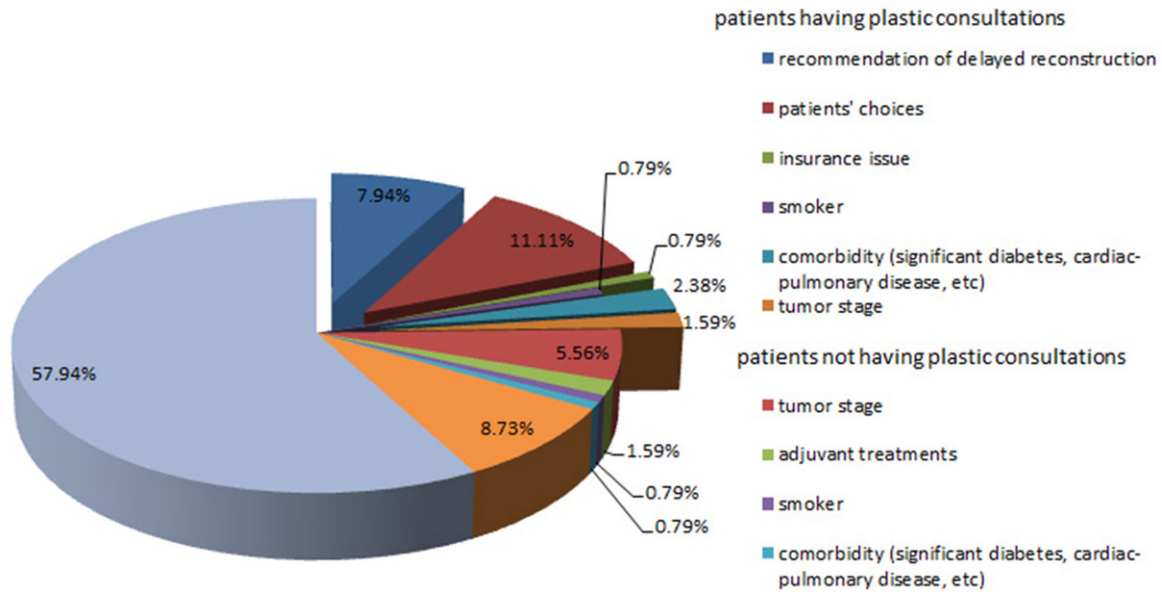| Characteristics	Bilateral mastectomy	Unilateral mastectomy	P value
N	179	122	
Tumor stage			<0.001*
T1	99 (55.3%)	25 (20.5%)	
T2	58 (32.4%)	57 (46.7%)	
T3	19 (10.6%)	34 (27.9%)	
T4	3 (1.7%)	6 (4.9%)	
Lymph node stage			<0.001*
N0	102 (57.0%)	3 (2.5%)	
N1	56 (31.3%)	73 (59.8%)	
N2	12 (6.7%)	25 (20.5%)	
N3	2 (1.1%)	19 (15.6%)	
Nx	7 (3.9%)	2 (1.6%)	
Histological grade			0.006*
I (MBRS 3-5/9)	54 (30.2%)	17 (13.9%)	
II (MBRS 6-7/9)	78 (43.6%)	59 (48.4%)	
III (MBRS 8-9/9)	44 (24.6%)	45 (36.9%)	
Not provided	3 (1.7%)	1 (0.8%)	
Hormonal receptor			
ER (+)	151 (84.4%)	94 (77.0%)	0.131
PR (+)	120 (67.0%)	69 (56.6%)	0.070
HER-2 (+)	20 (11.2%)	21 (17.2%)	0.171
Ki67			0.111
High (≥15%)	89 (49.7%)	73 (59.8%)	
Low (<15%)	83 (46.4%)	42 (34.4%)	
Not provided	7 (3.9%)	7 (5.7%)	
LVI			<0.001*
Yes	39 (21.8%)	69 (56.6%)	
No	140 (78.2%)	53 (43.4%)	
AJCC stage			<0.001*
I	75 (41.9%)	1 (0.8%)	
II	73 (40.8%)	52 (42.6%)	
III	31 (17.3%)	69 (56.6%)	
Subtypes			0.158
TNBC	23 (12.8%)	16 (14.3%)	
HER-2 (+)	20 (11.2%)	21 (18.8%)	
HR (+) & HER-2 (-)	136 (76.0%)	75 (67.0%)	

ER: estrogen receptor; PR: progesterone receptor; MBRS: Modified Bloom Richardson score; LVI: lymph vessel invasion; TNBC: triple negative breast cancer; *: P value <0.05.
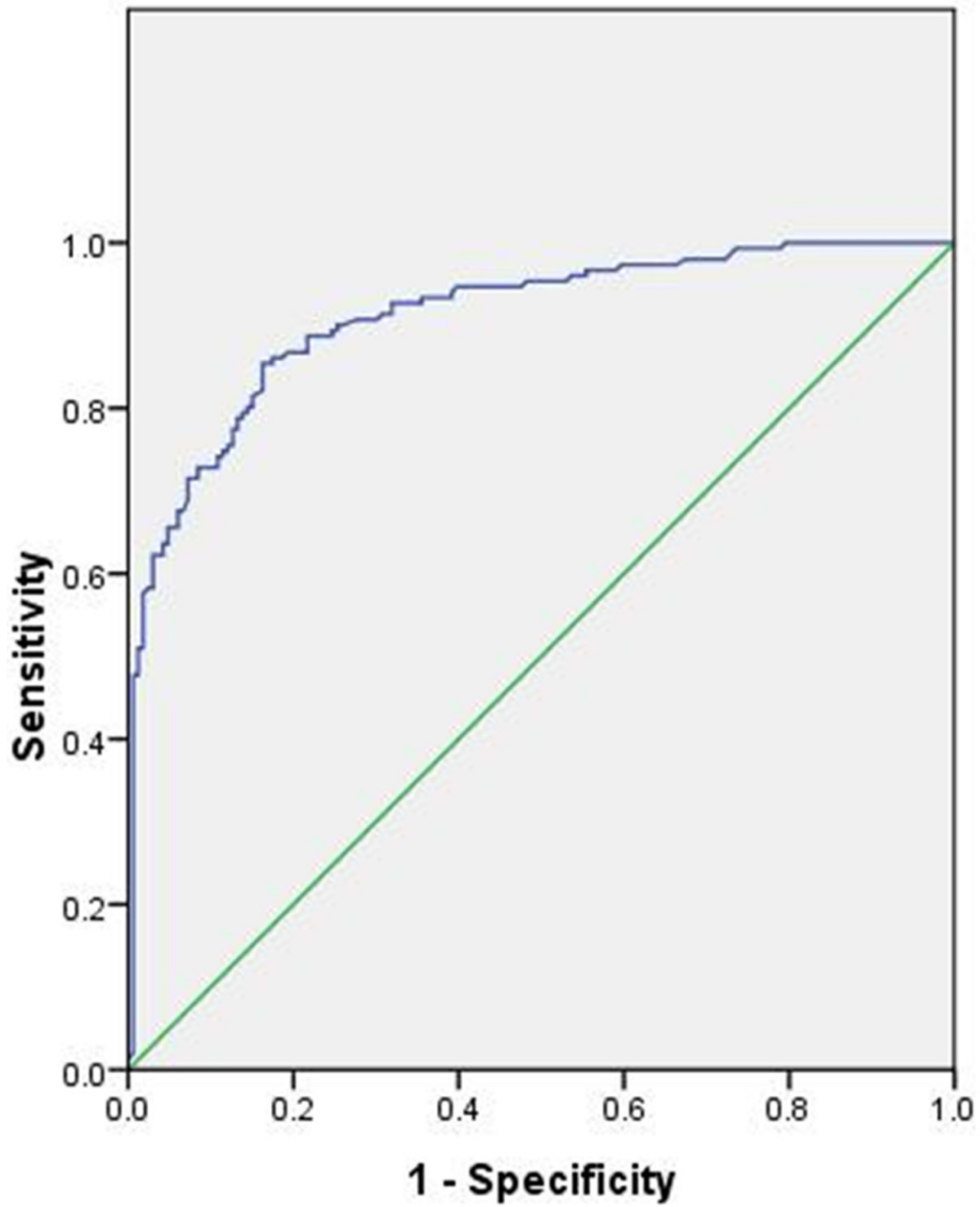
Appendix Figure 1. C-statistics of the logistic model (0.911, 95% CI 0.879~0.943, *P*<0.001).

Contralateral prophylactic mastectomy

patients having plastic consultations
- recommendation of delayed reconstruction
- patients' choices
- insurance issue
- smoker
- comorbidity (significant diabetes, cardiac-pulmonary disease, etc)
- tumor stage

patients not having plastic consultations
- tumor stage
- adjuvant treatments
- smoker
- comorbidity (significant diabetes, cardiac-pulmonary disease, etc)

Appendix Figure 2. Pie graph of the reasons for patients without reconstruction according to the medical notes.

Appendix Table 2. Differences of clinical-pathological characteristics and treatments in patients without reconstruction between patients with and without consultation with plastic surgeon (n=126)

Characteristics	Consultations for plastic surgery	Non-consultation for plastic surgery	P value
N	31	95	
Median age (Range)	53 (34-69)	64 (30-82)	<0.001*
Race			0.233
White	18 (58.1%)	58 (61.2%)	
Black	3 (9.7%)	3 (3.2%)	
Hispanic/Latino	2 (6.5%)	6 (6.3%)	
Asian/Pacific Islander	5 (16.1%)	25 (26.3%)	
American Indian/Alaskan Native	0	1 (1.1%)	
Others	3 (9.7%)	2 (2.1%)	
Menstruation			0.004*
Pre-menopausal	12 (38.7%)	13 (13.7%)	
Post-menopausal	19 (61.3%)	82 (86.3%)	
Family history			
Breast cancer	16 (51.6%)	39 (41.1%)	0.404
Ovarian cancer	3 (9.7%)	4 (4.2%)	0.362
Both	2 (6.5%)	3 (3.2%)	
BRCA test			0.562
Positive	1 (3.2%)	2 (2.1%)	
Negative	30 (96.8%)	97 (98.0%)	
BMI index			0.527
<18.5	2 (6.5%)	4 (4.2%)	
18.5-24.9	13 (41.9%)	36 (37.9%)	
25-29.9	7 (22.6%)	23 (24.2%)	
30-34.9	5 (16.1%)	14 (14.7%)	
≥35	4 (12.9%)	8 (8.4%)	
Unknown	0	10 (10.5%)	

Contralateral prophylactic mastectomy

Multiple breast biopsies			0.405
≤3	28 (90.3%)	90 (94.7%)	
>3	3 (9.7%)	5 (5.3%)	
History of breast augmentation			
Yes	2 (6.5%)	2 (2.1%)	
No	29 (93.5%)	93 (97.9%)	
Breast surgery			0.299
Bilateral mastectomy	16 (51.6%)	38 (40.0%)	
Unilateral mastectomy	15 (48.4%)	57 (60.0%)	
Lymph node surgery			0.764
SLNB	6 (19.4%)	24 (25.3%)	
ALND	24 (77.4%)	69 (72.6%)	
None	1 (3.2%)	2 (2.1%)	
MRI within 6 months before the surgery			0.461
Yes	9 (29.0%)	20 (21.1%)	
No	22 (71.0%)	75 (78.9%)	
Neo-adjuvant chemotherapy	9 (29.0%)	15 (15.8%)	0.118
Clinical tumor stage			0.019*
T1	11 (35.5%)	25 (26.3%)	
T2	10 (32.3%)	43 (45.3%)	
T3	8 (25.8%)	17 (17.9%)	
T4	0	10 (10.5%)	
Tx	2 (6.5%)	0	
Clinical lymph node status			1.000
Positive	10 (32.3%)	30 (31.6%)	
Negative	21 (67.7%)	65 (68.4%)	
Pathological tumor stage			0.165
T1	10 (32.3%)	18 (18.9%)	
T2	10 (32.3%)	45 (47.4%)	
T3	10 (32.3%)	24 (25.3%0	
T4	0	7 (7.4%)	
Tx	1 (3.2%)	1 (1.1%)	
Pathological lymph node stage			0.249
N0	8 (25.8%)	19 (20.0%)	
N1	11 (35.5%)	42 (44.2%)	
N2	10 (32.3%)	17 (17.9%)	
N3	1 (3.2%)	13 (13.7%)	
Nx	1 (3.2%)	4 (4.2%)	
Histological grade			0.672
I (MBRS 3-5/9)	5 (16.1%)	18 (18.9%)	
II (MBRS 6-7/9)	17 (54.8%)	42 (44.2%)	
III (MBRS 8-9/9)	9 (29.0%)	33 (34.7%)	
Not provided	0	2 (2.1%)	
Hormone receptor			
ER (+)	22 (71.0%)	74 (77.9%)	0.470
PR (+)	18 (58.1%)	53 (55.8%)	1.000
HER-2 (+)	4 (12.9%)	23 (24.2%)	0.217
Ki67			0.661
High (≥15%)	17 (54.8%)	57 (60.0%)	

	Contralateral prophylactic mastectomy		
Low (<15%)	11 (35.5%)	33 (34.7%)	
Not provided	3 (9.7%)	5 (5.3%)	
LVI			0.525
Yes	14 (45.2%)	35 (36.8%)	
No	17 (54.8%)	60 (63.2%)	
Radiation			0.252
Yes	17 (54.8%)	43 (45.3%)	
No	13 (41.9%)	39 (41.1%)	
Unknown	1 (3.2%)	13 (13.7%)	

BMI: body mass index; MRI: magnetic resonance imaging; SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; ER: estrogen receptor; PR: progesterone receptor; MBRS: Modified Bloom Richardson score; LVI: lymph vessel invasion; *P value <0.05.