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Trends in bilateral mastectomy for cases of unilateral breast cancer in a Brazilian institute over a 10-year period

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ABSTRACT

Introduction: There has been a substantial increase worldwide in the number of women with unilateral breast cancer who undergo bilateral mastectomy. Possible contributing factors include the advent of nipple-sparing mastectomy (NSM) and an improvement in breast reconstruction techniques. This study evaluated the trend in bilateral mastectomy at the Ceará Cancer Institute in Brazil. **Methods:** Patients with unilateral breast cancer who underwent mastectomy and immediate breast reconstruction were evaluated retrospectively between 2009 and 2018. Clinical, pathological and surgical factors were analyzed to determine their possible effects on the type of surgery performed. **Results:** Of 121 patients, 77 (63.6%) were submitted to unilateral mastectomy, while 44 (36.4%) underwent bilateral mastectomy. Most were treated with NSM (n = 66; 54.5%), with this technique being significantly associated with bilateral mastectomy ($p < 0.001$). Bilateral mastectomy increased significantly over the period ($p = 0.009$; $r^2 = 0.592$), but unilateral mastectomy did not ($p = 0.417$; $r^2 = 0.084$). Age < 45 years ($p = 0.007$) and negative axilla ($p = 0.003$) were also associated with bilateral mastectomy, while axillary dissection was associated with unilateral mastectomy ($p = 0.028$). Multivariate analysis showed the 2016-2018 period to be an independent factor associated with bilateral mastectomy. **Conclusions:** These results corroborate the international literature. From 2010 onwards, there was a trend towards an increase in bilateral mastectomy with breast reconstruction. These data may contribute to multidisciplinary debates, facilitating the establishment of guidelines. Further studies are required to improve understanding of this phenomenon in Brazil.

KEYWORDS: prophylactic mastectomy; unilateral breast neoplasms; mammaplasty.

INTRODUCTION

Breast-conserving surgery is the preferred treatment for early breast cancer. Survival rates after long periods of follow-up are comparable to those achieved with radical mastectomy.[1-6] Currently, the rates of local recurrence are low irrespective of the extent of the surgery;[7] nevertheless, many patients will still undergo mastectomy.

Skin-sparing (SSM) and nipple-sparing mastectomy (NSM) facilitate breast reconstruction and, although no prospective controlled studies have been conducted to evaluate the oncologic safety of these techniques, retrospective studies show adequate local control when compared to radical mastectomy.[8,9]

Recently, various countries have registered increased rates of bilateral mastectomy and a reduction in cases of unilateral mastectomy.[10] Possible explanations include cancer phobia, the possibility of detecting genetic susceptibility to breast cancer,[11] and of immediate breast reconstruction, particularly with the use of implants, following SSN or NSM, with the potential to achieve better breast symmetry,[12] and the greater attention given to the subject by the lay press. This trend, however, has yet to be evaluated in Brazil.

The purpose of the present study was to evaluate this trend in the surgical treatment of breast cancer, specifically bilateral mastectomy and its associated clinical factors, in a setting in which immediate breast reconstruction is available, in women with unilateral breast cancer who were to undergo mastectomy in a reference oncology institute in Brazil.

METHODS

This retrospective, longitudinal study included women with unilateral breast cancer. The internal review board of the Ceará Cancer Institute approved the study protocol under reference

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61.473. Medical records were reviewed and, between 2009 and 2018, patients submitted to mastectomy for the treatment of unilateral invasive breast cancer with recommendation for immediate breast reconstruction were selected. Patients with bilateral breast cancer, breast cancer recurrence or metastatic disease on an initial stage were excluded from the study. The factors evaluated were: whether mastectomy was SSM or NSM, unilateral or bilateral, and the year of the procedure. Data on age, tumor size (T), lymph nodes (N) and molecular subtypes were recorded. Hormone receptor (HR)-positive and HER2-negative tumors were considered luminal, while those expressing HER2 (or FISH/SISH-positive) were classified as HER2, and those that were HR-negative and HER2-negative were considered triple-negative (TN). The type of axillary surgery, adjuvant treatment (chemotherapy, hormone therapy and radiotherapy) and the presence of the inherited pathogenic mutations that predispose to cancer were also evaluated. Clinical outcomes were classified as local and/or regional recurrences, distant recurrences or death resulting from breast cancer. Follow-up of at least three months was required to determine any failure or major complications (skin necrosis, infection or hematoma that required reoperation) in breast reconstruction.

Data were expressed as absolute frequencies and percentages. Associations with the type of mastectomy were determined by using Fisher's exact test or Pearson's χ^2 test. To determine the factors independently associated with unilateral or bilateral mastectomy, the variables with $p < 0.20$ were selected using a forward stepwise approach to build a multinomial logistic regression model.

Linear regression was performed to establish the rate profile of bilateral and unilateral mastectomies over the evaluation period. The SPSS statistical software package for the social sciences, version 20.0 for Windows, was used. A significance level of 95% was adopted throughout the analysis.

RESULTS

The medical records of 341 patients were reviewed and 121 met the inclusion criteria. Between 2009 and 2018, 77 patients (63.6%) underwent unilateral mastectomy, while 44 (36.4%) underwent bilateral mastectomy. Most were treated with NSM (n = 66; 54.5%), a method significantly more common among the patients undergoing bilateral mastectomy ($p < 0.001$) (Table 1).

Bilateral mastectomies were more common in patients < 45 years of age ($p = 0.007$). Of those undergoing bilateral mastectomy, only two had a pathogenic mutation, BRCA, in both cases. T1 (n = 38; 36.2%) and N0 (n = 33, 56.9%) were the most prevalent tumor stage and node status, respectively. Distant metastases were found in 7 patients (8.0%). Node status was significantly associated with bilateral mastectomy ($p = 0.003$) (Table 2).

Table 1. Profile of mastectomies performed between 2009 and 2018.

Total	Mastectomy			
	Total	Unilateral	Bilateral	p-value
	121 (100%)	77 (63.6%)	44 (36.4%)	-
Surgery				
Nipple-sparing mastectomy	66 (54.5%)	31 (40.3%)	35 (79.5%)*	< 0.001
Skin-sparing mastectomy	55 (45.5%)	46 (59.7%)*	9 (20.5%)	
Year				
2009	2 (1.7%)	2 (2.6%)	0 (0.0%)	< 0.001
2010	8 (6.6%)	8 (10.4%)	0 (0.0%)	
2011	4 (3.3%)	3 (3.9%)	1 (2.3%)	
2012	2 (1.7%)	2 (2.6%)	0 (0.0%)	
2013	7 (5.8%)	6 (7.8%)	1 (2.3%)	
2014	23 (19.0%)	22 (28.6%)*	1 (2.3%)	
2015	19 (15.7%)	16 (20.8%)*	3 (6.8%)	
2016	13 (10.7%)	5 (6.5%)	8 (18.2%)*	
2017	10 (8.3%)	3 (3.9%)	7 (15.9%)	
2018	33 (26.3%)	10 (13.0%)	23 (52.3%)*	
Period				
2009-2015	65 (53.7%)	59 (76.6%)*	6 (13.6%)	< 0.001
2016-2018	56 (46.3%)	18 (23.4%)	38 (86.4%)*	

*$p < 0.05$. Fisher's exact test or Pearson's χ^2 test (n; %).

Most tumors were HR-positive (n = 63, 78.8%) and HER-negative (n = 70, 87.5%). Only 9 tumors (11.3%) were TN. Tumor phenotype was similar in the two groups (p > 0.05) (Table 2).

Adjuvant radiotherapy was administered to 53 patients (51.0%) and was not associated with unilateral or bilateral mastectomy (p = 0.116). Ten patients (11.1%) developed postoperative complications and three patients (2.5%) suffered local recurrence, unassociated with the type of mastectomy performed in both cases (p = 0.717 and p = 1.000, respectively) (Table 3). Positive sentinel lymph nodes were found in 62 patients (59.0%), with no difference between the two groups (p = 0.292). Thirty-two patients (30.5%) underwent axillary dissection, which was significantly associated with unilateral mastectomy (p = 0.028). Most of the patients (n = 71; 71.7%) underwent chemotherapy, with no association with the type of mastectomy performed (p = 0.102). Chemotherapy was neoadjuvant in 53% of cases. Most women received hormone therapy (n = 74; 85.1%), which was associated with unilateral mastectomy (p = 0.013). Six deaths occurred (7.5%), unassociated with the type of mastectomy performed (p = 0.092) (Table 3).

Bilateral mastectomy increased significantly (p = 0.009, r^2 = 0.592) over the period. Conversely, unilateral mastectomy did not (p = 0.417, r^2 = 0.084) (Figure 1). The number of bilateral mastectomies was significantly higher than unilateral mastectomies from 2016 onwards (p < 0.001) (Table 1). In the multivariate analysis, the 2016-2018 period was independently associated with bilateral mastectomy, with an odds ratio of 11.53 (95%CI 1.26–105.71) in relation to unilateral mastectomy (p = 0.031) (Table 4).

DISCUSSION

This study found increasing rates of bilateral mastectomy, particularly after 2016. Conversely, unilateral mastectomy did not increase significantly over this period. A study based on the Surveillance,

Table 2. Effect of age at diagnosis, clinical staging and tumor phenotype on the profile of the mastectomies performed.

	Mastectomy			
	Total	Unilateral	Bilateral	p-value
Age (years)				
< 45	39 (44.3%)	15 (31.3%)	24 (60.0%)*	0.007
≥ 45	49 (55.7%)	33 (68.8%)*	16 (40.0%)	
Tumor stage				
T1	38 (36.2%)	20 (32.8%)	18 (40.9%)	0.809
T2	52 (49.5%)	31 (50.8%)	21 (47.7%)	
T3	12 (11.4%)	8 (13.1%)	4 (9.1%)	
T4	3 (2.9%)	2 (3.3%)	1 (2.3%)	
Node status				
N0	33 (56.9%)	14 (40.0%)	19 (82.6%)*	0.003
N1	20 (34.5%)	18 (51.4%)*	2 (8.7%)	
N2	5 (8.6%)	3 (8.6%)	2 (8.7%)	
Metastases				
M0	80 (92.0%)	50 (89.3%)	30 (96.8%)	0.413
M1	7 (8.0%)	6 (10.7%)	1 (3.2%)	
Hormone receptor				
No	17 (21.3%)	6 (13.6%)	11 (30.6%)	0.066
Yes	63 (78.8%)	38 (86.4%)	25 (69.4%)	
HER2				
No	70 (87.5%)	41 (93.2%)	29 (80.6%)	0.104
Yes	10 (12.5%)	3 (6.8%)	7 (19.4%)	
Triple-negative				
No	71 (88.8%)	41 (93.2%)	30 (83.3%)	0.286
Yes	9 (11.3%)	3 (6.8%)	6 (16.7%)	

*p < 0.05. Fisher's exact test or Pearson's χ^2 test (n; %).

Table 3. Additional treatment and outcome according to the type of mastectomy performed.

	Mastectomy			
	Total	Unilateral	Bilateral	p-value
Radiotherapy				
No	51 (49.0%)	28 (43.1%)	23 (59.0%)	0.116
Yes	53 (51.0%)	37 (56.9%)	16 (41.0%)	
Complications				
No	80 (88.9%)	55 (87.3%)	25 (92.6%)	0.717
Yes	10 (11.1%)	8 (12.7%)	2 (7.4%)	
Local recurrence				
No	118 (97.5%)	75 (97.4%)	43 (97.7%)	1.000
Yes	3 (2.5%)	2 (2.6%)	1 (2.3%)	
Positive sentinel lymph node				
No	43 (41.0%)	28 (45.2%)	15 (34.9%)	0.292
Yes	62 (59.0%)	34 (54.8%)	28 (65.1%)	
Axillary dissection				
No	73 (69.5%)	38 (61.3%)	35 (81.4%)*	0.028
Yes	32 (30.5%)	24 (38.7%)*	8 (18.6%)	
Chemotherapy				
No	28 (28.3%)	17 (28.3%)	11 (28.2%)	0.102
Neoadjuvant	32 (32.3%)	15 (25.0%)	17 (43.6%)	
Adjuvant	39 (39.4%)	28 (46.7%)	11 (28.2%)	
Hormone therapy				
No	13 (14.9%)	4 (7.3%)	9 (28.1%)*	0.013
Yes	74 (85.1%)	51 (92.7%)*	23 (71.9%)	
Death				
No	74 (92.5%)	47 (88.7%)	27 (100.0%)	0.092
Yes	6 (7.5%)	6 (11.3%)	0 (0.0%)	

*p < 0.05. Fisher's exact test or Pearson's χ^2 test (n; %).

Epidemiology and End Results (SEER) program showed an increase in contralateral mastectomy in the United States from 1.8% in 1998 to 4.5% in 2003.[13] Simultaneously, conservative treatment remained stable, indicating that the preference for contralateral mastectomy is especially for women undergoing major surgery.[14]

The present rate of bilateral mastectomy was higher compared to earlier studies,[13,14] particularly in cases of NSM. Having selected patients for whom immediate breast reconstruction was available may have affected our results: preservation of the entire skin envelope of the breast facilitates reconstruction involves more discrete scars, and may affect the decision to perform bilateral surgery.[15] A retrospective study by the American National Cancer Database (NCDB) showed that in women submitted to surgery between 1998 and 2011, contralateral surgery increased 7% for each percentage point of increase in reconstruction[16].

More women have opted for bilateral mastectomy despite a paradoxical decline in the rates of contralateral disease in recent years. Following the introduction of systemic treatment, the annual risk of contralateral cancer fell from 0.5% to around 0.1% annually.[17] Overestimation of the risk may have affected the planning of surgeries. Germline mutations such as the BRCA1/2 gene mutations are known to play a role in the appearance of new breast tumors, with bilateral surgery often being recommended in such cases.[18] Nevertheless, in this study, only two patients were confirmed to have one of the inherited gene mutations.[19,20] Most of the prophylactic surgeries were probably performed based on family history and on the patients' personal decisions. A survey showed that only 38.1% of the patients with unilateral breast cancer knew that the contralateral prophylactic surgery had no effect on survival.[21]

Age also affected the results, with 56% of the women under 50 years of age undergoing bilateral surgery compared to 27% of the older patients, and a significant association being found between age < 45 years and bilateral surgeries. Likewise, data from the California Cancer Registry revealed that bilateral surgery was associated with younger age, with the rates increasing from 3,6% in 1998 to 33% in 2011, an increase of almost 10 times within little more than ten years.[22]

Neoadjuvant chemotherapy (NACT), traditionally used in cases of locally advanced cancer, has recently been indicated to facilitate breast conservation also in operable tumors.[23] Paradoxically, its use in the present study was associated with bilateral mastectomy in 53% of cases. A recent NCDB-based study reported similar results following the evaluation of almost 60,000 women submitted to NACT between 2010 and 2014.[24] Despite the increase in full pathological response over the time period, the rates of breast conservation increased slightly from 37.0% to 40.8% (p = 0.22) and bilateral mastectomy rates with immediate breast reconstruction increased from 8% to 13.1%, with a reduction in unilateral mastectomy. In the present study, bilateral surgery increased for patients with aggressive chemosensitive disease (70% of HER2 and 67% of the TN cases), although they would normally be potential candidates for NACT and conservative surgeries. Conversely, in luminal tumors, the bilateral surgery rate was lower: 30% of the cases. Better understanding is required regarding the reason why many patients who are eligible for breast-conserving surgeries decide that mastectomy is necessary. One of the possibilities is the fear of recurrence of the disease and the false impression that mastectomy is a "safer" treatment.[25]

In the present study, bilateral surgery was more closely associated with early-stage breast cancer. Patients with negative axilla were more likely to undergo bilateral surgery, whereas those who had undergone axillary dissection were more likely to have had a unilateral surgery. In general, the impact of a prophylactic surgery tends to be lower in the advanced stages of the disease, which may have affected these results.

Breast reconstruction failure, the most serious local complication in this procedure, was low in the present analysis, irrespective of laterality. In a cohort of 471 patients from Yale University, 58% underwent bilateral surgery, with complication rates being similar to those found with unilateral surgery (re-operation: 11.2% versus 10.8%).[26] Bilateral prophylactic mastectomy was associated with a longer hospitalization period, a factor that was not evaluated in the present study. Most cases of breast reconstruction today are performed with the use of implants, minimizing surgical complications. Women undergoing reconstruction with autologous flaps,[27] which prolongs surgery and increases associated morbidity, were not included in the present study.

Table 4. Multinomial logistic regression for predictive factors of bilateral mastectomy.

	p-value	Adjusted OR (95%CI)
Bilateral mastectomy		
Surgery (NSM) (SSM)	0.431	-
Year (2016-2018)	*0.031*	*11.53 (1.26–105.71)*
Age (< 45 years)	0.322	-
Node (+)	0.375	-
Hormone Receptor (-)	0.218	-
HER2 (+)	0.998	-
Radiotherapy (Yes)	0.874	-
Axillary dissection (No)	0.994	-
Chemotherapy (Yes)	0.938	-
Hormone therapy (No)	0.655	-
Death (No)	1.000	-

*p < 0.05; OR: odds ratio; 95%CI: 95% confidence interval for the adjusted OR; SSM: skin-sparing mastectomy; NSM: nipple-sparing mastectomy.

CONCLUSION

In conclusion, these results corroborate the international literature. From 2010 onwards, there was a trend towards an increase in bilateral mastectomy with breast reconstruction. These data may contribute to multidisciplinary debates, facilitating the

establishment of guidelines. Nevertheless, further studies are required to increase understanding of this phenomenon and the impact it produces in the country.

AUTHORS' CONTRIBUTION

F.P.: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing — original draft, writing — review & editing.

M.V.: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing — original draft, writing — review & editing.

P.G.: Data curation, formal analysis, methodology, resources, software, validation, visualization, writing — review & editing.

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