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Breast reconstruction and risk of lymphedema after mastectomy: A prospective cohort study with 10 years of follow-up[☆]

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Received 9 September 2015; accepted 4 June 2016

KEYWORDS

Breast neoplasia;
Reconstruction;
Incidence;
Lymphedema;
Risk factors

Summary Objective: The aim of this study is to assess the incidence and risk factors for lymphedema in women submitted to mastectomy, with or without breast reconstruction.

Methods: A cohort study was performed on women submitted to mastectomy with axillary lymphadenectomy in a single center. The follow-up included clinical evaluation and arm column measurements before surgery, at 30 days, 6 months, 5 years, and 10 years after surgery. For women subjected to late reconstruction, the time of occurrence of lymphedema (before or after reconstruction) was observed.

Results: We followed up on 622 patients submitted to mastectomy and axillary lymphadenectomy for an average period of 57 months after surgery. In total, 94 women were submitted to breast reconstruction, 47 (8%) of them immediate and 47 (8%) late reconstructions. Incidence

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of lymphedema in the whole group was 33% ($n = 204$). Among the patients submitted to reconstruction, 28% of them developed lymphedema, on average, 93 months (CI 95%, 88–98) after surgical treatment. In women not subjected to reconstruction, 179 (34%) developed lymphedema, on average, after 106 months (CI 95%, 96–116) ($p = 0.03$). Breast reconstruction reduced lymphedema risk in 36% (HR = 0.64, CI 96%, 0.42–0.98, $p = 0.04$). After adjustment for pathological staging and radiotherapy, this was not statistically significant (HR = 0.79, CI 95%, 0.52–1.21, $p = 0.28$).

Conclusion: Breast reconstruction does not increase the risk of lymphedema in long-term follow-up.

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Introduction

In Brazil, breast cancer is the most common cancer in women, corresponding to 22% of all new cancer cases per year.¹ The treatment of breast cancer patients, and therefore its aggressiveness, is determined by the characteristics of the disease at the time of diagnosis. The main procedures that can be performed alone or in combination are surgery (conservative or mastectomy), radiotherapy, chemotherapy, and hormone therapy.²

Whenever mastectomy is indicated, breast reconstruction is considered and can be undertaken either immediately or sometime after the initial procedure (delayed breast reconstruction).³ Different reconstruction techniques are currently employed, and the choice of method depends on the characteristics of the tumor, the clinical and emotional condition of the patient, and the qualification and infrastructure of the professionals and institution.⁴ Regardless of the breast reconstruction technique, different complications due to breast cancer treatment are reported in the literature.^{5–7} Lymphedema is one of the main complications after treatment of breast cancer. In our population, approximately 30% of women who underwent surgical treatment for breast cancer developed upper limb lymphedema within 5 years.⁸ The etiology and risk factors of lymphedema seem to be multifactorial and are not fully understood. In general, the main risk factors are lymphadenectomy and/or axillary radiotherapy, obesity, and invasive procedures performed on the limb homolateral to the breast cancer.^{8,9}

Only a few studies have assessed the incidence and risk factors for lymphedema in women subjected to immediate or delayed breast reconstruction.^{10–15} Some reports showed a reduction in lymphedema risk in women subjected to immediate reconstruction as compared with those without reconstruction.^{10,14,15} For those patients with lymphedema at the time of breast reconstruction, the reconstructive procedure has been shown to improve related symptoms.^{11,15,16}

The primary aim of this study was to assess the risk factors for lymphedema development and its long-term incidence in patients submitted to mastectomy, with or without breast reconstruction. In addition, we studied the frequency and factors associated with the choice of immediate and delayed breast reconstruction and the association between immediate breast reconstruction and

complications during the first year of follow-up. In addition, we analyzed the cumulative incidence of lymphedema in the 10-year follow-up period, according to the method of breast reconstruction.

Methods

This was a cohort study on women submitted to mastectomy with axillary lymphadenectomy for the treatment of breast cancer, in a single center (Brazilian National Cancer Institute) between August 1, 2001, and November 30, 2002. This was a subproject of a broader investigation that started in 2000.⁸

Women submitted to mastectomy within the established period were eligible for this study. We excluded patients who were submitted to prior oncologic treatment in other institutions for contralateral breast cancer, distant metastasis, lymphedema, or any other functional condition of the upper limbs prior to the surgical treatment for breast cancer.

The study had an initial population of 1243 women; 189 did not fulfill the eligibility criteria, resulting in a total of 1054 women who were assessed for lymphedema incidence five years after the surgical procedure.⁸ In order to analyze the 10-year evaluation, 70 women presenting early-onset edema and 27 other women who were monitored for less than six months after the surgical procedure were excluded. Moreover, seven other women were reinserted in the cohort study for this assessment. For this study, a total of 622 patients were included.

Patients were evaluated before surgery, at 30 days, six months, and then annually until five years after the surgery.¹⁷ Those who presented edema or any other functional disorder of the upper limb were requested to return for physical therapy for assessment and prescription of therapeutic procedures. Between the 5- and 10-year monitoring, a review of the patient charts was performed to identify the existence of the following information: minutes of medical and physical-therapist assessment; physical-therapy assessment with a difference of >2 cm being reported in the perimeter of the upper limb homolateral to surgery at any point when compared with the contralateral limb; treatment approach for lymphedema (use of elastic garments or compressive bandaging); and progression of the disease or death. Patients who had no diagnosis of lymphedema during the monitoring period, had stable

primary disease, or their last assessment was completed before 10 years after the surgical procedure were reviewed. The surviving women who did not return for the monitoring of physical-therapy assessment had their data collected from the chart until the last available information.

Exposure was considered as the performance of immediate or delayed breast reconstruction, according to data from surgical reports available in the hospital charts.

The outcome (lymphedema) was obtained by indirect volume measurements, determined by the upper limb circumference. The limb volume was calculated from the circumference measurements, treating each limb segment as a pair of circumferences. The limb volume was calculated as $V = h * (C^2 + Cc + c^2) / (\pi * 12)$, where V is the volume of the limb segment, C and c are circumferences between the points, and h is the distance between the circumferences (C , c). The final estimated volume excess corresponds to the sum of the differences between each point. Lymphedema was considered as a difference >200 ml between the volume of the affected limb and the volume of the contralateral limb.¹⁸

Patients in whom the onset of lymphedema was previous to delayed reconstruction were not considered to determine lymphedema incidence related to delayed reconstruction.

A descriptive analysis was performed. For the initial exploratory analysis, the Kaplan–Meier method was

performed, aiming to identify possible differences in curves for each exposure group and for the possible adjustment variables. The first occurrence of lymphedema was considered an event. Women completing 10 years of follow-up without lymphedema; those who were lost; and those with local recurrence, death, or metastasis at a distance were censored.

Multivariate Cox regression analysis (forward stepwise method) was performed. The order in which the variables were inserted into the regression model was defined by statistical significance ($p < 0, 20$), obtained in the univariate Cox regression analysis. Variables with clinical-epidemiological importance were included in the model as adjustment, even if they did not present statistical significance.

The research project was approved by the ethics committee of the Brazilian National Cancer Institute.

Table 1 Demographic and clinical characteristics at the time of breast cancer diagnosis ($n = 622$).

Variable	n	% valid ^a
Marital status		
Married	292	48%
Common-law spouse	02	0
Divorced/Separated	44	7%
Widow	119	19%
Single	157	26%
Education		
Illiterate	45	8%
Incomplete elementary school	280	47%
Complete elementary school	106	18%
Incomplete high school	22	4%
Complete high school	102	17%
Incomplete tertiary education	09	1%
Complete tertiary education	32	5%
Occupation		
Housewife	287	61%
Working outside	180	38%
Body mass index (BMI)		
Obesity (≥ 30)	215	35%
Overweight (25–29.99)	197	32%
Appropriate (18.5–24.99)	197	32%
Underweight (< 18.49)	13	2%
Surgery side		
Right	293	47%
Left	329	53%

^a Differences in sample sizes correspond to the absence of information.

Table 2 Histopathological and oncological treatment characteristics ($n = 622$).

Characteristics	N	% valid
Tumor stage		
0	26	4%
I	54	9%
IIA	175	28%
IIB	176	28%
IIIA	46	7%
IIIB	142	23%
No information	3	
Lymph node status		
Negative	287	47%
Positive	329	53%
No information	6	
Lymphadenectomy		
Level I and II	78	13%
Level III	509	87%
No information	35	
Mastectomy		
Halsted	12	2%
Madden	405	65%
Patey	205	33%
Lymph nodes removed		
>15 lymph nodes	215	35%
≤15 lymph nodes	405	65%
No information	3	
Chemotherapy^a		
No	143	23%
Neo adjuvant	212	34%
Adjuvant	383	62%
Radiotherapy^a		
No	303	49%
Neo adjuvant	17	3%
Adjuvant	302	49%
Hormone therapy^a		
No	204	33%
Neo adjuvant	20	3%
Adjuvant	414	67%

^a The sum does not correspond to the total population since the patients could have had more than one treatment.

Table 3 Characteristics of breast reconstruction.

Characteristics	N	% valid
Immediate reconstruction (n = 622)		
Not performed	575	92%
Transverse rectus abdominus musculocutaneous flap	36	6%
Latissimus dorsi	04	1%
Implants	01	0
Expander	03	0
No information	03	0
Late reconstruction (n = 575)^a		
Not performed	528	92%
TRAM (rectus abdominus muscle)	37	6%
Latissimus dorsi	04	1%
Expander	01	0
Prosthetics	01	0
Latissimus dorsi and prosthetics	04	1%

^a Excluding those patients with immediate reconstruction.

Results

This analysis included 622 women submitted to mastectomy for breast cancer, followed up for 57 ± 40 months after surgery. Demographic and clinical characteristics of this

population at the time of breast cancer diagnosis are presented in Table 1. The population was mostly composed of women who were 50 years old or older (58%), were married (48%), had not completed elementary school education (47%), had household chores as their main activity (61%), and were overweight (35%) (see Table 2).

Regarding oncological characteristics, the population presented a high frequency of tumors diagnosed in advanced stages of the disease (59% women presented at stage \geq IIB) and compromised axillary lymph nodes (53%). Radical mastectomy modified by Madden was the most frequent approach (65%), with complete axillary lymphadenectomy (NIII) (87%). Most patients were subjected to adjuvant treatment with chemotherapy (62%), radiotherapy (49%), and hormone therapy (67%).

In total, 94 women were submitted to breast reconstruction, with 47 (8%) being immediate and 47 (8%) delayed reconstructions. Pedicled transverse rectus abdominus myocutaneous flap was the most common technique used (Table 3).

The frequency of breast reconstruction and association with the characteristics of the women can be found in Table 4. Women who reported not having a partner at the time of breast cancer diagnosis presented a 41% less chance of being subjected to reconstruction (OR = 0.59, CI 95%, 0.37–0.92, $p = 0.02$). Patients with a low schooling level had a 50% less chance of having their breasts reconstructed

Table 4 Characteristics of the population according to breast reconstruction (n = 622).

Variable	No Reconstruction n = 528 n (%)	Immediate Reconstruction n = 47 n (%)	Late Reconstruction n = 47 n (%)	OR (CI 95%) ^a	p Value
Marital status					
No partner	282 (54%)	17 (37%)	21 (45%)	0.59 (0.37–0.92)	0.02
With a partner	239 (46%)	29 (63%)	26 (55%)		
Education					
Until completion of elementary school	377 (75%)	23 (52%)	31 (66%)	0.50 (0.31–0.79)	<0.01
Above completion of high school	128 (25%)	21 (48%)	16 (34%)		
Occupation					
Housewife	259 (65%)	09 (25%)	19 (58%)	0.37 (0.22–0.62)	<0.01
Working outside	139 (35%)	27 (75%)	14 (42%)		
BMI					
Overweight (BMI \geq 30)	194 (37%)	08 (17%)	13 (28%)	0.49 (0.29–0.83)	<0.01
Not overweight (BMI < 30)	334 (63%)	39 (83%)	34 (72%)		
Age					
<50 years old	191 (36%)	31 (66%)	36 (77%)	4.38 (2.71–7.08)	<0.01
\geq 50 years old	337 (64%)	16 (34%)	11 (23%)		
Lymph nodes removed					
\leq 15 lymph nodes	185 (35%)	18 (38%)	12 (25%)	0.86 (0.54–1.38)	0.56
\geq 15 lymph nodes	340 (65%)	29 (62%)	35 (74%)		
Lymph node status					
Negative	237 (45%)	28 (60%)	22 (48%)	1.40 (0.90–2.18)	0.14
Positive	286 (55%)	19 (40%)	24 (52%)		
Tumor stage					
\geq IIB	320 (61%)	17 (36%)	27 (57%)	1.77 (1.14–2.76)	0.01
Up to IIA	205 (39%)	30 (64%)	20 (43%)		

BMI = Body Mass Index; n = Number of Patients; OR = Odds Ratio; CI = Confidence Interval.

^a Odds ratio between reconstruction (yes versus no) and variables selected.

Table 5 Association between immediate reconstruction and complication in the first year after breast surgery.

Variable	Immediate reconstruction n (%)		OR (CI 95%)	P value
	Yes	No		
Seroma				
Yes	06 (37%)	369 (65%)	0.32 (0.12–0.90)	0.03
No	10 (62%)	199 (35%)		
Necrosis				
Yes	08 (47%)	288 (51%)	1.15 (0.44–3.03)	0.81
No	09 (53%)	281 (49%)		
Infection				
Yes	05 (31%)	75 (13%)	0.33 (0.11–0.99)	0.05
No	11 (69%)	494 (87%)		
Axillary web syndrome				
Yes	23 (49%)	366 (64%)	1.83 (1.01–3.32)	0.06
No	24 (51%)	209 (36%)		
Arm paresthesia				
Yes	06 (86%)	58 (83%)	0.81 (0.09–7.32)	1.00
No	01 (14%)	12 (17%)		
Winged scapula				
Yes	0 (0)	15 (21%)	—	0.33
No	07 (100%)	56 (79%)		
Arm pain				
Yes	02 (25%)	15 (22%)	0.85 (0.15–4.65)	1.00
No	06 (75%)	53 (78%)		
Arm flexion				
Incomplete	01 (12%)	13 (17%)	1.31 (0.15–11.66)	1.00
Complete or functional	07 (88%)	62 (83%)		
Arm abduction				
Incomplete	01 (12%)	12 (16%)	0.76 (0.09–6.77)	1.00
Complete or functional	07 (88%)	64 (84%)		
Cancer recurrence^a				
Yes	0 (0)	28 (5%)	—	0.26
No	47 (100)	547 (95%)		
Death^a				
Yes	08 (17%)	205 (36%)	0.37 (0.17–0.81)	0.01
No	39 (83%)	370 (65%)		

OR=Odds ratio; CI=Confidence interval.

^a All monitoring in the study.

(OR = 0.50, CI 95%, 0.31–0.79, $p < 0.01$), those reported as only taking care of the household chores presented a 63% less chance (OR = 0.37, CI 95%, 0.22–0.62, $p < 0.01$), and overweight subjects a 51% less chance (OR = 0.49, CI 95%, 0.29–0.83, $p < 0.01$). Reconstruction was most frequently performed in young patients (<50 years old), who presented a 4.38-fold higher chance of being subjected to such a procedure (OR = 4.38, CI 95%, 2.71–7.08, $p < 0.01$), and in patients with advanced tumors (\geq IIB) with a 1.77-fold higher chance (OR = 1.77, CI 95%, 1.14–2.76, $p < 0.01$).

While assessing the association between immediate breast reconstruction and complications in the first year of monitoring, it was observed that the patients subjected to immediate reconstruction had a 68% less chance of developing seroma (OR = 0.32, CI 95%, 0.12–0.90) and a 63% lower chance of evolving to death in the total monitoring period (OR = 0.37, CI 95%, 0.17–0.81). Other complications occurred regardless of the performance of immediate breast reconstruction (Table 5).

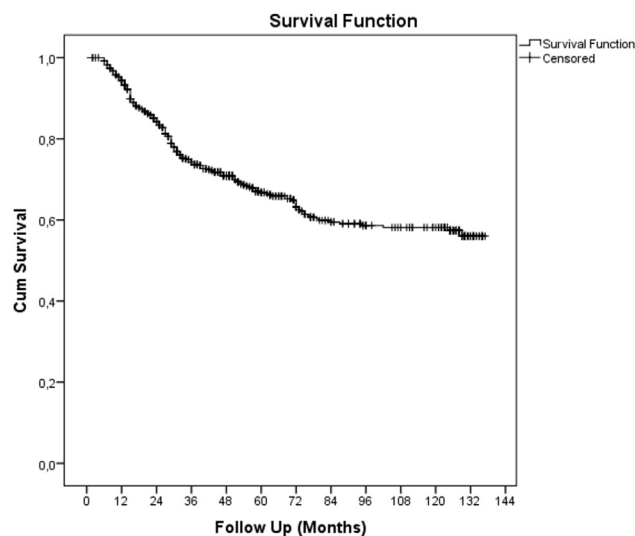


Figure 1 Lymphedema cumulative incidence after surgical treatment for breast cancer.

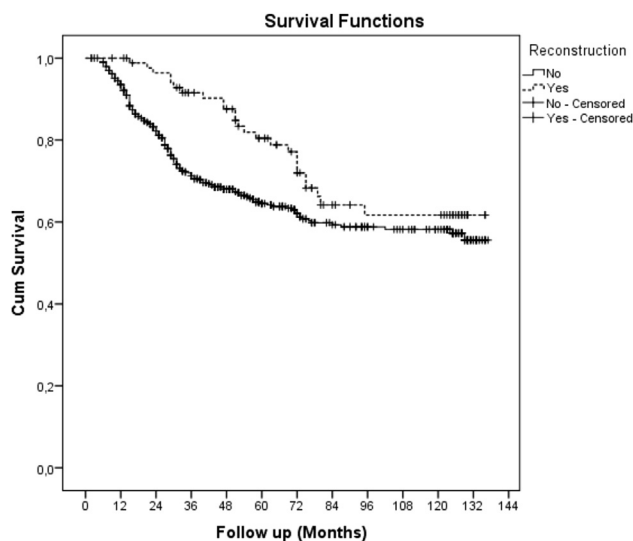


Figure 2 Lymphedema cumulative incidence after surgical treatment for breast cancer, according to the breast reconstruction ($p = 0,03$).

The overall incidence of lymphedema was 33% ($n = 204$). Lymphedema developed, on average, 95 months (CI 95%, 90–99) after surgical treatment (Figure 1). A total of 88 women (47 with immediate reconstruction and 41 with delayed reconstruction prior to the development of lymphedema) were submitted to breast reconstruction. Six of them were submitted to delayed reconstruction after the occurrence of lymphedema. Among those women submitted to reconstruction ($n = 88$), 25 (28%) developed lymphedema, on average, 93 months (CI 95%, 88–98) after surgical treatment. In women not subjected to reconstruction, 179 (34%) had lymphedema, on average, after 106 months (CI 95%, 96–116) ($p = 0.03$) (Figure 2).

In order to identify the adjustment variables in association with breast reconstruction and lymphedema, a Kaplan–Meier analysis was performed. Variables presenting $p < 0.20$ by the log-rank test were selected for the Cox regression (Table 6). In the Cox regression analysis, women submitting to breast reconstruction had a 36% lower risk of evolution to lymphedema compared with those not subjecting to the procedure (HR = 0.64, CI 96%, 0.42–0.98, $p = 0.04$). After adjustment for pathological staging and radiotherapy, there was a reduction in the risk of lymphedema in 21%; however, this difference was not statistically significant (HR = 0.79, CI 95%, 0.52–1.21, $p = 0.28$).

Discussion

This study analyzed the incidence of lymphedema in 622 patients submitted to mastectomy for breast cancer with or without breast reconstruction, who were followed up for approximately 10 years after the surgical procedure. Breast reconstruction was not very frequent, either immediately (8%) or delayed (8%), and marital status, education, occupation, body mass index, age, and tumor stage influenced its indication. Immediate reconstruction was related to a lower risk of seroma and lower death frequency. Only six

Table 6 Kaplan–Meier analysis between lymphedema and demographic and clinical characteristics.

Characteristics	Lymphedema (n)	Average time (months)	CI	Log rank
Age (years)				
<50	91	92	84–99	0.28
≥50	113	96	90–102	
Occupation				
Housewife	92	96	89–103	0.91
Working outside	62	94	85–102	
Nutritional status				
Overweight	80	91	83–99	0.16
Not overweight	124	96	91–102	
Cancer Staging				
Until IIA	72	103	97–110	<0.01
≥ II B	130	88	82–95	
Number of lymph nodes removed				
<15	60	99	91–107	0.23
≥15	142	93	87–99	
Chemotherapy in the affected arm				
Yes	98	80	72–88	<0.01
No	106	103	98–108	
Adjuvant radiotherapy				
Yes	139	78	71–85	<0.01
No	65	110	105–116	
Seroma				
Yes	135	91	85–97	0.07
No	61	98	91–106	
Axillary web syndrome				
Yes	113	100	94–105	0.01
No	91	86	79–94	

women presenting lymphedema were subjected to delayed reconstruction. After stage adjustment, the patients subjected to immediate or delayed breast reconstruction did not present increased risk of developing lymphedema in the 10-year period of post-surgical monitoring.

Mastectomy is associated with important physical, psychological, social, and sexual alterations.^{5,6,8} Breast reconstruction has the main objective of improving body image and satisfaction with oncological treatment, having a positive impact on the quality of life of these women.^{19–25} In Brazil, the federal legislation guarantees that every patient having a mastectomy has the right to breast reconstruction to be performed by the public health system.

However, even with the widely known benefits of breast reconstruction and a favorable legislation, in our study, it could be observed that of the 622 women subjected to a mastectomy in a single reference center for oncological treatment only 47 had immediate reconstruction and another 47 women had delayed reconstruction. A study performed on the American population submitted to mastectomy due to breast cancer in the initial stage showed an increase in the number of breast reconstruction cases from 12% in 1998 to 36% in 2011 ($p < 0.01$).²⁶ In Australia, among the patients subjected to mastectomy, 41% had reconstruction, with 97% of them being immediate.²⁷

Although the number of breast reconstructions is increasing, the low frequency can be due to demographic factors, clinical conditions, women's unawareness of the techniques, lack of access to plastic surgery services, and concern about and fear of complications due to such treatment.^{28,29} In the present study, the patients that were more likely to undergo reconstruction were those who were younger, better educated, employed, not overweight, and had more advanced tumors. Similar results were found in a study performed in the French population, where reconstruction was more frequent among younger women, those who worked away from home, non-smokers, those without metastatic cancer, and those who were not subjected to radiotherapy.³⁰ In Australian women, the factors associated with reconstruction were lower age, bilateral mastectomy, access to private hospitals, fewer home/work responsibilities, increased level of home support, and early discussion of reconstructive options.³¹ In another study on American patients, women who were more likely to have breast reconstruction were of a younger age, of lower body weight, white or Hispanic, without co-morbidities, and non-smokers.³²

In the present study, the most frequent technique used in the immediate and delayed breast reconstruction was pedicled transverse rectus abdominus musculocutaneous flap (TRAM) (77%). Similar results were also observed in another study published with data from the same institution, where 67% of women were submitted to reconstruction with TRAM (LEAL et al., 2003). Other studies reported a more frequent indication of reconstruction with expanders and breast implants.^{12,32–34} This divergence may result from the advanced diagnosis of breast cancer and its respective treatment, a very frequent characteristic in our institution, where 59% of women presented stage \geq IIb and 51% were subjected to (neo and/or adjuvant) radiotherapy.

Complications could follow surgical treatment for breast cancer.^{5,6,8} Moreover, women subjected to immediate breast reconstruction could have additional complications due to mastectomy and axillary dissection. Morbidity can involve, along with the chest and upper limb, the donor site in those patients who are subjected to reconstruction with autologous tissues. When it is performed with implants, the women can report increased pain in the reconstructed breast and decreased flexibility and strength in the pectoral muscles. In TRAM cases, pain can occur in different regions (abdomen, spine, neomama, and axilla), plus abdominal wall weakness and posture changes. When subjected to reconstruction with the latissimus dorsi muscle, shoulder pain, movement restriction, and functional changes to the upper limb can appear.³⁵

Our results showed no increased incidence of complications in the first year after surgery when comparing patients subjected to mastectomy with reconstruction and those without breast reconstruction. Immediate reconstruction was also a protective factor from the occurrence of seroma, with a 68% reduction in the risk of this complication (OR = 0.32, CI 95%, 0.12–0.90). Similar results were shown in an American study comparing women subjected to mastectomy with and without immediate reconstruction with implants, where no increase was found in the morbidity rates from the surgical wound in the first 30 days after surgery.³⁶ Another study performed in a single

institution showed no increase in general and neuropathic pain after immediate reconstruction when compared with patients subjected to mastectomy alone.³⁷

Lymphedema is one of the main complications from the treatment of breast cancer.⁸ In this study, lymphedema incidence was 33%, occurring on average 95 months after surgical treatment. Among those patients with immediate or delayed reconstruction, 28% had lymphedema, as did 34% of those without reconstruction. Card et al. (2012)³² in a cohort of 1148 patients found a lower rate of lymphedema (7%), of which 4% were women submitted to breast reconstruction and 10% were mastectomy patients. In our results, there was a higher incidence of lymphedema. The differences in the incidences of lymphedema can be justified by the method used to diagnose lymphedema and the characteristics of the populations.³⁸

In the multiple regression analysis, after removing the effects of possible confounding variables, there was a 21% reduction in the risk of lymphedema among those who had reconstruction; however, this difference was not statistically significant (HR = 0.79, CI 95%, 0.52–1.21, $p = 0.28$). Our results corroborate those reported in other series, where women submitting to breast reconstruction present a lower incidence of lymphedema when compared with those who did not have their breasts reconstructed.^{13,15,32}

Although delayed breast reconstruction is not contraindicated in patients with lymphedema, our study observed that only six women had their breasts reconstructed after the onset of lymphedema. The study demonstrated improvement in lymphedema symptoms and the number of women submitting to delayed reconstruction.^{11,15,16,39}

This study presents some limitations, among them the small number of patients exposed to reconstruction. This fact prevented stratified analyses by the surgical technique. Moreover, a few specific variables related to reconstruction were not collected. However, our results demonstrate the low frequency at which breast reconstruction was performed in a single reference center for oncologic treatment in Brazil. At the same time, it is possible that breast reconstruction could lead to a decrease in morbidity, such as lymphedema.

Conclusion

Immediate breast reconstruction was performed in 8% of women and delayed reconstruction was performed in 8%. Only six women were submitted to delayed reconstruction after the occurrence of lymphedema.

The incidence of lymphedema in the total population was 33%. Lymphedema developed, on average, 95 months after surgical treatment. Among those submitted to reconstruction, 25 (28%) developed lymphedema, on average, 93 months after surgical treatment. On the other hand, in women not submitted to reconstruction, 179 (34%) presented lymphedema, on average, after 106 months. In the Cox regression analysis, women submitting to breast reconstruction had a 36% lower risk of developing lymphedema compared with those who did not have reconstruction. After adjustment for pathological stage and radiotherapy, breast reconstruction was not statistically associated with the occurrence of lymphedema.

Conflict of interest

There is no conflict of interest.

Funding source

The authors declare that there was no funding source.

Ethical approval

The research project was subjected to and approved by the ethics committee of the Brazilian National Cancer Institute.

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