

Factors associated to complications in reconstruction in patients with breast cancer treated with mastectomy

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Abstract

Introduction: Breast cancer is the most common invasive neoplasm in women. When taken to mastectomy, breast reconstruction is an integral part of treatment. **Objectives:** The purpose of this study is to determine which factors are associated to post-operative complications of breast reconstruction in patients with breast cancer treated with mastectomy. **Methods:** 306 patients taken to breast reconstruction were divided into three groups depending on technique: pedicled flaps, prosthetic material and deep inferior epigastric perforators (DIEP). Descriptive and comparative statistics were performed to find associations between the type of reconstruction and complications. **Results:** The factors associated to general were bleeding and reintervention. Reintervention was associated to loss of reconstruction. Factors associated to reoperation were immediate complications, late complications, and radiotherapy. Factors associated to loss of reconstruction were smoker status, presence of late complications, and reintervention. **Conclusion:** There is a higher percentage of immediate complications and loss of reconstruction with prosthetics. DIEP is an alternative with lower probability of loss of reconstruction. Multidisciplinary teams should establish the decision of the best type of reconstruction.

Key words: Breast cancer. Mastectomy. Breast Reconstruction.

Factores asociados a complicaciones en la reconstrucción en pacientes con cáncer de mama tratadas con mastectomía

Resumen

Introducción: El cáncer de mama es la neoplasia invasora más común en mujeres. Cuando son llevadas a mastectomía, la reconstrucción mamaria es también una parte integral del tratamiento. **Objetivos:** Determinar factores asociados a complicaciones postoperatorias de reconstrucción mamaria en pacientes con cáncer de mama tratadas con mastectomía. **Métodos:** 306 pacientes llevadas a reconstrucción mamaria fueron divididas en tres grupos dependiendo de la técnica: colgajo pediculado, prótesis y colgajo DIEP. Se realizaron análisis descriptivos y comparativos entre el tipo de reconstrucción y las complicaciones postoperatorias. **Resultados:** Los factores asociados a complicaciones en general fueron sangrado y reintervención. Los factores asociados a la reintervención fueron complicaciones inmediatas, tardías y radioterapia. Los factores asociados a la pérdida de la reconstrucción fueron el tabaquismo, complicaciones tardías y reintervención.

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Conclusión: *Hay un mayor porcentaje de pacientes con complicaciones inmediatas y pérdida de la reconstrucción en técnicas que involucran prótesis. El colgajo DIEP es una alternativa con menor probabilidad de pérdida de la reconstrucción. Un equipo multidisciplinario debe decidir el mejor tipo de reconstrucción para cada paciente.*

Palabras clave: *Cáncer de mama. Mastectomía. Reconstrucción mamaria.*

Introduction

Breast cancer is the most common invasive neoplasm in women and is their second most prevalent cause of death by cancer. Worldwide, approximately 1.4 million women were diagnosed with breast cancer in 2018, out of which 458 thousand died due to the disease^{1,2}. Treatment for breast cancer should be a multidisciplinary effort that includes surgery, chemotherapy, and radiotherapy. Surgical management for breast cancer consists of conservative surgery with axillary evaluation or mastectomy with axillary lymph node dissection. Many of these patients will desire breast reconstruction, which should nowadays be considered an integral part of treatment^{3,4}.

The ideal reconstruction technique in patients is based in the use of implants, expanders with implants, or reconstruction with autologous tissue; free flaps or pedicled flaps. Free flaps require a microsurgical technique to perform the anastomosis, most commonly executed with deep inferior epigastric perforators (DIEPs)⁵⁻⁷. The most common technique is immediate two-step reconstruction with tissue expander and implant. The effect of radiotherapy in reconstructed patients has been well documented, with an increased incidence of capsular contractures, exposition, infections, and some other post-operative complications such as tissue necrosis, wound dehiscence, and seromas⁸. Autologous reconstructions leads to fewer complications than those involving implants in patients treated with radiotherapy⁹. Breast reconstruction posterior to mastectomy represents an essential part of breast cancer treatment. Improvements in treatment outcomes have resulted in women's interest in esthetic results, without ignoring prognosis, posterior to cancer treatment¹⁰.

The objective of this work was to describe factors associated to post-operative complications in patients with breast cancer with reconstructive surgery treated at Mexico City's National Cancer Institute (INCan).

Materials and methods

We performed a retrospective analysis of the clinical files of all patients with breast cancer treated with

mastectomy and unilateral reconstruction at our institution between January 2013 and December 2016. All patients with breast cancer taken to immediate and delayed reconstruction in any modality were included in this analysis. Mastectomies were either simple mastectomy with sentinel lymph node biopsy or radical modified mastectomy. Reconstructive procedures were performed by three teams of expert plastic surgeons specialized in microvascular surgery.

We recollected information on general variables (age, body mass index [BMI], smoke status, and menopause), oncologic variables (clinical stage, tumor size, histologic and molecular subtype, lymph node positivity, and type of treatment), and surgical variables (type of reconstruction, surgical complications, etc.). Patients were divided into three groups according to the type of reconstruction; the first including patients treated with pedicled flaps; the second, patients reconstructed with prosthetic material (definite implant or tissue expander), and the third with DIEP free flaps. Patients without an oncologic diagnosis, with conservative surgery (oncoplastic surgery, lumpectomy, or partial mastectomy), or with insufficient data for analysis were excluded from the study. Complications included bleeding, wound dehiscence or exposition, seroma, infection, and loss of reconstruction and were classified as early or late. Early complications were defined as those which occurred within 30 days after the reconstructive procedure. Late complications were defined as those which occurred after 30 days of the reconstructive procedure. Overweight was defined as a BMI ≥ 25 kg/m². We considered type 2 diabetes mellitus and high blood pressure as comorbidities.

For clinical variables, descriptive statistics were done with central tendency measures and data dispersion according to their distribution. Data distribution was analyzed with the Shapiro–Wilk test. For categorical variables, absolute and relative frequencies were used. For continuous variables with non-normal distribution, the median and interquartile range (IQR) were used, and for continuous variables with a normal distribution, the mean and standard deviation were used. The comparative analysis was performed with Chi-squared or Fisher's exact test for contingency tables, Student's

t-test for continuous variables with a normal distribution, and Mann–Whitney U-test for continuous variables with a non-normal distribution. A logistic regression was calculated to obtain the risk associated with flap complications, reinterventions, and flap loss, through a univariate and multivariate analysis. Statistical analysis was performed with STATA 14.1 (College Station, TX) software, and statistical significance was considered when $p < 0.05$. The study was approved the Institutional Review Board, with approval reference INCAN/CI/0480/18.

Results

A total of 306 out of 320 patients who had a mastectomy with breast reconstruction were included in the analysis. The mean age was 46.03 (standard deviation [SD] 9.5) years, 136 (44.41%) were overweight, and 259 (84.64%) presented comorbidity. Most patients were diagnosed on clinical Stage II ($n = 152$, 49.67%). Immediate reconstruction was performed in 251 (82.02%) patients. The number of patients that received adjuvancy was 286 (93.46%) and 84 (27.45%) received neoadjuvancy (Table 1). General complications, either immediate or late, occurred in 68/306 (22.22%) patients, out of which 39/306 (12.75%) had immediate complications, and 63/306 (20.59%) had late complications. There were 21/306 (6.9%) patients who had a reintervention and 25/306 (8.2%) losses of reconstruction. There was a total of 171 (55.9%) prosthetic reconstructions, 55 (18%) with pedicled flaps, and 80 (26.19%) with DIEP flaps.

A difference was found between the three groups regarding BMI ($p = 0.02$), being overweight in 94 (54.97%) patients in the prosthesis group, 38 (59.1%) in the pedicled flap group, and 57 (71.25%) in the DIEP flap group. Lymph node positivity was found in 56 (32.75%) patients in the prosthesis group, 26 (47.27%) in the pedicled flap group, and 24 (30%) in the DIEP flap group ($p = 0.006$). As for the duration of surgical procedure, the prosthesis group had a median of 180 (IQR 120-200) min, 180 (IQR 120-240) min for the pedicled flaps, and 360 (IQR 165-480) min for DIEP flaps, with a statistically significant value ($p < 0.001$). There was also a statistically significant difference ($p < 0.001$) regarding bleeding; with a median of 150 mL (IQR 100-250) for the prosthesis group, 150 (IQR 100-300) mL for the pedicled flap group, and 300 (IQR 200-400) mL for the DIEP flap group. The presence of immediate complications was also different among the groups ($p = 0.03$), with 22 (12.07%)

Table 1. General characteristics of patients with breast cancer treated with mastectomy at INCAN from 2013 to 2016 ($n = 306$)

Continuous variables	Mean \pm SD
Age (years)	46.03 \pm 9.5
Categorical variables	Frequency (%)
Body mass index	
Under 25 kg/m ²	117 (38.24)
Over 25 kg/m ²	189 (61.77)
Presence of comorbidities	47 (15.36)
Clinical stage	
0	18 (5.88)
I	69 (22.55)
II	152 (49.67)
III	65 (21.24)
IV	2 (0.65)
Tumor size	
Tis	21 (6.86)
T1	86 (28.10)
T2	146 (47.71)
T3	38 (12.42)
T4	12 (3.92)
Not available	3 (0.98)
Menopause	49 (16.01)
Histology	
Ductal	263 (86.95)
Non-ductal	43 (14.00)
Smoker	66 (21.57)
Molecular subtype	
Luminal A	147 (48.4)
Luminal B	75 (24.51)
Her2+	40 (13.07)
Triple negative	44 (14.38)
Positive lymph nodes	104 (33.99)
Neoadjuvancy	84 (27.45)
Axillary dissection	52 (16.99)
Adjuvant therapy	286 (93.46)
Adjuvant chemotherapy	133 (43.14)
Adjuvant radiotherapy	110(35.95)
Adjuvant hormonal therapy	136 (77.2)

SD: standard deviation, Tis: carcinoma *in situ*.

events in the prosthesis group, 1 (1.82%) in the pedicled flap group, and 16 (20%) in the DIEP flap group. There was also a difference ($p = 0.04$) in the loss of reconstruction, with 20 (11.7%) events in the prosthesis group, 2 (3.64%) in the pedicled flap group, and 3 (3.75%) in the DIEP flap group. Finally, a total of 7

Table 2. Comparison between the types of reconstructions in patients with breast cancer treated with mastectomy from 2013 to 2016 (n = 306)

	Prosthetic material n = 171 (55.9%)	Pedicled flap n = 55 (18.0%)	DIEP n = 80 (26.1%)	p-value*
Age (years), mean ± SD	45.85 ± 9.5	46.07 ± 9.3	46.4 ± 9.7	0.500
Body mass index				
Under 25 kg/m ²	77 (45.03)	17 (30.91)	23 (28.75)	0.020
Over 25 kg/m ²	94 (54.97)	38 (59.1)	57 (71.25)	
Tumor size				
Tis	11(6.43)	5 (9.09)	5 (6.25)	0.580
T1	44 (25.73)	16 (29.09)	26 (3.25)	
T2	81 (47.37)	26 (47.27)	39 (48.75)	
T3	27 (15.79)	5 (9.09)	6 (7.5)	
T4	5 (2.92)	3 (5.45)	4 (5)	
Not available	3 (1.75)	0 (0)	0	
Menopause	28 (16.37)	8 (14.55)	13 (16.25)	0.950
Histology				
Ductal	144 (84.21)	50 (90.91)	69(83.25)	0.710
Non-ductal	27 (15.79)	5 (9.09)	11 (13.75)	
Smoker	38 (22.23)	13 (23.63)	15 (18.75)	0.890
Positive lymph nodes	56 (32.75)	26 (47.27)	24 (30)	0.006
Surgical time, minutes (IQR)	180 (120-200)	180 (120-240)	360 (165-480)	< 0.001
Bleeding	150 (100-250)	150 (100-300)	300 (200-400)	< 0.001
Immediate reconstruction	143 (83.63)	46 (83.64)	62 (77.5)	0.470
Immediate complications	22 (12.07)	1 (1.82)	16 (20)	0.030
Late complications	40 (23.39)	7 (12.73)	16 (20)	0.230
Loss of reconstruction	20 (11.7)	2 (3.64)	3 (3.75)	0.040
Reintervention	7 (4.09)	1 (1.82)	13 (16.25)	< 0.001

DIEP: deep inferior epigastric perforator flap reconstruction; SD: standard deviation; Tis: carcinoma *in situ*; IQR: interquartile range .

(4.09%) patients were reintervened in the prosthesis group, 1 (1.82%) in the pedicled flap group, and 13 (16.25%) in the DIEP flap group, with a statistically significant difference (p < 0.001). No statistically significant difference was found regarding age, tumor size, menopause, tumor histology, smoker status, realization of immediate reconstruction, and late complications (Table 2).

The independent factors associated to general complications were a non-ductal histology (odds ratio [OR] 2.58, CI 95% 1.16-5.77; p = 0.02) and bleeding during surgery (OR 1.01, CI 95% 1.00-1.05; p = 0.025) (Table 3). The independent factors associated to reoperation were the presence of immediate complications (OR 11.98, CI 95% 2.51-57.18; p = 0.002), the presence of late complications (OR 1.66, CI 95% 1.33-2.09; p = 0.002), and the presence of radiotherapy (OR 5.38, CI 95% 1.14-25.36; p = 0.03) (Table 4).

The independent factors associated to loss of reconstruction were smoker status (OR 16.05, CI 95% 1.60-160.34; p = 0.018), triple-negative tumors (OR 7.24, CI 95% 1.15-45.68; p = 0.035), presence of late complications (OR 2.47, CI 95% 1.65-3.67; p < 0.001), and being reintervened (OR 20.62, CI 95% 1.68-252.34; p = 0.018). DIEP type free flap reconstructions were a protective factor against loss of reconstruction (OR 0.0016, CI95% 0.00006-0.040; p < 0.001) (Table 5).

Discussion

In this work, we have shown factors that relate to complications in breast reconstruction surgeries in patients with breast cancer who have undergone mastectomy. Our most important findings are that prosthesis techniques have a higher correlation

Table 3. Factors associated to general complications in patients with breast cancer treated with mastectomy from 2013 to 2016 (n = 306)

	Univariate			Multivariate		
	OR	CI 95%	p-value	OR	CI 95%	p-value
Tumor size						
Tis	1	Ref.	Ref.	1	Ref.	Ref.
T1	4.22	0.53-33.96	0.170	--	--	
T2	4.95	0.64-38.47	0.130	--	--	
T3	11.66	1.41-96.59	0.023	7.7	0.88-68.13	0.065
T4	14.28	1.41-144.36	0.024	9.13	0.83-100.96	0.070
Not available	9.99	0.43-228.69	0.150	--	--	
Histology						
Ductal	1	Ref.	Ref.	1	Ref.	Ref.
Non-ductal	2.58	1.29-5.17	0.007	2.58	1.16-5.77	0.020
Smoker status						
Never smoked	1	Ref.	Ref.	1	Ref.	Ref.
Ex-smoker	1.47	0.58-3.71	0.410	1.34	0.41-4.34	0.620
Current smoker	1.33	0.61-9.92	0.470	1.21	0.48-3.03	0.680
Adjuvant radiotherapy	1.72	0.99-3.00	0.050	1.25	0.63-2.46	0.520
Surgical time	1	0.99-1.00	0.640	0.99	0.99-1.02	0.220
Bleeding	1.002	0.9-1.01	0.060	1.01	1.00-1.05	0.025

OR: odds ratio; CI 95%: 95% confidence interval; Tis: carcinoma *in situ*; Ref: reference value.

Table 4. Factors associated to surgical reintervention in patients with breast cancer treated with mastectomy from 2013 to 2016 (n = 306)

	Univariate			Multivariate		
	OR	CI 95%	p-value	OR	CI 95%	p-value
Smoker status						
Never smoked	1	Ref.	Ref.	1	Ref.	Ref.
Ex-smoker	1.96	0.52-7.26	0.32	2.5	0.46-13.47	0.28
Current smoker	1.22	0.33-4.4	0.77	0.97	0.11-7.93	0.98
Adjuvant radiotherapy	1.36	0.55-3.35	0.49	5.38	1.14-25.36	0.03
Procedure						
Prosthetic	1	Ref.	Ref.	1	Ref.	Ref.
Pedicled flap	0.43	0.05-3.60	0.44	1.55	0.14-17.34	0.72
DIEP	4.54	1.73-11.89	0.002	5.58	1.24-25.11	0.2
Surgical time	1.01	1.001-1.01	0.018	1.01	0.99-1.01	0.87
Immediate complications	23.9	8.74-65.39	< 0.001	11.98	2.51-57.18	0.002
Late complications	1.84	1.53-2.22	< 0.001	1.66	1.33-2.09	< 0.001

OR: odds ratio; CI 95%: 95% confidence interval; Ref: reference value; DIEP: deep inferior epigastric perforator flap reconstruction.

with loss of reconstruction and that although the DIEP technique leads to reintervention, it does not correlate with loss of reconstruction. Few studies in Mexico have reported the results of these kinds of patients. A previous work by Drucker et al. reported

an increase in complications in patients with reconstruction that received radiotherapy, concluding that it is a better option to reconstruct with autologous tissue or delay the reconstructive procedure¹¹.

Table 5. Factors associated to loss of reconstruction in patients with breast cancer treated with mastectomy at from 2013 to 2016. (n = 306)

	Univariate			Multivariate		
	OR	CI 95%	p-value	OR	CI 95%	p-value
Smoker status						
Never smoked	1	Ref.	Ref.	1	Ref.	Ref.
Ex-smoker	3.93	1.39-11.1	0.010	16.05	1.607-160.34	0.018
Current smoker	0.69	0.15-3.11	0.630	0.37	0.04-3.36	0.380
Molecular subtype						
Luminal A	1	Ref.	Ref.	1	Ref.	Ref.
Luminal B	1.51	0.50-4.52	0.460	2.53	0.49-12.98	0.120
Her 2+	1.41	0.35-5.57	0.630	0.67	0.82-5.59	0.710
Triple negative	3.86	1.35-2.99	0.010	7.24	1.15-45.68	0.035
Adjuvant radiotherapy	1.72	0.75-3.92	0.190	3.19	0.79-14.50	0.510
Procedure						
Prosthetic	1	Ref.	Ref.	1	Ref.	Ref.
Pedicled flap	0.28	0.06-1.26	0.090	0.81	0.083-7.84	0.850
DIEP	0.29	0.08-1.02	0.050	0.0016	0.0006-0.040	< 0.001
Immediate complications	9.88	4.06-24.05	< 0.001	2.79	0.43-17.84	0.270
Late complications	1.72	1.46-2.02	< 0.001	2.47	1.65-3.67	< 0.001
Reintervention	12.61	4.63-34.29	< 0.001	20.62	1.68-252.34	0.018

OR: odds ratio; CI 95%: 95% confidence interval; Ref: reference value; DIEP: deep inferior epigastric perforator flap reconstruction.

In our study, a total of 22% of the patients had general complications, but with a low percentage of reintervention and loss of reconstruction. Factors associated to general complications where higher intraoperative bleeding and being reintervened. Qin et al. published in 2018 a rate of up to 26.5% of complications, finding a higher rate in patients reconstructed with flaps instead of any other technique. Furthermore, they found no difference in complications such as infection or wound dehiscence. Being overweight was also reported as an independent factor (OR 1.76, CI95% 1.28-2.69) for complications¹². This was not reproduced in our work, however. Other authors, like Ilonzo et al., found in a study that included 25 thousand patients, a higher rate of complications in patients reconstructed with autologous tissue, compared to patients in which prosthetic material was used (tissue expander or definite implant). Complications related to infection or bleeding were not influenced by the reconstructive technique, just like our work has shown. Furthermore, although patients with DIEP flaps presented a higher median bleeding, this had no clinical implications. Nevertheless, in the previously mentioned work, the types of flaps used for reconstruction were not analyzed independently¹³.

Although some publications have found smoking to be a risk factor for complications, we did not reproduce this result, did find it to correlate with loss of the reconstruction.

In addition, some publications, like Ryckie G. Wade, have also found smoking to be unrelated to complications¹⁴. In addition, we observed some other factors that influence complications, such as the triple negative tumors, and some molecular subtypes. These patients requiring more aggressive therapy might explain this, since adjuvant therapy, like radiotherapy, was a factor for reintervention.

Another factor that calls for attention is tumor size, since larger tumors are associated to more complications. An explanation for this is that these patients with larger tumors will require more aggressive therapy. Analyses like that one published by Qin et al. in 2018 showed that adjuvant and neoadjuvant chemotherapy did not increase the risk of complications with an OR of 1.04 (CI95% 0.72-1.43, p = 0.355). As for the demographic characteristics of patients, the same author found that age over 40 years, smoking status, or alcohol consumption have no effect on complications. However, the presence of comorbidities such as type 2 diabetes mellitus or obesity does increase the risk of complications, with respective ORs of 1.28 (CI95% 1.06-1.55, p = 0.043) and 1.76 (CI95% 1.28-2.69, p = 0.25)¹¹. Our study did not find these two comorbidities to be related to complications. Dorsi flaps, which in congruence with published literature, present minimal complications, are a type of useful tissue for rescue surgery of other reconstruction

techniques. It is important to mention, however, that complication can correspond to donor site, receptor, or complications related to mastectomy directly. It is important to take in account that DIEP is a protective factor to avoid the loss of the reconstructive procedure, justifying the reason why it is convenient to increase the number of reconstructive procedures of this type.

Weaknesses of our study are the retrospective nature of the analysis and the heterogeneous characteristics of the cohort, since we have included patients with various types of reconstructions, which were grouped as prosthetic and pedicled. Strengths of our study are the number of patients, one of the largest cohorts in our settings. The factors associated to each type of reconstruction were analyzed independently. In Mexico, there are few centers with the adequate surgical conditions to perform an immediate reconstruction, which makes this information limited in our setting. There are few of these analyses, and the ones available have few patients. Some other variables should be considered in future research, such as distance and time it takes patients to transfer, sociocultural, and economic status.

Conclusion

There is a higher percentage of patients with immediate complications and loss of reconstruction in techniques involving prosthetics, although the patients most likely to be taken to reintervention are the ones with DIEP reconstruction. Among the factors associated to loss of reconstruction are reintervention, and presence of immediate and late complications. DIEP is an alternative with lower probability of loss of reconstruction. Individually, the decision of the best type of reconstruction should be established by a multidisciplinary team, including the reconstructive plastic surgery team. An integral approach to patients whose disease encompasses various specialties could ensure an optimal therapeutic decision and increased quality of life.

Conflicts of interest

Authors declare no conflicts of interest.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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