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RESEARCH ARTICLE

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Neoadjuvant chemotherapy impact on outcomes in immediate breast reconstruction with latissimus dorsi flap and silicone implant

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Abstract

Background and Objectives: Neoadjuvant chemotherapy (NCH) has demonstrated efficacy in downsizing tumors and facilitating less extensive surgery. However, immediate breast reconstruction (IBR) after NCH has raised concerns regarding higher complication rates. This study evaluates the impact of NCH on outcomes following IBR with a latissimus dorsi flap and implant (LDI) after mastectomy.

Methods: Cases from a prospective maintained database were reviewed, and patients classified according to whether or not they received NCH. Risk factors and major and minor complications in both groups were then analyzed.

Results: Among the 196 patients who underwent 198 IBR procedures, 38.4% received NCH and 66.1% did not. The overall complication rate was 46.7% in the non-NCH group and 53.3% in the NCH group ($p = 0.650$). The presence of comorbidities increased the likelihood of any complication (odds ratio [OR]: 3.46; 95% confidence interval [CI]: 1.38–8.66; $p = 0.008$) as well as major complications (OR: 3.35; 95% CI: 1.03–10.95; $p = 0.045$). Although patients in the NCH group experienced more major complications (10.5% vs. 4.9%; $p = 0.134$) and early loss of breast reconstruction (3.9% vs. 0.8%; $p = 0.128$), these findings were not statistically significant.

Conclusion: This study found no statistically significant association between NCH and higher risk of complications or loss of IBR with LDI after mastectomy.

KEYWORDS
breast reconstruction, locally advanced breast cancer, neoadjuvant chemotherapy, outcome

1 | INTRODUCTION

Breast reconstruction (BR) plays a vital role in the management of patients with breast cancer (BC) who undergo radical mastectomy,[1,2] but the safety of immediate breast reconstruction (IBR) in advanced stages of the disease remains under debate.[3] While the oncological safety of IBR has been extensively investigated and established in early-stage BC,[4,5] comprehensive evaluation of outcomes following BC treatment and IBR when neoadjuvant adjuvant treatment is required remains an ongoing topic of discussion within the literature.[6–12]

Previous studies have shown the efficacy of neoadjuvant chemotherapy (NCH) in downstaging tumors and allowing less extensive surgery to address BC.[12–15] Despite these benefits, many patients still

require mastectomy after NCH.[15,16] Although NCH is generally considered safe for patients undergoing IBR, existing studies have primarily focused on surgical outcomes without detailed analysis of risk factors for complications and the impact of NCH on BR following BC treatment. Some clinical series have reported no significant increases in morbidity or complications associated with surgical treatment and IBR after NCH,[10–12,17,18] but these studies often had limited sample sizes and lacked a comprehensive assessment of potential risk factors for complications related to the harmful potential of NCH.

The primary objective of this study was to evaluate the safety of NCH in patients with BC who underwent mastectomy and IBR using the latissimus dorsi flap and implant (LDI) technique; the secondary objective was to identify potential risk factors for surgical complications.

2 | MATERIAL AND METHODS

This retrospective cohort was performed in accordance with the 1964 Declaration of Helsinki and its subsequent amendments. It was approved by the Research Ethics Council (Brazil Platform System, approval no. CAAE: 46253215.2.0000.0072), and adhered to the STROBE guidelines.[19] Informed consent was obtained from all patients on admission to the hospital for use of clinical data for scientific purposes and publication.

Medical records of all women 18 years of age or older, with BC, who had undergone mastectomy followed by IBR in a tertiary teaching hospital from August 1, 2010 to March 31, 2020 were retrospectively reviewed for eligibility.

Patients who had undergone any type of mastectomy (modified radical mastectomy, skin-sparing mastectomy, or nipple-sparing mastectomy) followed by IBR with LDM flap and silicone implant were included in the cohort. Other types of reconstruction were not addressed.

Patients with previous surgery complications, short-term follow-up loss, and incomplete clinical data were excluded. The participants were classified into two groups according to whether or not they received NCH (groups I and II, respectively). Clinical, surgical, and oncological data were collected, including age, body mass index (BMI), clinical diseases, smoking, previous radiation therapy (RT), hospital stay (days), area of skin resection, breast weight, duration of surgery, histological type and grade, tumor size, pathological staging, and immunohistochemistry subtype based on the 2011 St. Gallen Consensus.[20] This information was collected from a dedicated database specifically designed for BC patients to ensure a systematic and prospective approach to data collection. Baseline characteristics of the patients are presented in Tables 1 and 2.

NCH regimens followed institutional protocols; the most common regimens were 4 cycles of doxorubicin and cyclophosphamide every 14 or 21 days, followed by 4 cycles of docetaxel every 21 days or 12 cycles of paclitaxel every 7 days. Patients with amplification of the HER2 gene received targeted therapy for 12 months. The time elapsed between NCH completion and date of surgery was divided into three groups: <4 weeks, 5–8 weeks, and >8 weeks (Table 3).

Surgical complications were classified as minor (treatable on an outpatient basis) or major (requiring a prolonged hospital stay or readmission). Data on surgical site infection, skin dehiscence, dorsal seroma, hematoma, mastectomy skin flap necrosis, latissimus dorsi flap (LD) necrosis, early loss of BR, and clinical complications related to the surgical procedure were collected before adjuvant treatment initiation.

2.1 | Statistical analysis

Quantitative variables were presented as means, medians, standard deviation, and quartiles, while qualitative variables were presented as absolute and relative frequencies. The association between qualitative variables was assessed using Pearson's chi-squared test or Fisher's exact test, and quantitative variables were analyzed using Student's *t*-test or the Mann–Whitney test. Univariate and multiple binary logistic regression were used to evaluate factors associated with complications and calculating odds ratios and 95% confidence intervals. The final models were constructed using the backward stepwise method, initially including all variables (complete model) and subsequently eliminating nonsignificant variables. The models were adjusted for the primary variable (NCH) and age, and their validity was assessed by constructing a receiver operating characteristic (ROC) curve and calculating the area under the curve (AUC). The significance level was considered to be 5%, and the analyses were performed using SPSS v.25 and Stata/MP 14.0 for Windows software.

2.1.1 | Propensity score matching

Propensity score matching was used to estimate the association between NCH and the early outcomes. To minimize selection bias in this retrospective study, 1:1 matching was performed according to four related covariates (age, histological grade, grouped staging, and immunohistochemistry subtype) to generate propensity scores, and calculated via logistic regression model; this was followed by nearest neighbor matching with a match tolerance of 0.2. Standardized differences between both groups of no more than 20% were accepted. Surgical outcomes were then investigated between the two matched cohorts.

3 | RESULTS

A total of 205 BC patients were initially screened: 196 (95.6%) met the inclusion criteria and 9 (4.4%) were excluded. The study population consisted of 76 patients (38.4%) in Group I (NCH) and 122 patients (61.6%) in Group II (no NCH) (Figure 1). The mean follow-up duration for both groups was 51.4 months, with a minimum

TABLE 1 Demographics, risk factors, and surgical aspects of patients undergoing breast reconstruction with and without neoadjuvant chemotherapy.

Characteristics	Neoadjuvant chemotherapy		Total	p value
	No	Yes		
	n = 122	n = 76	n = 198	
	n (%)	n (%)	n (%)	
Age				**0.007**[a]
Mean (SD)	46.8 (10.2)	42.8 (10.2)	45.2 (10.3)	
Median (Q_1–Q_3)	47 (39–53)	42.5 (34.5–49)	45 (37.8–53)	
BMI (kg/m^2)				0.857[b]
Normal	47 (38.5)	32 (42.1)	79 (39.9)	
Overweight	46 (37.7)	26 (34.2)	72 (36.4)	
Obese	29 (23.8)	18 (23.7)	47 (23.7)	
Hypertension				0.337[b]
No	96 (78.7)	64 (84.2)	160 (80.8)	
Yes	26 (21.3)	12 (15.8)	38 (19.2)	
Diabetes mellitus				0.139[b]
No	108 (88.5)	72 (94.7)	180 (90.9)	
Yes	14 (11.5)	4 (5.3)	18 (9.1)	
Tobacco use				0.645[b]
No	113 (92.6)	69 (90.8)	182 (91.9)	
Yes	9 (7.4)	7 (9.2)	16 (8.1)	
Previous radiation therapy				0.054[b]
No	110 (90.2)	74 (97.4)	184 (92.9)	
Yes	12 (9.8)	2 (2.6)	14 (7.1)	
Comorbities				0.666[c]
Up to 1 comorbidity	100 (82.0)	65 (85.5)	165 (83.3)	
2–3 comorbidities	20 (16.4)	11 (14.5)	31 (15.7)	
More than 3 comorbidities	2 (1.6)	0	2 (1.0)	
Hospital stay (days)				0.211[d]
Mean (SD)	2.2 (0.6)	2.4 (2.5)	2.2 (1.6)	
Median (Q_1–Q_3)	2 (2–2)	2 (2–2)	2 (2–2)	
Breast skin resection (cm^2)				**0.006**[d]
Mean (SD)	53.7 (49.8)	72.3 (67.3)	60.9 (57.7)	
Median (Q_1–Q_3)	38.6 (19.6–72.3)	50.2 (36.5–85.2)	45.3 (25.1–75.4)	
NSM	4 (3.3)	0	4 (2.0)	**0.026**[c]
SSM	57 (46.7)	25 (32.9)	82 (41.4)	
Mastectomy	61 (50.0)	51 (67.1)	112 (56.6)	
Surgical specimen weight (g)				0.757[d]
Mean (SD)	509.0 (235.1)	541.0 (287.4)	521.3 (256.2)	
Median (Q_1–Q_3)	470 (345–651)	480 (315–680)	470 (337.5–662.5)	
Implant weight				0.816[d]
Mean (SD)	372.3 (99.6)	367.5 (89.5)	370.5 (95.6)	
Median (Q_1–Q_3)	370 (290–445)	372.5 (320–435)	370 (597.5–445)	

TABLE 1 (Continued)

Characteristics	Neoadjuvant chemotherapy: No *n* = 122 *n* (%)	Neoadjuvant chemotherapy: Yes *n* = 76 *n* (%)	Total *n* = 198 *n* (%)	*p* value
Surgery duration (hours)				0.400[d]
Mean (SD)	5.6 (1.1)	5.7 (1.0)	5.6 (1.0)	
Median (Q_1–Q_3)	5.5 (5–6)	5.6 (5–6.4)	5.5 (5–6)	
Normal (<7 h)	104 (85.2)	66 (86.8)	170 (85.9)	0.601[b]
Prolonged (≥7 h)	18 (14.8)	10 (13.2)	28 (14.1)	
Oncological surgery type				<0.001[c]
Mastectomy	6 (4.9)	2 (2.6)	8 (4.0)	
Mastectomy and ALNB	62 (50.8)	15 (19.7)	77 (38.9)	
Mastectomy and ALND	51 (41.8)	56 (73.7)	107 (54.0)	
Mastectomy. ALND, and CPM	3 (2.5)	3 (3.9)	6 (3.0)	

Note: Bold values indicates statistically significant at $p < 0.05$.

Abbreviations: ALNB, axillary lymph node biopsy; ALND, axillary lymph node dissection; BMI, body mass index; CPM, contralateral prophylactic mastectomy; NSM, nipple-sparing mastectomy; SSM, skin-sparing mastectomy; Q1, first quartile; Q3, third quartile.

[a]Student's *t*-test.

[b]Pearson's chi-squared test.

[c]Fisher's exact test.

[d]Mann–Whitney test.

period of 3 months to collect data on early complications (Tables 2 and 3).

3.1 | Clinical and oncological aspects

Patients in the NCH group were significantly younger (mean age 42.8 vs. 46.8 years; $p = 0.007$) with more advanced oncological stage at diagnosis as well as more aggressive immunohistochemistry features compared to the patients in the non-NCH group. The remaining variables were similar between the two groups (Tables 1 and 2). Most patients in Group I (89%) received NCH protocols involving doxorubicin and cyclophosphamide followed by taxane. The median interval between the completion of chemotherapy and surgery was 36 days, and 14 patients (18.4%) underwent surgery after more than 8 weeks (Table 3).

3.2 | Surgical aspects

The average surgical duration was 5.5 h, with no significant difference observed between the groups ($p = 0.400$). Fourteen percent of the surgeries lasted 7 h or more, which was defined as prolonged surgical time (exceeding 1 SD above the mean). The prevalence of prolonged surgical time did not differ significantly between Group I and Group II ($p = 0.601$). Patients in Group I had higher rates of modified radical mastectomy ($p = 0.026$), axillary lymph node dissection ($p < 0.001$), and a larger area of breast skin resection ($p = 0.006$) compared to Group II (Table 1).

3.3 | Postoperative complications and risk factors

The overall complication rate (major and minor) was 46.7% for Group II and 53.3% for Group I ($p = 0.650$). In the univariate analysis, higher BMI ($p = 0.029$), diabetes ($p = 0.038$), and number of comorbidities ($p = 0.007$) were identified as statistically significant risk factors (Table 4). In the multiple regression analysis, number of comorbidities was the only factor that increased the likelihood of overall complications (Table 5). Forty-five percent of patients experienced no early complications, 40.4% had one complication, 12.1% had two complications, and 2% had three complications. The incidences of minor and major complications were 63.3% and 7.1%, respectively. The most common complication was seroma at the LD donor site, observed in 33.3% of cases, followed by wound dehiscence (16.2%) and mastectomy skin flap necrosis (12.6%). In the univariate analysis, no statistically significant risk factors for the occurrence of dorsal seroma were identified. However, in the multiple analysis, being overweight was found to increase the chance of this complication 2.04-fold (OR: 2.04, 95% CI: 1.01–4.13; $p = 0.047$) (Table 5). With regard to mastectomy skin flap necrosis, NCH was not identified as a significant risk factor in the univariate analysis, while hypertension ($p = 0.031$), diabetes ($p = 0.014$), smoking ($p = 0.035$), number of comorbidities ($p = 0.002$), previous RT ($p = 0.019$), area of breast skin resection ($p = 0.021$), and prolonged surgical time ($p = 0.012$) were found to be

TABLE 2 Oncological aspects of patients undergoing breast reconstruction with and without neoadjuvant chemotherapy.

Characteristic	Neoadjuvant chemotherapy: No *n* = 122 *n* (%)	Neoadjuvant chemotherapy: Yes *n* = 76 *n* (%)	Total *n* = 198 *n* (%)	*p* Value
Histological type				**0.001**[a]
IDC	95 (77.9)	69 (90.8)	164 (82.8)	
DCIS	18 (14.8)	0	18 (9.1)	
ILC	8 (6.6)	6 (7.9)	14 (7.1)	
Other	1 (0.8)	1 (1.3)	2 (1.0)	
Histological grade				**<0.001**[b]
G1	10 (9.6)	3 (3.9)	13 (7.2)	
G2	77 (74.0)	37 (48.7)	114 (63.3)	
G3	17 (16.3)	36 (47.4)	53 (29.4)	
Tumor size (mm)				**<0.001**[c]
Mean (SD)	25.0 (15.9)	43.3 (21.9)	32.0 (20.5)	
Median (Q_1–Q_3)	22 (15–30)	40 (30–55)	27 (19.8–40)	
Stage (AJCC)				**<0.001**[a]
0	17 (13.9)	0	17 (8.6)	
I	30 (24.6)	0	30 (15.2)	
II	48 (39.3)	35 (46.1)	83 (41.9)	
III	26 (21.3)	40 (52.6)	66 (33.3)	
IV	1 (0.8)	1 (1.3)	2 (1.0)	
Estrogen receptor				**0.005**[b]
No	27 (22.1)	31 (40.8)	58 (29.3)	
Yes	95 (77.9)	45 (59.2)	140 (70.7)	
Progesterone receptor				**0.024**[b]
No	34 (27.9)	33 (43.4)	67 (33.8)	
Yes	88 (72.1)	43 (56.6)	131 (66.2)	
HER-2				0.634[b]
Negative	92 (75.4)	55 (72.4)	147 (74.2)	
Positive	30 (24.6)	21 (27.6)	51 (25.8)	
Immunohistochemistry subtype				**<0.001**[b]
Luminal A	32 (26.7)	12 (15.8)	44 (22.4)	
Luminal B HER-2−	54 (45.0)	22 (28.9)	76 (38.8)	
Luminal B HER-2+	15 (12.5)	14 (18.4)	29 (14.8)	
HER-2+	12 (10.0)	6 (7.9)	18 (9.2)	
HR−. HER2−	7 (5.8)	22 (28.9)	29 (14.8)	

Note: Bold values indicates statistically significant at $p < 0.05$.

Abbreviations: DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; Q1, first quartile; Q3, third quartile.

[a]Fisher's exact test.

[b]Pearson's chi-squared test.

[c]Mann–Whitney's test.

TABLE 3 Neoadjuvant chemotherapy (NCH) characteristics.

Characteristics	*n* = 76	*n* (%)
Time to surgery after NCH (days)		
Mean (SD)	43.8 (27.3)	
Median (Q_1–Q_3)	36 (27–48)	
≤4 weeks		21 (27.6)
5–8 weeks		41 (53.9)
>8 weeks		14 (18.4)
Type of NCH		
ACT		65 (89.0)
Without anthracycline		3 (4.1)
Only anthracycline		2 (2.7)
Other		3 (4.1)

Abbreviations: ACT, anthracycline, cyclophosphamide, and taxane; NCH, neoadjuvant chemotherapy; Q1, first quartile; Q3, third quartile.

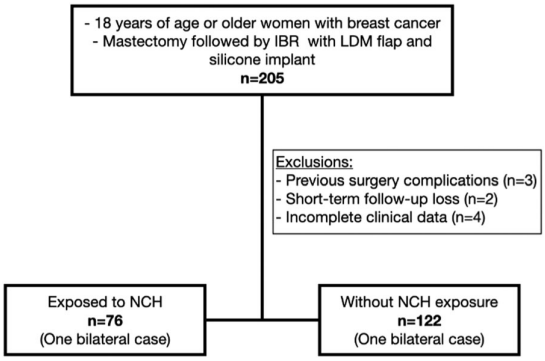

FIGURE 1 Flowchart for study participants (196 patients; *n* = 198 breasts).

statistically significant. In the multiple regression model, smokers, patients with diabetes, and patients who previously underwent RT had a greater chance of mastectomy skin flap necrosis ($p < 0.05$), and patients subjected to prolonged surgery (≥7 h) were 5.15 times more likely to experience this complication (Table 5). No statistically significant risk factors for wound dehiscence were observed in the univariate analysis, but the multiple regression model showed that patients with hypertension were 3.31 times more likely to experience this outcome (Table 5).

Major complications included six cases (3%) of hematoma requiring reoperation, four cases (2%) of infection requiring intravenous antibiotic therapy, three of which (1.5%) progressed to implant extrusion. Three cases (1.5%) of mastectomy flap necrosis required debridement, and one case (0.5%) of latissimus dorsi necrosis required debridement and implant removal. There was no statistically significant difference in the incidence of major complications between Group I and Group II (10.5%

TABLE 4 Overall major and minor surgical complications in patients undergoing breast reconstruction.

	Complication		
	No	Yes	
	n = 90	*n* = 108	
Characteristics	*n* (%)	*n* (%)	*p* Value
Age			
Mean (SD)	44.9 (10.3)	45.5 (10.4)	0.670[a]
Median (Q_1–Q_3)	44 (38–52)	46.5 (37–53)	
BMI (kg/m^2)			
Mean (SD)	26.0 (4.1)	27.4 (4.5)	**0.029**[b]
Median (Q_1–Q_3)	25.8 (23.3–27.8)	27.3 (23.9–30.5)	
Normal	40 (50.6)	39 (49.4)	**0.047**[c]
Overweight	36 (50.0)	36 (50.0)	
Obese	14 (29.8)	33 (70.2)	
Hypertension			
No	78 (48.8)	82 (51.2)	0.056[c]
Yes	12 (31.6)	26 (68.4)	
Diabetes mellitus			
No	86 (47.8)	94 (52.2)	**0.038**[c]
Yes	4 (22.2)	14 (77.8)	
Tobacco use			
No	84 (46.2)	98 (53.8)	0.505[c]
Yes	6 (37.5)	10 (62.5)	
Radiation therapy			
No	85 (46.2)	99 (53.8)	0.448[c]
Yes	5 (35.7)	9 (64.3)	
Comorbidities			
<2	82 (49.7)	83 (50.3)	**0.007**[c]
2 or more	8 (24.2)	25 (75.8)	
Breast skin resection			
NSM	1 (25.0)	3 (75.0)	0.801[d]
SSM	38 (46.3)	44 (53.7)	
Mastectomy	51 (45.5)	61 (54.5)	
Surgery duration (hours)			
Normal (<7 h)	79 (46.5)	91 (53.5)	0.479[c]
Prolonged (≥7 h)	11 (39.3)	17 (60.7)	
Oncological surgery type			
Mastectomy	3 (37.5)	5 (62.5)	0.868[d]
Mastectomy and ALNB	37 (48.1)	40 (51.9)	
Mastectomy and ALND	48 (44.9)	59 (55.1)	

(Continues)

TABLE 4 (Continued)

Characteristics	Complication No *n* = 90 *n* (%)	Complication Yes *n* = 108 *n* (%)	*p* Value
Mastectomy, ALND, and CPM	2 (33.3)	4 (66.7)	
Surgical specimen weight (g)			
Mean (SD)	482.1 (235.8)	554.0 (268.7)	0.127[b]
Median (Q_1–Q_3)	450 (294–650)	485 (348–693)	
NCH			
No	57 (46.7)	65 (53.3)	0.650[c]
Yes	33 (43.4)	43 (56.6)	

Note: Bold values indicates statistically significant at $p < 0.05$.
Abbreviations: ALNB, axillary lymph node biopsy; ALND, axillary lymph node dissection; BMI, body mass index; CPM, contralateral prophylactic mastectomy; NSM, nipple-sparing mastectomy; SSM, skin-sparing mastectomy; Q1, first quartile; Q3, third quartile.
[a]Student's *t*-test.
[b]Mann–Whitney test.
[c]Pearson's chi-squared test.
[d]Fisher's exact test.

vs. 4.9%; $p = 0.134$). Four cases (2.0%) of clinical complications were observed in the early postoperative period: one case each of anemia requiring transfusion, non-dialysis acute renal failure, deep vein thrombosis, and intestinal pseudo-obstruction.

3.4 | Failure of reconstruction

A total of four IBR failures was observed in the entire population. In Group I, three implants (3.9%) had to be removed due to complications, while in Group II one implant (0.8%) failed. The rate of IBR failure did not show a significant difference between the two groups ($p = 0.128$).

3.5 | Propensity score matching

After constructing the propensity scores using binary logistic regression, 40 pairs ($n = 80$) were obtained. Characteristics after pairing were customized as shown in Table 6a. No statistically significant association was found between NCH and dorsal seroma, mastectomy skin necrosis, skin dehiscence, any complication, major complication, or minor complication (Table 6b).

4 | DISCUSSION

NCH has shown promise in reducing tumor size and metastasis risk. Current indications for this therapy have expanded to include treatment of early stages of BC.[12,13] Several studies have shown

TABLE 5 Risk factors related to complications.

Characteristics	$OR_{adjusted}$ (CI 95%)	*p* Value
Overall surgical complications		
Age (years)	0.99 (0.96–1.02)	0.552
Comorbidities (ref: <2 comorbidities)	3.46 (1.38–8.66)	**0.008**
NCH (ref: No)	1.15 (0.64–2.10)	0.638
Dorsal seroma		
Age (years)	1.01 (0.98–1.04)	0.476
BMI (kg/m^2) (ref: Normal)		
Overweight	2.04 (1.01–4.13)	**0.047**
Obese	2.14 (0.98–4.68)	**0.057**
NCH (ref: No)	1.39 (0.74–2.61)	0.300
Mastectomy skin flap necrosis		
Age (years)	1.02 (0.97–1.07)	0.443
Diabetes mellitus (ref: No)	4.59 (1.34–15.74)	**0.016**
Tobacco use (ref: No)	5.07 (1.44–17.86)	**0.012**
Radiation therapy (ref: No)	4.57 (1.21–17.29)	**0.025**
Surgery duration (ref: Normal < 7 h)		
Prolonged (≥7 h)	5.15 (1.74–15.29)	**0.003**
NCH (ref: No)	0.79 (0.28–2.22)	0.659
Wound dehiscence		
Age (years)	0.97 (0.92–1.01)	0.113
Hypertension (ref: No)	3.31 (1.21–9.05)	**0.020**
NCH (ref: No)	0.74 (0.32–1.70)	0.477
Major complication		
Comorbidities (ref: <2 comorbidities)	3.35 (1.03–10.95)	**0.045**
NCH (ref: No)	2.46 (0.80–7.53)	0.115

Note: Bold values indicates statistically significant at $p < 0.05$.
Abbreviations: BMI, body mass index; NCH, neoadjuvant chemotherapy.

NCH comparable to adjuvant chemotherapy in terms of overall survival and disease-free survival rates.[15,21] Yet the impact of NCH on postoperative morbidity, particularly in relation to IBR, remains under debate. Some surgeons have hypothesized that NCH significantly increases postoperative complications, based on their personal experience. Our study consequently investigated different surgical outcomes in patients who received NCH compared to those who underwent the same surgical procedure without prior chemotherapy. Potential risk factors for surgical complications were also explored. To minimize potential biases associated with different IBR techniques, we specifically focused on patients who underwent mastectomy and IBR with LDI.

Chemotherapy in general can interfere with the normal process of wound healing. Previous research from experimental and clinical

TABLE 6a Variables considered for analysis after pairing.

Characteristics	Neoadjuvant chemotherapy Yes *n* = 40 *n* (%)	Neoadjuvant chemotherapy No *n* = 40 *n* (%)	Total *n* = 80 *n* (%)	*p* Value
Age				0.842[a]
Mean (SD)	45.1 (9.8)	45.5 (9.2)	45.3 (9.5)	
Median (Q_1–Q_3)	46 (38–51.5)	44.5 (38–52.5)	45.5 (38–52)	
Histological grade				0.999[b]
G1	4 (10.0)	3 (7.5)	7 (8.8)	
G2	25 (62.5)	26 (65.0)	51 (63.8)	
G3	11 (27.5)	11 (27.5)	22 (27.5)	
Stage (AJCC)				0.822[c]
I–II	22 (55.0)	23 (57.5)	45 (56.3)	
III–IV	18 (45.0)	17 (42.5)	35 (43.8)	
Immunohistochemistry subtype				0.827[b]
Luminal A	12 (30.0)	9 (22.5)	21 (26.3)	
Luminal B HER-2−	15 (37.5)	17 (42.5)	32 (40.0)	
Luminal B HER-2+	5 (12.5)	7 (17.5)	12 (15.0)	
HER-2+	4 (10.0)	2 (5.0)	6 (7.5)	
HR−. HER2−	4 (10.0)	5 (12.5)	9 (11.3)	

[a]Student's *t*-test.
[b]Fisher's exact test.
[c]Pearson's chi-squared test.

studies suggests that chemotherapy may hinder early matrix formation, reduce collagen production, and impair fibroblast proliferation.[22–24] Animal experiments have shown that NCH leads to decreased wound breaking strength at 2 weeks[23]; clinical studies have similarly associated NCH with prolonged wound healing and complications after abdominoperineal resection.[24] However, some authors investigating IBR have reported similar rates of wound and overall complications in patients who received NCH and those who did not.[25] Despite these findings, concerns have been raised about IBR in patients treated with NCH.[11,25,26] Mitchem et al. found a higher risk of tissue expander extrusion in patients exposed to NCH compared to those who did not receive chemotherapy.[11] In a comprehensive analysis of 1195 BR procedures, Mehrara et al. observed an increase in wound healing problems and fat necrosis in patients who underwent NCH.[26] A meta-analysis by Verghese et al. concluded that although IBR is generally safe in patients exposed to NCH, subgroup analysis revealed an elevated rate of alloplastic implant extrusion in patients undergoing NCH (RR: 1.54; 95% CI: 1.04–2.26; $p = 0.03$).[25]

Our findings are in line with the existing literature. In our series, 54% of patients experienced overall surgical complications in the early postoperative period, with 7.1% classified as major complications. Only 2% of cases resulted in complete loss of IBR. While exposure to NCH did not emerge as a statistically significant risk factor for overall complications ($p = 0.650$) or major complications ($p = 0.134$), patients who underwent NCH showed higher rates of major complications (10.5% vs. 4.9%; $p = 0.134$) and early loss of BR (3.9% vs. 0.8%; $p = 0.128$), even though this finding did not achieve statistical significance (potentially attributed to insufficient statistical power in the study). Conversely, the number of comorbidities was associated with a 3.46-times higher risk of overall complications and a 3.35-fold increase in the likelihood of major complications.

In terms of outcomes, rates of complications and early loss of BR varied significantly in previous studies, with no established risk factors[27–29]: Pinsolle et al. observed at least one complication in 52% of IBR with LDI and reconstruction loss rate of 2.5%,[27] while Wilkins et al. reported early complications in 42.5% of IBR with LDI and an early loss rate of 2.7%.[28] Factors such as bilateral surgery, older age, and BMI > 30 were associated with overall and major complications, while chemotherapy (neoadjuvant or adjuvant) and radiation therapy did not increase the risk of complications.[28] Fisher et al. also identified obesity, smoking, American Society of Anesthesiologists Classification (ASA) > 2, and prolonged surgical time as significant risk factors for complications related to BR.[29]

In our series, the most frequently observed complication of IBR with LDI was dorsal seroma, which significantly impacted the overall complication rate. Reported rates of donor site seroma associated with LD BR vary widely, ranging from 7.6% to 53.6%[12,27,29–33]; this

TABLE 6b Association between neoadjuvant chemotherapy and outcome.

Characteristics	Neoadjuvant chemotherapy Yes *n* = 40 *n* (%)	No *n* = 40 *n* (%)	Total *n* = 80 *n* (%)	*p* Value
Dorsal seroma				
No	26 (65.0)	29 (72.5)	55 (68.8)	0.469[a]
Yes	14 (35.0)	11 (27.5)	25 (31.3)	
Mastectomy skin necrosis				0.999[b]
No	36 (90.0)	36 (90.0)	72 (90.0)	
Yes	4 (10.0)	4 (10.0)	8 (10.0)	
Skin dehiscence				0.793[a]
No	30 (75.0)	31 (77.5)	61 (76.3)	
Yes	10 (25.0)	9 (22.5)	19 (23.8)	
Any complication				0.822[a]
No	17 (42.5)	18 (45.0)	35 (43.8)	
Yes	23 (57.5)	22 (55.0)	45 (56.3)	
Major complication				0.201[b]
No	39 (97.5)	35 (87.5)	74 (92.5)	
Yes	1 (2.5)	5 (12.5)	6 (7.5)	

[a]Pearson's chi-squared test.
[b]Fisher's exact test.

variation likely stems from use of different diagnostic methods which in turn over- or underestimate this complication. Dorsal seroma occurred in approximately 33% of our sample and was considered when patients required at least one aspiration puncture for treatment. Fortunately, all cases could be managed conservatively without the need for hospitalization or reoperation. Our findings correspond with the literature, which did not find NCH to be a significant risk factor for dorsal seroma ($p = 0.408$). Furthermore, we identified a significant association between higher BMI and the occurrence of this outcome ($p = 0.025$), in line with previous studies.[30]

Mastectomy skin flap necrosis is a relatively common complication associated with IBR, and occurs more frequently in skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM).[5,28–30,32,34–36] Reported rates of this complication in the literature range from 3.6% to 21.6%, with no clearly established risk factors.[5] Peled et al. conducted a prospective study involving 428 patients who underwent NSM with various IBR techniques (81% tissue expanders) and observed that 11.9% developed mastectomy skin flap necrosis.[36] Losken et al. published a series of bilateral mastectomy (77% SSM) and IBR with LDI and found that previous RT was the only significant risk factor for mastectomy skin flap necrosis.[37] In our cohort, mastectomy skin flap necrosis occurred in 12.6% of cases; the multivariate analysis determined that diabetes, smoking, previous RT, and prolonged surgical time were associated with an increased likelihood of experiencing this complication.

As mentioned previously, greater risk of complications associated with the healing process is a significant concern for patients undergoing NCH. Previous series have reported complication rates ranging from 1.4% to 13%, with no established risk factors.[25,30] In the present study, exposure to NCH was not significantly associated with increased risk of wound dehiscence, but hypertension emerged as a significant risk factor for the occurrence of this outcome in the multiple regression model.

The optimal interval between NCH and surgery remains a subject of debate in the literature, as large randomized clinical trials addressing this issue are unlikely due to ethical concerns. In clinical practice, surgery is typically performed at the end of the cytotoxic window, generally between 3 and 4 weeks after the final chemotherapy cycle.[4,6–10,38,39] Sanford et al. observed poorer oncological outcomes in patients who underwent surgery 8 weeks after their last NCH session.[38] Similarly, a meta-analysis by Cullinane et al. determined that patients who underwent surgery within 8 weeks after their final NCH cycle had better overall and disease-free survival, and observed no survival benefit when the interval between NCH and surgery was less than 4 weeks.[39] In our cohort, the median interval between the last chemotherapy cycle and surgery was 36 days, with 14 patients (18%) undergoing surgery after more than 8 weeks. Factors specific to IBR (such as additional consultations with the plastic surgery team and institutional availability of plastic surgeons and operating rooms) may contribute to delays in the surgical timeline, as noted by Kupsta et al.[40]

The present study has some limitations that should be considered. First, it is a single-center study based on a retrospective analysis of a prospective maintained database. While retrospective cohort studies offer cost advantages, they are susceptible to biases, underestimation of risks, and limitations related to sample selection and statistical power. In terms of postoperative outcomes, however, this present cohort benefited from the consistent surgical technique performed by the same team, which also facilitated follow-up. Additionally, the data were analyzed by two observers, making it less likely that events and complications would be underestimated. All patients had sufficient follow-up for data collection, since the main objective was to evaluate early complications and reoperations. Furthermore, as noted by some authors, indicating NCH inherently creates two heterogeneous groups for statistical analysis[8,25]: patients who undergo NCH often have larger and more aggressive tumors, and are typically younger and healthier women who can better tolerate the side effects of this treatment. For this reason, it can be challenging or even impossible to find two comparable groups, representing another limitation of this study, although we implemented propensity score matching analysis in an attempt to mitigate selection bias. Lastly, it is important to acknowledge that the lack of statistical significance for less frequent outcomes (such as major complications and early IBR losses) could be attributed to the limited sample power.

The strengths of the present study include a solely oncological patient population undergoing the same IBR technique after mastectomy, with distinct risk factors. Data are limited on risk factors and complication rates in patients undergoing IBR with LDI, and even scarcer for patients who receive NCH before this specific BR technique. Our series represents one of the largest samples evaluating early outcomes in this field, which is particularly relevant given the limited data on a widely used BR technique in clinical practice, especially in middle- and low-income countries, where the availability of hospitals equipped to undertake advanced IBR procedures like microsurgeries is limited. Finally, this study also provides valuable insights that could potentially inform discussions with patients regarding the appropriateness of IBR and the optimal sequence within the NCH scenario.

5 | CONCLUSIONS

In this specific cohort, exposure to NCH was not found to be a statistically significant risk factor for increased rates of early surgical complications or loss of IBR with LDI after mastectomy, suggesting that this procedure can be safely performed. However, it should be noted that patients with a history of NCH experienced more major complications and early loss of IBR, although this difference did not reach statistical significance. Nevertheless, the findings indicate that patients with two or more comorbidities are more likely to experience overall and major complications.

AUTHOR CONTRIBUTIONS

Gabriel Salum D'Alessandro and **Fabiana Midori Takeuchi**: Data collection, data analysis or interpretation, and writing the paper. **Alexandre Mendonça Munhoz**: Data analysis or interpretation, writing the paper. **João Carlos Sampaio Góes** and **Alejandro Povedano**: Data analysis or interpretation

CONFLICT OF INTEREST STATEMENT

Alexandre Mendonça Munhoz serves as a consultant/board member for Establishment Labs, Holdings, Inc., but received no financial support or assistance in the preparation of this article. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Newman LA, Kuerer HM, Hunt KK, et al. Feasibility of immediate breast reconstruction for locally advanced breast cancer. *Ann Surg Oncol*. 1999;6:671-675.
2. Gieni M, Avram R, Dickson L, et al. Local breast cancer recurrence after mastectomy and immediate breast reconstruction for invasive cancer: a meta-analysis. *Breast*. 2012;21:230-236.
3. Taqi K, Pao JS, Chen L, et al. Immediate breast reconstruction in locally advanced breast cancer: is it safe? *Breast Cancer Res Treat*. 2021;190(2):175-182.
4. Taylor CW, Horgan K, Dodwell D. Oncological aspects of breast reconstruction. *Breast*. 2005;14:118-130.
5. Munhoz AM, Montag E, Filassi JR, Gemperli R. Immediate nipple-areola-sparing mastectomy reconstruction: an update on oncological and reconstruction techniques. *World J Clin Oncol*. 2014;5(3):478-494.
6. Decker MR, Greenblatt DY, Havlena J, Wilke LG, Greenberg CC, Neuman HB. Impact of neoadjuvant chemotherapy on wound complications after breast surgery. *Surgery*. 2012;152:382-388.
7. Bowen ME, Mone MC, Buys SS, Sheng X, Nelson EW. Surgical outcomes for mastectomy patients receiving neo-adjuvant chemotherapy: a propensity-matched analysis. *Ann Surg*. 2017;265:448-456.
8. Song J, Zhang X, Liu Q, et al. Impact of neoadjuvant chemo-therapy on immediate breast reconstruction: a meta-analysis. *PLoS One*. 2014;9:e98225.
9. Cohen O, Lam G, Choi M, Karp N, Ceradini D. Does the timing of chemotherapy affect post-mastectomy breast reconstruction complications? *Clin Breast Cancer*. 2017;17:307-315.
10. Hu YY, Weeks CM, In H, et al. Impact of neoadjuvant chemotherapy on breast reconstruction. *Cancer*. 2011;117:2833-2841.
11. Mitchem J, Herrmann D, Margenthaler JA, Aft RL. Impact of neoadjuvant chemotherapy on rate of tissue expander/implant loss and progression to successful breast reconstruction following mastectomy. *Am J Surg*. 2008;196:519-522.
12. D'Alessandro GS, Povedano A, dos Santos LKIL, Munhoz AM, Gemperli R, de Sampaio Góes JC. Effect of neoadjuvant chemotherapy on women undergoing breast cancer surgery and immediate breast reconstruction with latissimus dorsi flap and silicone implants. *Eur J Plast Surg*. 2017;40(4):299-308.
13. Kaufmann M, Hortobagyi GN, Goldhirsch A, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. *J Clin Oncol*. 2006;24:1940-1949.
14. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO guideline. *J Clin Oncol*. 2021;39(13):1485-1505.
15. Alberro JA, Ballester B, Deulofeu P, et al. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomized trials. *Lancet Oncol*. 2018;19(1):27-39.
16. Grigor EJM, Stein MJ, Arnaout A, Ghaedi B, Ramsay T, Zhang JJ. The effect of neoadjuvant chemotherapy on safety outcomes following immediate breast reconstruction. *J Plast Reconstr Aesthet Surg*. 2022;75(8):2520-2525.
17. Azzawi K, Ismail A, Earl H, Forouhi P, Malata CM. Influence of neoadjuvant chemotherapy on outcomes of immediate breast reconstruction. *Plast Reconstr Surg*. 2010;126(1):1-11.
18. Warren Peled A. Impact of chemotherapy on postoperative complications after mastectomy and immediate breast reconstruction. *AArch Surg*. 2010;145(9):880-885.
19. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453-1457.
20. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ. Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert

Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol*. 2011;22(8):1736-1747.
21. Mauri D, Polyzos NP, Salanti G, Pavlidis N, Ioannidis JPA. Multiple-treatments meta-analysis of chemotherapy and targeted therapies in advanced breast cancer. *J Natl Cancer Inst*. 2008;100(24):1780-1791.
22. Guo S, DiPietro LA. Factors affecting wound healing. *J Dent Res*. 2010;89(3):219-229.
23. Mullen BM, Mattox DE, Von Hoff DD, Hearne EM. The effect of preoperative adriamycin and dihydroxyanthracenedione on wound healing. *Laryngoscope*. 1981;91(9):1436-1443.
24. Althumairi AA, Canner JK, Gearhart SL, Safar B, Sacks J, Efron JE. Predictors of perineal wound complications and prolonged time to perineal wound healing after abdominoperineal resection. *World J Surg*. 2016;40(7):1755-1762.
25. Varghese J, Gohari S, Faheem M, Kümmel S, Johnson L, Schmid P. A systematic review and meta-analysis on the effect of neoadjuvant chemotherapy on complications following immediate breast reconstruction. *Eur J Surg Oncol*. 2021;47(1):e1.
26. Mehrara BJ, Santoro TD, Arcilla E, Watson JP, Shaw WW, Da Lio AL. Complications after microvascular breast reconstruction: experience with 1195 flaps. *Plast Reconstr Surg*. 2006;118(5):1100-1109.
27. Pinsolle V, Grinfeder C, Mathoulin-Pelissier S, Faucher A. Complications analysis of 266 immediate breast reconstructions. *J Plast Reconstr Aesthet Surg*. 2006;59(10):1017-1024.
28. Wilkins EG, Hamill JB, Kim HM, et al. Complications in postmastectomy breast reconstruction: one-year outcomes of the mastectomy reconstruction outcomes consortium (MROC) study. *Ann Surg*. 2018;267(1):164-170.
29. Fischer JP, Nelson JA, Au A, CT T, Serletti JM, Wu LC. Complications and morbidity following breast reconstruction—a review of 16,063 cases from the 2005-2010 NSQIP datasets. *J Plast Surg Hand Surg*. 2014;48(2):104-114.
30. Munhoz A, Aldrighi C, Montag E, et al. Periareolar skin-sparing mastectomy and latissimus dorsi flap with biodimensional expander implant reconstruction: surgical planning, outcome and complications. *Plast Reconstr Surg*. 2007;119(6):1637-1649.
31. Munhoz A, Montag E, Fels KW, et al. Outcome analysis of breast-conservation surgery and immediate latissimus dorsi flap reconstruction in patients with T1 to T2 breast cancer. *Plast Reconstr Surg*. 2005;116(3):741-752.
32. Slavin SA, Schnitt SJ, Duda RB, et al. Skin-sparing mastectomy and immediate reconstruction: oncologic risks and aesthetic results in patients with early-stage breast cancer. *Plast Reconstr Surg*. 1998;102(1):49-62.
33. Spear SL, Newman MK, Bedford MS, Schwartz KA, Cohen M, Schwartz JS. A retrospective analysis of outcomes using three common methods for immediate breast reconstruction. *Plast Reconstr Surg*. 2008;122(2):340-347.
34. Petersen A, Eftekhari ALB, Damsgaard TE. Immediate breast reconstruction: a retrospective study with emphasis on complications and risk factors. *J Plast Surg Hand Surg*. 2012;46(5):344-348.
35. Munhoz AM, Aldrighi CM, Montag E, et al. Clinical outcomes following nipple-areola-sparing mastectomy with immediate implant-based breast reconstruction: a 12-year experience with an analysis of patient and breast-related factors for complications. *Breast Cancer Res Treat*. 2013;140(3):545-555.
36. Peled AW, Foster RD, Stover AC, et al. Outcomes after total skin-sparing mastectomy and immediate reconstruction in 657 breasts. *Ann Surg Oncol*. 2012;19(11):3402-3409.
37. Losken A, Nicholas CS, Pinell XA, Carlson GW. Outcomes evaluation following bilateral breast reconstruction using latissimus dorsi myocutaneous flaps. *Ann Plast Surg*. 2010;65(1):17-22.
38. Sanford RA, Lei X, Barcenas CH, et al. Impact of time from completion of neoadjuvant chemotherapy to surgery on survival outcomes in breast cancer patients. *Ann Surg Oncol*. 2016;23(5):1515-1521.
39. Cullinane C, Shrestha A, Al Maksoud A, et al. Optimal timing of surgery following breast cancer neoadjuvant chemotherapy: a systematic review and meta-analysis. *Eur J Surg Oncol*. 2021;47(7):1507-1513.
40. Kupstas AR, Hoskin TL, Day CN, Habermann EB, Boughey JC. Effect of surgery type on time to adjuvant chemotherapy and impact of delay on breast cancer survival: a national cancer database analysis. *Ann Surg Oncol*. 2019;26(10):3240-3249.

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