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Local safety of immediate reconstruction during primary treatment of breast cancer. Direct-to-implant versus expander-based surgery

Egidio Riggio[a,*], **Elisa Toffoli**[a], **Caterina Tartaglione**[a], **Giuseppe Marano**[b], **Elia Biganzoli**[b,c]

[a] *Unit of Plastic and Reconstructive Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milan, Italy*
[b] *Laboratory of Medical Statistics, Biometry and Bioinformatics G.A. Maccacaro, Department of Clinical Science and Community Health, University of Milan, 20133 Milan, Italy*
[c] *Unit of Medical Statistics, Biometry and Bioinformatics, Fondazione IRCCS Istituto Nazionale dei Tumori, 20133 Milan, Italy*

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Summary *Introduction:* After mastectomy, immediate breast reconstruction is paramount. With the growing number of nipple-sparing mastectomies, the chances of successful one-stage reconstruction with implants are also increasing. Local safety is one of the main issues. This study investigated the factors that could lead to major or minor complications after expander-based versus direct-to-implant (DTI) reconstruction.
Methods: The studied factors were age, body mass index (BMI), hypertension, smoking, diabetes, type of mastectomy (nipple-sparing/total), implant size, neoadjuvant/adjuvant chemotherapy, and radiotherapy. The study sample included 294 immediate reconstructions over 3 years. The primary outcome was the incidence of complications, major or minor depending on the necessity of revision surgery. For the DTI pocket, we applied a variant of the conventional submuscular technique.
Results: In DTI reconstructions (median follow-up 26 months), the complication rate was 17.2% (4.3% major and 12.8% minor) with no significant association with clinical variables. In expander-based reconstructions (median follow-up 19 months), the complication rate was 18.3% (12.5% major and 5.8% minor). Univariate analysis showed a significant association

* Corresponding author.
E-mail address: egidio.riggio@istitutotumori.mi.it (E. Riggio).

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between overall complications and radiotherapy ($P = 0.01$) as well as between major complications and expander size ($P < 0.005$), BMI ($P < 0.005$), and radiotherapy ($P < 0.01$); radiotherapy and BMI retained significance in multivariate analysis. Neoadjuvant/adjuvant chemotherapy did not affect the complication rate.

Conclusions: There was evidence of an association between major complications and clinical variables in the expander-based cohort. Larger expander size was a predictor of failure, especially combined with radiation. Direct-to-implant reconstruction proved to be safe. We describe a reliable method of reconstruction and a safe range of implant sizes even beyond 500 g.

Introduction

Breast cancer surgery has evolved from radical operations toward less and less disfiguring procedures with better cosmetic results. Immediate breast reconstruction after mastectomy has become ever more important for the body image of women with breast cancer.[1] The choice of reconstructive treatment depends on the type of mastectomy, the local conditions after mastectomy, the clinical history of the patient (metabolic diseases, coagulation disorders, smoking, etc.), the patient's preference, and the need for postoperative radiotherapy.

With the radical procedures of the past, the feasibility of immediate reconstruction with implants was limited due to the insufficient soft-tissue coverage.[2] Now that the indications for skin-sparing and nipple-sparing mastectomies are growing,[3-5] mainly because of mammography screening and earlier detection,[6,7] the placement of a permanent implant is often possible at the time of mastectomy.[3,8] Immediate reconstruction with implants is increasingly preferred by surgeons and patients. It gives a less disfiguring cosmetic result and reduces the operative time and costs as well as the psychological impact of cancer on patients.[9,10]

Reconstruction can be performed by the traditional two-stage approach with the insertion of tissue expanders followed by a permanent implant, or the one-stage approach with implant placement at the time of mastectomy. This emerging approach has been sparsely reported on and is not yet accepted as the standard of care. One-stage reconstructive surgery has several advantages including shorter operative times, a lower cost, and less discomfort to the patient.[11,12] The use of acellular dermal matrix (ADM) increases the cost and may be associated with a wide range of early complications.[13-15]

We performed a study to assess the safety of direct-to-implant (DTI) reconstruction versus the traditional procedure in patients affected by primary breast cancer and undergoing total or nipple-sparing mastectomy and adjuvant therapies. The primary outcome was local safety in terms of complications and revision surgeries. A statistical analysis was performed to evaluate the two surgical approaches in terms of type and number of local complications and in relation to potential risk factors (both patient and disease related) and interference by chemotherapy and radiation.

Materials and methods

Ethics statement

This observational study was approved by the Institutional Ethics Committee of Fondazione IRCCS Istituto Nazionale dei Tumori (INT), Milan, Italy (registration number: INT 134-2016) and complied with the Declaration of Helsinki. The patients gave informed consent to their clinical data being used for research and being published. The study records were extracted from the institutional electronic database and clinical charts. Demographics, treatments, and complications were recorded prospectively.

Patients and data collection

The study population comprised 262 women undergoing 294 immediate reconstructions after mastectomy (32 bilateral cases) at INT from December 2011 to June 2014. The observation period ran from June 2014 to March 2015.

The mastectomies (166 total and 128 nipple-areola complex [NAC] sparing) were performed by oncology surgeons on staff. Axillary sentinel lymph node biopsy or node dissection was performed as necessary. Reconstructions were consecutively performed by the first author (E.R.) with immediate placement of a permanent implant or tissue expander using complete musculofascial coverage. Skin-reducing and radical mastectomies, reconstructions with composite pockets (use of ADM and other meshes) as well as second operations for expander substitution and final aesthetic outcome were excluded in order to obtain a homogeneous sample.

Reconstructions were divided into two groups: immediate reconstruction with permanent implant (direct-to-implant, DTI) versus expander-based reconstruction (EBR) in two stages. 61 patients underwent DTI (including nine bilateral cases) for a total of 70 reconstructions. All implants were Natrelle® 410 highly cohesive silicone-filled models produced by Allergan Inc. (Irvine, CA, USA). Two hundred and one patients underwent EBR (23 bilateral cases) for a total of 224 reconstructions. The expanders included 213 Natrelle®, 133 (Allergan), and 11 CPX (Mentor, Santa Barbara, CA, USA) models.

To determine which factors might lead to complications, we analyzed the association of complications with several variables selected on the basis of our clinical experience. The variables potentially associated with complications

were patient characteristics (age, body mass index [BMI]), risk factors (hypertension, smoking, diabetes), type of mastectomy (NAC-sparing or total), implant volume and weight, neoadjuvant and adjuvant chemotherapy, and adjuvant radiotherapy.

Complications were classified as major or minor depending on the necessity (or not) of revision surgery. Major complications (requiring a new operation with implant replacement) included necrosis, infection, inflammation and seroma, implant damage, exposure, and rupture or severe lateral displacement. Minor complications included inflammation, infection, wound pain, abnormal scars, and minor lateral displacement of the implant. The study observed the occurrence of total adverse events (i.e., major and minor complications), because these are good indicators of the reliability of the surgical procedure, and analyzed the complications as total (minor + major) and major alone, because the latter were expected to be more clinically relevant.

Surgical techniques

EBR reconstruction consisted of the creation of a conventional totally submuscular pocket. The expanders were saline single-lumen and integrated-valve tissue expanders; no adjustable/expandable implants (Becker type) were used. The intraoperative fill with saline solution amounted to a mean of 35% of the nominal device volume. The refill was completed after 3–6 times in 2–3 months.

DTI reconstruction included a dual-plane variant of the conventional submuscular pocket with a lower fascial dissection (Fig. 1) that allowed insertion of larger implants.[16,17] All implants were anatomically shaped with highly cohesive silicone gel. Because of its shape and cohesiveness, the implant could progressively expand the lower pole and move the pectoralis muscle upward, producing results similar to those achievable with ADM.

Statistical analysis

The main aim of the analysis was to evaluate in the DTI and EBR groups the association between complications and the following variables: age and implant volume (continuous variables), BMI ($< 25\,kg/m^2$; $\geq 25\,kg/m^2$), diabetes (no; yes), hypertension (no; yes), smoking habit (nonsmoker; exsmoker; smoker), type of mastectomy (total; NAC-sparing), radiotherapy (no; yes), and chemotherapy (no therapy; adjuvant; neoadjuvant; adjuvant plus neoadjuvant). Data recorded from 294 reconstructions were used. The study outcomes were total complications and major complications. In the DTI group, analyses were performed only for total complications; in accordance with the event-per-variable rule,[18] major complications were not considered because of the paucity of observed events ($n = 3$).

Continuous variables were summarized using median, quartiles (Q_1, Q_3), interquartile range (IQR), minimum and maximum; categorical variables were summarized by frequency counts and percentages. The associations between outcomes and variables of interest were first evaluated by univariate logistic models, with complications (total or major) as the response variable (1 = present; 0 = absent). For each model, the null hypothesis of no association was assessed by the two-tailed Wald test. In the second step, multivariate logistic models were estimated for major and total complications in the EBR group. In the multivariate models, the variables that showed at least a moderate association with the outcome (odds ratio [OR] > 2.5 for categorical variables; $P < 0.05$ for continuous variables) were included as independent variables. Age was included independent of its statistical significance in order to obtain age-adjusted estimates of the multivariate ORs.

A robust estimation method[19] was used to fit the logistic regression models (both univariate and multivariate) given the unbalanced distribution of some covariates (e.g., diabetes). The association between outcomes and variables was evaluated using the two-tailed Wald test. Results were reported in terms of the estimated ORs of complications with the respective 95% confidence intervals and the *P* values of the association tests. For each test, statistical significance was deemed for $P < 0.05$. The analyses were performed using the r software version 3.2.4,[20] with the logistic package added.[21]

Results

The DTI group included 70 reconstructions, 8 after total mastectomy and 62 after NAC-sparing mastectomy. Tables 1 and 2 list the patient and tumor characteristics, reconstruction techniques, and risk factors. The median duration of follow-up was 26–25 months. Table 3 details the observed complications. No category of complication was found to be predominant. Regarding the association between complications and clinical variables, no statistically significant associations emerged (Table 4). One major complication occurred in one of four irradiated breasts.

The EBR group included 224 reconstructions, 158 after total mastectomy and 66 after a NAC-sparing procedure. Patient and tumor characteristics, reconstruction techniques, and risk factors are listed in Tables 1 and 2. The median duration of follow-up was 18.82 months. Twenty-eight major complications and 13 minor complications occurred, with severe infection and expander exposure being the most frequent (Table 3). In the 44 irradiated breasts, the overall complication rate was 31.8% while the major complication rate was 25%; the failure rate was 11.36%, with expander exposure accounting for 5 of 11 major complications compared with 10 of 17 major complications in the 180 nonirradiated breasts.

With regard to total complications, in univariate analysis (Table 4), a moderate association with radiotherapy ($P = 0.013$) and a minor association with BMI and expander volume were found. In addition, an association was found with diabetes (OR = 4.69; $P = 0.05$). When these variables were included in the multivariate model, only the association with radiotherapy proved significant ($P < 0.05$) (Table 5 and Fig. 2).

Regarding the outcome of major complications, univariate analysis showed a significant association between major complications and expander size (OR = 1.44; $P < 0.005$), radiotherapy (OR = 3.2; $P < 0.005$), and BMI ≥ 25 (OR = 3.54; $P = 0.0018$), while the association with smoking was less marked (OR = 2.34; $P = 0.05$) (Table 4). The analysis indicated that a patient with a 700-mL expander had a 5.6

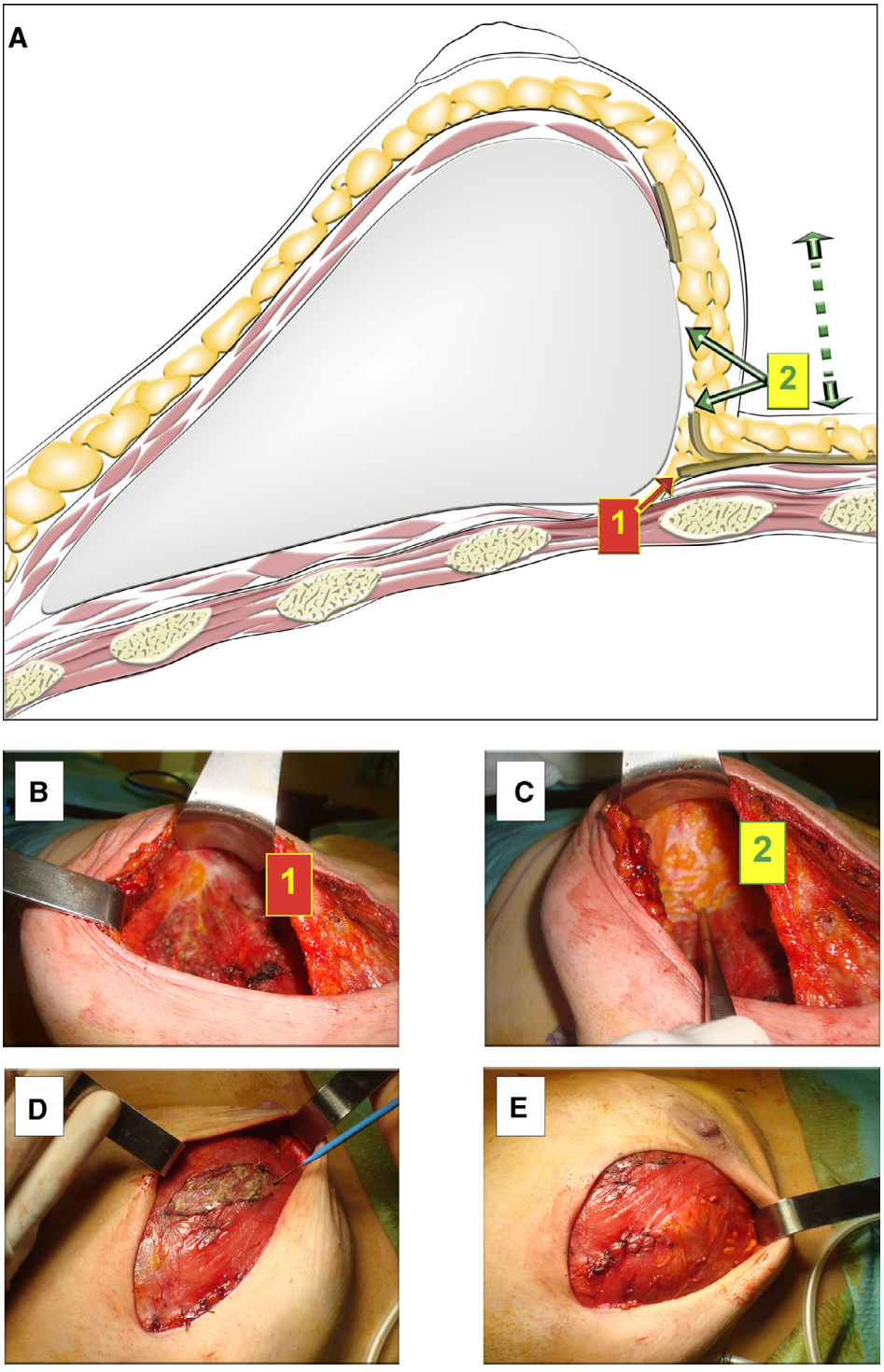

Fig. 1 Technical details of direct-to-implant (DTI) reconstruction. (A) Illustration of the breast frame around the implant and surgical focal points: muscle insertions and deep fascia (1), superficial fascia and its attachments (2) and the respective levels of scoring *(short arrows 1 and 2)*; release effect of the soft tissue by scoring the two fascial systems from the medial to lateral side of the lower breast *(vertical dashed arrow)*. (B) Scoring of the pectoralis major and serratus anterior muscles with the deep fascia along the inframammary fold can produce a pocket extension of 1–2 cm (1); the serratus is split and a thin upper layer of muscle with its fascia is raised laterally. (C) The following step of scoring the superficial fascia and its attachments (2) can produce further vertical extension of the lower pocket, up to 3–5 cm. (D) After implant placement, one or two partial, superficial myotomies can be carried out medially to the muscle suture line to reduce tension along the suture line. (E) The muscle layer at the upper two-thirds (pectoralis major and serratus anterior) and a composite layer of skin, fat, and fascia at the bottom third with no interruption of the implant envelope and its vascular supply.

Table 1 Characteristics of reconstructions and patients of the direct-to-implant and expander-based groups.

	Group	
Reconstructions	DTI ($n=70$)	EBR ($n=224$)
Type of mastectomy *n* (%)		
- Total	8 (11.4%)	158 (70.5%)
- NAC-sparing	62 (88.6%)	66 (29.5%)
Complications *n* (%)		
- Total:	12 (17.2%)	41 (18.3%)
- Minor	9 (12.9%)	13 (5.8%)
- Major	3 (4.3%)	28 (12.5%)
Device weight/volume (g/mL)		
median, range	370, 125-525	500, 250-800
Q_1 - Q_3 (IQR)	301-410 (109)	350-650 (300)
Patients	**DTI ($n=61$)**	**EBR ($n=201$)**
Age (years)		
Median, range	46, 23-74	48, 27-75
Q_1 - Q_3 (IQR)	39-50 (11)	43-57 (14)
BMI (kg/m^2)		
Median, range	20.6, 16.6-27.8	23.0, 16.0-37.6
Q_1 - Q_3 (IQR)	19.2-22.9 (3.7)	20.7-26.4 (5.7)
Hypertension *n* (%)		
- No	57 (93.4%)	174 (86.6%)
- Yes	4 (6.6%)	27 (13.4%)
Diabetes *n* (%)		
- No	61 (100%)	195 (97.0%)
- Yes	0 (0.0%)	6 (3.0%)
Smoking *n* (%)		
- No	47 (77.0%)	127 (63.1%)
- Yes	2 (3.3%)	14 (7.0%)
- Ex	12 (19.7%)	41 (20.4%)
- Not available	0 (0.0%)	19 (9.5%)
Chemotherapy *n* (%)		
- No	24 (39.3%)	42 (20.9%)
- Adjuvant	31 (50.9%)	130 (64.7%)
- Neoadjuvant	5 (8.2%)	17 (8.5%)
- Adjuvant + neoadjuvant	1 (1.6%)	12 (6.0%)
Radiotherapy *n* (%)		
- No	57 (93.4%)	163 (81.1%)
- Yes	4 (6.6%)	38 (18.9%)

BMI - body mass index; DTI - direct-to-implant reconstruction; EBR - expander-based reconstruction; IQR - interquartile range; NAC - nipple-areola complex; Q - quartile.

Table 2 Oncological data of the direct-to-implant and expander-based groups.

	Group	
Tumors	DTI ($n=70$)	EBR ($n=224$)
Hereditary risk - No disease *n*	11	15
Histological type n (%)	59	209
- Malignant phyllodes tumor	1 (1.7%)	4 (1.9%)
- IDC	25 (42.3%)	106 (50.7%)
- IDC + DCIS	11 (18.6%)	27 (12.9%)
- IDC + ILC	2 (3.4%)	11 (5.2%)
- IDC + ILC + DCIS	1 (1.7%)	1 (0.5%)
- ILC - DCIS	3 (5.0%)	25 (11.9%)
- Paget + DCIS	13 (22.0%)	28 (13.4%)
- Tubular carcinoma + DCIS	1 (1.7%)	-
- Cribriform carcinoma	1 (1.7%)-	4 (1.9%)
- Mucinous carcinoma	-	2 (0.9%)
- Nonmalignant papilloma	-	1 (0.5%)
TNM *n* (%)	58	204
- Tis	4 (6.9%)	12 (5.9%)
- T1	38 (65.5%)	103 (50.5%)
- T2	16 (27.6%)	67 (32.8%)
- T3	-	12 (5.9%)
- T4	-	10 (4.9%)
- N0	37 (63.8%)	98 (48.0%)
- N1	20 (34.5%)	74 (36.2%)
- N2	1 (1.7%)	16 (7.8%)
. N3	-	6 (2.9%)
- M0	58 (100.0%)	202 (99.0%)
- M1	-	2 (0.9%)
Grading n (%)	58	204
- G 1	2 (3.4%)	8 (3.9%)
- G 2	24 (41.4%)	89 (43.6%)
- G 3	28 (48.2%)	101 (49.5%)
- G 1/2/3	1 (1.7%)	0 (0.0%)
- G 1/2	1 (1.7%)	3 (1.5%)
- G 2/3	2 (3.4%)	3 (1.5%)
*Molecular profile** *n* (%)	58	204
- Luminal A	24 (41.3%)	72 (35.3%)
- Luminal B HER2-negative	17 (29.3%)	73 (35.8%)
- Luminal B HER2-positive	6 (10.3%)	16 (7.8%)
- HER2	4 (6.9%)	23 (11.2%)
- Triple negative	7 (12.0%)	20 (9.8%)
Recurrence after surgery* *n* (%)		
Local recurrences	0/59	5/208 (2.4%)
Distant metastases	0/59	10/208 (4.8%)

* According to St. Gallen Consensus 2013.
DCIS - ductal carcinoma in situ; DTI - direct-to-implant reconstruction; EBR - expander-based reconstruction; IDC - invasive ductal carcinoma; ILC - invasive lobular carcinoma; TNM - tumor-node-metastasis staging .

times higher risk than a patient with a 300-mL expander, while the odds of major complications were seven times greater in a patient with a BMI of 35 than in a patient with a BMI of 21.

The variables included in the multivariate analysis were the same as those selected in the analysis of total complications. A moderately significant association of major complications was found for radiotherapy ($P<0.05$) and BMI ($P<0.05$) (Table 5 and Fig. 2).

Limitations

Given the small sample size and the confounding bias inherent in nonrandomized analysis, these results should be considered with caution. We decided therefore not to pursue a comparison analysis but an analysis of the incidence

Table 3 Details of minor and major complications.

Group: DTI ($n=70$)		Group: EBR ($n=224$)	
Minor complications *n* (%)		Minor complications *n* (%)	
- Poor aesthetic result	2 (2.9%)	- Infection	3 (1.3%)
- Implant displacement	1 (1.4%)	- Seroma	1 (0.4%)
- Skin inflammation	2 (2.9%)	- Wound dehiscence	1 (0.4%)
- Seroma	1 (1.4%)	- Stretched skin and scar tension	2 (0.9%)
- Rippling on the medial quadrants due to tissue thinning	1 (1.4%)	- Pain in axillary and dorsal regions	1 (0.4%)
- Breast pain, alteration of scapular and humeral movement	1 (1.4%)	- Skin necrosis	1 (0.4%)
- Skin necrosis with fistula formation	1 (1.4%)	- Skin inflammation	2 (0.9%)
		- Hematoma	1 (0.4%)
		- Expander displacement (lateral)	1 (0.4%)
Total	9 (12.9%)	**Total**	13 (5.8%)
Interval from surgery to occurrence mean (range)	126 days (7–360)	*Interval from surgery to occurrence mean (range)*	76 days (1–90)
Major complications *n* (%)		**Major complications** *n* (%)	
- Poor aesthetic result	1 (1.4%)	- Infection	11 (4.9%)
- Implant rotation with hypercorrection of the upper quadrants, Baker 2/3		- Skin inflammation	3 (1.3%)
- Implant micro-leakage detected by MRI	1 (1.4%)	- Exposure of tissue expander	8 (3.6%)
	1 (1.4%)	- Breakage / damage of tissue expander	3 (1.3%)
		- Recurrent seroma	1 (0.4%)
		- Skin necrosis	1 (0.4%)
		- Severe lateral displacement of expander	1 (0.4%)
Total	3 (4.3%)	**Total**	28 (12.5%)
Interval from surgery to occurrence mean (range)	669 days (300–1080)	*Interval from surgery to occurrence mean (range)*	180 days (11–750)

DTI – direct-to-implant reconstruction; EBR – expander-based reconstruction; MRI – magnetic resonance imaging.

of complications in order to establish their association with different variables. The clear difference between the two groups must be assessed considering the associations observed with the other variables.

Discussion

The strengths of our study are the prospectively collected preoperative and operative variables and the meticulous collection of postoperative complications, which allowed us to control for the described risk factors. Many of the earlier studies analyzed single risk factors and single complications, often in a composite group of reconstructive techniques and different types of devices. Given the similarity of the surgical techniques, with fully vascularized muscular or musculofascial coverage of the device, the types of complications were expected to be homogeneous in the present study. Accordingly, the descriptive analysis indicated a similar incidence of complications correlated with both surgical procedures (DTI: 17.2%; EBR: 18.3%).

The complication rates were highly similar to the perioperative complication rate of 17.6% reported over a 2-year period in a study of 1170 expander/implant reconstructions.[22] In contrast, Woederman et al reported 39% of patients being affected by mild and severe postoperative complications after 195 single-stage implant reconstructions and 205 two-stage reconstructions, and suggested the high rate to be associated with the large number of reconstructions in patients who smoked, obese patients, and patients with larger, more ptotic breasts.[23]

Interestingly, in the present study, with roughly the same total complications, we found opposite ratios of minor and major complications, namely 12.9% versus 4.3% (DTI) and 5.8% versus 12.5% (EBR), respectively. These results suggest greater safety of the one-stage procedure. Age, hypertension, and type of mastectomy (total or NAC-sparing) did not increase the likelihood of complications in either groups. In the EBR group, diabetes and smoking mildly increased the rate of total and major complications, respectively. The results concerning the main risk factors are discussed in the following subsections.

Radiotherapy

Univariate analysis in the EBR sample confirmed the predictive role of radiotherapy in the onset of complications observed in previous studies,[24–29] as it increased the risk of total complications (OR = 2.6; $P=0.01$) and major complications (OR = 3.2; $P<0.01$). The impact was found to be similar in multivariate analysis. The rate of major complications (25%) and the failure rate of 11.36% were comparable with the data reported in the literature.

Table 4 Association between complications and patient and reconstruction characteristics: univariate analyses.

	DTI: Total complications		EBR: Total complications		EBR: Major complications	
	Frequencies n/N (%)	Estimates OR (95% CI); *P*	Frequencies n/N (%)	Estimates OR (95% CI); *P*	Frequencies n/N (%)	Estimates OR (95% CI); *P*
Type of mastectomy						
- Total	2/8 (25.0%)	ref	28/158 (17.7%)	ref	20/158 (12.7%)	ref
- NAC-sparing	10/62 (16.1%)	0.52 (0.11, 3.13); 0.440	13/66 (19.7%)	1.16 (0.55, 2.34); 0.70	8/66 (12.1%)	0.98 (0.40, 2.25); 0.966
Chemotherapy						
- No	4/27 (14.8%)	ref	5/45 (11.1%)	ref	3/45 (6.6%)	ref
- Adjuvant	6/36 (16.7%)	1.11 (0.30, 4.44); -	33/147 (22.4%)	2.15 (0.87, 6.30); -	23/147 (15.6%)	2.29 (0.79, 8.90); -
- Neoadjuvant	2/6 (33.3%)	2.90 (0.41, 18.54); -	2/18 (11.1%)	1.12 (0.19, 5.19); -	1/18 (5.5%)	1.04 (0.10, 6.89); -
- Adjuvant + neoadj.			1/14 (7.1%)	0.82 (0.08, 4.64); -	1/14 (7.1%)	1.35 (0.12, 9.10); -
		Overall association: P = 0.526		*Overall association: P* = 0.236		*Overall association: P* = 0.391
- No	4/27 (14.8%)	ref	5/45 (11.1%)	ref	3/45 (6.7%)	ref
- Yes	8/42 (19.0%)	1.29 (0.38, 4.91); 0.692	36/179 (20.1%)	1.87 (0.77, 5.44); 0.177	25/179 (14.0%)	2.00 (0.70, 7.74); 0.211
Radiotherapy						
- No	11/65 (16.9%)	ref	27/180 (15.0%)	ref	17/180 (9.4%)	ref
- Yes	1/5 (20.0%)	1.58 (0.15, 9.67); 0.657	14/44 (31.8%)	2.65 (1.24, 5.56); 0.013*	11/44 (25.0%)	3.21 (1.37, 7.32); 0.0080*
Diabetes						
- No	0/65 (0%)	-	38/218 (17.4%)	ref	26/218 (11.9%)	ref
- Yes			3/6 (50.0%)	4.69 (0.96, 22.90): 0.056	2/6 (33.3%)	4.04 (0.68, 19.21); 0.115
Hypertension						
- No	11/66 (16.7%)	ref	35/194 (18.0%)	ref	25/194 (12.9%)	ref
- Yes	1/4 (25.0%)	2.07 (0.19, 14.08); 0.499	6/30 (20.0%)	1.19 (0.43, 2.91); 0.717	3/30 (10.0%)	0.85 (0.22, 2.49); 0.779
Smoking *n* (%)						
- No	9/54 (16.7%)	ref	21/139 (15.1%)	ref	14/139 (10.1%)	ref
- Yes or ex	3/16 (18.8%)	0.96 (0.17, 3.98); 0.956	16/65 (24.6%)	1.84 (0.88, 3.78); 0.102	13/65 (20.0%)	2.23 (0.98, 5.02); 0.054
Age		1.01 (0.95, 1.07); 0.734		1.03 (0.995, 1.06);0.097		1.02 (0.99, 1.06); 0.243
Overweight (BMI $\geq$ 25)						
- No	11/63 (17.5%)	ref	20/141 (14.2%)	ref	10/141 (7.1%)	ref
- Yes	1/7 (14.3%)	1.05 (0.10, 5.77); 0.957	21/83 (25.3%)	2.04 (1.03, 4.04) 0.040*	18/83 (21.7%)	3.54 (1.59, 8.23) 0.0018*
Device weight/volume		0.99 (0.54, 1.89); 0.983		1.25 (1.0051, 1.55); 0.045*		1.44 (1.12, 1.88); 0.0045*

CI - confidence interval; DTI - direct-to-implant reconstruction; EBR - expander-based reconstruction; NAC - nipple-areola complex; OR - odds ratio; ref - reference category for the calculation of OR.

Reported are the frequency of complications (n) and overall reconstructions (N) (categorical variables only); the estimated ORs of complications with the respective 95% CIs; and *P* values from association tests. For chemotherapy, *P* values were reported only for the test of overall association. Since in each case the overall association was not significant, comparisons between groups were not performed.

In the DTI group only one patient received both adjuvant and neoadjuvant therapy and was therefore excluded.

* $P < 0.05$

Table 5 Association between complications and patient and reconstruction characteristics: multivariate analyses.

	EBR: Total complications		EBR: Major complications	
	Estimates OR (95% CI)	*P* value	Estimates OR (95% CI)	*P* value
Radiotherapy	2.46 (1.13, 5.24)	0.0235*	2.95 (1.23, 6.94)	0.0165*
Age	1.01 (0.98, 1.05)	0.4026	1.01 (0.97, 1.04)	0.7918
Overweight	1.51 (0.68, 3.34)	0.3079	2.56 (1.02, 6.59)	0.0445*
Expander volume	1.11 (0.86, 1.42)	0.4477	1.20 (0.90, 1.61)	0.2222
Diabetes	2.90 (0.54,15.56)	0.2046	1.93 (0.29,10.45)	0.4663

CI - confidence interval; EBR - expander-based reconstruction; OR - estimated odds ratio of complications.
* $P < 0.05$

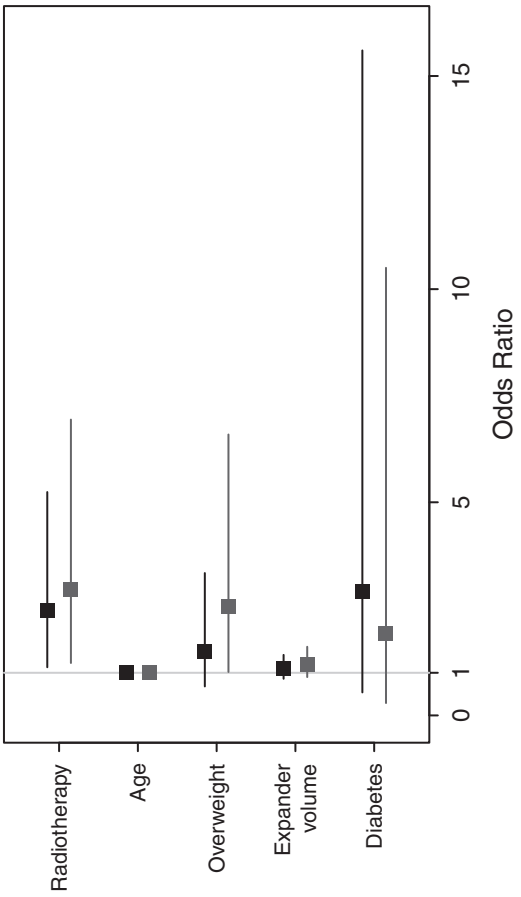

Fig. 2 Estimated odds ratios (ORs) from multivariate models (expander-based group). Black: outcome = total complications; grey: outcome = major complications.

In a series of 104 patients treated with radiotherapy before expander exchange, Ascherman et al reported the following rates of major complications necessitating reoperation: 18.5% for irradiated and 4.2% for nonirradiated breasts, with overall complication rates of 40.7% and 16.7% and implant failure rates of 14.8% and 0%, respectively.[30] Roostaeian et al found significantly higher complication rates after radiation therapy in expander- and implant-based reconstructions, where an acellular dermal sling was added to the subpectoral pocket, with more complications and revisions in the expander group.[31] Sbitany et al. observed higher but acceptable early complication rates in two-stage reconstructions, including those where ADM was added.[32] Cordeiro et al. reported failure rates before expander exchange that were slightly lower than ours: 8.5% of irradiated versus 3.6% of nonirradiated breasts. Univariate analysis revealed a lower failure rate in the permanent implant group than the expander group.[24] Our outcome in the DTI group was likewise encouraging, with no implant failure and the odds of major complications after radiotherapy close to 1. By contrast, we found significant odds of all major complications after expander irradiation (OR = 3.33), although this is still acceptable compared to the high odds of reconstruction failure (OR = 5.75) reported by Cordeiro et al.[24]

Other studies reported diverging outcomes of two-stage reconstruction. Nava et al recorded a 20% failure rate in 50 irradiated expanders (which became 40% after the exchange with permanent implants) compared with 2.3% in the non-irradiated group after a median follow-up of 50 months.[25] Aristei et al. found a lower rate of implant failure after expander irradiation, 11.9% after a median follow-up of 50 months.[29]

Chemotherapy

Complications after surgery may delay or interfere with chemotherapy protocols, and chemotherapeutic agents can impair cellular functions necessary for recovery from surgery and for regular tissue expansion. Nevertheless, we did not record any significantly higher risk for patients treated with adjuvant chemotherapy. The overall complication rates of DTI were similar: 16.7% (36 adjuvant treatments) and 14.8% (no treatment). The significance of the 33% complication rate in DTI patients treated with neoadjuvant therapy (OR = 2.90) is limited by the small number of cases. Nevertheless, given the lack of reoperations in this group, recipients of neoadjuvant chemotherapy may still be good candidates for DTI. The EBR group showed a higher complication rate in the 147 cases treated with adjuvant chemotherapy (22.4%; OR = 2.15) compared with 11.1% of 18 cases treated with neoadjuvant therapy and 11.1% of 45 cases without chemotherapy. Peled et al.[33] found no significant difference in a prospective series of patients treated with neoadjuvant or adjuvant chemotherapy and McCarthy et al.[22] analyzed all chemotherapy treatments as a single risk factor without finding them to be significantly predictive of complications. In the EBR group of the present study, the OR for overall complications

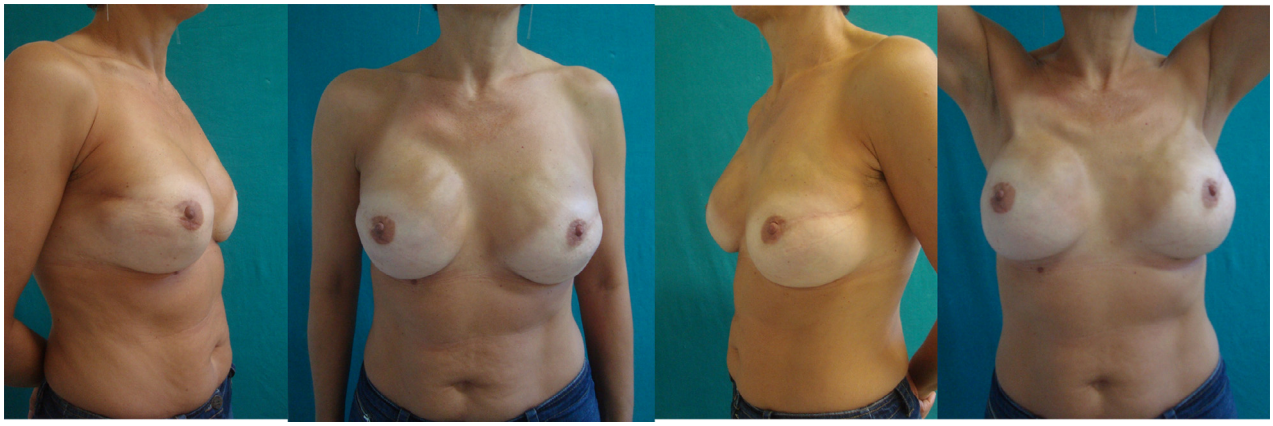

Fig. 3 Left breast, invasive ductal carcinoma and right breast, ductal carcinoma in situ: bilateral NAC-sparing mastectomy, sentinel lymph node biopsy and immediate reconstruction (without ADM) using highly cohesive silicone-filled implants with moderate-height/extra-full projection (Allergan Natrelle 410 Style MX, 445 g). Breast weight: 410 g left and 400 g right. Patient's views after 24 months.

after neoadjuvant treatment (1.03) was comparable to the 0.49 of 30-day postoperative morbidity reported by Abt et al.[34] Another study estimated 32% expander loss among 34 patients receiving neoadjuvant chemotherapy but lacked information on the complication rate in a control group.[35] Decker et al. reported a trend toward increased wound complications in patients undergoing mastectomy with immediate reconstruction who had received neoadjuvant chemotherapy.[36] Donker et al. studied short-term complications correlated with neoadjuvant therapy and found a rate of 15% in 48 immediate breast reconstructions with permanent implants versus 29% in control patients who did not receive neoadjuvant treatment.[37]

BMI

We found a significant association between higher BMI and the risk of complications in the EBR cohort. Our outcome is similar to that observed by McCarthy et al, with an OR for reconstructive failure of 6.9 in obese patients.[22] Other authors suggested that high BMI and immediate reconstruction were correlated with increased complication rates.[38]

Device size

To the best of our knowledge, expander/implant size has not been previously assessed as a predictor of surgical complications following implant-based breast reconstruction. It is, however, known that large-volume breasts can increase the risk of surgical failure.

Greater size of the immediate permanent implant was not associated with more complications in the present study. Highly cohesive silicone implants may be safely inserted in an uninterrupted musculofascial pocket and without a biological sling within the limit of 525 g (Fig. 3). With our single-stage technique, the OR of complications using a small-size implant (190 g) was the same as when sizes of 370 or 470 g were used.

By contrast, increases in expander volume in EBR are known to be associated with a higher incidence of complications, probably as a result of the wider dimensions of the pocket and the skin envelope, enhancing the production of serum and the risk of bacterial contamination. The impact of expander size on major complications might be related to that reported for BMI. The analogous trends of these variables can be partly explained by the correlation between body mass and breast volume.

Conclusions

EBR is as yet the most popular method of immediate breast reconstruction. However, this study provided evidence of a significant association between complications and clinical variables in the expander cohort but not the implant-based cohort. The association with radiotherapy was the most significant in univariate and multivariate analysis, followed by overweight. Univariate analysis of major complications showed a significant association between complications and expander size, BMI, and radiotherapy. In particular, we observed that larger expander volume was a significant predictor of failure, especially following breast irradiation. The combination of large expanders and planned radiation appeared to be contraindicated in overweight patients, for whom reconstruction should be postponed until after radiation. By contrast, DTI reconstruction of the breast proved safe, with no risk of major complications. There was a non-significant increase in mild complications after NAC-sparing mastectomy and after neoadjuvant chemotherapy. In this paper, we have described a reliable method of reconstruction, without using ADM, and a safe range of implant sizes even beyond 500 g. Its degree of surgical safety will need to be compared more thoroughly to standard EBR in future clinical trials. This is particularly important when heterologous or alloplastic materials are used in pocket preparation.

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Conflict of interest

None.

Funding

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