

Local Safety of IMMEDIATE RECONSTRUCTION DURING PRIMARY TREATMENT OF BREAST CANCER. Direct-to-Implant vs. Expander- based surgery.

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INTRODUCTION

Over time, breast cancer surgery has evolved from radical surgical procedures toward less and less disfiguring procedures and consequently improved cosmetic results.

Immediate breast reconstruction after mastectomy has become ever more significant 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, smoke, etc.), the patients' preference and the need of postoperative radiotherapy.

In the past, the limitation of immediate reconstruction with implants was due to inappropriate soft-tissue coverage with the following wound dehiscence and implant exposure, poor aesthetic outcomes and poor symmetry with high and tight breasts.² Currently, the indications to radical mastectomy are decreasing while skin-sparing and nipple-sparing mastectomies are growing.^{3,4,5} This is mainly because mammography screening helps detect breast cancer early,^{6,7} when it is most easily to treat.

Thanks to the more conservative mastectomies, the saving of the breast skin has been improved allowing the possibility of successful placement of a permanent implant at the time of mastectomy.^{3,8} Therefore, immediate breast reconstruction with implants is increasingly required by both the patients and the surgeons. This type of surgery gives a less disfiguring cosmetic result, reducing the psychological impact of cancer on patients. Oncological radicality and aesthetic outcome (satisfying breast shape and symmetry after immediate reconstruction) represent a great challenge for the surgeon.

According to the American Society of Plastic Surgeons, the post-mastectomy reconstruction with implants represents the 77% of all reconstructions. The remaining 33 % is represented by autologous tissues reconstructions (TRAM, Latissimus Dorsi and DIEP).⁹ Hershman et al. reported that the immediate in-hospital complication rate was significantly higher in patients who underwent autologous flaps when compared to those with implant reconstruction.¹⁰

There are two approaches of immediate reconstruction with implants: two-stage and one-stage. The traditional one is achieved in two stages with the use of tissue expanders and permanent implants. The emerging approach is performed in one stage by using permanent implants with or without the use of mesh. The immediate use of implants at the time of mastectomy, which eliminates the need for a second surgery procedure, has been sparsely reported and is not yet accepted as the standard of care. The one-stage reconstructive surgery has several advantages, such as lower surgical times compared to reconstructions with autologous tissue, reduction of surgical procedures and lower costs.^{11,12} In addition, it should be noted that this surgical procedure involves a minor discomfort to the patient in terms of

ambulatory accesses for the filling of expander. However, additional cost is incurred if breast reconstruction is associated with Acellular Dermal Matrix (ADM).^{13, 14} ADM is frequently used in expander based breast reconstruction because facilitates complete implant coverage providing support to the inferior-lateral pole of the implant. ADM gives a faster tissue expansion, a reduction of post-operative pain and an improvement of the aesthetic outcome,^{15,16} reducing concerns for complications such as rippling and malposition.^{17,18} By contrast the overall early complications can reach a wide spectrum.¹⁹

We performed a retrospective study aimed at:

- analyzing how patient characteristics are associated to surgical outcome, after breast reconstruction with implants or tissue expanders;
- identifying predictive factors which could help patient selection for type of reconstruction.

The study provided first evidence to assess the safety of the direct-to-implant reconstruction and the traditional procedure with expander insertion in patients affected by primary breast cancer and undergoing total or nipple-sparing mastectomy and adjuvant therapies. The outcome was the local safety in terms of complications and revision surgeries. A statistical analysis was performed to analyze the two surgical approaches in terms of type and number of local complications and in relation to potential risk factors as patient and disease factors, and interferences produced by chemotherapy and radiation.

Materials and methods

Ethical statement

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

Patients and data collection

The series is composed of 262 females undergoing 294 immediate reconstructions after mastectomy (32 bilateral cases) at the Istituto Nazionale dei Tumori (Milan, Italy) from December 2011 to June 2014. The

observational period was from June 2014 to March 2015. All data were collected prospectively. No patient was lost to follow-up.

The mastectomies (166 Total and 128 Nac-sparing) were performed by the staff of oncologic surgeons. Axillary sentinel lymph node biopsy or node dissection was performed as necessary. Reconstructions were consecutively performed by the senior author (E.R.) with immediate placement of permanent implant or tissue expander using complete musculofascial coverage. Skin-Reducing and radical mastectomies, reconstructions with composite pocket (use of ADM and other meshes), the second operation for expander- substitution and final aesthetic outcomes were excluded from the study, in order to have a homogeneous sample.

Reconstructions were divided into two groups: immediate reconstruction with permanent implant (direct-to-implant, DTI) versus expander-based reconstruction in two stages (EBR). Sixty-one patients underwent DTI (9 bilateral cases, for a total of 70 reconstructions). All implants were 410 high-cohesive models from Allergan Inc. (Irvine, US). 201 patients underwent EBR (23 bilateral cases, for a total of 224 reconstructions). The expanders were: 213 Allergan style 133 and 11 Mentor CPX (Mentor, Santa Barbara, US).

In order to suggest which factors could show a major or minor propensity to risk of complications in the treated patients, it has been considered the association of complications with some variables selected on the basis of clinical experience. The analyzed variables, potentially associated with the outcome, were patient characteristics (age, BMI), risk factors (hypertension, smoking, diabetes), characteristics of surgical treatment (type of mastectomy: nipple sparing or total mastectomy), prosthetic volume/weight, primary and secondary chemotherapy, and radiotherapy.

Complications were divided in two groups based on their severity, major and minor depending on the necessity of a revision surgery or not. Major complications included necrosis, infection, inflammation, seroma, damage, exposure, rupture and lateral dislocation of the implant, which required a new surgery with implant replacement. Minor complications mainly included inflammation, infection, pain of the wound, abnormal scars and mild lateral dislocation of the implant, but they did not require any implant removal. The study observed the occurrence of the totality of adverse effects (i.e. major and minor complications), because they represent good indicators of reliability of the surgical procedure, and analyzed the complications as total (minor + major) and major alone, because they were expected to be more clinically relevant.

Surgical techniques

DTI reconstruction: submuscular pocket with full release of lower insertions and deep fascia (harvest of pectoralis major muscle and thin-layer fibers of serratus anterior muscle and fascia); full release of the superficial fascial system above the inframammary fold (Riggio and Nava);²⁰ implant insertion; two drains (submuscular and subcutaneous/axillary). The DTI pocket includes a variant of the conventional submuscular pocket that, through a full superficial fasciotomy, allows direct extension of the lower pole and insertion of larger implants (Riggio et al).²¹ All breast implants were anatomically shaped with high-cohesive silicone gel.

EBR reconstruction: submuscular pocket (harvest of pectoralis major and serratus anterior, with release of lower insertions and deep fascia); expander insertion; two drains (submuscular and subcutaneous/axillary). Intraoperative fill with saline solution is meanly 35% of the nominal device volume. The following fills start 2-3 weeks after surgery, and carry on at every 1- 2 weeks. The full expansion can be reached after 2-3 months. This time can be longer in patients under chemotherapy. The pocket is totally autologous and vascularized, with no interruption of the lower envelope for implants and expanders as well. All breast expanders were saline single-lumen and integrated-valve tissue expanders. Adjustable/expandable breast implants (i.e. Becker-type) were not used.

STATISTICAL ANALYSIS

The main aim of the analysis was to evaluate, in the DTI and in the EBR group, the association between complications and the following variables: age and prosthetic volume (continuous variables), BMI (<25 Kg/m²; ≥25 Kg/m²) diabetes (no; yes), hypertension (no; yes), smoking habit (non smoker; ex smoker; smoker), type of mastectomy (total; nac sparing), radiotherapy (no;yes) and chemotherapy (no therapy; Adjuvant; Neoadjuvant; Adjuvant plus neoadjuvant). To such aim, data recorded from 294 reconstructions were used. The outcomes were: total complications and major complications. For the DTI group the analyses were performed only for total complications; major complications were not considered because of the paucity of observed outcomes (n=3).

Continuous variables were summarized using median, quartiles (Q₁, Q₃), interquartile range (IQR), minimum and maximum; categorical variables were summarized by frequency counts and percentages. The association among outcomes and variables of interest was firstly evaluated through univariate logistic models, with complication (total or major) as response variable (1=present; 0=absent). For each model, the null hypothesis of no association was assessed by the Wald test (two-tailed). In a second step multivariable logistic models were estimated for major and total complications in the EBR group. The decision of excluding the outcomes of the DTI group was made

according to the event per variable (EPV) rule²². The EPV rule is designed to avoid estimation bias, by “ruling out” situations in which the number of observed events is relatively low. In multivariable models, the variables that showed at least a moderate association with the outcome (Odds Ratio>2.5 for categorical variables; $p<0.05$ for continuous variables) were included as independent variables. Age was included in the model independently on its statistical significance, in order to obtain age-adjusted estimates of the multivariate Odds Ratios.

A robust estimation method²³ was used to fit the logistic regression models (both the univariate and the multivariate ones), due to the unbalanced distribution of some covariates (e.g. diabetes). The association between outcomes and variables was evaluated through the Wald test (two-tailed). Results were reported in terms of estimated odds ratios of complication, with 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 3.2.4²⁴, with the `logistf` package added.²⁵

RESULTS

DTI group (61 patients) included 70 reconstructions, of which 8 (11.4%) after total mastectomy and 62 (88.6%) after nipple-sparing mastectomy (Table 1). The median age of patients was 46 years (range: 23-74 years). BMI varied from 16.6 to 27.8 with a median of 20.6. Considering the factors of cardiovascular risk, none of the patients were diabetic, 4 patients (6.6%) were hypertensive, 2 patients (3.3%) were smoker and 12 patients (19.7%) had a past smoker. The volume of the implant used varied from 125 ml to 525 ml with a median of 370 ml.

Four patients (6.6%) on 61 underwent radiotherapy. Chemotherapy was performed according to adjuvant treatment in 31 patients (50.9%), neoadjuvant in 5 patients (8.2%) and both therapies were performed in 1 patient (1.6%).

Median follow-up was of 26.25 months. Twelve complications (17.2%) were identified; 3 (4.3%) of which were major complications and 9 (12.85%) minor complications. The major complications were reported in 2 cases (2.9%) following total mastectomy and in one (1.4%) following nipple-sparing mastectomy. Nine minor complications (12.9%) were observed only in patients who underwent nipple-sparing mastectomy. No category of complication was found to be predominant (Table 2). Regarding the association between complications and clinical variables, no significant associations at the level of 5% emerged. (Table 3).

EBR group (201 patients) included 224 reconstructions, of which 158 (70.5%) after total mastectomy and 66 (29.5%) after nipple-sparing mastectomy (Table 1). The median age of patients was 48 years (range, 27-75 years). BMI varied from 16 to 37.6 with a median of 23. Considering the factors of cardiovascular risk, 6 patients (2.7%) were diabetic, 27 patients (13.4%) were hypertensive, 14 patients (7.0%) were smoker and 41 patients (20.4%) had a past as a smoker. The volume of the tissue expanders varied from 250 ml to 800 ml with a median of 500 ml.

Thirty-eight patients out 201(18.9%) were subjected to radiotherapy. Chemotherapy was performed according to adjuvant treatment in 130 patients (64.7%), according to neoadjuvant treatment in 17 patients (8.5%) while both therapies were performed in 12 patients (6.0%).

Median follow-up time was of 18.82 months. Forty-one complications (18.3%) were identified. Twenty-eight (12.5%) were major complications and 13 (5.8%) were minor (Table 2). Major complications were reported in 19 cases (8.5%) following total mastectomy and 9 (4.01%) after nipple-sparing mastectomy. Five of 13 minor complications (2.23%) were observed in cases who underwent nipple-sparing mastectomy. Eight complications (3.57%) occurred in cases who underwent total mastectomy. Severe infection (4.95%) and expander exposure (3.6%) were largely the most frequent categories of complication reported (Table 2). Expander explantations were 5 above 11 major complications in 44 radiated breasts compared to 10 above 17 in 180 nonirradiated breasts.

Concerning total complications: in the univariate analysis (Table 3) a moderate association with radiotherapy ($p = 0.013$) and a mild association with BMI and expander volume were found. Also, a moderate association was found with diabetes ($OR=4.7$) even though not significant at the level of 5%. The variables above were then included in the multivariate model, where, only the association with radiotherapy was significant ($p<0.05$) (Table 4).

Regarding the outcome of major complications, the univariate analysis showed a significant association between complications and implant size ($p<0.005$), BMI ($p<0.005$), and radiotherapy ($p<0.01$) (Table 3). A moderate association was found also with radiotherapy ($OR= 3.2$, $p<0.005$) and BMI ($OR=3.5$, $p<0.005$) So, the variables included in the multivariate analysis were the same as those selected in the analysis of total complications. Here, moderately significant association of major complications were shown by radiotherapy ($p<0.05$) and BMI ($p<0.05$) (Table 4).

Limitations

These results should be considered with caution considering the small sample and confounding bias inherently present in un-randomized analysis. The clear difference found between the two groups must be assessed with caution considering the associations observed with the other variables. More

sophisticated analyses should be required in order to compare these samples and correct the potential bias such as propensity score or an analysis of the projections of the marginal estimates.

DISCUSSION

Strengths of our study are the benefit of prospectively collected preoperative and operative variables and meticulous collection of postoperative complications, which allowed us to control for the described risk factors. Many of the earlier studies analyze single risk factor and single complication often in a composite group of reconstructive techniques and different types of devices. Given the similarity of the surgical techniques which rest on muscular or musculo-fascial, fully vascularized, coverage of the device, also the types of complications were expected to be homogeneous in the current study. Accordingly, the descriptive analysis might suggest a similar percentage in the incidence of complications correlated to both surgical procedures (DTI: 17.2%; EBR: 18.3%).(Table1) The insertion of a device with fixed volume does not jeopardize the safety of the immediate reconstruction and there is no evidence that shows more interferences with clinical risk factors and adjuvant therapies.

The complication rate are well comparable with the perioperative complication rate of 17.6% reported over a 2-year period in a study from Memorial Sloan-Kettering Cancer Center (1170 consecutive tissue expander/implant reconstructions performed in 884 patients.²⁶ In contrast, Woederman et al. described a 39% of 309 patients affected by mild and severe postoperative complications after 195 single-stage implant reconstructions and 205 two-stage reconstructions and suggested the association of the high rate with the high number of single-stage reconstructions in patients such as smokers, obese patients, and those with larger, more ptotic breasts.²⁷

In this study, even if with the same total number of complications, we have interestingly found opposite ratios of minor and major complications, 12.9 vs. 5.8 (DTI) and 4.3 vs. 12.5 (EBR) respectively. These results that stand for the greater safety of the 1-stage surgery must be evaluated with extreme caution considering the small sample and confounding bias inherently present in an un-randomized analysis. Therefore we decided not to pursue a comparison analysis but an analysis of the incidence of complications, in order to study their association with different variables.

Age, hypertension and type of mastectomy (total or nipple-sparing) do not increase the likelihood for complications in both groups. Smoke slightly

increases the rate of major complications exclusively in EBR group, 20% vs. 10.1% (Odds ratio 2.34; $p = 0.05$). Diabetes mildly interferes with total complications in EBR group (OR 4.69; $p = 0.05$).

Concerning the main risk factors the results are discussed here.

Radiotherapy

Univariate analysis in the EBR sample confirms the predictive role of radiotherapy in the generation of all complications.²⁸⁻³³ It increases the incidence of total complications ($p = 0.01$; odds ratio 2.6). (Table 8) This evidence is more marked if we consider only the major complications ($p < 0.01$; odds ratio 3.2). (Table 10) The impact of radiotherapy is similarly found in the multivariate analysis.

In the subgroup of 44 radiated breasts following EBR the rate of major complications (reoperation) is 25%. The overall rate is 31.8%. In DTI the rate is lower, 20.0% (1 of 5 radiated breasts), although it is not significant. The total reconstructive failure, i.e. the expander removal, occurred in 15 of 41 overall complications. In particular, the failure rate was 11.36% (5 of 44 irradiated expanders) vs. 5.55% (10 of 180 nonirradiated expanders).

In a series of 104 patients with two-stage reconstruction, of whom 27 underwent radiotherapy before expander exchange (some was radiated before salvage mastectomy and expander), Ascherman et al. reported the following rates of major complication, i.e. reoperation rates (18.5% for irradiated and only 4.2% for nonirradiated breasts, $p = 0.025$), and of overall complication rates (40.7% for irradiated and 16.7% for nonirradiated breasts, $p = 0.01$). In addition there were higher rates of implant failure in irradiated breasts (14.8 percent versus 0 percent, $p = 0.001$). The small rates of major complication may be explained by the use of a total submuscular coverage.³⁴ Roostaeian et al.³⁵ significantly found very higher complication rates after radiation therapy in expander- or implant-based reconstructions where an acellular dermal sling was added to the subpectoral pocket. They reported more complications and revisions in the expander group, $p < 0.01$ (respectively 5 and 6 of 7 patients treated with radiotherapy), and for revision in the implant group, $p = 0.05$ (4 of 6 radiated patients).

Cordeiro et al.²⁸ focused the analysis on the expander/implant explantation. They reported failure rates before expander exchange mildly lower than ours: 8.5% of irradiated vs. 3.6% of nonirradiated breasts). The univariate analysis demonstrated that the radiotherapy to the expander group had a higher failure rate than the radiotherapy to the permanent implant group (18.1 percent versus 12.4 percent), although this difference was not significant. Our outcome in DTI group is also encouraging (no implant failure; odds of major complications after radiotherapy near 1 likewise with nonsignificant p). By contrast, in the current study, the analysis shows

significant odds of all major complications after expander radiation (3.33) but that are still acceptable in comparison of very high (5.75), found by Cordeiro et al., taking into account the limit of a single complication (explantation) but after the two stages of surgery for irradiated breasts. Also Sbitany et al.¹⁹ described that the overall early complication rates are higher but acceptable compared with nonirradiated patients in two-stage reconstruction even in those case with acellular dermal matrix added to the muscular expander pocket.

Other studies showed diverging outcomes of the two-stage reconstruction. Nava et al.²⁹ recorded 10 explantations in a group of 50 irradiated expanders (20%) that became 40% after the exchange with permanent implant and compared to 2.3% of nonirradiated group, after a median FU of 50 months. On the contrary, Aristei et al.³³ found a low rate of implant failure, 11.9% after a median FU of 50 months, in 101 patients of whom 90 underwent radiation of temporary tissue expanders.

The study of radiation effects should not limit to one type of complication, even if it is the most severe, and the lack of analysis of covariates could partially invalidate the outcome of a study.

Chemotherapy

Neoadjuvant and/or adjuvant chemotherapy, primary surgery with or without immediate reconstruction, local recurrence control and overall survival are strictly related in breast cancer care. Complications after surgery may delay and interfere with chemotherapeutic protocols as well as chemotherapeutic agents may impair cellular functions necessary for regular recovery from surgery and for usual tissue expansion. Nevertheless, we do not record any significant higher risk for patients treated with chemotherapy before and after surgery. DTI overall complication rates were analogous: 16.7% (36 adjuvant treatments) and 14.8% (no treatment). The 33% of complications in DTI cases treated by neoadjuvant therapy (odds ratio 2.90) is limited by the few cases. Nevertheless, due to the lack of reoperations, recipients of neoadjuvant chemotherapy may still be good candidates to DTI. EBR group shows higher rate of complications in the 147 cases treated by adjuvant chemotherapy (22.4%; odds ratio 2.15) compared to the 11.1% of 18 cases treated by neoadjuvant therapy and the 11.1% of 45 cases without chemotherapy.

Peled et al. found no significant difference in a prospective series of patients treated by neoadjuvant and adjuvant chemotherapy (expander or implant removal rates were 26% vs. 22% compared to 18% control group).³⁶

The EBR overall complication odds ratio after neoadjuvant treatment (1.03) is comparable with the 0.49 of 30-day postoperative morbidity reported by Abt et al. in a large series.³⁷ In a different way, Mitchem et al. prospectively observed 32% of expander loss out of 34 patients receiving neoadjuvant

chemotherapy but the study lacked information on the complication rate in a control group).³⁸

Decker et al.³⁹ reported a trend toward increased wound complications in patients undergoing mastectomy with immediate reconstruction (odds ratio, 1.58; $p = 0.06$). Dorken et al.⁴⁰ studied short-term complications correlated to neoadjuvant therapy and found a rate of 15% in 48 immediate breast reconstructions predominantly using permanent implants compared to a 29% in the control cases with $p = 0.042$ (study limitations: age-related differences among the groups with $p < 0,001$; no estimation of adjuvant chemotherapy in the control group).

Our outcome is also comparable to that reported by McCharty et al.²⁶ who analyzed all chemotherapeutic treatments as one risk factor without finding them to be significantly predictive of complications (12% vs. 16% without chemotherapy, OR 0.8, $p = 0.26$).

BMI

DTI and EBR median values are normal. EBR interquartile range lightly includes part of the overweight range (Table 2). Moderate association between BMI and increased risk of complications is reported in the study. In particular, this is significant in the univariate analysis of the EBR cohort (OR 4.6, $p = 0.0003$ for major complications in the preobese patients). Our outcome, where the odds for major complications of a patient with BMI = 35 are seven times greater than that with BMI = 21, is analogous to that found by McCharty et al.²⁶ (OR of 6.9 in obese patients compared with nonobese patients for reconstructive failure: seven times greater).

Other authors as Alderman and Wilkins suggested that BMI and immediate reconstruction were correlated with increased complication rates following various types of reconstruction.⁴¹

Device size.

To the best of our knowledge, expander/implant size has not been previously assessed as predictor of surgical complications following implant-based breast reconstruction. It is by contrast known that large-volume breasts may be significant risk factors for surgical failure.

The size of the immediate permanent implant is not associated to increasing number of complications (OR 1.02). It is valuable for immediate breast reconstruction that high-cohesive silicone implants may be safely inserted in an uninterrupted musculofascial pocket and without biological sling, within the limit of 525 g. According to our single-stage technique, OR using a small size (190 g) is the same as using size of 370 or 470 g.

By contrast in EBR, when the expander volume increases there is a negative trend of overall complications (odds ratio: 1.2; $p < 0.05$) and, particularly, of

major complications (OR 1.2; $p < 0.005$). A patient with a 700cc expander has a risk 5.6 times higher than a patient with a 300cc expander. Major volume increase, up to 800cc, implies higher incidence of complications and are probably associated to the wider dimensions of the pocket and of the skin envelope which enhances the production of serum and the risk of bacterial contamination. The size impact on major complications might be strictly associated to that reported for BMI. The analogous trends of these variables can be partly explained by the correlation between body mass and breast volume. Generally, a woman with high BMI is supposed to have large breasts and possible vascular alterations of the skin associated to a state of overweight.

In univariate analysis of the DTI group there are no significant associations between total complications and the considered variables. The effects of the expansion may explain the greater impact of the radiotherapy occurred in the EBR group. The expansion, in fact, involves a certain amount of tissue thinning even if skin viability and capillary blood are not compromised by the progressive tissue remodeling. The thinnest layer of expanded skin and tissue envelope might have a more negative effect on irradiation boosts.

Vascular changes are also found in the DTI group because the preserved skin envelope is initially subjected to hypoperfusion even when the subcutaneous vascular network is still present. Nevertheless, the report of minor vascular complications in DTI may be explained with two distinguishing factors. The first is given by the fact that an uninterrupted muscolofascial layer likely works as a pressure relief so to avoid that skin flaps are subjected to the direct pressure of permanent implant of highly cohesive silicone. The second factor is given by the graded elongation of muscular fibers in the first weeks that facilitates the skin remodeling with retraction instead of the delayed expansion occurred in the EBR group. This hypothesis should be investigated by biomechanical models in future research.

Conclusion

The expander-based reconstruction is the most popular method of immediate reconstruction. In this study there was evidence of significant association between complications and clinical variables for the expander cohort and not for the implant-based cohort. The association with radiotherapy was the most significant in univariate and multivariate analyses, less for overweight. The univariate analysis of major complications showed a significant association between complications and implant size, BMI and radiotherapy. In particular, we have observed that larger expander volume is a significant predictor of failure, especially following radiation. The association of very large expander and planned radiation could represent a contraindication for the restricted group of overweight patients. The direct-to-

implant reconstruction of the breast is a safe procedure, without risk of severe complications. Non-significant increase is present only for mild complications after nipple-sparing mastectomy and after neo-adjuvant therapy. Here we have described a method and a safe range of implant size to be used overcoming the 500 grams. In the future its grade of surgical safety should be better compared to the standard expander-based reconstruction in clinical trials. In particular this determination is necessary when eterologous or alloplastic materials are used in the pocket preparation.

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Table 1 – Characteristics of reconstructions and patients for the direct to implant (DTI) and the expander-based reconstructions (EBR) groups.

1. Reconstructions	GROUP	
	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%)
Volume (ml) :		
median, range	370, 125-525	500, 250-800
Q ₁ - Q ₃ (IQR)	301-410 (109)	350-650 (300)
2. 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)
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%)
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%)
Smoke: n (%)		
- NO	47 (77.0%)	127 (63.1%)
- YES	2 (3.3%)	14 (7.0%)
- EX	12 (19.7%)	41 (20.4%)
- not available		19 (9.5%)

Table 2 – details about major and minor complications

GROUP: DTI (N=70)		GROUP: EBR (N=224)	
1. MINOR COMPLICATIONS: n (%)		1. MINOR COMPLICATIONS: n (%)	
- Poor aesthetic result	2 (2.9%)	- Infections	3 (1.3%)
- Implant displacement	1 (1.4%)	- Seroma	1 (0.4%)
- Phlogosis	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 thinned tissue	1 (1.4%)	- Pain in axillary and dorsal region	1 (0.4%)
- Breast pain, alteration of the scapular and humeral movement	1 (1.4%)	- Necrosis	1 (0.4%)
- Skin necrosis with fistula formation	1 (1.4%)	- Phlogosis	2 (0.9%)
		- Hematoma	1 (0.4%)
		- Lateralization of tissue expander	1 (0.4%)
TOTAL	9 (12.9%)	TOTAL	13 (5.8%)
2. MAJOR COMPLICATIONS: n (%)		2. MAJOR COMPLICATIONS: n (%)	
- Poor aesthetic result	1 (1.4%)	- Infections	11 (4.9%)
- Implant rotation with hypercorrection of the upper quadrants Baker 2/3	1 (1.4%)	- Phlogosis	3 (1.3%)
- NMR showed a microcracking of the right implant	1 (1.4%)	- Exposure of tissue expander	8 (3.6%)
		- Breakage / damage of tissue expander	3 (1.3%)
		- Recurrent seroma	1 (0.4%)
		- Skin necrosis	1 (0.4%)
		- Lateralization of tissue expander	1 (0.4%)
TOTAL	3 (4.3%)	TOTAL	28 (12.5%)

Table 3 – association between complications and patient and reconstruction characteristics: univariate analyses Reported in the table are: frequencies of complications (n) and overall reconstructions (N) (categorical variables only); estimated odds ratios of complication with respective 95% C.I.s; p-value 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. OR = odds ratio, p = p-value, NR = not reported, ref = reference category for the calculation of Odds Ratios
1 in the DTI group only one patient with both adjuvant and neoadjuvant therapy was present: thus, was excluded. * p<0.05

	DTI: total complications:		EBR: total complications		EBR: major complications:	
	frequencies: n/N (%)	Estimates: OR (95% C.I.) ; p	frequencies: n/N (%)	Estimates: OR (95% C.I.) ; p	frequencies: n/N (%)	Estimates: OR (95% C.I.) ; 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) ; -
- Adj + Neoadj			1/14 (7.1%)	0.82 (0.08, 4.64) ; -	1/14 (7.1%)	1.35 (0.12, 9.10) ; -
		<i>overall association: p= 0.526</i>		<i>overall association: p= 0.236</i>		<i>overall association: p= 0.391</i>
- 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
Smoke: 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≥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 *
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 *

TABLE 4 – association between complications and patient and reconstruction characteristics: multivariate analyses

OR = Estimated odds ratios of complication with respective 95% C.I.s. * p<0.05

	EBR: total complications:		EBR: major complications	
	Estimates: OR (95% C.I.)	p-value	Estimates: OR (95% C.I.)	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 *
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