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ORIGINAL ARTICLE

# Pre-pectoral breast reconstruction: early and long-term safety evaluation of 146 unselected cases of the early pre-pectoral era of a single-institution, including cases with previous breast irradiation and post-mastectomy radiation therapy

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## Abstract

We re-evaluated acute and early-late toxicity-related factors among pre-pectoral immediate tissue expander/implant (TE/I) breast reconstruction (BR) unselected, first-era, cases, including previous breast radiation treatment and post-mastectomy radiation therapy (PMRT). A retrospective analysis of 146 (117 therapeutic and 29 prophylactic) pre-pectoral reconstructions, between 2012 and 2016, considered patient-related (age, body mass index [BMI], smoke-history, comorbidity, BRCA mutation), and treatment-related characteristics (previous irradiation, axillary surgery, PMRT, pre- and postoperative chemotherapy, endocrine therapy, and target-therapy). Safety was evaluated as acute and early-late complications, and TE/I failures. At multivariate analysis of the 146 cases (117 patients submitted to BR) a significant factor related to acute toxicity was: BMI ≥ 25 (31.3% [≥ 25] vs 8.8% [< 25]; OR 4.44, 95% CI 1.56–12.6; $p = 0.003$), while previous breast surgery on ipsilateral side presented a borderline significance (31.6% [previous surgery] vs 7.4% [no previous surgery]; OR 3.74, 95% CI 0.97–14.40; $p = 0.055$). Factors significantly related to TE/I failure were: current or previous smoking exposition (13.8% [smokers] vs 2.6% [non-smokers]; OR 7.32, 95% CI 1.37–39.08; $p = 0.02$) and preoperative chemotherapy (18.8% [yes] vs 3.5% [no]; OR 8.16, 95% CI 1.29–51.63; $p = 0.026$). At 4-year median follow-up, 3 deaths, 5 locoregional recurrences, and 14 distant metastases occurred. Immediate pre-pectoral BR is safe and effective, with low rates of acute and early-late complications. BMI and previous breast surgery were related to higher complications but not failure; smoking and preoperative chemotherapy were related to TE/I explant. Previous RT and PMRT were related neither to early-late toxicity nor failure.

**Keywords** Pre-pectoral breast reconstruction · Post-mastectomy radiation therapy · Implant based breast reconstruction

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## Introduction

Implant-based breast reconstruction (IBBR), either one- or two-stage by means of tissue expander (TE), is nowadays the most frequent reconstructive choice particularly in conservative mastectomies [1, 2]. After initial diffusion of subcutaneous implant and expander placement in the early era of prosthetic reconstruction [3–5], the development of modified radical mastectomy, e.g. saving the pectoralis major muscle, allowed the introduction of retro-pectoral implant reconstruction, which largely replaced the subcutaneous approach, due to a significant lower rate of postsurgical complications, such as prosthesis extrusion and capsular contracture [6, 7].

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The introduction of biological or synthetic soft tissue replacement devices allowed the so called direct-to-implant (DTI) one-step IBBR with a dual plane retro-pectoral technique, using matrixes as a hammock in the lower pole [8]. Later on, because of the good results of soft tissue replacement devices in a dual plane approach, the rationale in favor of using such devices as a full coverage of TE/I was developed and published first by means of synthetic meshes [9], and immediately after by acellular dermal matrixes (ADMs) [10], thus starting again the era of a subcutaneous approach, this time considered a conservative reconstruction with a complete muscle sparing technique. More recently, many experiences and series have been published in literature reporting the growing popularity of this novel approach in BR [11–25]. And nowadays several algorithms and selection criteria have been proposed to identify the candidates of this new, very popular, approach [26].

The aim of the present study is to go back to the very beginning of the pre-pectoral (pre-pec) era, where patients were mostly unselected, to evaluate the acute and early-late toxicity predictive factors and safety in patients receiving pre-pectoral immediate TE/I based reconstruction. Such an analysis was motivated by the intent to analyze the risk of pre-pec IBBRs in relation to radiation therapy, performed either before or after the reconstruction itself, which is a hot issue in the present era of the pre-pec IBBRs. All the preoperative characteristics and also the post-operative treatments, such as postmastectomy radiation therapy (PMRT), were analyzed as risk factors for complication and failures in an early group of patients of a single Institution, which was one of the first to adopt such an approach. Going back to a very early age of this experience, when selection criteria were quite loose, allowed to assess if RT is a possible risk factor, with a multivariate analysis that considered many other features.

## Patients and methods

### Patients

We performed a retrospective analysis of 117 consecutive patients who underwent therapeutic or prophylactic pre-pectoral IBBR from October 2012 to May 2016 at our Center (117 therapeutic and 29 prophylactic). Patients underwent DTI pre-pectoral reconstructions or two-stage TE pre-pectoral implant-based BR.

We recorded individual patient-related features (i.e., age, body mass index [BMI], smoke-history, comorbidity, BRCA mutation, previous RT), and BC-related treatments characteristics (i.e., axillary surgery, adjuvant post-mastectomy radiotherapy [PMRT], preoperative and postoperative chemotherapy, endocrine therapy, and target therapy).

Toxicity profile was evaluated in terms of complications related to IBBR; we recorded acute toxicity, late toxicity, and TE/I explantation rate, considered as a failure. As previously published [9, 12, 13] acute toxicities were classified as follows: BR failure (i.e., TE/I explantation) and surgical complications, namely, skin-nipple necrosis, seroma, wound dehiscence, surgical site infection, hematoma, and atopic versus graft reaction. Early-late toxicities (assessed at 2 years from the DTI reconstruction, and at least after one year form second stage in every TE case) were classified as follows: chronic seroma, infection, capsular contracture, extrusion/damage of the implant.

### Treatments

Surgical techniques for DTI [9] and for two-stage TE reconstructions have been previously described [13]. Patients scheduled at our institution for conservative mastectomies, either nipple-sparing or skin-sparing mastectomy, were thoroughly informed of different reconstruction options, either autologous or prosthetic. The pre-pec approach was thoroughly described and an informed consent was signed by every patient. The pre-pectoral technique was started at our institution in 2011 as a pilot protocol approved by the Hospital Drugs and Devices Service Committee, designed in accordance with the Hospital Ethical Committee rules on non-randomized clinical studies, and it was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

If a TE approach was chosen, patients were informed of the muscle-sparing subcutaneous option with synthetic mesh coverage only (totally subcutaneous, pre-pectoral TE adjustment, and wrapped in a titanium-coated polypropylene synthetic mesh bag, TiLOOP® Bra, pfm medical, Cologne Germany). In case of two-stage IBBR mesh wrapping around TE was loose, considering final expansion diameter of TE. Outpatient expansions were done every week or every 2 weeks for the first 2 months, with 40–50 mL of sterile solution each time [13]. On the other hand, in case of DTI the synthetic mesh wrapping was tight around the chosen implant adjusting the mesh itself by means of a purse string suture [12]. A specific digital database was adopted in 2012 to prospectively collect all the consecutive pre-pectoral cases performed, encompassing all baseline characteristics, oncological parameters, therapies and follow-up, surgical complications, outpatient visits, re-interventions, second stage reconstructions in case of TE, and long-term outcomes. All further surgical procedures and postoperative radiation therapies, occurred between the first reconstruction and last follow-up, were investigated and registered.

All patients with a 2-year minimum follow-up were submitted to both an objective and a subjective long-term outcomes evaluation. At the objective long-term evaluation a

score was given to the capsular contracture according the 4-grade Baker scale [27]. TE reconstruction cases were all at 1 year from second-stage by the time of the 2-year long-term evaluation. PMRT (when indicated) was always performed between first and second surgical stage. The subjective evaluation was conducted using the postoperative section of BREAST-Q reconstruction module (Memorial Sloan-Kettering Cancer Center and The University of British Columbia© 2006, all rights reserved). Our experiences in subjective assessment was previously published and did not represent the aim of the present study [13].

All patients were discussed case-by-case by our breast cancer multidisciplinary team. Systemic therapies indications, included preoperative chemotherapy and postoperative chemotherapy/endocrine therapy, followed national and international oncological guidelines. When indicated, PMRT volumes and doses consisted of affected chest-wall plus ipsilateral axillary 3–4 level irradiation (50 Gy in 25 fractions), independently of axillary surgical treatment. Axillary 1–2 levels and internal mammary nodes were never irradiated in present series, since at our Institution the radiation treatment volumes include not operated axillary levels without internal mammary nodes. Internal mammary nodes are included only if positive or suspicious at diagnostic imaging. PMRT included the definitive implant or tissue expander and was delivered between 10 and 20 weeks from surgery (in any case before the second-stage reconstruction); in case of postoperative chemotherapy, PMRT was delivered at the end of treatment (between 4 and 6 weeks from the last cycle). Conversely, PMRT was given concomitant to adjuvant endocrine therapy (in case of both aromatase inhibitors and tamoxifen).

### Pathology methods

Every case was diagnosed by specialized pathologists, dedicated to breast diseases. Diagnosis was made according to the AJCC and WHO criteria. Starting from macroscopic examination, in order to correctly diagnose possible site/s of microinvasion, handling of surgical specimens included ''bread-slicing'' method: mastectomies specimens were serially sectioned at 1.5–2 mm intervals from superficial to deep aspects. Tissue sections were chosen for microscopic examination on corresponding mammographic patterns in case of mastectomy. Focus or foci of microcalcifications were completely and sequentially submitted to histological examination. Cancer subtype (Luminal A, Luminal B HER-2 negative, Luminal B HER-2 positive, HER-2 positive and Triple Negative) was determined by ER, PR receptors, and HER-2 status. Ki-67 stain was used for distinction of Luminal A and B. Hormone receptor status was reported as negative when < 1% of tumors cells stained at IHC. HER2 status was determined only by IHC in cases scored as 0 or 1 + (negative) and 3 + (positive), otherwise a FISH test was adopted.

### Statistical analysis

The association between selected individual characteristics and selected toxicities was firstly evaluated by a simple chi-square test (Table 1). Secondly, a univariate logistic analysis was performed to estimate the association between each individual parameter and selected toxicities (Tables 2 and 3). The risk of toxicity was calculated by odd ratios (OR) and 95% confidence intervals (95% CI). A logistic multivariate analysis including parameters resulted to be statistically significant at univariate analysis was finally performed.

Survival analyses were performed in relation to specific events: local recurrences (LR), distant metastasis (DM), and death. Overall survival (OS) was defined as the time from the surgery to time of death or last follow-up. Progression-free survival (PFS) as time to specific events (LR or DM) was measured from the date of surgery to the date of event. Patients who died before experiencing a disease occurrence were considered censored at their dates of death. Event rates and their 95% CI were calculated according to the Kaplan–Meier method.

Differences between groups of patients were evaluated using the log-rank test. Univariate Cox proportional regression model was used to obtain the hazard ratios (HR) and corresponding 95% CI for specific events. A multivariate Cox proportional regression model was used to identify independent factors of specific events. All two-sided p-values less than 0.05 were considered significant. Statistical analyses were performed using SPSS Statistics software (version 22; SPSS Statistics, IBM Corporation, Armonk, NY, USA).

## Results

### Patients' characteristics and surgical complication rates

We analyzed 117 patients, 88 had a unilateral mastectomy, while 29 had a bilateral mastectomy, with an overall number of 146 consecutive pre-pectoral IBBRs, 117 therapeutic and 29 prophylactic mastectomies. A bilateral procedure was performed in 6 patients with bilateral cancer, in 6 patients with a BRCA mutation and in 17 women who chose to remove the contralateral breast. The 12 bilateral mastectomies in 6 BRCA-mutation carriers and the 17 contralateral mastectomies represented the 29 cases of prophylactic mastectomies (until recently, a prophylactic mastectomy was offered, at our Institution, both to BRCA-mutation carries and to those women scheduled

**Table 1** Main features of the whole series

| | Cases *n* | Acute toxicity *n* (%) | TE/I explant *n* (%) | Late toxicity *n* (%) |
|---|---|---|---|---|
| Group age, years | | | | |
| < 45 | 35 | 5 (14.3) | 2 (5.7) | 0 |
| 46–55 | 64 | 7 (10.9) | 2 (3.1) | 2 (3.1) |
| > 55 | 47 | 8 (17.0) | 3 (6.4) | 0 |
| *p* value | | 0.65 | 0.70 | 0.27 |
| Smoking habits | | | | |
| Never smoker | 117 | 15 (12.8) | 3 (2.6) | 1 (0.8) |
| Former smoker and smokers | 29 | 5 (17.2) | 4 (13.8) | 1 (3.4) |
| *p* value | | 0.55 | **0.029** | 0.36 |
| Hypertension | | | | |
| No | 119 | 15 (12.6) | 5 (4.2) | 2 (1.7) |
| Yes | 27 | 5 (18.5) | 2 (7.4) | 0 |
| *p* value | | 0.53 | 0.61 | 1.0 |
| Diabetes | | | | |
| No | 143 | 17 (11.9) | 7 (4.9) | 2 (1.4) |
| Yes | 3 | 3 (100.0) | 0 | 0 |
| *p* value | | **0.002** | 1.0 | 1.0 |
| Previous breast RT | | | | |
| No | 117 | 10 (8.5) | 6 (5.1) | 1 (0.8) |
| Yes on ipsilateral side | 29 | 10 (34.5) | 1 (3.4) | 1 (3.4) |
| *p* value | | **0.001** | 1.0 | 0.36 |
| Previous breast surgery | | | | |
| No | 92 | 8 (27.6) | 5 (5.4) | 0 |
| Ipsilateral | 38 | 12 (31.6) | 2 (5.3) | 2 (5.3) |
| Contralateral | 16 | 0 | 0 | 0 |
| *p* value | | **0.001** | 0.64 | 0.06 |
| BMI ($kg/m^2$) | | | | |
| < 25 | 114 | 10 (8.8) | 5 (4.4) | 2 (1.7) |
| ≥ 25 | 32 | 10 (31.2) | 2 (6.2) | 0 |
| *p* value | | **0.003** | 0.65 | 1.0 |
| Bilateral breast cancer | | | | |
| No | 140 | 20 (14.3) | 7 (5.0) | 2 (1.4) |
| Yes | 6 | 0 | 0 | 0 |
| *p* value | | 1.0 | 1.0 | 1.0 |
| Mastectomy intent | | | | |
| Prophylactic | 29 | 3 (10.3) | 1 (3.4) | 0 |
| Therapeutic | 117 | 17 (14.5) | 6 (5.1) | 2 (1.7) |
| *p* value | | 0.77 | 1.0 | 1.0 |
| Skin-reducing | | | | |
| No | 133 | 18 (13.5) | 5 (3.7) | 2 (1.5) |
| Yes | 13 | 2 (15.4) | 2 (15.4) | 0 |
| *p* value | | 0.69 | 0.12 | 1.0 |
| Nipple-sparing | | | | |
| No | 28 | 3 (10.7) | 1 (3.6) | 0 |
| Yes | 118 | 17 (14.4) | 6 (5.1) | 2 (1.7) |
| *p* value | | 0.72 | 1.0 | 1.0 |
| Mastectomy | | | | |
| Nipple/areola-sparing mastectomy | 110 | 16 (14.5) | 5 (4.5) | 2 |
| Skin-reducing nipple-sparing mastectomy | 8 | 1 (12.5) | 1 (12.5) | 0 |
| Skin-reducing mastectomy | 5 | 1 (20.0) | 1 (20.0) | 0 |

**Table 1** (continued)

| | Cases *n* | Acute toxicity *n* (%) | TE/I explant *n* (%) | Late toxicity *n* (%) |
|---|---|---|---|---|
| Skin-sparing mastectomy | 23 | 2 (8.7) | 0 | 0 |
| *p* value | | 0.87 | 0.19 | 0.88 |
| Axillary surgery | | | | |
| None | 34 | 7 (20.6) | 1 (2.9) | 0 |
| SNB | 77 | 8 (10.4) | 4 (5.2) | 0 |
| ALND | 35 | 5 (14.3) | 2 (5.7) | 2 (5.7) |
| *p* value | | 0.35 | 0.84 | **0.04** |
| Adjuvant RT | | | | |
| No | 108 | 14 (13.0) | 4 (3.7) | 0 |
| Chest wall and regional node irradiation | 37 | 5 (13.5) | 3 (8.1) | 2 (5.4) |
| *p* value | | 0.28 | 0.18 | **0.024** |
| Chemotherapy* | | | | |
| None | 86 | 12 (13.9) | 3 (3.5) | 1 (1.2) |
| Postoperative | 43 | 5 (11.6) | 1 (2.3) | 1 (2.3) |
| Preoperative | 16 | 3 (18.7) | 3 (18.7) | 0 |
| *p* value | | 0.78 | **0.022** | 0.77 |
| Adjuvant endocrine therapy* | | | | |
| No | 53 | 5 (9.4) | 1 (1.9) | 1 (1.9) |
| Yes | 92 | 15 (16.3) | 6 (6.5) | 1 (1.1) |
| *p* value | | 0.32 | 0.42 | 1.0 |
| (Neo)adjuvant trastuzumab* | | | | |
| No | 121 | 17 (14.0) | 6 (5.0) | 1 (0.8) |
| Yes | 24 | 3 (12.5) | 1 (4.2) | 1 (4.2) |
| *p* value | | 1.0 | 1.0 | 0.31 |
| Device | | | | |
| Tissue expander | 64 | 10 (15.6) | 4 (6.2) | 0 |
| Implant | 82 | 10 (12.2) | 3 (3.7) | 2 (2.4) |
| *p* value | | 0.63 | 0.70 | 0.50 |
| Total | 146 | 20 | 7 | 2 |

Association analysis by $\chi^2$ test between selected parameters and toxicity in 146 mastectomies and pre-pectoral IBBR. In bold *p* value < 0.05

*TE/I* tissue expander/implant, *RT* radiotherapy, *BMI* body mass index, *SNB* sentinel node biopsy, *ALND* axillary lymph node dissection

*Information not available in one case

to a mastectomy for cancer who required such a procedure for the contralateral side too, after a psychiatric evaluation. Nowadays a prophylactic mastectomy can be performed to BRCA-mutation carriers only after a genetic and psycho-oncologic counselling).

Most patients were aged more than 45 years. A minority of the series had received previous breast RT and previous breast surgery for BC.

Concerning postoperative treatments, 37 patients received PMRT, 92 endocrine treatments, and 43 chemotherapy. Main patient characteristics and association analysis by chi-square test between selected parameters and surgical outcomes (acute toxicity, TE/I explant, early late toxicity) are summarized in Table 1.

We recorded 20 representative acute complications, namely: 11 infections, 3 skin flap necroses, 3 wound dehiscences, 1 hematoma, 2 nipple necroses.

At univariate analysis, previous breast RT (34.5% [RT] vs 8.5% [no RT]; $p = 0.001$), previous ipsilateral breast surgery (31.6% [previous surgery] vs 7.4% [no previous surgery]; $p = 0.001$), and BMI ≥ 25 (31.3% [≥ 25] vs 8.8% [< 25]; $p = 0.002$) emerged as significant risk factors for acute toxicity ($n = 20$). At multivariate logistic analysis between individual parameters only BMI ≥ 25 (OR 4.44, 95% CI 1.56–12.6; $p = 0.005$) confirmed the statistical significance, while previous breast surgery on ipsilateral side was borderline (OR 3.74, 95% CI 0.97–14.40; $p = 0.055$). Main results are described in Table 2.

**Table 2** Association analysis by logistic models between individual parameters and acute toxicity ($n=20$) in 146 mastectomies and pre-pectoral IBBR

| | Cases | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | | OR (95% CI) | *p* | OR (95% CI) | *p* |
| Group age, years | | | | | |
| < 45 | 35 | 1 | | | |
| 46–55 | 64 | 0.74 (0.22–2.52) | 0.63 | – | |
| > 55 | 47 | 1.23 (0.37–4.15) | 0.74 | | |
| Smoking habits | | | | | |
| Never smoker | 117 | 1 | | – | |
| Former smoker and smokers | 29 | 1.42 (0.47–4.28) | 0.54 | | |
| Hypertension | | | | | |
| No | 119 | 1 | | – | |
| Yes | 27 | 1.58 (0.52–4.79) | 0.42 | | |
| Diabetes | | | | | |
| No | 143 | 1 | | – | |
| Yes | 3 | Not evaluable | 0.99 | | |
| Previous breast RT | | | | | |
| No | 117 | 1 | | 1 | |
| Yes on ipsilateral side | 29 | **5.63 (2.07–15.4)** | **0.001** | 2.22 (0.56–8.74) | 0.26 |
| Previous breast surgery | | | | | |
| No previous surgery on IBBR side | 108 | 1 | | 1 | |
| Previous surgery on ipsilateral side | 38 | **5.77 (2.14–15.58)** | **0.001** | 3.74 (0.97–14.40) | 0.055 |
| BMI (kg/m$^2$) | | | | | |
| < 25 | 114 | 1 | | 1 | |
| ≥ 25 | 32 | **4.73 (1.76–12.7)** | **0.002** | **4.67 (1.59–13.75)** | **0.005** |
| Bilateral breast cancer | | | | | |
| No | 140 | 1 | | – | |
| Yes | 6 | Not evaluable | 0.99 | | |
| Mastectomy intent | | | | | |
| Prophylactic | 29 | 1 | | – | |
| Therapeutic | 117 | 1.47 (0.40–5.41) | 0.56 | | |
| Skin-reducing | | | | | |
| No | 133 | 1 | | – | |
| Yes | 13 | 1.16 (0.24–5.68) | 0.85 | | |
| Nipple-sparing | | | | | |
| No | 28 | 1 | | | |
| Yes | 118 | 1.40 (0.38–5.16) | 0.61 | | |
| Mastectomy | | | | | |
| Nipple/areola-sparing mastectomy | 110 | 1 | | | |
| Skin-reducing nipple-sparing mastectomy | 8 | 0.84 (0.10–7.27) | 0.87 | – | |
| Skin-reducing mastectomy | 5 | 1.47 (0.15–14.0) | 0.74 | | |
| Skin-sparing mastectomy | 23 | 0.56 (0.12–2.62) | 0.46 | | |
| Axillary surgery | | | | | |
| None | 34 | 1 | | – | |
| SNB plus ALND | 112 | 0.51 (0.18–1.39) | 0.19 | | |
| Postoperative RT | | | | | |
| No | 108 | 1 | | – | |
| Chest wall and regional node irradiation | 37 | 1.05 (0.35–3.14) | 0.93 | | |
| Chemotherapy* | | | | | |
| None | 86 | 1 | | – | |
| Postoperative plus preoperative | 59 | 0.97 (0.37–2.53) | 0.95 | | |
| Adjuvant endocrine therapy* | | | | | |

**Table 2** (continued)

| | Cases | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | | OR (95% CI) | *p* | OR (95% CI) | *p* |
| No | 53 | 1 | | – | |
| Yes | 92 | 1.87 (0.64–5.48) | 0.25 | | |
| (Neo)adjuvant trastuzumab* | | | | | |
| No | 121 | 1 | | – | |
| Yes | 24 | 0.87 (0.24–3.25) | 0.84 | | |
| Device | | | | | |
| Tissue expander | 64 | 1 | | – | |
| Implant | 82 | 0.75 (0.29–1.93) | 0.55 | | |

Univariate and multivariate logistic analysis: odds ratio (OR), 95% CI and *p* value. In bold *p* value < 0.05
*RT* radiotherapy, *BMI* body mass index, *SNB* sentinel node biopsy, *ALND* axillary lymph node dissection
*Information not available in one case

**Table 3** Association analysis by logistic models between individual parameters and tissue expander/implant (TE/I) explant ($n = 7$) in 146 mastectomies and pre-pectoral IBBR

| Feature | Cases | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | | OR (95% CI) | *p* | OR (95% CI) | *p* |
| Smoking habits | | | | | |
| Never | 117 | 1 | | 1 | |
| Smokers or former smokers | 29 | 6.08 (1.28–28.88) | **0.023** | 7.32 (1.37–39.08) | **0.02** |
| Chemotherapy | | | | | |
| None | 86 | 1 | | 1 | |
| Postoperative | 43 | 0.66 (0.07–6.53) | 0.72 | 0.69 (0.07–7.14) | 0.76 |
| Preoperative | 16 | 6.39 (1.16–35.08) | **0.033** | 8.16 (1.29–51.63) | **0.026** |

Univariate and multivariate logistic analysis: odds ratio (OR), 95% CI and *p* value. In bold *p* value $p < 0.05$

At univariate analysis, significant risk-factor related to TE/I removal, 7 cases (reconstruction failure), were current or previous smoking exposition (13.8% [smokers] vs 2.6% [non-smokers]; $p = 0.023$) and preoperative chemotherapy (18.8% [yes] vs 3.5% [no]; $p = 0.033$). At multivariate logistic analysis both features confirmed the statistical significance ($p = 0.02$ and $p = 0.026$, respectively). The main results are reported in Table 3.

We recorded only two capsular grade III-IV contractures as late complication events at the 2-year follow up visit. No other cases of seroma, infection or different late complications were registered.

### Survival

At a 4.0 year median follow up time (mean 3.9 years; range 3–5.5), 3 deaths, 5 LR, and 14 DM occurred among the series. At time of analysis, OS was 78.1%, LR free-survival was 95.0%, and DM free-survival was 71.6%. Kaplan–Meier survival analysis for significant parameters are summarized in Table 4.

## Discussion

Two-stage retro-pectoral implant-based BR has been the most common method for breast reconstruction for decades starting from the '80s.

Lately, at the beginning of the new millennium, the introduction of matrixes, either synthetic or biologic, has opened the era of dual-plane techniques for an immediate implant positioning, the so called DTI. Eventually, in the last decade, recent advances in surgical techniques and matrixes technology have made pre-pectoral implant-based BR, either DTI or two-stage using TEs, feasible, showing enthusiastic results [28].

In a narrative review describing new insights on pre-pectoral BR [29], the authors showed that the subcutaneous pre-pectoral approach is safe, feasible, and has excellent short-term cosmetic and patient satisfaction outcomes. Even though further studies are strongly required to compare short- and long-term outcomes with the previous standard of care, early postoperative pain and quality of life evaluations seems to be equivalent between groups [30].

**Table 4** Kaplan–Meier survival analysis in 117 patients treated with pre-pectoral IBBR at a 3-year median follow up time: patients at start, events (deaths, local recurrence, distant metastases), *p* values from log-rank test

| Variable | Cases | Deaths $n=3$ | Local recurrence $n=5$ | Distant metastases $n=14$ |
|---|---|---|---|---|
| Group age, years | | | | |
| < 45 | 23 | 2 (8.7) | 2 (8.7) | 2 (8.7) |
| 46–55 | 53 | 0 | 2 (3.8) | 7 (13.2) |
| > 55 | 41 | 1 (2.4) | 1 (2.4) | 5 (12.2) |
| *p* value | | 0.10 | 0.46 | 0.73 |
| Smoking habits | | | | |
| Never smoker | 95 | 2 (2.1) | 4 (4.2) | 13 (13.7) |
| Former smoker and smokers | 22 | 1 (4.5) | 1 (4.5) | 1 (4.5) |
| *p* value | | 0.96 | 0.90 | 0.29 |
| Hypertension | | | | |
| No | 92 | 2 (2.2) | 5 (5.4) | 9 (9.8) |
| Yes | 25 | 1 (4.0) | 0 | 5 (20) |
| *p* value | | 0.47 | 0.28 | 0.064 |
| BRCA mutation-carrier | | | | |
| No | 111 | 3 (2.7) | 5 (4.5) | 13 (11.7) |
| Yes | 6 | 0 | 0 | 1 (16.7) |
| *p* value | | 0.82 | 0.61 | 0.66 |
| Diabetes | | | | |
| No | 114 | 3 (2.6) | 5 (4.4) | 14 (12.3) |
| Yes | 3 | 0 | 0 | 0 |
| *p* value | | 0.87 | 0.72 | 0.57 |
| Previous breast RT | | | | |
| No | 97 | 3 (3.1) | 4 (4.1) | 12 (12.4) |
| Yes on ipsilateral side | 20 | 0 | 1 (5.0) | 2 (10.0) |
| *p* value | | 0.44 | 0.91 | 0.68 |
| Previous breast surgery | | | | |
| No | 78 | 2 (2.6) | 3 (3.8) | 10 (12.8) |
| Ipsilateral | 33 | 0 | 1 (3.0) | 3 (9.1) |
| Contralateral | 6 | 1 (16.7) | 1 (16.7) | 1 (16.7) |
| *p* value | | 0.22 | 0.26 | 0.80 |
| BMI ($kg/m^2$) | | | | |
| < 25 | 90 | 2 (2.2) | 5 (5.5) | 11 (12.2) |
| ≥ 25 | 27 | 1 (3.7) | 0 | 3 (11.1) |
| *p* value | | 0.50 | 0.22 | 0.95 |
| Bilateral breast cancer | | | | |
| No | 111 | 3 (2.7) | 5 (4.5) | 14 (12.6) |
| Yes | 6 | 0 | 0 | 0 |
| *p* value | | 0.82 | 0.59 | 0.34 |
| Mastectomy | | | | |
| Nipple/areola-sparing mastectomy | 84 | 2 (2.4) | 4 (4.8) | 7 (8.3) |
| Skin-reducing nipple-sparing mastectomy | 5 | 0 | 1 (20.0) | 0 |
| Skin-reducing mastectomy | 5 | 0 | 0 | 1 (20.0) |
| Skin-sparing mastectomy | 23 | 1 (4.3) | 0 | 6 (26.1) |
| *p* value | | 0.75 | 0.12 | 0.21 |
| Axillary surgery | | | | |
| None | 19 | 0 | 1 (5.3) | 2 (10.5) |
| SNB | 63 | 1 (1.6) | 2 (3.2) | 2 (3.2) |
| ALND | 35 | 2 (5.7) | 2 (5.7) | 10 (28.6) |
| *p* value | | 0.85 | 0.84 | **0.008** |
| Adjuvant RT | | | | |

**Table 4** (continued)

| Variable | Cases | Deaths $n=3$ | Local recurrence $n=5$ | Distant metastases $n=14$ |
|---|---|---|---|---|
| No | 83 | 1 (1.2) | 3 (3.6) | 6 (7.2) |
| Chest wall and regional node irradiation | 33 | 2 (6.1) | 2 (6.1) | 8 (24.2) |
| *p* value | | 0.57 | 0.74 | **0.036** |
| Chemotherapy* | | | | |
| None | 65 | 0 | 1 (1.5) | 1 (1.5) |
| Postoperative | 40 | 1 (2.5) | 3 (7.5) | 8 (20.0) |
| Preoperative | 11 | 2 (18.2) | 1 (9.1) | 5 (45.4) |
| *p* value | | 0.11 | 0.24 | **0.0001** |
| Adjuvant endocrine therapy* | | | | |
| No | 34 | 0 | 2 (5.9) | 5 (14.7) |
| Yes | 82 | 3 (3.6) | 3 (3.6) | 9 (11.0) |
| *p* value | | 0.23 | 0.59 | 0.59 |
| (Neo)adjuvant trastuzumab* | | | | |
| No | 93 | 3 (3.2) | 4 (4.3) | 11 (11.8) |
| Yes | 23 | 0 | 1 (4.3) | 3 (13.0) |
| *p* value | | 0.36 | 0.95 | 0.90 |
| Total | 117 | 3 (2.5) | 5 (4.3) | 14 (12.0) |

In bold $p$ value $< 0.05$

*RT* radiotherapy, *BMI* body mass index, *SNB* sentinel node biopsy, *ALND* axillary lymph node dissection

*Information not available in one case

In the last 5 years the pre-pectoral approach has reached a sky-rocketing success in the breast reconstruction scenario, and, even in the absence of any level IA evidence, many selection criteria and algorithm have been proposed. Nonetheless, a cloudy area of surgical management entails the relationship between pre-pec IBBR and radiation therapy, either as a previous treatment or as a PMRT treatment, with a scarce presence in the literature. We decided to go back to our very early cases, at the very beginning of the pre-pec era, which we started in 2011, when selection criteria were quite loose. Analyzing an early population we have had the opportunity to include many different characteristics and risk factors in a quite large series, with also a significant number of cases with previous breast RT and with PMRT, to perform a multivariate analysis with many unselected patients and draw quite comprehensive conclusions.

We confirmed the overall safety of the pre-pectoral approach, showing 13.7% of acute postoperative complications with 4.8% TE/I failure rate, and 1.4% late surgical complications at the 2-year assessment.

An increasing number of women who undergo IBBR either one or two-stage will require PMRT [31], since the meta-analysis of Early Breast Cancer Trialists' Collaborative Group (EBCTCG) confirmed a significant reduction of both LR and BC mortality in patients with pathological nodal involvement [32]. Moreover, regional nodal irradiation improved outcomes for most of high-intermediate risk BC patients [33, 34].

Concerning the role of adjuvant treatments great attention focused on PMRT over time, and the impact of its timing to a TE or a permanent implant has not been clarified yet. Patients receiving PMRT after pre-pectoral BR showed a capsular contracture rate and severity significantly lower as compared to those receiving PMRT after retro-pectoral breast reconstruction [35–37].

Sinnott and colleagues [35] in a recently published study on 274 patients showed a capsular contracture rate difference of 36.1% (52.2% vs 16.1%; $p=0.0018$) and a 61.1% difference of Baker grades 3 or 4 severity (83.3% vs 22.2%; $p=0.0092$) in favor of pre-pectoral BR. Ricci and colleagues [36] published a review including 20 studies (range 2000–2016) and 2348 patients showing that PMRT delivered on TE resulted in higher rates of reconstructive failure as compared to PMRT applied to permanent implants (20% vs 13.4%, OR 2.33; $p=0.0083$), but lower rates of capsular contracture (24.5% vs 49.4%, OR 0.53; $p=0.083$).

Although the risk of reconstructive failure is significantly higher for patients with TE radiation compared to patients with permanent implant radiation, the aesthetic results and capsular contracture rates are slightly better [37]. Therefore, immediate TE/I reconstruction seems to be a reasonable surgical option also in the setting of PMRT [31].

In our study 37 cases received PMRT (25.3%), 19 irradiated the TE and 18 the permanent implant. At the 2-year late complication assessment only two patients showed grade III-IV capsular contracture (5.4% of patients receiving PMRT),

both in case of immediate permanent implant reconstruction. The lower rate of capsular contracture in TE IBBR pre-pec cases submitted to PMRT could be explained, in our experience, to the fact that a fat graft procedure on the irradiated skin flap is always performed during the second stage procedure in such cases, thus permitting a regenerative process to the irradiated tissues. Moreover, thanks to the recent advance in surgical and radiation techniques [38], PMRT seemed not to be the only risk factor for unsatisfactory postoperative outcomes in pre-pectoral reconstructions.

Indeed, in our single-center experience, we evidenced BMI ≥ 25 at diagnosis (OR 4.44, CI 95% 1.56–12.6; $p = 0.005$) as an independent risk-factor of acute surgical complications development. Previous breast surgery on the IBBR side was almost close to significance (OR 3.74, 95% CI 0.97–14.40; $p = 0.055$). Smoking habits (OR 7.32, CI 95% 1.37–39.08; $p = 0.02$) and preoperative chemotherapy (OR 8.16, CI 95% 1.29–51.6; $p = 0.026$) resulted as independent risk-factors of TE/I explant (reconstruction failure).

Therefore, patient selection for the pre-pectoral technique seems to be crucial and it is dependent on patient-related factors (such as smoking, comorbidities, previous treatments such as RT, breast size, BMI, and lifestyle), as well as adjuvant prescribed treatments (local and systemic therapies) [29, 39–43].

Concerning survival outcomes, a direct comparison between published studies is limited mainly due to different reconstruction techniques used, several missing data on RT (schedule, volume, quality assurance) and systemic therapies (drugs, regimens, doses, setting) [44–48]. However, in a meta-analysis on 19 studies immediate breast reconstruction after mastectomy showed at least equivalent overall survival and disease-free survival as compared to mastectomy alone [49].

Although the short-term follow up did not allowed any definitive conclusions on survival, not surprisingly our study identified a more extensive local treatment (i.e., PMRT, ALND) and systemic treatments needs (i.e., preoperative chemotherapy) as independent risk factors for DM development.

## Conclusions

In our experience, pre-pectoral IBBR, either one or two-stage, was safe independent of device (TE or implant) and postoperative treatments. Preoperative information should be carefully considered to assess the overall procedural risks and to individualize the reconstructive management, particularly BMI and previous ipsilateral breast treatments. On the other hand, a foreseen PMRT doesn't seem to be a possible hindrance to the pre-pec IBBR. However, further investigations and mature follow-up are warranted to confirm these results.

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## Declarations

**Conflict of interest** All authors have no conflict of interest to declare.

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