International Prospective REgistry on Pre-pectorAl breast REconstruction (I-PREPARE EUBREAST-11R)

Introduction/Rationale

Remarkably, while breast cancer surgery experienced a progressive de-escalation in the last decades, mastectomy rates remain around 30-40%. This rate could be mainly due to the increased use of preoperative breast MRI, high genetic risk, patient's choice for contralateral prophylactic mastectomy (CPM), younger breast cancer population, higher disease stage and aggressive tumour biology. In detail, up to 1/3 of breast cancer patients aged from 22 to 44 years undergo a CPM and about 40% of mutation carriers decide for bilateral risk reducing mastectomy(1-3).

Hence, more and more women undergoing mastectomy have to see their body image impaired with a great detriment to their psychosocial functioning and quality of life even though immediate breast reconstruction (IBR) could provide excellent aesthetic results (4-6). Surgery can profoundly affect body image and self-esteem, and IBR at the time of mastectomy is therefore to be offered for most patient to improve quality of life.

In many countries, implant-based breast reconstruction is the most commonly performed reconstructive procedure, most-often independent of whether radiation therapy is planned after mastectomy(7).

After the initial experience with subcutaneous implant positioning directly under the mastectomy flap in the 1970s, this technique was abandoned due to a high rate of implant loss (28%), flap necrosis (13.5%) and capsular contracture (56%)(8, 9). For this reason, the positioning of the implant in an "artificially" created pocket under the pectoralis muscle became the standard of care, pushing IBR to evolve into a subpectoral two-stage (tissue expander followed by definitive implant) approach. However, over time the surgical technique has improved, implant loss and flap necrosis rates have decreased (9% and <5%, respectively) and polyurethane implants have reduced capsular contracture rates (0.4-1%% at more than ten-year follow-up)(10-12). In particular, when considering irradiated breasts the capsular contracture occurs more frequently than in non-irradiated ones (HW=12.5, $p<0.001$), and the relative risk was higher (HR 0.3, $p=0.003$) with textured implants compared with the polyurethane ones(13). Firstly, biological and synthetic meshes have been used to complete the subpectoral pocket inferiorly and allow the placement of a definitive implant immediately after mastectomy. Secondly, the same devices have been applied to cover the implant and position it superficial from the pectoralis major, thus again subcutaneously, thereby avoiding to lift the muscle with great benefits in terms of complications (no animation deformity, no chronic pain, no loss of muscular function), patients' wellbeing, postoperative pain and recovery. Furthermore, as several studies reported higher rates of infection and seroma as well as increased healthcare cost when meshes were used, new reconstructive solutions have been proposed (7, 14-19). In 2019, de Vita et al. have reported their preliminary experience with polyurethane breast implants in pre-pectoral positioning for IBR without any kind of implant coverage. Results on 21 patients are encouraging with no major complications, satisfactory cosmetic outcomes and excellent patient satisfaction (20). Similarly, Manrique et al. reported the experience from the Mayo Clinic on 21 patients with equally good results when compared with pre-pectoral reconstruction with matrices, but reduced costs and operative time (21). Data on pre-pectoral breast reconstruction shows a promising technique restoring a natural-looking breast with a simple one-stage technique and an acceptable complication rate (22).

In 2019 a joint consensus on pre-pectoral reconstruction has been published by UK, European and USA breast and plastic surgeons, they conclude that any preferred surgical technique should be applied with no specific indications to each surgical method (with or without biological or synthetic meshes, not mentioning to polyurethane-covered implants) and recommend to auditing results. In particular, they suggested to collect both early and late data on patient-reported outcomes, re-admission, re-surgery, implant-loss, infection and revision surgery. In fact, the pre-pectoral approach is under-represented in audit trials (around 2% in iBRA study) and literature mainly reports comparative studies with the subpectoral reconstruction or single-centre case series (10, 18, 23-29). Parallel to increased rates of IBR there is an increase in the rate of patients who are referred for radiation therapy after mastectomy (30-33). Radiation in the setting of breast reconstruction (regardless of the timing of reconstruction), increases the risk of complications, such as capsular contracture (2.5 times more compared to without radiation), and lead to poorer aesthetic outcomes. This often results in more subsequent surgeries, and in some published series more than 20% risk of removing the implant (34-39).
The need to improve patients' quality of life (reduction of psychological distress and avoidance of the postmastectomy syndrome) led to refinement of the surgical techniques to produce aesthetic outcomes as close as possible to that of the pre-mastectomy breast shape and the contralateral intact breast. Even though these new surgical procedures are considered oncologically safe for breast cancer patients and for risk reducing surgeries in high-risk patients, they were not evaluated in prospective randomized trials. The 2016 Cochrane Database Systematic Reviews stated that there is no prospective data to support oncological safety of these procedures (40). Therefore, it is our aim to prospectively evaluate the utilization of the pre-pectoral approach, and evaluate oncological and aesthetic outcomes related to each type of surgical technique and the use of postmastectomy radiation therapy. Based on these premises the EUBREAST study group decided to initiate a prospective cohort study as an international project that aims at comparatively evaluating data on different surgical techniques of pre-pectoral breast reconstruction with or without radiation

Study design
International prospective cohort study

Study aims
Primary endpoint:

- Implant-loss at three months postoperatively defined as the unplanned removal or loss of the implant as a result of infection or other complication

Secondary endpoints:

- Infection defined as *minor* if oral antibiotic was required, *major* if surgical revision and/or hospitalisation was necessary;
- Re-admission and re-operation rates (reference value for both: 18% at 3 months (10));
- Subgroup analysis according to technique and device used (to update after all feasibility questionnaires come back);
- Quality of life through BREASTQ Breast Reconstruction Module questionnaires before and

after breast reconstruction at 6 and 12, 24 months;

- Early onset complication at 3 month follow up: seroma, hematoma/bleeding, skin flap or T junction necrosis, nipple necrosis, wound dehiscence, implant malposition (i.e. rotation, displacement etc..);
- late-onset complications at 6-12-24 months: seroma, capsular contracture, wrinkling/rippling, implant malposition (i.e. rotation, displacement etc..), implant upper pole visibility, implant loss;
- Further surgery at 24 months for aesthetic improvement, oncological needs or complications;
- Time to postoperative anti-cancer therapy (radiation and/or systemic therapy);

Tertiary endpoints (5-year follow up according to budget availability):

- Further surgery after 24 months for aesthetic improvement, oncological needs or complications;
- Loco-regional recurrence, disease free survival, breast cancer specific survival, distant-disease free survival, overall survival
- Development of seroma/implant-associated anaplastic T-cell-NHL

Inclusion criteria

- Female patients older than 18 years old
- Signed informed consent form
- Patients undergoing mono or bilateral therapeutic mastectomy
- Patients undergoing pre-pectoral implant-based breast reconstruction with implant or expander with or without mesh

Exclusion criteria

- Male patients
- Patients not suitable for surgical treatment
- Patients undergoing subpectoral reconstruction
- Patients undergoing breast reconstruction with autologous tissue.

Registration

All patients who are candidates for implant-based reconstruction should be informed about the possible participation to this clinical study. The inclusion and exclusion criteria are verified by the investigator and an informed consent is obtained from the patient.

The therapeutic pattern should be followed according to institutional and national standards. Since this is a non-interventional trial, the study sites do not deviate from their own study protocol at any timepoint.

Data reported will be divided into:

Data on patient: age, BMI, smoking history, comorbidities, medications, breast measurements (width, height, projection), breast cup size, ptosis, previous radiotherapy or surgery, subcutaneous tissue thickness on mammogram or MRI, high genetic or familial risk.
Data on tumour: clinical/imaging TNM stage, grading, subtype, histotype, risk-reducing vs therapeutic indication.
Data on surgery: nipple- or skin-sparing mastectomy, use of biological or synthetic meshes or polyurethane implants only, operative time, drain duration, thickness of the mastectomy flap, eventual flap evaluation through ICG, surgeon's experience, implant size and type.
Data on neo/adjuvant treatment: primary systemic therapy, planned endocrine, biological and/or chemo- therapy, planned radiation therapy, time to the first adjuvant treatment (radiation therapy/chemotherapy), dose, target volumes and fractionation of radiation therapy
Complication data: onset time, type of complications, treatment, Clavien-Dindo Classification
Quality of life data: preoperative and postoperative PROMs at 0-6-12-24 months.

The follow-up on patient status is conducted at baseline and after 3, 6, 12, 24 months.

Data management and analysis
Data management and analysis are conducted by the EUBREAST study group and its affiliates. All patients who fulfil inclusion criteria should be recorded in the study identification list and their pseudo-anonymized data reported on the eCRF available on REDCap.

Statistical considerations
Descriptive statistics will be used to analyse data. Two multivariate analyses will be carried out to evaluate risk factors for complications and lower patient satisfaction.
We will use a single-arm design to assess the safety of PPBR based on the primary outcome of implant loss rate at 3 months. It is expected that the implant loss rate will be 9% or lower based on previous literature(10); 12% or greater will be regarded as unacceptably high. The assessment will be based on 1,112 patients. For this sample size calculation, power was set to 90%, and the two-sided alpha was set to 0.05. Allowing for a 10% loss to follow-up at 3 months, we aim at recruiting 1,236 patients.

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