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ORIGINAL ARTICLE

Volume replacement procedure adopting biomaterial: early considerations from a multicentric study

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Abstract

Breast cancer remains the most prevalent female cancer, affecting 2.3 million women worldwide in 2022 (WHO). Breast-conserving surgery aims to remove cancerous tissue while preserving the breast, often incorporating oncoplastic techniques for better cosmetic outcomes. The use of biomaterials for volume replacement, such as the REGENERA™ biomimetic polyurethane-based patented scaffold, could make these procedures less invasive, with faster recovery and shorter operative times. This article presents preliminary data from a multicentric trial exploring the use of REGENERA™ in breast reconstruction after breast-conserving surgery. This study included patients operated from 14th June 2023 to 15th May 2024. The involved centers are: Breast Surgery Unit, Santa Chiara Hospital, Pisa (Italy, ITA01), European Institute of Oncology, Milan (Italy, ITA02), and Hospital A Coruña, A Coruña (Spain, ESP01). For each patient, we evaluated the incidence of adverse events, changes in breast appearance (using photographs and anthropomorphic measurements), interference with ultrasounds and MRI, investigator's satisfaction, patient's pain (through VAS scale), and quality of life (using BREAST-Q questionnaire). Our early experience included 16 patients meeting the inclusion/exclusion criteria from the 3 centers (3 patients from ESP01, 7 from ITA01, and 6 from ITA02). No complications or allergies related to the device were observed, with a mean follow-up of 3 months. The only complication observed was 3 seromas accounting for 18.75% of patients, justifying the use of drains when REGENERA™ is used. BREAST-Q questionnaire results at 1-month follow-up showed no statistical significant improvements except for the Psychosocial Well-Being Chest section, which moved from a pre-operative score of 23 to a post-operative score of 52.33. The REGENERA™ scaffold shows promise as a novel biomaterial for volume replacement in breast-conserving surgery, with high patient satisfaction and minimal complications. Further research and long-term follow-up are necessary to fully evaluate its efficacy and safety.
Trial registration: ClinicalTrials.gov (NCT05941299).

Keywords Breast surgery · Oncoplasty · Volume replacement · Breast oncological surgery · Reconstructive surgery

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Introduction

Breast cancer remains the most prevalent female cancer, affecting 2.3 million women worldwide in 2022 (WHO) [1]. Surgical procedures are essential in treatment, with various reconstruction techniques based on tumor extent and location. Modern breast surgery trends emphasize minimal effective treatment, leading to increased adoption of breast-conserving surgery, which aims to remove cancerous tissue while preserving the breast [2].

Breast-conserving surgery (BCS) offers survival rates equivalent to mastectomy and has led to more oncoplastic procedures, combining oncologic and plastic surgery to enhance cosmetic results.

Oncoplastic breast surgery (OBS), compared to traditional BCS, is technically more demanding, time-consuming, and frequently bilateral with the need of a symmetrization. OBS includes volume displacement and volume replacement techniques.

While volume displacement procedures involve reshaping the remaining breast tissue after tumor excision being suitable either for smaller defects or bigger defects in big size breasts volume, volume replacement techniques are employed for larger defects and specifically when the tumor/breast size ration is insufficient for local tissue rearrangement [3]. These methods adopt mainly autologous tissue to replace the excised breast. Traditional volume replacement techniques include the use of autologous fat, use of local and loco-regional flaps, and the use of microsurgery [4].

Such procedures are more time-consuming and advanced, requiring specific surgical skills.

The adoption of biomaterials for volume replacement could make procedure less invasive, with a faster recovery, and a shorter operative time [5]. In particular REGENERA™, a patented biomimetic polyurethane-based scaffold, has been used in non-malignant breast lesion surgeries [6]. This article presents preliminary data obtained from a multicenter trial that explores its use in breast reconstruction after breast conservative surgery, presenting early experiences and considerations of this promising procedure, after a short follow-up.

Materials and methods

The purpose of this pre-market, pivotal, non-comparative, multi-center study is to assess whether the positive safety and performance results obtained during the first-in-human (FIH) study [6] are confirmed in patients treated for malignant lesions, undergoing adjuvant treatments such as radiotherapy.

In this study, we included patients operated from 14st June 2023 to 15th May 2024.

The involved centers are: Santa Chiara Hospital, Pisa (Italy), named as center ITA01, European Institute of Oncology—IEO, Milan (Italy) named as center ITA02, and Hospital A Coruña, A Coruña (Spain) named as center ESP01.

Inclusion and exclusion criteria are described in Table 1. The procedure is, in summary, intended for invasive no special type (NST) breast cancer, unifocal or multifocal with a max diameter of 4 cm of the pathologic area.

For each patient, we evaluated the incidence of adverse events, changes in breast appearance (using photographs and anthropomorphic measurements), interference with ultrasounds and MRI, investigator's satisfaction, patient's pain (through VAS scale), and quality of life (using BREAST-Q questionnaire).

Device

REGENERA™ is a polymeric bioresorbable scaffold. The REGENERA™ matrix is characterized by an interconnected open pore/void structure, having an average pore/void diameter from 0.9 to 5 mm.

A network of channels propagates through the device interconnected with the porous structure. The biomaterial constituting REGENERA™ is composed of a patented biodegradable cross-linked poly(urethane-ester-ether) foam coated with a bio adhesive macromolecule [Poly(L-lysine); PLL] and hydrophobized by oleic acid (18:1 n-9), a monounsaturated fatty acid. The shape and geometry of REGENERA™ have been set to facilitate its insertion to the implantation site and to fulfill the volume deficit caused by the excision of lesioned soft tissue after lumpectomy. [6]

The biocompatibility of REGENERA™ has been adequately demonstrated in accordance with ISO 10993-1:2018 and the FDA Guidance on ISO 10993-1, as well as the CDRH Guidance for Breast Implants.

Surgical procedure

Before surgery, patients received a single dose of antibiotics (first generation cephalosporin), were positioned supine on the operative table, with the arms stretched out in the line with the shoulder and underwent general anesthesia.

Quadrantectomy incision was rather a radial or a periareolar incision according to the quadrant location. After quadrant removal and sentinel lymph node sampling, breast or plastic surgeon prepared the device for implantation. The scaffold was removed from its sterile package and rehydrated by physiologic solution for about 10 min. The scaffold was then placed in the cavity and fixed with Vicryl 3/0 to the surrounding breast. The implant was either covered with

Table 1 Inclusion criteria and exclusion criteria Inclusion criteria are:

Inclusion criteria are:

- Female aged 40−70 years
- Diagnosis of malignant breast lesion: monolateral nodular infiltrative carcinoma, without microcalcification, single or multifocal, included in an area with a maximum diameter of 4 cm,
- non-metastatic (M0).
- Clinically negative axilla
- Eligibility for BCS (lumpectomy or quadrantectomy), leaving a volume deficit compatible with a REGENERA implant (available in two sizes) volume of 70ml or 100 ml.
- Confirmation of malignant lesion (pT1, pT2, pN0, pN1) with no discordance between biopsy and radiological imaging.
- Adequate hematopoietic functions.

Exclusion criteria are:

- Subject with actual concomitant benign breast lesion (B2 and B3), unless present in the same mammary quadrant or in the contralateral breast.
- Subject with actual concomitant malignancies, lobular neoplasm, metastatic breast carcinoma, sarcoma, malignant phyllodes lesions, or Paget's disease.
- Axillary dissection planned as part of the breast lesion surgery.
- History of surgery, chemotherapy, neoadjuvant chemotherapy, or irradiation of the breast parenchyma object of the study.
- Skin retraction at the breast to be operated.
- Infection of the surgical site confirmed pre-operatively by clinical examination.
- Abnormal blood sugar and glycosylated hemoglobin.
- Hard smoker (more than 10 cigarettes a day).
- Subjects who are known to be carriers of BCRA mutation.
- Immunocompromised patients (HIV).
- Pregnant or breastfeeding woman or woman who has nursed a child within 3 months prior to enrolment in the study.

remaining glandular tissue or with glandular flaps to avoid its exposition.

A drainage of Blake type was positioned at the surgeon's discretion, as it was in semi-aspiration which reduces the aggressive suction effect on the device by maintaining a lower and controlled negative pressure with an average duration of 5–7days. The skin was closed with subcutaneous and intradermal suture. The procedure was performed on a day surgery basis.

Results

In our early experience, we included 16 patients meeting the inclusion/exclusion criteria coming from the three different centers (three patients from center ESP-01, seven patients from center ITA-01, and six patients from center ITA-02). Each patient signed the informed consent. Study of population and detail of surgery are described in Tables 2–3.

We did not observe any major complications or allergies related to the device with a mean follow-up of 3 months.

The only complication we observed were three seromas accounting for 18.75% of patients and, for this reason, we decide to put drainage in case of REGENERA™ adoption.

Breast-Q questionnaires results at 1-month follow-up are presented in Table 4. In particular, we did not observe any statistically significant improvement except for Psychosocial Well-Being Chest section that moved from a pre-operative value of 23 points to a post-operative value of 52,33.

Table 2 Study population

		N	%
	Age	53 (43–70)	–
	BMI	24,3 (17,84–42,45)	–
Quadrant	Upper outer quadrant	11	68,8
	Lower outer quadrant	1	6,2
	Lower inner quadrant	2	12,5
	Central	2	12,5
	Monofocal	14	87,5
	Multifocal	2	12,5
Stadiation	T1b	3	18,7
	T1c	9	56,3
	T2	4	25
	No	12	75
	N1	4	25
Histology	Ductal	8	50
	Mucinous	1	6,2
	Apocrine	1	6,2
	Others	6	37,6
Lymphovascular invasion	No	13	81,3
	Yes	3	18,7
Tumor phenotypes	LUMINAL A	10	62,5
	LUMINAL B	3	18,7
	HER2	3	18,7
	TRIPLE NEGATIVE	0	0

Table 3 Surgical characteristics

		N	%
Time of surgery			
		74 min (range 45–145)	
Incision			
	Radial	10	62,5
	Periareolar	6	37,5
Type of cavity closure			
	No cavity closure	3	18,7
	Minor mobilization of local tissue flaps	10	62,5
	Moderate-to-extensive tissue rearrangement	3	18,7
Duration of the implanting procedure			–
	Min	28,6 min (range 5–49)	
Size			
	70 ml	13	81,3
	100 ml	3	18,7
Percentage of tissue removed			
	< 20% of breast removed	7	43,7
	≥ 20% and ≤ 50%)	9	56,3
Weight of the resected tissue			
		44,7 gr (range 16–94)	

Table 4 Breast-Q questionnaires' values

Breast-Q section	Pre-operative mean value	Pre-operative SD	Post-operative mean value	Post-operative SD	*p* value
Psychosocial well-being	72,81	18,9	66,07	21,03	*p* 0.35
Sexual well-being	62,93	17,04	64,31	24,4	*p* 0.17
Satisfaction with breast	61,19	21,8	63,64	18,6	*p* 0.7
Physical well-being chest	23,00	21,3	52,33	17,1	*p* < 0.01
Breast symptoms	66,73	13,5	65,6	5,3	*p* 0.7
Cancer worry	45,47	17,2	41,67	15,3	*p* 0.5

Discussion

Breast-conserving surgery combined with radiotherapy has become the preferred treatment for early-stage breast cancer. The aim of breast conservation has expanded significantly due to the variety of oncoplastic surgical procedures available. [7]

In case of small breasts or high tumor-volume-to-breast-size ratio, volume replacement procedures could be adopted with perforator flaps which are versatile and useful in filling the defects especially in the outer aspect of the breast. Significant advantages include minimal donor site morbidity and the potential for avoiding any symmetrization procedures.

In scientific literature, there are several case series based on limited number of patients [8]. In particular, Meybodi and colleagues present data on the modified LICAP technique, presenting data from 22 cases [9]. This study reported good esthetic outcomes with no flap necrosis and complications in only four patients (one with seroma and three with wound infections). Neamonitou et al. presented a multicenter trial on 41 patients showing extremely low complication rate such as 2.4% of hematoma, 7.1 % of seroma, and 4.9% of reoperation for positive margins [8]. On the other hand, Kim et al., in a study involving 19 patients showed higher complication rate such as 11% wound dehiscence, 21% necrosis in 21%, and 16% fat necrosis [10].

Different experience beyond groups could explain differences in complication rate. These techniques are appreciated for their results even though they appear time-consuming and advanced, requiring specific surgical skills.

Biological scaffolds represent a promising alternative in volume replacement procedures. This scaffold provides a supportive matrix that facilitates tissue REGENERA™ and integration with the patient's own tissues. In our study, we implant a biomaterial scaffold composed of a cross-linked poly(urethane-ester-ether)-based matrix in tissue loss after quadrantectomy in woman with a malignant lesion of the breast.

In a previous first-in-human (FIH) study, we evaluated the safety and performance of REGENERA™ in 15 patients treated with excision or lumpectomy of a benign tumor [6]. The technique resulted easy to adopt, easily repeatable, and associated with minimal surgical morbidity. The low post-operative complication rate, recorded up to 2 years after surgery, combined with the positive psychological impact generated by a valid reconstructive option after lumpectomy, documented the potential for improving patients' quality of life during post-operative recovery.

This study (TENS-BBC/003/2021) was, therefore, designed to expand the use of the REGENERA™ medical device for subjects diagnosed with a malignant tumor to evaluate its relationship with other anticancer treatments, particularly radiotherapy.

An evaluation of the irradiation treatment potentially affecting the physico-chemical properties was performed in collaboration with the radiotherapy unit of the European Institute of Oncology—IEO with encouraging results: the biocompatibility was preserved as the mechanical properties. After performing the tests, direct cytotoxicity tests were carried out and no cytotoxic effect detected.

No difference was detected between devices subject to irradiation treatment when compared to the hydrated control devices.

We are convinced to share with the scientific community our preliminary results with this biomaterial scaffold that are encouraging. Patients who received the scaffold for volume replacement reported high satisfaction with their breast shape and feel, comparable to traditional methods but with fewer complications such as donor site morbidity. The scaffold's ability to integrate with host tissues also suggests potential for better long-term outcomes.

In our preliminary experience, the main surgical complication is seroma development, mainly observed in the first post-operative period (5–7 days) and for this reason, we decided to routinely use drains to reduce seroma formation. We did not observe any hematoma, infection, or allergic reactions.

The biomaterial scaffold represents a significant innovation in oncoplastic surgery, addressing some limitations of current volume replacement techniques. Its application may reduce the need for extensive autologous tissue harvesting, minimizing surgical morbidity and recovery time. Further research and long-term follow-up are necessary to fully evaluate the efficacy and safety of this new technology. The

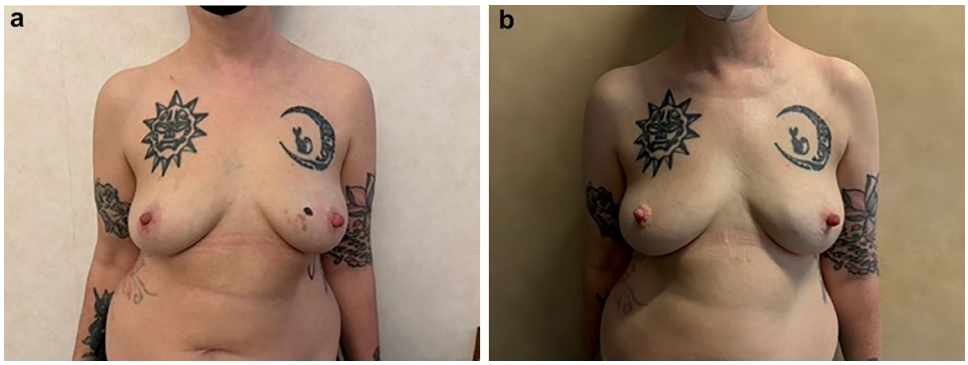

Fig. 1 **a-b** Pre-operative and 3-month post-operative pictures of a patient affected by pT1c (1.9 cm) pN0 ductal carcinoma of the inner quadrants. The patient underwent a quadrantectomy (weight of the removed gland: 50 g) and reconstruction with 70 ml of REGENERA™

procedure accounts for a mean of 74 min including sentinel lymph node biopsy (SLNB), significantly faster that chest wall perforators procedures that in certain report accounts for a mean operative time of 126 min. [11]

Correct indication is quintessential. In our early experience, REGENERA™ seems to be best suitable for moderate- to medium-size breast without ptosis where volume replacement technique could be troublesome (Fig. 1). Indeed, it could be adopted also in bigger breast with ptosis when the patient refuses to perform volume displacement procedures (Fig. 2).

In our protocol, we consider essential to gather information about patient's satisfaction with Breast-Q questionnaires. Although we cannot drive any definitive conclusion, given the extremely short follow-up, we can affirm the level of satisfaction is good.

In our experience, we find REGENERA™ particularly useful to reconstruct the inner quadrants where glandular remodeling is particularly complex. [12]

One of the main positive aspect of this preliminary experience is that the adoption of this device allows to perform wider oncological removal, confirmed by the 100% radical margins in our case series.

The main limitation of our study is obviously the short follow-up and the reduced number of patients.

Another limit of the study is the selection of the device's dimensions. The use of a small-sized device was a result of a consecutive case selection, without any selection bias. Larger breast sizes are more likely to be selected for volume displacement procedures, which explains the lower incidence of larger breasts in the current patient cohort.

The first objective of our paper is to present the preliminary experience in the adoption of REGENERA™ device in anticipation of the increase in patient recruitment and appropriate follow- up.

In conclusion, we are convinced that REGENERA™ device could represent a great innovation in breast oncological surgery allowing to reconstruct defects after breast oncological resection and representing a possible alternative to volume replacement with faster operative time, faster recovery, less morbidity, and good patient satisfaction. We are proceeding with gathering data regarding a higher number of patients and analyzing more robust evidence on the relationship between the device and radiotherapy to provide a definitive confirmation of its adoption.

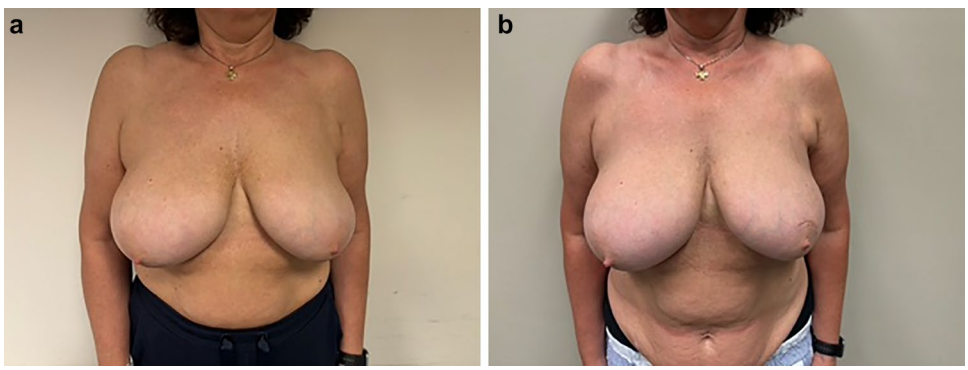

Fig. 2 **a-b** Pre-operative and 3-month post-operative pictures of a patient affected by pT1c (1.5 cm) pN0 ductal carcinoma of the superior quadrants. After the removal of the tumor (weight of removed tissue: 90 g), the patient was reconstructed with 100 ml of REGENERA™. The patient declined volume displacement procedures to correct breast ptosis

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Data availability All data were gathered in the structure's database.

Declarations

Conflict of interest The authors have nothing to disclose.

Ethical approval and Informed consent The project has been discussed in ethical committee with the number-IEO 1807-Titolo: "Volume replacement procedure adopting biomaterial: early considerations from a multicentric study". Responsabile: Prof Rietjens Mario.

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