Title: Regenerative Collagen Scaffold for Breast Volume Restoration in Breast-Conserving Surgery

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INTRODUCTION

Breast-conserving surgery (BCS) has become the standard surgical approach for early-stage breast cancer, offering oncologic outcomes equivalent to mastectomy while preserving the native breast mound. Despite its advantages, excision of tumor-bearing tissue frequently results in postoperative volume deficits, contour deformities, and asymmetry, which can significantly compromise cosmetic outcomes and patient quality of life. These deformities are particularly impactful in small- to moderate-volume breasts, where even modest tissue loss may produce visible distortion [1].

Traditional strategies for managing post-BCS volume loss include volume displacement techniques, regional or local flaps, autologous fat grafting, and, less commonly, implant-based approaches. While effective in selected cases, these methods are associated with important limitations. Flap-based reconstruction increases operative complexity and donor-site morbidity, fat grafting is limited by unpredictable resorption and the need for repeat procedures, and implants are generally unsuitable for partial defects and may interfere with radiotherapy and oncologic surveillance [2]. Consequently, there remains an unmet clinical need for minimally invasive, biologically compatible solutions capable of restoring volume while preserving breast architecture and oncologic safety.

The ideal volume restoration strategy following breast cancer resection in BCS would combine several key features: (1) immediate structural support to prevent cavity collapse, (2) biological integration promoting neovascularization and tissue regeneration, (3) minimal additional surgical morbidity, (4) compatibility with adjuvant radiotherapy, (5) preservation of imaging interpretability for cancer surveillance, and (6) predictable, durable cosmetic outcomes. Currently, no single technique fulfills all these criteria, highlighting a critical gap in oncoplastic breast surgery that regenerative biomaterials may address.

Regenerative medicine approaches have gained increasing attention as alternatives to traditional reconstruction. Among these, collagen-based scaffolds have emerged as promising tools due to their ability to provide immediate structural support while simultaneously promoting host tissue integration, neovascularization, and gradual remodeling. Type I collagen, the principal structural protein of the extracellular matrix, plays a central role in wound healing and tissue regeneration by supporting fibroblast migration, angiogenesis, and organized tissue deposition [3, 4].

An evolution in collagen biomaterials, un-crosslinked High-purity Type I collagen (HPTC) with added bioactivity through phosphorylation is characterized by reduced antigenicity, and predictable biodegradation and reliable tissue integration. Extensive clinical experience with HPTC-based constructs in complex wound environments has demonstrated their capacity to facilitate durable tissue regeneration across a range of indications. Early work describing novel collagen application techniques over meshed split-thickness skin grafts highlighted improved graft stability and wound coverage in challenging defects, establishing the biological versatility of collagen scaffolds in surgical reconstruction [1]. Subsequent clinical series demonstrated the successful use of collagen-based matrices as alternatives to flap coverage for exposed bone and tendon, further supporting their load-bearing and regenerative capabilities [2].

Randomized controlled trials conducted by our group and others have consistently shown superior or comparable outcomes with HPTC-based skin substitutes compared with dehydrated human amnion/chorion membrane (dHACM) in diabetic foot ulcers, venous leg ulcers, and pressure ulcers, with advantages in healing rate, tissue quality, and safety profile [3-7]. These findings have been reinforced by multicenter trials and systematic reviews demonstrating favorable histopathological remodeling, angiogenesis, and epithelialization with HPTC use in chronic wounds [8]. Beyond wound care, collagen-based biomaterials have also shown efficacy in complex surgical scenarios, including the management of infected prosthetic meshes, where collagen matrices facilitated tissue incorporation and infection resolution without foreign-body complications [9].

Collectively, this body of evidence underscores the biological consistency of HPTC scaffolds across diverse tissue environments, suggesting potential applicability beyond surface wounds to deeper soft-tissue defects. The breast excision cavity following BCS represents a uniquely suitable target for such regenerative scaffolds, as it requires immediate volume support, predictable integration, compatibility with adjuvant radiotherapy, and preservation of imaging interpretability for cancer surveillance [10,11].

Despite encouraging preclinical and early clinical data on collagen-based fillers for soft-tissue reconstruction, prospective human studies evaluating HPTC scaffolds specifically for breast volume restoration after BCS remain limited [12, 13]. Furthermore, standardized radiologic and volumetric outcome measures assessing scaffold integration and volume

maintenance in the breast are lacking. Addressing these gaps is essential to establish the clinical role of regenerative scaffolds within oncoplastic breast surgery.

The present prospective, multicenter clinical trial was therefore designed to evaluate the safety, efficacy, radiologic integration, volumetric stability, cosmetic outcomes, and patient-reported satisfaction associated with implantation of a high-purity Type I collagen scaffold for immediate volume restoration following breast-conserving surgery. By integrating objective imaging-based metrics with validated patient-reported outcomes, this study aims to provide comprehensive evidence supporting the use of HPTC scaffolds as a regenerative alternative to conventional volume-replacement techniques in breast cancer surgery.

MATERIALS AND METHODS

Study Design and Setting

This prospective, single-arm, multicenter clinical trial was conducted at two tertiary care academic institutions in Karnataka, India: JSS Medical College and Hospital, Mysuru. And Adichunchanagiri Institute of Medical Sciences (AIMS), B. G. Nagara. The study was designed to evaluate the safety, volumetric efficacy, radiologic integration, cosmetic outcomes, and patient-reported satisfaction following implantation of a High Purity Type I collagen (HPTC) scaffold for immediate volume restoration after breast cancer resection surgery. The trial was registered prospectively with ClinicalTrials.gov (ID: NCT07219316) and approved by the Institutional Ethics Committee (Approval No.: AIMS/IEC/240/2025).

The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Approval was obtained from the Institutional Ethics Committees of both participating centers prior to patient enrollment. Written informed consent was obtained from all participants. The methodological framework, outcome hierarchy, and statistical rigor were modeled on previously published multicenter HPTC trials to ensure internal validity and reproducibility.

Patient Selection and Eligibility Criteria

Women aged 18 to 70 years undergoing BCS for stage 0–II breast carcinoma or high-risk premalignant breast lesions were screened for eligibility. Patients were required to have a unifocal lesion suitable for wide local excision with an anticipated postoperative breast volume deficit of at least 20%, as estimated intraoperatively by the operating surgeon. Adequate skin envelope viability and the ability to undergo serial MRI examinations were mandatory.

Exclusion criteria included multicentric disease requiring mastectomy, prior radiotherapy to the ipsilateral breast, active local or systemic infection, known hypersensitivity to collagen-based products, autoimmune or connective tissue disorders, uncontrolled systemic illness, pregnancy or lactation, and inability to comply with postoperative follow-up or patient-reported outcome assessments.

Sample Size Determination

This study was designed as a prospective feasibility and early efficacy trial. Sample size was determined based on precision estimation for the primary composite endpoint rather than traditional hypothesis testing. Assuming a true success rate of 75% (based on oncoplastic literature), a sample of 40 patients provides an expected 95% confidence interval width of approximately 25%, which was deemed acceptable for preliminary efficacy assessment and effect size estimation to inform future definitive trials. The sample size also ensures adequate power (>80%) to detect a clinically meaningful difference of 15% in volume retention compared to the benchmark of 75%, assuming a standard deviation of 10% and $\alpha = 0.05$.

Surgical Technique and Intervention

All patients underwent standard oncologic breast-conserving surgery performed by experienced breast or plastic surgeons at the respective centers. Following tumor excision with confirmed hemostasis and margin adequacy, the excision cavity was carefully assessed for volume deficit and three-dimensional geometry.

A high purity Type I collagen scaffold was trimmed intraoperatively to conform precisely to the dimensions of the surgical cavity and implanted without tension. The scaffold was positioned in direct contact with surrounding viable breast tissue to facilitate cellular infiltration and neovascularization. No additional fixation beyond absorbable sutures was routinely required. Layered parenchymal and skin closure was performed using standard techniques. The use of surgical drains was left to the discretion of the operating surgeon based on oncologic considerations rather than scaffold placement.

Postoperative management, including antibiotics, wound care, chemotherapy, and radiotherapy, followed institutional breast cancer treatment protocols.

Outcome Measures

Primary Outcome: Breast Volume Restoration Success

The primary efficacy endpoint was breast volume restoration success at two months postoperatively, defined as a composite outcome incorporating both objective volumetric preservation and patient-perceived cosmetic satisfaction. Success required achievement of at least 80% objective breast volume retention relative to the immediate postoperative baseline, together with a patient satisfaction score of ≥ 7 on a 10-point Likert scale. This composite

endpoint was selected to ensure that structural volume preservation translated into clinically meaningful cosmetic benefit and patient acceptance.

Objective Breast Volume Retention

Objective breast volume retention was assessed using a dual-modality approach comprising three-dimensional surface photogrammetry and magnetic resonance imaging (MRI) volumetry. Baseline measurements were obtained within 48 hours postoperatively and repeated at 2, 4, and 8 weeks. Breast volumes were calculated for the operated breast and normalized against the immediate postoperative volume to derive percentage volume retention. MRI volumetry served as the reference standard, while 3D surface imaging provided adjunctive validation and assessment of symmetry.

Volume retention was expressed as a continuous variable and analyzed longitudinally to assess temporal stability and controlled scaffold resorption.

MRI Integration Score (MIS)

Radiologic integration of the HPTC scaffold was evaluated using a predefined MRI Integration Score (MIS), a composite semi-quantitative scoring system developed to assess biological scaffold performance. MRI examinations were performed immediately postoperatively and at 4 and 8 weeks using standardized T1-weighted, T2-weighted, and dynamic contrast-enhanced sequences.

The MIS evaluated four domains: scaffold–host tissue integration, neovascularization based on enhancement patterns, scaffold resorption and volume replacement, and tissue quality within the scaffold region. Each domain was scored from 0 to 3, yielding a total score ranging from 0 to 12, with higher scores indicating superior integration and regenerative remodeling.

Cosmetic Outcome: BREAST-Q

Cosmetic outcomes were assessed using the BREAST-Q questionnaire [14], a validated patient-reported outcome measure specific to breast surgery. The “Satisfaction with Breasts” domain was prespecified as the primary cosmetic endpoint. Questionnaires were administered preoperatively and at 4 and 8 weeks postoperatively. Raw scores were converted to standardized scores ranging from 0 to 100 according to BREAST-Q scoring manuals, with higher scores indicating greater satisfaction [14].

Improvement over baseline and attainment of an absolute score ≥70 at final follow-up were considered clinically meaningful cosmetic outcomes.

Safety and Complications

Safety assessment included prospective recording of all adverse events and postoperative complications, including seroma, surgical site infection, hematoma, wound dehiscence, scaffold migration or exposure, and delays in adjuvant oncologic therapy. Device-related serious adverse events were specifically monitored. All events were managed according to institutional protocols and documented throughout the follow-up period.

Data Collection and Follow-up

Baseline demographic data, tumor characteristics, operative details, and immediate postoperative imaging were recorded at enrollment. Follow-up assessments were conducted at 2, 4, and 8 weeks postoperatively, during which volumetric measurements, MRI evaluation, BREAST-Q questionnaires [14], and complication surveillance were completed. Data were recorded in standardized case record forms at both centers to ensure uniformity.

Statistical Analysis Plan

Statistical analysis was performed using IBM SPSS Statistics (version 28.0). Continuous variables were summarized as mean ± standard deviation, while categorical variables were expressed as frequencies and percentages. Longitudinal changes in breast volume retention, MRI Integration Score, and BREAST-Q scores were analyzed using repeated-measures analysis of variance. One-sample t-tests were used to compare observed volume retention against predefined clinical benchmarks. Correlations between objective volumetric outcomes and patient-reported satisfaction were assessed using Pearson correlation coefficients. A two-sided p value of less than 0.05 was considered statistically significant.