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Review Article

Nanofibrillar Collagen Scaffolds in Chronic Lymphoedema: A Review of Indications, Applications, and Clinical Outcomes

Sotirios Foutsizoglou

MBBS, FRCS(Eng), FEBOPRAS, BSc(Hons), MSc(Biostats), PGDip(Micro)
Consultant Plastic and Reconstructive Surgeon

*Corresponding author
Sotirios Foutsizoglou Private Practice, London UK

Email: s.foutsi@me.com

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Abstract

Background: Chronic lymphoedema remains difficult to manage, particularly in advanced disease, where physiologic procedures may improve drainage but do not reverse established fibroadipose change and reductive procedures reduce tissue excess without restoring lymphatic function.

Objective: To review the indications, applications, and reported clinical outcomes of implantable nanofibrillar collagen scaffolds in stage I–III lymphoedema.

Methods: This narrative review summarizes the English-language literature on chronic lymphoedema, lymphangiogenesis, biomaterials, lymphaticovenous anastomosis, vascularized lymph node transfer, and implantable nanofibrillar collagen scaffolds, including BioBridge™. The review focuses on mechanistic studies, translational evidence, operative applications, and reported clinical outcomes relevant to contemporary reconstructive practice.

Results: The available literature consists mainly of preclinical studies, translational reports, retrospective clinical cohorts, observational comparative studies, and review articles. Collectively, these reports suggest that scaffold implantation may support lymphangiogenesis, formation of new lymphatic collectors, reduction of dermal backflow, and improvement in volumetric and symptom-based outcomes, particularly when combined with lymphaticovenous anastomosis or vascularized lymph node transfer. More recent animal models and longer-term observational clinical data further support the biologic plausibility and emerging clinical rationale of scaffold-assisted lymphatic reconstruction, although the evidence remains heterogeneous and largely non-randomised.

Conclusion: Nanofibrillar collagen scaffolds represent a promising biomaterial-based adjunct in lymphoedema surgery and are supported by an expanding preclinical and early clinical literature. However, the current evidence base remains limited by retrospective design, small sample sizes, heterogeneous treatment pathways, and inconsistent outcome reporting. Prospective multicentre studies are needed to clarify patient selection, durability, and comparative clinical benefit.

Keywords: Lymphoedema; BioBridge; nanofibrillar collagen scaffold; lymphangiogenesis; lymphaticovenous anastomosis; vascularized lymph node transfer; review

Introduction

Lymphoedema is a chronic disorder characterised by interstitial accumulation of protein-rich lymphatic fluid resulting from impaired lymph transport. Over time, persistent lymph stasis promotes adipose deposition, fibrosis, and progressive tissue remodelling, transforming a fluid-predominant process into a structurally complex disease [1].

Lymphoedema may be primary, owing to congenital abnormalities of the lymphatic system, or secondary, following acquired lymphatic injury or obstruction. Although filariasis remains the leading global cause of secondary lymphoedema, in high-income settings the condition is most commonly associated with cancer and its treatment, particularly lymphadenectomy and radiotherapy [2].

Clinically, lymphoedema ranges from early pitting oedema and limb heaviness to advanced fibrofatty enlargement with skin thickening, recurrent infection, and functional impairment. Beyond physical morbidity, it imposes a substantial psychosocial burden and adversely affects quality of life, with longitudinal breast-cancer survivorship data demonstrating persistence of self-reported lymphoedema symptoms over time [3,4].
Management remains challenging. Conservative therapy is central to care, while surgical approaches such as lymphaticovenous anastomosis and vascularized lymph node transfer may improve lymphatic drainage in selected patients [5]. However, no universally accepted treatment algorithm exists, outcomes are variable, and advanced disease is often only partially reversible [6,43].

These limitations have prompted interest in regenerative adjuncts capable of supporting lymphatic repair. Among these, implantable nanofibrillar collagen scaffolds have emerged as a biomaterial-based strategy intended to enhance lymphangiogenesis and complement existing surgical approaches. This review examines the indications, operative integration, and

early clinical evidence for these scaffolds in chronic lymphoedema.

Pathophysiology of lymphoedema

The lymphatic system maintains interstitial fluid homeostasis by returning protein-rich fluid to the venous circulation, while also contributing to immune-cell trafficking, lipid absorption, and clearance of cellular debris and inflammatory mediators [7-9]. Consequently, congenital maldevelopment or acquired injury to lymphatic vessels and nodes disrupts several essential physiologic functions and forms the basis of primary and secondary lymphoedema.

In healthy tissue, intrinsic lymphangion contractility is usually sufficient to propel lymph centrally, with only limited contribution from muscular activity, respiration, passive movement, and arterial pulsation [10,11]. Lymphoedema develops when this autoregulated transport fails because lymphatic drainage can no longer match capillary filtration, leading to lymphatic hypertension, valvular incompetence, lymphostasis, and accumulation of protein-rich fluid in the interstitium [12].

Whether due to congenital abnormalities or acquired obstruction, impaired lymphatic flow reduces transport capacity and increases intralymphatic pressure. The resulting fluid stasis initiates a self-perpetuating cycle of tissue injury in which persistent oedema further compromises lymphatic function and promotes progression from a fluid-predominant to a structurally remodelled disease state [12].

With chronic disease, lymphatic stasis promotes persistent inflammation, adipose deposition and fibrosis. Exposure of adipocytes to lymph-derived lipids and inflammatory mediators contributes to adipocyte hypertrophy, while cytokine signalling activates fibroblasts and stimulates extracellular-matrix and collagen deposition [13,14]. These changes progressively compress residual lymphatic channels, further impair drainage and drive irreversible remodelling of the skin and subcutaneous tissues. Advanced disease may therefore be associated with hyperkeratosis, fissuring, recurrent cellulitis, ulceration and, rarely, lymphangiosarcoma [15].

These pathophysiological changes have important therapeutic implications. Early lymphoedema is predominantly fluid-rich and may respond more favourably to compression therapy or physiologic microsurgical procedures. By contrast, later-stage disease is characterised by established fibrosis and fibroadipose hypertrophy, which are less reversible and may require adjunctive reductive procedures [16,17]. This progressive transition from fluid accumulation to structural tissue remodelling helps to explain why lymphatic regeneration has become a major therapeutic objective in reconstructive lymphoedema surgery.

Classification of lymphoedema

Lymphoedema is commonly classified as primary or secondary according to aetiology, and it is also staged clinically according to severity. The International Society of Lymphology staging system remains widely used (Table 1). Stage 0 denotes a latent or subclinical state; stage I is characterised by early pitting oedema that may regress with limb elevation; stage II reflects more persistent swelling with progressive fibrosis and reduced reversibility; and stage III includes marked enlargement, skin change, and advanced tissue remodelling [18]. Surgical management may differ substantially between primary and secondary disease, particularly in congenital forms of lymphoedema.

Table 1. International Society of Lymphology classification of peripheral lymphoedema.

Stage	Clinical features	Typical characteristics
Stage 0 (latent/subclinical)	No visible swelling despite impaired lymph transport.	Patients may report heaviness or tightness; the condition may remain clinically occult for months or years before oedema becomes apparent.
Stage I	Early accumulation of protein-rich fluid with soft pitting oedema.	Swelling may reduce with limb elevation; there is little or no established fibrosis.
Stage II	Persistent swelling that does not reliably resolve with elevation.	Pitting may be present in the earlier part of this stage, but progressive fibrosis and adipose deposition develop over time.
Stage III (lymphostatic elephantiasis)	Advanced lymphoedema with marked tissue enlargement and irreversible skin and soft-tissue change.	Features may include fibrosis, skin thickening, hyperkeratosis, papillomatosis, and recurrent infection.

The International Society of Lymphology system is the most widely used staging framework for peripheral lymphoedema, although other systems such as the Campisi, Filippetti, and Cheng classifications are also used in surgical practice and research (Table 2).

Table 2. Lymphoedema grading systems

Classification	Stage/grade/class	Defining characteristics	Management
Campisi clinical staging	Stage IA — latent/subclinical	No clinically evident oedema despite impaired lymphatic transport demonstrable by lymphoscintigraphy; early structural changes may be present.	Surveillance, education, risk-factor modification and early conservative management where symptoms or progression occur. Microsurgical assessment may be considered in selected progressive cases.
	Stage IB — initial	Oedema decreases completely or partially with rest, elevation or a draining position.	Complete decongestive therapy (CDT), compression, exercise and skin care [22]. Consider early lymphatic–venous microsurgery when symptoms persist or disease progresses despite appropriate conservative treatment.

	Stage IIA — increasing	Progressive reduction in lymphatic transport, recurrent lymphangitis, developing fibroinduration and emerging functional impairment.	CDT and compression remain fundamental. Lymphatic–venous anastomoses or other physiologic microsurgical procedures may be considered, particularly while usable lymphatic collectors remain.
	Stage IIB — column-shaped fibrolymphoedema	Established fibrolymphoedema with a cylindrical limb, lymphostatic skin changes, markedly impaired lymphatic transport and increasing disability.	Intensive decongestive treatment followed by selected lymphatic microsurgery. Liposuction or another reductive procedure may be required for substantial fibroadipose deposition.
	Stage IIIA — elephantiasis	Scleroindurative pachydermitis, papillomatous or verrucous changes, absent lymphatic transport and severe disability.	Intensive conservative treatment to reduce and stabilise the disease before surgery. Selected patients may require staged physiologic surgery combined with liposuction, debulking or excisional procedures.
	Stage IIIB — extreme elephantiasis	Extreme limb enlargement and deformity with total or near-total functional disability.	Multidisciplinary, individualised management. Intensive decongestion, infection and skin management, followed by carefully selected staged debulking or excisional surgery, with microsurgical reconstruction where technically feasible.
Filippetti postoperative outcome classification	Class 1 — poor	Inadequate postoperative reduction in limb dimensions and persistence of clinically important symptoms.	The classification does not prescribe treatment. A poor result should prompt reassessment of the diagnosis, compression and rehabilitation programme, treatment adherence and suitability for adjunctive or revision intervention.
	Class 2 — fair	Partial improvement in limb dimensions and pre-existing symptoms.	Continue conservative maintenance treatment and monitor progress. Additional physiologic or reductive treatment may be considered for significant residual disease.
	Class 3 — good	Substantial reduction in limb dimensions with marked symptomatic improvement.	Continue long-term maintenance measures, including appropriate compression, exercise, skin care, weight management and clinical follow-up.
Cheng Lymphoedema Grading	Grade 0	Circumference difference 0–9%; approximately 0–1 cellulitis episode annually; normal or partial obstruction with patent lymphatic ducts.	CDT and compression. Lymphovenous anastomosis (LVA) may be considered in selected symptomatic patients with patent lymphatics, particularly when compression cannot be maintained.
	Grade IA	Circumference difference 10–19%; partial obstruction; patent lymphatic ducts on ICG lymphography.	LVA, together with continued conservative lymphoedema management.

	Grade IB	Circumference difference 10–19%; advanced partial or early total obstruction with diffuse dermal backflow and no suitable patent superficial lymphatics.	Vascularised lymph-node transfer (VLNT), with perioperative and long-term conservative management.
	Grade IIA	Circumference difference 20–29%; partial obstruction with identifiable patent lymphatic ducts.	LVA when functional lymphatic collectors are demonstrated.
	Grade IIB	Circumference difference 20–29%; advanced partial or total obstruction with diffuse dermal backflow.	VLNT where suitable lymphatic collectors for LVA are absent.
	Grade III	Circumference difference 30–39%; approximately 3–4 cellulitis episodes annually; predominantly total lymphatic obstruction.	VLNT with additional staged procedures, commonly liposuction or debulking after restoration or stabilisation of lymphatic drainage.
	Grade IV	Circumference difference >40%; generally more than four cellulitis episodes annually; severe total lymphatic obstruction.	VLNT with staged reductive surgery, including liposuction or debulking. Extensive disease may require multiple or combined procedures.

Note: -Campisi and colleagues emphasise that lymphatic microsurgery generally produces better results when performed during earlier disease stages. In advanced disease, non-operative treatment may be required first to reduce and stabilise the lymphoedema before microsurgery or reductive surgery is undertaken [19].

-The *Filippetti* classification system describes postoperative outcomes, rather than directing treatment. The suggested actions in the management column are therefore practical clinical implications, not components of the original classification. The original study categorised results as poor, fair or good according to limb-dimensional reduction and improvement in lymphangitis, pain and functional deficits [20].

-The *Cheng* system was specifically designed to support treatment selection: patent lymphatic ducts favour LVA, diffuse dermal backflow without usable collectors favours VLNT, and Grades III–IV commonly require VLNT followed by staged liposuction or debulking [21].

The existence and use of many other classification systems have made standardisation impossible and the interpretation of lymphoedema interventions as well as the evaluation of clinical studies difficult. In addition, staging does not fully capture the biological heterogeneity of lymphoedema. Another point of discrepancy is the technique used to measure limb volume. Generally speaking, optometric (or perometry) and water volumetry (or plethysmography) are considered more accurate and reliable than tape measurements [23,24]. Standardized approaches to limb-volume quantification are therefore important for consistent outcome reporting in breast cancer-related lymphoedema research [25].

Imaging findings, distribution of dermal backflow, fibrosis burden, prior oncologic treatment, and responsiveness to conservative therapy may all influence surgical planning. For this reason, modern reconstructive practice increasingly integrates clinical staging with indocyanine green lymphography and other imaging modalities when selecting candidates for physiologic procedures and regenerative adjuncts.

Current surgical management of lymphoedema

Complex decongestive therapy remains the cornerstone of lymphoedema management, and surgery is generally reserved for patients with persistent symptoms or functional limitation despite conservative treatment [22]. Current surgical treatment is generally divided into physiologic and reductive approaches, with preventive microsurgical strategies such as Lymphatic Microsurgical Preventive Healing Approach (LYMPHA) also described in selected oncologic settings [26,27]. Physiologic procedures include lymphaticovenous anastomosis [28-30], surgical approaches for congenital lymphoedema,31 vascularized lymph node transfer [32-34], and other microsurgical reconstructive approaches such as lymph-vessel transplantation [35,36,38]. These techniques aim to restore drainage or create alternative pathways for lymph transport and are most effective when residual lymphatic function can still be recruited. Reductive strategies, such as liposuction, decrease fibroadipose tissue burden and can improve limb contour and volume control, particularly in advanced disease, but they do not restore lymphatic function [37].

LVA is most applicable in earlier-stage disease, when functional lymphatic channels remain available for bypass. Advances in supermicrosurgery and the use of indocyanine green lymphography have improved the identification of suitable lymphatics and facilitated minimally invasive anastomosis to adjacent venules [28]. Although LVA can improve symptoms and reduce limb volume in selected patients, outcomes depend heavily on disease stage, imaging findings, and surgical expertise [29].

Preventive or early-intervention strategies such as LYMPHA have also been proposed, particularly at the time of axillary or groin node dissection, with the aim of reducing postoperative lymphatic complications [26]. While conceptually attractive, their adoption remains limited by resource requirements, technical complexity, and the relative lack of long-term prospective data [27].

In more advanced disease, particularly when diffuse dermal backflow or nodal basin damage is present, VLNT is often favoured because it may both absorb lymphatic fluid and promote lymphangiogenesis through local growth-factor release [5,27]. Reported outcomes are encouraging, but results vary across studies and depend on disease stage, anatomic site, donor-site selection, and adjunctive postoperative therapy [32,34].

In end-stage lymphoedema, irreversible adipose deposition and fibrosis limit the effectiveness of purely physiologic reconstruction. Combined strategies are therefore often required, integrating VLNT or bypass procedures with reductive interventions such as liposuction or, rarely, excisional surgery [35,36].

Liposuction is particularly useful for patients with substantial adipose hypertrophy and fixed volume excess, as it can achieve immediate debulking without further compromising remaining lymphatic pathways when performed appropriately [37]. By contrast, the Charles procedure is now reserved for exceptional cases of massive elephantiasis because of its ablative nature, high morbidity, and additional disruption of residual lymphatic function [38].

In practice, treatment is increasingly multimodal. Many centres now combine reductive and physiologic procedures in staged algorithms tailored to disease stage and tissue characteristics, while longitudinal survivorship data underscore the chronic persistence of lymphoedema symptoms over time [39]. This evolving field has created interest in adjunctive biomaterials that may bridge obstructed lymphatic territories, support lymphangiogenesis, and potentially improve the durability of reconstructive outcomes. Nanofibrillar collagen scaffolds have emerged within this context as a promising regenerative strategy.

Materials and methods

Review design

This article was conducted as a review of the published literature addressing chronic lymphoedema, lymphatic reconstruction, lymphangiogenesis, biomaterials, and implantable nanofibrillar collagen scaffolds. The objective was to provide a focused synthesis of the mechanistic rationale, operative applications, and reported clinical outcomes of scaffold-assisted lymphoedema surgery, rather than to perform a formal systematic review or meta-analysis.

The review was structured to capture both foundational and translational literature relevant to reconstructive practice, including preclinical studies, technical reports, retrospective clinical cohorts, and prior review articles. Emphasis was placed on publications describing BioBridgeTM or aligned nanofibrillar collagen scaffolds in the context of lymphatic regeneration, lymphaticovenous anastomosis, vascularized lymph node transfer, and multimodal surgical treatment pathways.

Information sources and search strategy

A targeted literature search was undertaken in English-language sources to identify publications relevant to chronic lymphoedema and nanofibrillar collagen scaffolds. Search terms included combinations of "lymphoedema" or "lymphedema," "lymphangiogenesis," "nanofibrillar collagen scaffold," "BioBridge," "lymphaticovenous anastomosis," "vascularized lymph node transfer," "lymphatic reconstruction," and "biomaterials." Reference lists of included articles were also reviewed to identify additional pertinent publications. To update the present review, the search was extended to capture newer preclinical and clinical reports published through 2025 that addressed scaffold-assisted lymphatic regeneration, comparative surgical outcomes, and experimental disease models.

The search was designed to capture mechanistic, translational, and clinical evidence relevant to contemporary reconstructive surgery. Because the literature on scaffold-assisted lymphatic regeneration remains limited and heterogeneous, the search strategy prioritised sensitivity over strict filtering in order to include key experimental studies, pilot clinical experiences, and contextual review literature.

Eligibility criteria and study selection

Publications were considered eligible if they addressed at least one of the following domains: the pathophysiology of lymphoedema relevant to regenerative surgery; biomaterial-based lymphatic repair; preclinical or translational studies of aligned collagen scaffolds; operative integration of nanofibrillar scaffolds with lymphaticovenous anastomosis or vascularized lymph node transfer; or reported clinical outcomes after scaffold-assisted treatment. Both original investigations and relevant review articles were considered.

Articles were excluded if they were not relevant to lymphatic regeneration or reconstructive management of lymphoedema, did not address nanofibrillar collagen scaffolds or the surrounding clinical context, or provided insufficient methodological or outcome detail to inform the aims of this review. In cases where multiple publications addressed overlapping patient cohorts or closely related technical experiences, emphasis was placed on the most informative and clinically relevant reports.

Data extraction and analysis

Data were extracted narratively from the included literature with attention to study design, patient population, disease stage, operative context, scaffold use, comparator treatment where applicable, and reported clinical or imaging outcomes. Particular consideration was given to whether scaffolds were used as standalone adjuncts or within multimodal treatment algorithms combining reductive and physiologic procedures.

The findings were synthesised descriptively because of marked heterogeneity across the available literature, including variation in study design, staging systems, operative sequencing, outcome definitions, and duration of follow-up. No formal quality scoring or quantitative pooling was undertaken. The review therefore emphasises patterns of evidence, biologic plausibility, technical themes, and major limitations of the current literature.

Results

Lymphatic Regeneration Using Nanofibrillar Collagen Scaffolds

Current surgical strategies for lymphoedema can reduce limb volume or improve lymphatic drainage, but they do not reliably restore damaged lymphatic pathways along the affected extremity. This limitation is particularly relevant in patients with advanced disease, prior radiotherapy, or extensive soft-tissue fibrosis, in whom surgical dissection is more difficult and long-term volume control is less predictable [34]. These challenges have stimulated interest in regenerative adjuncts designed to support lymphatic repair.

Among these, implantable aligned nanofibrillar collagen scaffolds such as BioBridge have emerged as a biomaterial-based adjunct intended to facilitate lymphangiogenesis and improve the durability of surgical outcomes when combined with physiologic and/or reductive surgery [40,41].

BioBridge® Collagen Matrix is manufactured by Fibralign Corporation using Fibralign's proprietary Nanoweave® technology. It is a sterile, implantable matrix composed of aligned type I porcine collagen nanofibrils. Its architecture is designed to mimic native extracellular collagen alignment and provide directional guidance for cellular migration and lymphatic endothelial organisation [41]. Initial preclinical work in porcine and rat models showed that these scaffolds can support formation of new lymphatic collectors, improve lymphatic drainage, and, in prevention models, reduce the development of postoperative lymphoedema [42,43]. More recent experimental work has extended this mechanistic rationale to a rabbit model, in which implantation of aligned nanofibrillar collagen scaffolds after popliteal lymph node excision reduced dermal backflow and was associated with the appearance of new linear lymphatic channels on indocyanine green lymphography in both preventive and treatment settings [44]. Taken together, these studies reinforce the biologic plausibility of scaffold-guided lymphatic regeneration across multiple animal systems.

Clinical evidence

Early clinical reports suggest that scaffold placement may enhance outcomes when integrated into multimodal surgical treatment. In retrospective series, BioBridge has most commonly been used alongside liposuction, lymphaticovenous anastomosis, and/or vascularized lymph node transfer in patients with stage II–III secondary lymphoedema, with reported improvements in excess limb volume reduction, maintenance of postoperative volume control, and imaging evidence of new lymphatic collector formation (Fig. 1) [45,46].

The most frequently cited clinical experience is the so-called "triple therapy" algorithm, in which liposuction is followed by a physiologic procedure and subsequent BioBridge implantation. Reported outcomes from these retrospective cohorts are encouraging, including sustained reduction in excess limb volume over follow-up of approximately two years [45]. However, because scaffold placement is embedded within a multimodal approach, the independent contribution of the device remains difficult to assess.

Comparative retrospective data suggest greater oedema reduction and improved formation of new lymphatic collectors when nanofibrillar collagen scaffolds are added to lymphaticovenous anastomosis and/or vascularized lymph node transfer than when these procedures are performed alone [46]. This is also reinforced by a more recent observational study comparing vascularized lymph node transfer alone with combined vascularized lymph node transfer plus nanofibrillar collagen scaffolds, which reported greater postoperative volume reduction, improved indocyanine green downstaging, fewer infectious episodes, and imaging evidence of new lymphatic vessel formation in the combined-treatment group over longer-term follow-up [47]. Although these findings strengthen the emerging clinical rationale for scaffold use, they remain hypothesis-generating because of small sample sizes, heterogeneity in treatment pathways, and the

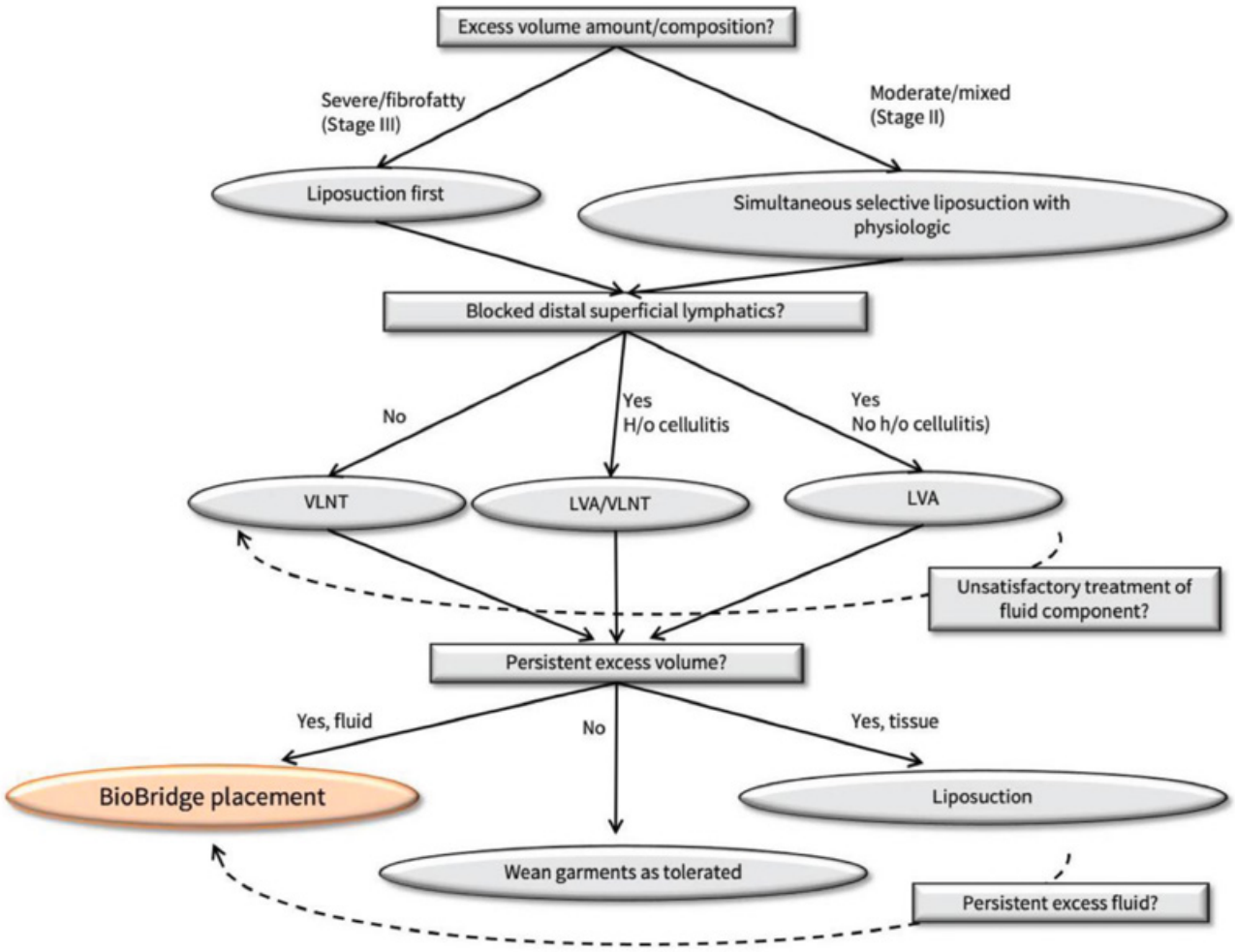

Figure 1. Treatment algorithm for Stage II-III lymphedema.

Figure 1. [45] Multimodal treatment algorithm for late-stage II–III lymphoedema. Reproduced from Deptula et al. (2022), subject to the terms of the Creative Commons Attribution licence.

Surgical Technique

Implantation of nanofibrillar collagen scaffolds is usually performed as an adjunct to physiologic lymphoedema surgery rather than as an isolated intervention. The operative objective is to place the aligned collagen scaffold within the superficial subcutaneous plane so that it bridges fibrotic, scarred, irradiated or otherwise obstructed lymphatic territories and connects regions of preserved distal lymphatic function with a proximal drainage pathway, such as a vascularised lymph node transfer, lymphaticovenous anastomosis site, or adjacent functional nodal basin [46].

Preoperative planning should be guided by clinical staging, previous operative history, distribution of fibrosis or scarring, and lymphatic imaging. Indocyanine green lymphography is commonly used to identify residual functional lymphatic collectors and to determine the trajectory of scaffold placement. The planned track is marked on the skin from distal to proximal, usually following a course from intact distal lymphatic collectors across the obstructed or scarred segment towards the nearest viable lymphatic drainage pathway (Fig. 2). In most reported techniques, two to four subcutaneous scaffold tracks are created, depending on limb size, disease distribution, and the extent of fibrosis [46,48].

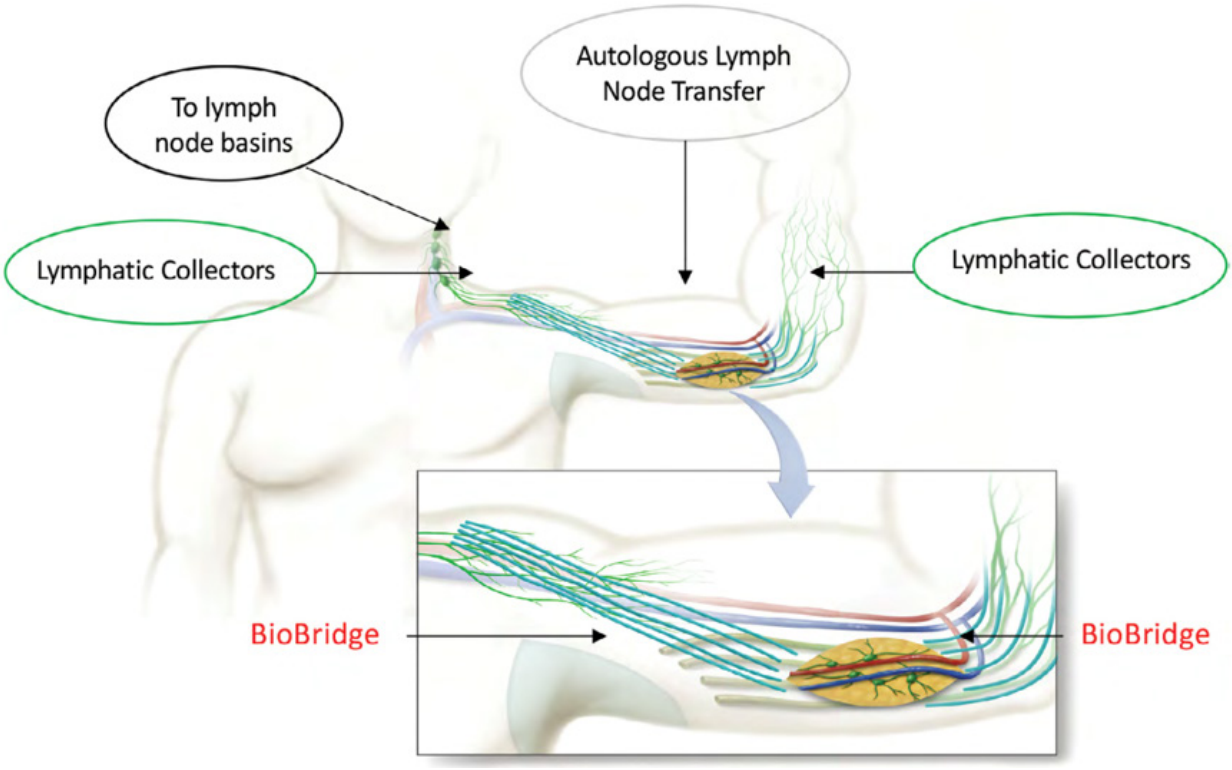

Figure 2. Schematic illustration of BioBridge placement in the upper limb after scar release. The scaffold is tunnelled subcutaneously from regions of preserved distal lymphatics across fibrotic segments toward the vascularized lymph node flap and proximal nodal basin [46].

The procedure may be performed under local or general anaesthesia depending on the extent of surgery and whether scaffold placement is combined with liposuction, scar release, LVA, or VLNT. When scar release or debulking is required, this is generally performed before scaffold insertion to create a more permissive soft-tissue bed and reduce mechanical obstruction to lymphatic regeneration. Care is taken to avoid injury to functioning lymphatic channels, superficial veins, flap pedicles, and areas of compromised skin.

Following skin preparation and draping, small stab incisions are made along the pre-marked trajectory. A subcutaneous tunnelling device, such as the SecurusEP, is then passed through the superficial subcutaneous plane, exiting at the next planned point along the track. The scaffold is moistened with sterile saline and gently drawn into the tunnel, avoiding twisting, folding, excessive tension, or compression. Where longer trajectories are required, several scaffold segments may be placed in series, with the exit point of one segment serving as the entry point for the next, thereby creating a continuous scaffold pathway across the obstructed lymphatic territory.

When used after or in conjunction with vascularized lymph node transfer, the scaffold is typically positioned to connect preserved distal lymphatics with the transferred lymph node flap and, where appropriate, with the next functional nodal basin. In the upper limb, this may involve tunnelling from the hand, wrist, or forearm toward the vascularised lymph node flap and then proximally towards the axillary or cervical lymphatic territory, depending on the reconstructive strategy and location of scarring [46,47]. Particular care is required to avoid compression or distortion of the vascular pedicle.

When used in patients who have undergone lymphaticovenous anastomosis, ICG lymphography may be used to identify functioning lymphatic channels and dermal backflow patterns. The scaffold is positioned close to, but not directly across or under tension on, the anastomotic site, and is tunnelled toward a functional proximal nodal basin. In the upper limb, this may include the axillary or cervical region; in the lower limb, the ipsilateral or contralateral groin may be targeted depending on lymphatic mapping and disease distribution.46 The intended effect is to augment collateral lymphatic drainage and provide a directional scaffold for lymphatic endothelial migration and organisation.

At the end of the procedure, the stab incisions are closed with tissue adhe-

sive or fine sutures according to surgeon preference. A light sterile dressing is applied. Compression therapy and complex decongestive therapy are usually continued postoperatively according to the treating team's lymphoedema protocol, although excessive focal compression over a transferred lymph node flap, vascular pedicle, or recent anastomosis should be avoided. Postoperative follow-up should include assessment of limb volume, symptoms, cellulitis frequency, compression requirements, and, where available, repeat lymphatic imaging to evaluate changes in dermal backflow and lymphatic collector formation.

Reported outcomes

Clinical evidence remains preliminary and is derived mainly from retrospective cohorts and small observational studies. A systematic scoping review by Yesantharao and Nguyen identified 32 relevant articles, eight of which specifically investigated nanofibrillar collagen scaffolds for secondary lymphoedema; four of these were clinical investigations ranging from case reports to retrospective cohort studies. Across the included studies, scaffold implantation was associated with improvement in lymphoedema symptoms, particularly when combined with physiologic microsurgical procedures such as vascularized lymph node transfer or lymphaticovenous anastomosis [49].

Nguyen et al. performed a retrospective cohort study of patients with stage I–III secondary lymphoedema who had undergone lymphaticovenous anastomosis and/or vascularized lymph node transfer, with or without delayed implantation of nanofibrillar collagen scaffolds. The BioBridge cohort included 18 patients and was compared with 11 retrospective controls. Excess volume reduction at 12 months was significantly greater in the scaffold group than in controls, reported as 111.5 ± 34.5% versus 70.0 ± 19.0%, respectively. The average rate of oedema reduction increased 3.5-fold after lymphaticovenous anastomosis and 7.6-fold after vascularized lymph node transfer following scaffold placement. In patients undergoing concurrent liposuction and scaffold implantation, 88% maintained normal limb volumes at 13 months, and 77.8% of the overall scaffold cohort achieved and maintained normal limb volume at a mean total follow-up of 29 months. Lymphatic mapping also demonstrated more new lymphatic collectors and reduced dermal backflow after scaffold implantation [46].

Deptula et al. reported a retrospective series of 14 patients with late-stage II–III lymphoedema treated using a multimodal "triple therapy" algorithm comprising liposuction, physiologic surgery, and subsequent scaffold placement. Baseline median excess limb volume was 29% (interquartile range 19.8–43.3%). After liposuction and physiologic procedures, median excess volume improved to 0.5% at 14.4 months from the first-stage operation; after completion of triple therapy with scaffold placement, it improved further to −1.0% at 24.6 months. These findings suggest that scaffold placement may contribute to sustained volume normalisation in selected patients with residual fluid-predominant disease after debulking and physiologic reconstruction [45].

Early clinical experience with scaffold implantation combined with lymph node fragment transfer has also been reported. In the cohort summarised by Yesantharao and Nguyen, scaffold placement with lymph node fragments, with or without adipose-derived stromal cells, resulted in a mean limb volume reduction of approximately 20% at 6 months, compared with approximately 1% in patients treated with lymph node fragment transfer alone. One-third of scaffold-treated patients reportedly achieved normal limb-volume ratios [49].

Cè et al. described a preliminary experience in three patients with primary lymphoedema treated with BioBridge implantation combined with either lymph node transfer or venolymphatic anastomosis. No postoperative complications were reported. At 1 year, clinical and imaging follow-up demonstrated reduction in limb size, reduction in bioimpedance values, decreased circumferential measurements on magnetic resonance lymphography, and the appearance of new lymphatic structures parallel to the implanted scaffold. In two patients in whom volume excess was calculated, excess volume decreased from 25% to 6% and from 26% to 2%, respectively [50].

Dionyssiou et al. reported longer-term observational data comparing vascularized lymph node transfer alone with vascularized lymph node transfer combined with nanofibrillar collagen scaffold implantation in 24 patients with secondary upper- or lower-limb lymphoedema. Twelve patients underwent vascularized lymph node transfer alone and 12 underwent combined vascularized lymph node transfer with scaffold implantation. Mean follow-up was 42 months in the vascularized lymph node transfer group and 27 months in the combined-treatment group. Preoperative-to-postoperative oedema volume difference improved from 36% to 25% in the vascularized lymph node transfer group and from 33% to 14% in the combined-treatment group. Infection episodes decreased from 1.75 to 0.33 episodes per patient-year after vascularized lymph node transfer alone and from 2.17 to 0.42 episodes per patient-year after combined treatment. The combined-treatment group also demonstrated significantly better postoperative volume difference and indocyanine green lymphography change, with imaging evidence of new lymphatic vessel formation at the scaffold implantation site [47].

Additional case-level evidence has been reported in anatomically complex lymphoedema. Barrantes et al. described treatment of genital lymphoedema using a lymphatic-system pedicled superficial circumflex iliac perforator transfer combined with nanofibrillar collagen scaffold placement. Scaffold implantation was used to enhance distal lymphangiogenesis, and the patient's Genital Lymphedema Score improved from 5/9 to 1/9, with substantial symptomatic relief [51].

Overall, the clinical literature suggests that nanofibrillar collagen scaffold implantation may be associated with reduced limb volume, improved maintenance of postoperative volume reduction, fewer infectious episodes, reduced dermal backflow, and imaging evidence of new lymphatic collector formation. The strongest signal appears to occur when scaffolds are used as an adjunct to vascularized lymph node transfer, lymphaticovenous anastomosis, and/or staged multimodal surgery rather than as an isolated intervention. However, the available evidence remains limited by small sample sizes, retrospective design, heterogeneous disease stages, variable surgical sequencing, inconsistent outcome definitions, and the frequent use of concurrent procedures such as liposuction, scar release, lymphaticovenous anastomosis, and vascularized lymph node transfer. Therefore, the independent contribution of scaffold implantation cannot yet be determined with confidence. Key published clinical outcomes are summarised in Table 3.

Table 3. Clinical outcomes of nanofibrillar collagen scaffold implantation in lymphoedema surgery.

Study	Design / population	Scaffold use	Follow-up	Main clinical outcomes
Nguyen et al [46].	Retrospective cohort; stage I–III secondary lymphoedema; 18 scaffold patients vs 11 controls	Delayed scaffold placement after LVA and/or VLNT, with liposuction where indicated	Mean total follow-up 29 months	Greater excess volume reduction vs controls: 111.5 ± 34.5% vs 70.0 ± 19.0%; 3.5-fold increased oedema reduction rate after LVA and 7.6-fold after VLNT; 77.8% maintained normal limb volume; more new collectors and reduced dermal backflow
Deptula et al [45].	Retrospective cohort; 14 late stage II–III patients	Triple therapy: liposuction, physiologic surgery, then scaffold placement	24.6 months after completion of triple therapy	Median excess volume improved from 29% to 0.5% after first-stage treatment and to −1.0% after scaffold placement/triple therapy
Early lymph node fragment/scaffold cohort [49].	Small clinical cohort summarised in scoping review	Scaffold plus lymph node fragment transfer, with or without adipose-derived stromal cells	6 months	Mean limb volume reduction approximately 20% vs 1% with lymph node fragment transfer alone; one-third achieved normal limb-volume ratio
Cè et al [50].	Three-patient preliminary clinical series; primary lymphoedema	Scaffold with lymph node transfer or venolymphatic anastomosis	1 year	No postoperative complications; bioimpedance and circumference reduction; volume excess decreased from 25% to 6% and from 26% to 2% in two calculable cases; MR lymphography showed new lymphatic structures parallel to scaffold
Dionyssiou et al [47].	Observational comparative study; 24 patients, VLNT alone vs VLNT + scaffold	Scaffold added to VLNT	Mean 42 months VLNT alone; 27 months combined group	Volume difference improved from 36% to 25% with VLNT alone and from 33% to 14% with VLNT + scaffold; infection episodes decreased in both groups; combined group had better postoperative volume difference and ICG change; new lymphatic vessel formation seen at scaffold site
Barrantes et al [51].	Case report; genital lymphoedema	Scaffold combined with lymphatic-system pedicled SCIP transfer	Case-level follow-up	Genital Lymphedema Score improved from 5/9 to 1/9 with substantial symptomatic relief

Discussion

Collagen-based scaffolds are well established in reconstructive surgery, particularly in implant-based breast reconstruction, where acellular dermal matrices have been widely adopted. This familiarity may make translation of nanofibrillar collagen scaffolds into lymphoedema surgery conceptually appealing. However, analogy to other reconstructive biomaterials should be interpreted cautiously. The biologic environment of chronic lymphoedema is distinct, characterised by persistent inflammation, fibrosis, adipose deposition, and impaired lymphatic transport, and it cannot be assumed that safety or performance data from other reconstructive settings are directly transferable. In addition, published experience with nanofibrillar collagen scaffolds in patients with a history of malignancy remains limited, and longer-term oncologic and device-related safety data are still lacking.

BioBridge is an implantable adjunct intended to support lymphatic tissue repair when used alongside physiologic and/or reductive surgery in patients with later-stage lymphoedema. Although the mechanistic rationale is compelling, the clinical evidence remains preliminary. The longest reported follow-up in the available literature now extends beyond two years, but remains insufficient to determine long-term durability in a chronic disease known for recurrence and progression over time [47]. Moreover, the published literature is dominated by retrospective cohorts and institutional pilot experiences, frequently involving small samples, highly select-

ed patients, and limited comparator groups. These features increase the risk of selection bias, performance bias, and overestimation of treatment effect, thereby constraining the generalisability of current outcome data.

In preclinical and translational studies, BioBridge has been reported to support lymphangiogenesis, enhance lymphatic drainage, and provide a structural platform for lymphatic regeneration [40-44,48].

Deptula et al. reported that BioBridge placement appeared to confer the greatest benefit in patients with persistent excess limb volume after lymphaticovenous anastomosis or vascularized lymph node transfer [45]. These findings are noteworthy, but they should be interpreted in light of substantial methodological limitations. The retrospective design, small cohort size, absence of random allocation, and limited control of confounding make it difficult to determine the independent contribution of scaffold implantation relative to concomitant procedures such as liposuction, LVA, or VLNT. In effect, the reported benefit may reflect the multimodal treatment algorithm as a whole rather than the scaffold component alone. The study therefore supports feasibility and hypothesis generation, but not definitive causal inference.

Patients with suboptimal response to physiologic surgery, or those seeking further improvement, were offered delayed BioBridge implantation in comparative retrospective series [46]. Although these studies suggest greater oedema reduction and improved maintenance of volume reduction when scaffolds are added to LVA and/or VLNT, interpretation remains challenging. Study populations were heterogeneous with respect to disease stage, prior interventions, anatomic site, and adjunctive therapies, while outcome calculations were not standardised across reports. Such variability complicates cross-study comparison and raises uncertainty regarding which patient subgroups are most likely to benefit. Furthermore, delayed scaffold placement after an unsatisfactory initial response introduces an important indication bias, as the treated and untreated groups may not have been clinically equivalent at baseline.

Dionyssiou et al. described simultaneous breast and lymphoedema reconstruction with adjunctive collagen scaffold placement in combination with pedicled or free vascularized lymph node transfer [47]. Reported improvements in infection episodes, pain, heaviness, function, and dermal backflow are clinically encouraging in the broader combined-treatment literature [47]. Nevertheless, these outcomes derive from complex reconstructive settings in which several therapeutic components were delivered concurrently. As a result, attribution of benefit specifically to the scaffold remains uncertain. This is a recurrent problem across the literature: when BioBridge is embedded within a multimodal surgical pathway, the incremental value of the device is difficult to isolate without prospective study designs and predefined outcome hierarchies.

Nanofibrillar collagen scaffolds may be considered a minimally invasive physiologic adjunct for secondary lymphoedema and, unlike microsurgical bypass or transfer procedures, do not themselves require supermicrosurgical anastomosis. BioBridge is manufactured by Fibralign, and its per-unit cost is reported to be in the range of several thousand dollars. Future work should therefore address cost-effectiveness alongside clinical efficacy, particularly in high-volume lymphoedema centres and in resource-constrained settings. In parallel, other biomaterials known to influence lymphatic endothelial cell proliferation, sprouting, and orientation—including fibrin, polycaprolactone, hyaluronic acid, hydrogels, and gelatin—deserve comparative evaluation as potentially less costly regenerative platforms.

Overall, BioBridge appears most biologically plausible in patients with persistent fluid-predominant disease in whom residual lymphatic function can still be recruited or regenerated. By contrast, its role is likely to be more limited in advanced fibrofatty lymphoedema, where tissue remodelling may be less reversible and reductive strategies remain central. This distinction is clinically important, because the current literature often groups heterogeneous stages of disease together despite fundamentally different pathophysiologic substrates. More precise phenotyping of lymphoedema—incorporating disease stage, imaging characteristics, fibrosis burden, and prior treatment history—will be necessary to define rational indications for scaffold implantation and to avoid overextending conclusions derived from small, selected cohorts.

A further limitation of the literature is the inconsistency of outcome assessment. Although volumetric reduction is commonly reported, methods vary considerably between studies and include circumferential calculations, relative excess volume formulas, symptom reporting, and imaging-based endpoints [49]. Circumferential measurements, in particular, are prone to interobserver variability and may inadequately capture regional tissue composition or distinguish fluid reduction from changes in adipose or fibrotic burden [23]. The absence of standardised endpoints limits both reproducibility and meta-analytic synthesis. Future studies would benefit from harmonised outcome reporting incorporating validated patient-reported measures, objective limb-volume assessment, complication profiles, compression requirements, and imaging evidence of lymphatic regeneration.

In the future, a larger prospective, randomized, controlled study is needed to truly evaluate the efficacy of these scaffolds as a viable treatment for secondary lymphoedema and to further define the synergistic impact of adding nanofibrillar collagen scaffolds to lymphaticovenous anastomosis and vascularized lymph node transfer procedures to treat lymphoedema. There may also be a role for BioBridge in lymphoedema prevention. Although the preventive impact of BioBridge has not yet been tested in human clinical trials, implantation of BioBridge in a rat hind-limb model has been shown to reduce established lymphoedema and dermal backflow when connected to a contralateral lymph node basin [42].

Finally, further studies from a tissue engineering perspective are needed to optimize nanofibrillar collagen scaffolds and maximize their potential for lymphangiogenesis (e.g., supplementing the scaffolds with biochemical stimuli such as vascularized endothelial growth factor, or seeding the scaffolds with stem cells). While most current efforts focus on recreating lymphatic vasculature, future work should also investigate the feasibility of engineering constructs to regenerate the lymph node itself to obviate the need for lymph node.

Conclusion

Chronic lymphoedema is a progressive and disabling condition that continues to impose a substantial physical, psychosocial, and healthcare burden. In oncology populations, particularly after nodal surgery and radiotherapy, management remains challenging despite advances in microsurgical reconstruction. Nanofibrillar collagen scaffolds have emerged as a potentially valuable adjunct to procedures such as lymphaticovenous anastomosis and vascularized lymph node transfer by promoting lymphatic regeneration and helping to sustain limb-volume reduction. However, the current evidence base remains preliminary and is derived largely from small, heterogeneous cohorts with limited follow-up and non-standardised outcome assessment. Accordingly, multicentre prospective studies, ideally randomised where feasible, are needed to define indications, quantify benefit, clarify long-term safety, and determine the place of these biomaterials within contemporary lymphoedema treatment algorithms.

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Ethics declaration
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Author contributions
Sotirios Foutsizoglou: Conceptualization, literature review, data curation, analysis and interpretation, writing—original draft, and writing—review and editing.

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