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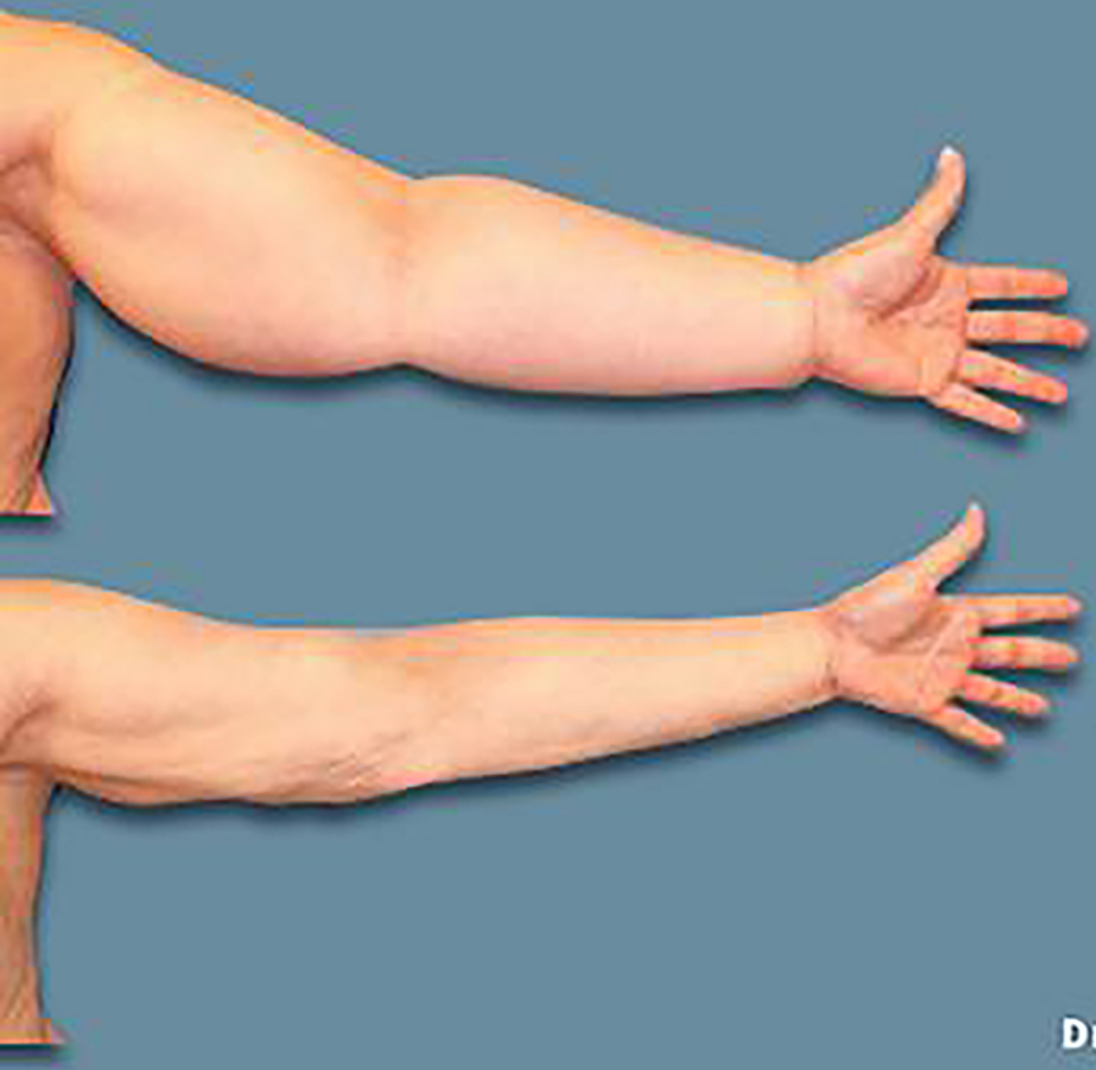
PLASTIC AND AESTHETIC RESEARCH

Recent Advances in Breast Cancer-related Lymphedema



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Topic: Recent Advances in Breast Cancer-related Lymphedema

Dr. Suami (MD, PhD) trained in Japan as a reconstructive microsurgeon. He was admitted to the Japan Society of Plastic and Reconstructive Surgery in 1999. Dr Suami started lymphatic research in 2001 when he worked in the Reconstructive Microsurgery Research Unit at the University of Melbourne, Australia. Dr Suami developed a novel radiographic technique to demonstrate the lymphatic system in a cadaver model in 2003 and in 2005 he was awarded the Basic Science Award from the Plastic Surgery Education Foundation in the USA. In 2009, Dr Suami joined the Department of Plastic Surgery at the MD Anderson Cancer Centre in Houston, Texas as Assistant Professor and a director of the microsurgery research centre. Here he developed a large animal model for lymphoedema and assisted with indocyanine green fluorescence lymphography in over 250 surgical lymphoedema cases. Dr Suami was recruited to the Faculty of Medicine and Health Sciences at Macquarie University in 2015 and works with the Australian Lymphatic Education, Research and Treatment (ALERT).

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Topic: Recent Advances in Breast Cancer-related Lymphedema

Mario F. Scaglioni studied medicine at the University of Pavia, Italy. After completing his doctorate in Pavia, he became a specialist in Plastic, Reconstructive and Aesthetic Surgery at the University Politecnica delle Marche, Italy. Moreover, he subspecialized in Reconstructive Microsurgery. He obtained two years (2011-2012) fellowship in Breast Reconstruction and Head & Neck reconstruction respectively, under the supervision of Prof. Eyal Gur at the Sourasky Medical Center in Tel Aviv, Israel. Afterwards (2013), he spent 1 year at MD Anderson Cancer Center, Houston Texas, as microsurgery research fellow. Under the mentoring of Prof. Suami, he studied the anatomy of the lymphatic system and its application in lymphedema surgery. Then (2014), he moved for one more year to Chang Gang Memorial Hospital, Taiwan as a microsurgery fellow under the mentoring of Prof. Fu-Chan Wei and Prof. Yur-Ren Kuo, worldwide recognized microsurgeons. In 2015, he was appointed as consultant in Plastic and Reconstructive surgery at University Hospital Zurich (USZ). In 2017 he received his Venia Legendi (PD) at the University of Zurich. In 2018 he has been appointed as senior consultant at the Clinic of Hand and Plastic Surgery at the Lucerne Cantonal Hospital (LUKS). In December 2021 he has been appointed Titular Professor at Faculty of Health Sciences and Medicine at the University of Lucerne. Since January 2022 he has promoted as Co-Chief of the Clinic of Hand and Plastic Surgery in LUKS. He published more than 90 scientific papers in international peer-review Journals and contributed to several book chapters; he is an international well recognized reconstructive microsurgeon.

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Dr. Akitatsu Hayashi is a skilled plastic surgeon with a diverse and extensive background in the field. He graduated from the University of Juntendo in 2010 and began his residency at the Center Hospital of the National Center for Global Health and Medicine shortly thereafter. Dr. Hayashi specialized in Plastic Surgery at The University of Tokyo Hospital in 2012, further honing his expertise at Asahi Hospital in 2015. His career then led him to pivotal roles such as serving as a medical instructor in the Department of Lymphatic Surgery at Lymfecentrum, AZ Sint-Maarten Hospital in October 2017 and later joining the Breast Center at Kameda Medical Center in February 2018. Dr. Hayashi's subspecialties include a focus on lymphedema after cancer surgery, microsurgery, and super microsurgery, showcasing his dedication to intricate and specialized surgical interventions.

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Plastic and Aesthetic Research

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Systematic Review

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Nanofibrillar collagen scaffolds for lymphedema treatment: current applications and future directions

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Abstract

Aim: Biosynthetic scaffolds represent cutting-edge therapeutic efforts for secondary lymphedema. In particular, nanofibrillar collagen scaffolds have shown efficacy in both preclinical and clinical contexts, and there has been growing interest in these scaffolds in recent years. This study systematically reviewed the current literature on nanofibrillar collagen scaffolds for lymphedema treatment to synthesize findings and highlight areas for further research.

Methods: This was a systematic scoping review of the literature on nanofibrillar collagen scaffolds for lymphedema treatment.

Results: Upon review of the literature, 32 relevant articles were identified, of which seven articles specifically investigating nanofibrillar collagen scaffolds were selected for inclusion. Of these articles, three investigated scaffold placement in small or large animal models, while four were clinical investigations ranging from case reports to retrospective cohort studies. Across all studies, scaffold implantation was associated with significant improvement in lymphedema symptoms compared to untreated controls, especially when used in combination with physiologic microsurgical procedures such as vascularized lymph node transfer. However, even when used alone or in combination with lymph node fragments, subcutaneous placement of these scaffolds improved lymphedema symptoms. Additionally, in a rodent model of lymphedema, scaffold placement at the time of lymph node harvest forestalled the development of lymphedema, highlighting the preventative capacity of these scaffolds as well.

Conclusion: Nanofibrillar collagen scaffolds have been demonstrated to effectively treat and/or prevent secondary lymphedema in both preclinical and clinical investigations. Ultimately, these scaffolds represent a promising intersection of tissue engineering and lymphedema therapy, and further clinical investigation is warranted.

Keywords: Biomaterials, lymphedema, biosynthetic scaffold, lymphangiogenesis, regenerative medicine, adipose-derived stem cells

INTRODUCTION

Secondary lymphedema is a relatively common and highly morbid iatrogenic complication after cancer resection, especially in those who undergo concomitant radiation therapy[1]. In fact, amongst breast cancer patients, some studies report secondary lymphedema incidence rates of greater than 50%[2]. Thus, this disease poses a substantial clinical and psychosocial burden amongst cancer survivors. Although diagnosis and treatment of lymphedema have improved over the years, sustainable, replicable therapy has remained a challenge.

Several techniques for the treatment of lymphedema have been developed, primarily aimed at redirecting interstitial fluid back into lymphaticovenous channels to restore lymphatic flow. These treatments range from conservative measures involving mechanical compression (i.e., complete decongestive therapy) to microsurgical techniques designed to transpose lymphatic networks (i.e., vascularized lymph node transfer) or to redirect lymphatic flow into the venous system (i.e., lymphovenous anastomosis)[3]. More recently, biomaterials-based treatments have emerged with a focus on augmenting/accelerating lymphatic regeneration. Such treatments include nanofibrillar collagen scaffolds, which mimic the collagen extracellular matrix in vasculature and can be seeded with stem cells or growth factors to help stimulate lymphangiogenesis[4].

As survival improves amongst cancer patients, management of sequelae such as secondary lymphedema has become paramount in ensuring long-term quality of life. There has been a recent surge in biomaterials research for lymphedema treatment, with investigations spanning the gamut from preclinical studies through clinical trials. This paper systematically reviews the current literature on biosynthetic nanofibrillar collagen scaffolds for lymphedema treatment by reviewing recent innovations in the field and exploring areas for further research.

METHODS

This was a systematic scoping review of the English-language literature investigating nanofibrillar collagen scaffolds for the treatment of secondary lymphedema. A structured literature search was performed with the MeSH terms listed in the Supplementary Tables 1-4, using databases including PubMed, MEDLINE, EMBASE, Scopus, the Cochrane Central Register of Controlled Trials, and Web of Science. Covidence management software (Melbourne, Australia) was utilized to screen, perform quality assessments, and extract data from included literature. Studies were selected using predefined inclusion criteria created using a Population, Intervention, Comparison, Outcome, Timing, and Setting (PICOTS) framework. Inclusion criteria were as follows: (1) English-language; (2) original research article (i.e., not a review article or meta-analysis) published after 1990; and (3) primarily investigating nanofibrillar collagen scaffolds for secondary lymphedema treatment (including preclinical, translational, and clinical investigations). Reference sections of articles meeting study criteria were also reviewed to identify any further relevant articles for study inclusion.

The study workflow was designed according to PRISMA guidelines[5]. Two independent study team members screened article titles, abstracts, and full texts for every article identified through a comprehensive literature search. Only articles primarily investigating nanofibrillar collagen scaffolds for lymphedema treatment were selected for final inclusion in the review. Any discrepancies in screening results were resolved through reviewer consensus. Two independent team members assessed the risk of bias for each article included in the final study cohort using the validated Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) scale for clinical work and the SYRCLE's risk of bias tool for animal studies[6,7]. Study objectives, design, interventions, results, and conclusions were extracted for each included study. Study data were tabulated to synthesize the literature on the use of biosynthetic nanofibrillar collagen scaffolds for lymphedema treatment.

RESULTS

In total, 32 English language articles were identified from the initial query, of which eight articles specifically investigating nanofibrillar collagen scaffolds for secondary lymphedema were selected for inclusion in the final review. Figure 1 demonstrates the algorithm for the selection of the final set of articles included in this study.

All included articles were either preclinical investigations of biosynthetic nanofibrillar collagen scaffolds for lymphedema treatment in animal models of lymphedema, or clinical cohort studies of these scaffolds in human subjects. The overall risk of bias was moderate for two studies and low for six studies [Supplementary Figure 1]. Additionally, all articles provided details on surgical techniques used to implant the scaffolds, whether in animal models or human subjects, as well as postoperative outcomes regarding changes in lymphedema symptoms following implantation of the biosynthetic scaffolds.

DISCUSSION

Novel tissue engineering efforts in lymphedema treatment have focused on designing scaffolds to guide and enhance lymphangiogenesis to regenerate lymphatic channels after iatrogenic injury. A number of biomaterials have been studied in the context of promoting lymphatic regeneration, ranging from endothelial cell-seeded polyglycolic acid scaffolds, fibrin/fibrin-collagen matrices, and fibrin hydrogels to bioengineered dermal grafts/acellular dermal matrices and decellularized adipose tissue matrices[8-11]. In particular, nanofibrillar collagen scaffolds have demonstrated particular efficacy in enhancing lymphangiogenesis[4]. From a review of both preclinical and clinical investigations, these nanofibrillar biosynthetic collagen scaffolds have been demonstrated to improve outcomes in secondary lymphedema across both preventative and therapeutic contexts [Figure 2].

Biosynthetic scaffolds: background

Lymphatic vessels have a unique architecture that is challenging to recapitulate[12]. A current focus of tissue engineering for lymphedema treatment involves the fabrication of biosynthetic scaffolds, which can be implanted in affected extremities to encourage lymphangiogenesis. These scaffolds are designed to function as three-dimensional templates for endothelial cell proliferation by acting as analogues to the extracellular matrix found in the native lymphatic vasculature. The biodegradable scaffolds are designed to be replaced by functional lymphatic channels over time. Furthermore, they can be used in combination with pro-lymphangiogenic growth factors or cell-based therapy by seeding the scaffold with growth factors or stem cells known to be involved in lymphangiogenesis[13,14].

Multiple biomaterials have been investigated as scaffolds for lymphangiogenesis, including polyglycolic acid/polylactic acid, human acellular dermal matrix, decellularized adipose tissue matrix, fibrin matrices in

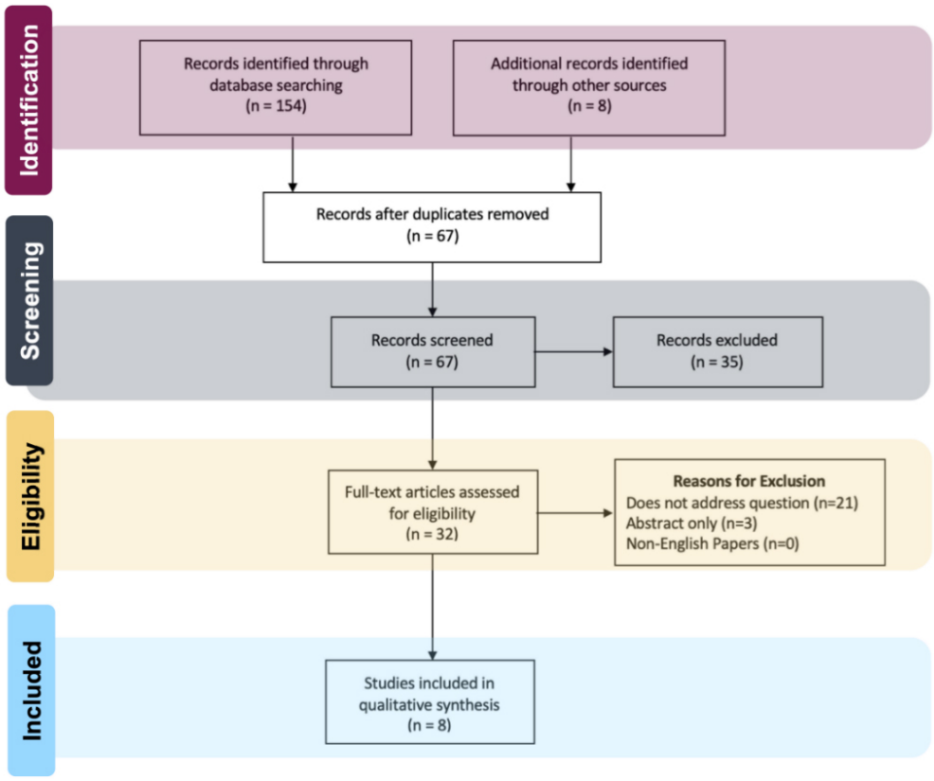

Figure 1. PRISMA study selection diagram.

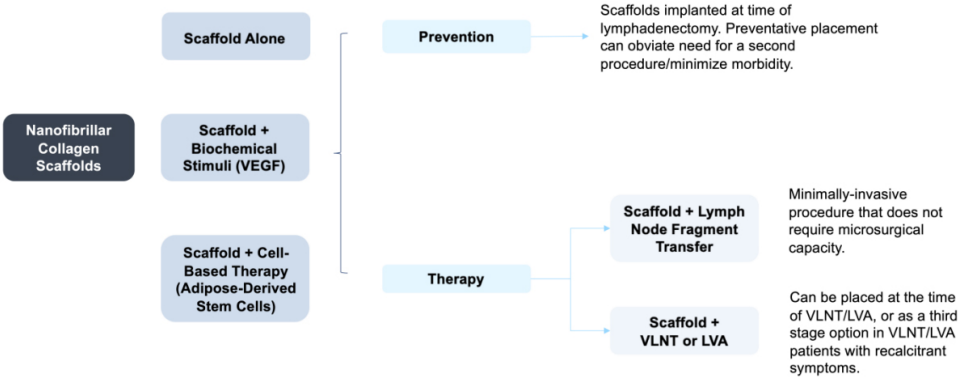

Figure 2. Utility of nanofibrillar biosynthetic scaffolds for lymphedema. VEGF: Vascular endothelial growth factor; VLNT: vascularized lymph node transfer; LVA: lymphaticovenous anastomosis.

arterio-venous loop systems, and type 1 collagen nanofibrils[11,13,15-19]. In particular, nanofibrillar collagen scaffolds, marketed as BioBridge (Fibralign Corporation, Union City, CA), have shown promise in enhancing lymphatic regeneration when used alone or when seeded with stem cells. These scaffolds are a class II device cleared through the 510(K) pathway, composed of medical grade type 1 monomeric collagen fibrils that are aligned to create membranes with high mechanical tensile strength and a stable structure. These scaffolds are fabricated into thin, ribbon-like structures that are implanted subcutaneously to bypass areas of lymphatic obstruction caused by scar tissue/fibrosis.

Given their biomimetic properties that guide cellular organization and enhance cell survival, nanofibrillar collagen scaffolds have multiple uses in regenerative medicine, ranging from nerve and vascular regeneration (e.g., neovascularization in ischemic limbs) to bone tissue engineering[20-22]. With regards to lymphedema, specifically, BioBridge scaffolds mimic native extracellular matrices, enabling endothelial cell infiltration and remodeling to recreate lymphatic vasculature. Furthermore, the nanofibrillar structure of these scaffolds guides directional local interstitial flow, which is known to be a factor in stimulating lymphangiogenesis[23]. The nanofibrillar collagen encourages endothelial cell cytoskeletal reorganization along the direction of the scaffold and provides support to enhance endothelial cell survival[24]. Ultimately, endothelial cells migrate into the scaffold, attach, and proliferate, leading to the directional development of mature lymphatic vasculature.

Nanofibrillar collagen scaffolds have been used alone and in combination with other therapies. When implanted at the time of vascularized lymph node transfer, for instance, nanofibrillar collagen scaffolds have been shown to accelerate the engraftment of lymphatic tissue by increasing endothelial cell migration and formation of lymphatic vasculature[25-27]. Lymph node transfer is thought to stimulate lymphangiogenesis in the surrounding tissue, and the scaffold augments this process by providing soft tissue support for the directional growth of lymphatic channels, as previously described[28]. However, BioBridge scaffolds have also been successfully used alone-the nanofibrillar structure of these scaffolds holds intrinsic capacity to engender lymphangiogenesis through the aforementioned mechanisms (e.g., stimulating flow of interstitial fluid, encouraging migration of endothelial cells, and enhancing expression of lymphangiogenetic factors in the surrounding milieu such as vascular endothelial growth factor)[29,30]. This highlights the immense potential that biomaterial design and tissue engineering hold for lymphedema treatment, as optimally-designed scaffolds can act in a standalone capacity to enhance lymphatic regeneration[31].

Nanofibrillar collagen scaffolds: preclinical investigations

Preclinical investigations of nanofibrillar collagen scaffolds have spanned both small and large animal models [Table 1]. In a rat model of acquired lymphedema, implantation of the BioBridge scaffold seeded with adipose-derived stem cells demonstrated significant positive effects when utilized in a preventative capacity or as a treatment in animals with established disease[32]. In this study, rodents underwent surgical excision of hind limb lymphatics and were assigned into either an untreated control group or one of two treatment groups - (1) BioBridge placement prior to irradiation (i.e., preventative placement); and (2) implantation of BioBridge scaffolds seeded with adipose-derived stem cells after lymphedema symptoms were established (i.e., therapeutic placement). When BioBridge was implanted pre-emptively at the time of inguinal and popliteal lymph node excision, rats did not develop hind limb lymphedema in the affected extremity, unlike untreated controls, as determined by computed tomography-based volumetric analysis at the 1-month postoperative timepoint. Additionally, when BioBridge scaffolds seeded with stem cells were implanted in rodents with established lymphedema, affected limb volume was significantly reduced compared to untreated controls at 4 months postoperatively, with enhanced lymphatic regeneration confirmed by near-infrared fluoroscopy.

Nanofibrillar collagen scaffolds have also demonstrated promising results in large animal models. Hadamitzky *et al.* investigated the BioBridge scaffold in a validated porcine model of secondary lymphedema, which is generated by surgically resecting hindlimb lymphatics and delivering a single dose of radiotherapy to the groin[33]. In this study, animals were randomized to one of three groups - (1) control (no treatment); (2) BioBridge with autologous lymph node fragment transfer; or (3) BioBridge supplemented with vascular endothelial growth factor-C (VEGF-C), a growth factor known to enhance lymphatic sprouting, at a concentration (1.5 micrograms/mL) that optimized VEGF-C loading and release profiles[34]. Three-month post-treatment outcomes were investigated using bioimpedance ratios and by CT contrast

Table 1. Summary of preclinical investigations

Study (reference)*	Objectives	Study design	Treatments	Number of animals	Timeline/Duration	Study outcomes
Small animal						
Nguyen *et al.*, 2022[32]	To investigate the efficacy of BioBridge implantation both preventatively and as a treatment in a rodent model of acquired lymphedema. Outcomes were measured using CT-based volumetric analysis and near-infrared fluoroscopy to detect lymphatic regeneration	Randomized Factorial Design (2 treatment groups)	(1) Untreated controls (2) BioBridge after lymphadenectomy but prior to radiation (preventive) (3) BioBridge + autologous adipose-derived stem cells (treatment)	*n* = 7 prevention group; *n* = 5 treatment group	BioBridge was implanted immediately in the preventive group, and 1 month after the establishment of lymphedema in the treatment group, study data were collected up to 4 months after scaffold implantation	BioBridge implantation at the time of lymph node excision prevented lymphedema development. BioBridge seeded with stem cells also had therapeutic effects in rodents with established lymphedema, with demonstrated regeneration of lymphatic vasculature
Large animal						
Hadamitzky *et al.*, 2016[33]	To investigate the efficacy of BioBridge scaffold placement +/- concurrent vascularized lymph node transfer in a porcine model of acquired lymphedema. Outcomes were assessed using bioimpedance, histologic evaluation, and computed tomography imaging of lymphatic vessels in the treated limb	Randomized Factorial Design (2 treatment groups)	(1) Untreated controls (2) BioBridge + VEGF-C (3) BioBridge + lymph node fragments	*n* = 4 control; *n* = 4 BioBridge + VEGF-C; *n* = 8 BioBridge + lymph node fragments	BioBridge was implanted 3 months after establishment of lymphedema; study data were collected up to 3 months after scaffold implantation	BioBridge treatment with or without lymph node transfer significantly improved bioimpedance ratios and increased quantifiable lymphatic collectors in the treated area, indicating targeted regeneration of functional lymphatic vessels. VEGF-C, on the other hand, was found to hinder directional lymphangiogenic sprouting

*See References section for full citation; citation number on References list provided here in parentheses. VEGF-C: Vascular endothelial growth factor-C; VLNT: vascularized lymph node transfer.

lymphangiography. This study demonstrated that BioBridge implantation significantly enhanced lymphatic regeneration when placed alone or in combination with autologous lymph node fragment transfer. Animals treated with BioBridge demonstrated a significantly greater density of lymphatic vessels. In fact, the highest density of lymphatic vessels in treated animals was found within 100 microns of the scaffold, demonstrating the specific impact that the scaffold had on augmenting lymphatic regeneration. Upon computed tomography imaging and bioimpedance testing, the BioBridge treatment group with concurrent autologous lymph node fragment transfer demonstrated functional improvement in lymphedema symptoms compared to the control group. In experimental groups treated with VEGF-C impregnated scaffolds, however, it was found that exogenous VEGF-C resulted in nonfunctional lymphangiogenesis. The presence of growth factor distributed uniformly along the length of the scaffold obscured the directionality of lymphatic regeneration, resulting in ineffectual lymphangiogenesis.

Nanofibrillar collagen scaffolds: clinical investigations

Nanofibrillar collagen scaffolds have also been investigated in humans, with preliminary results demonstrating the safety of scaffold placement as well as success in improving lymphedema symptoms [Table 2]. Study eligibility criteria are reported in Table 2 - including studies that investigated BioBridge placement in lymphedema patients across a variety of stages (stage I-III), as both a primary treatment and a secondary procedure in patients who had already undergone prior physiologic therapy (e.g., LVA, VLNT).

Table 2. Summary of clinical investigations

Study (reference)*	Objectives	Study design	Study population/eligibility criteria	Treatments/Number of subjects	Timeline/Follow up	Study outcomes
Nguyen *et al.*, 2021[35]	To investigate the utility of BioBridge scaffolds in augmenting the effects of LVA and/or VLNT for secondary lymphedema. Cohorts were compared based on limb volume and indocyanine green fluorescence lymphatic mapping	Retrospective cohort investigation, 2016-2019	Patients with stage 1 to stage 3 secondary lymphedema are patients with a unilaterally affected extremity, who had undergone prior LVA and/or VLNT	*n* = 18 BioBridge cohort; *n* = 11 retrospective controls	BioBridge placed on average 16.7 months (range, 1-72 months) after LVA/VLNT; Mean follow-up was 29 months	Limb volume was significantly reduced in the BioBridge cohort, with those who underwent prior VLNT demonstrating more pronounced results. These results were sustained upon longitudinal follow-up
Hadamitzky *et al.*, 2017[40]	To investigate the efficacy of BioBridge placement in combination with autologous lymph node fragment transfer, with or without adipose-derived stromal cells	Prospective cohort investigation	Patients with secondary lymphedema of a unilateral extremity	*n* = 8 BioBridge + lymph node fragment transfer (5 with scaffolds alone, 3 with adipose stromal cells); *n* = 4 lymph node fragment transfer	BioBridge and lymph node fragments were implanted concurrently, time from lymphedema diagnosis was not specified. Follow-up to 6 months post-implantation was reported	Use of BioBridge resulted in a 20% average limb volume reduction, compared to 1% in those treated with lymph node fragment transfer alone
Deptula *et al.*, 2022[36]	To investigate BioBridge efficacy in patients with advanced secondary lymphedema and to create a treatment algorithm for BioBridge placement	Retrospective cohort investigation	Patients with late stage 2 to stage 3 secondary lymphedema are patients with a unilaterally affected extremity who had undergone prior LVA and/or VLNT	*n* = 14 BioBridge cohort	Patients were considered for BioBridge placement 1-2 years after liposuction/physiologic procedure. Follow-up was at least 24 months	In patients with excess fluid volume after liposuction and physiologic treatment (LVA, VLNT), subsequent BioBridge placement normalized limb volumes, with sustained results more than 2 years after surgery
Inchauste *et al.*, 2020[39]	To investigate BioBridge with concurrent VLNT in a lymphedema patient with peripheral vascular disease	Retrospective case report	Patient with stage 3 lower extremity secondary lymphedema, with concurrent neuropathy and femoral artery thrombosis	*n* = 1	Patient was treated with VLNT and BioBridge ~30 years after the onset of lymphedema symptoms; outcomes at 3 months post-implantation were reported	BioBridge placement resulted in volume reduction, improved neuropathic pain, and improved ambulation in the affected extremity
Dionyssiou *et al.*, 2021[41]	To propose an algorithmic approach to concurrent	Retrospective cohort investigation	Partial or total mastectomy patients with stage 1-3 lymphedema refractory	*n* = 69	BioBridge implanted at the time of delayed breast/lymphatic reconstruction; mean	Simultaneous breast and lymphedema reconstruction

breast reconstruction and lymphedema treatment with vascularized lymph node transfer and scaffold placement	to medical therapy	time since lymphedema diagnosis not reported; mean follow-up was 4 years	with lymph node transfer and scaffold placement was effective in achieving sustained volume reduction, reducing infections, and improving patient satisfaction

*See References section for full citation; citation number on References list provided here in parentheses. LVA: Lymphaticovenous anastomosis; VLNT: vascularized lymph node transfer.

Nguyen *et al*. investigated delayed implantation of BioBridge scaffolds in secondary lymphedema patients who had undergone prior lymphaticovenous anastomosis and/or vascularized lymph node transfer[35]. Included patients were largely stage 1 to stage 2 lymphedema patients with a unilaterally affected extremity, who either had a suboptimal response to their initial physiologic procedure or desired further improvement in their lymphedema symptoms. After scar release and liposuction, if indicated, BioBridge scaffolds were tunneled subcutaneously to create a connection between intact native lymphatic tissue and the site of the prior lymphaticovenous anastomosis or vascularized lymph node transfer. Patients in the BioBridge cohort had a significantly greater reduction in the volume of the affected limb compared to historical controls (111% *vs*. 70% edema reduction, respectively), with lymphatic mapping demonstrating evidence of lymphangiogenesis and decreased dermal backflow in the BioBridge cohort. Furthermore, both surgical subgroups (lymphaticovenous anastomosis and vascularized lymph node transfer) demonstrated positive results with BioBridge placement, although a greater treatment response was noted in the vascularized lymph node transfer group compared to the lymphaticovenous anastomosis group (7.6-fold versus 3.5-fold increase in edema reduction, respectively). These successful results were sustained upon long-term follow-up - more than 75% of patients who underwent BioBridge implantation maintained normal limb volumes at an average of 29 months post-implantation.

Retrospective clinical investigations have studied secondary BioBridge placement in secondary lymphedema patients with more advanced disease, intending to create treatment algorithms to optimize outcomes[36,37]. Brazio *et al*. retrospectively reviewed outcomes of patients with stage II-III lymphedema undergoing physiologic procedures versus liposuction, with downstream scaffold placement in some cases[37]. They found that patients with predominantly non-pitting lymphedema benefitted most from liposuction prior to physiologic procedure/scaffold placement, while those with primarily pitting edema were best treated with physiologic procedure first and liposuction as a possible second stage[37]. Building on this study, Deptula *et al*. investigated outcomes in late stage 2 to stage 3 secondary lymphedema patients who underwent prior physiologic procedures to devise an algorithm that identifies ideal candidates for downstream BioBridge placement[36]. All included patients were treated with a proposed "triple therapy" involving initial debulking with liposuction, followed by a physiologic procedure (lymphaticovenous anastomosis or vascularized lymph node transfer) and then BioBridge placement. BioBridge placement as part of this "triple" therapy was found to have the greatest impact in patients with persistent excess limb volume due to continued fluid accumulation after lymphaticovenous anastomosis or vascularized lymph node transfer. In fact, BioBridge placement in appropriately selected patients completely normalized limb volume in the affected extremity, with sustained results noted at the two-year postoperative timepoint from the initial BioBridge placement. Unlike standard debulking therapies such as liposuction alone, which require ongoing compression therapy to prevent relapse, this triple therapy recreates lymphatic flow and thus allows patients to ultimately wean

compression garments and achieve endogenous volume control in the affected extremity through the physiologic restoration of lymphatic circulation[36,38].

While the previously described work demonstrated successful placement of BioBridge as a delayed therapy after a physiologic procedure, a recent case report in a patient with stage III right lower extremity secondary lymphedema has demonstrated that BioBridge implantation is also successful in normalizing limb volume when implanted concurrently with vascularized lymph node transfer[39]. Notably, this patient also had radiation-related peripheral vascular disease and peripheral neuropathy in the affected limb, and had undergone prior revascularization with a saphenous vein graft due to radiation-induced femoral artery thrombosis. In this patient, BioBridge scaffolds were placed subcutaneously after scar release at the time of vascularized lymph node transfer to provide soft tissue support and to bridge the lymph node transfer to healthy native lymph tissue. Ultimately, vascularized lymph node transfer in combination with BioBridge placement resulted in sustained limb volume reduction, improved neuropathic pain, and improved ambulation three months post-procedurally, demonstrating that nanofibrillar collagen scaffolds can also be safely placed at the time of microsurgical physiologic lymphedema procedures.

Preliminary data in secondary lymphedema patients have also demonstrated that BioBridge scaffolds seeded with adipose-derived stromal cells in combination with non-vascularized autologous lymph node fragment transfer resulted in sustained improvement in lymphedema symptoms[40]. A majority of patients treated with seeded BioBridge scaffolds and lymph node fragment transfer demonstrated substantial volume reduction in the affected extremity at 6 months postoperatively (mean volume reduction reported was 20%, with 1/3 of the patients reporting complete normalization of limb volumes), compared to a 1% volume reduction in controls who received lymph node fragment transfer alone. These results highlight the specific, synergistic effect of BioBridge scaffolds in enhancing lymphangiogenesis, given that lymph node fragment transfer alone was not enough to create measurable improvements in lymphedema symptoms.

Finally, Dionyssiou *et al.* (2021) investigated simultaneous breast and lymphedema reconstruction[41]. In this study, collagen scaffolds were subcutaneously inserted in the upper limb, in combination with pedicled or free vascularized lymph node transfer, to enhance lymphangiogenesis during partial or total breast reconstruction. Treated patients had fewer episodes of infection, significantly reduced pain and heaviness, significantly improved overall function, and evidence of dermal backflow reduction at 1 year postoperative follow-up. No complications specifically related to collagen scaffold placement were reported.

Nanofibrillar collagen scaffolds in the context of current lymphedema treatment

Regenerative medicine holds immense promise for secondary lymphedema and represents the cutting-edge therapies in this field that have the potential for curative treatment[13,42,43]. Tissue engineering efforts with nanofibrillar collagen scaffolds offer a number of advantages over current standard-of-care therapies for secondary lymphedema as it provides a biomaterial structure that can mimic native extracellular matrix and drive lymphatic regeneration in synergy with cellular and biochemical growth factors[44]. Unlike physiotherapy with drainage and compression or ablative surgical procedures, these scaffolds have the potential to obviate the need for repeat surgery or lifelong therapy, and they directly address the pathophysiology of the disease rather than simply providing symptomatic treatment[15]. Compared to physiologic procedures (e.g., vascularized lymph node transfer, lymphaticovenous anastomosis), nanofibrillar collagen scaffolds are minimally invasive, placed subcutaneously in affected limbs to encourage lymphatic flow across scar tissue, and do not require microsurgical anastomoses or a donor site.

Ultimately, nanofibrillar collagen scaffolds have been demonstrated to stimulate lymphangiogenesis when used alone, in combination with cell-based therapy, and in combination with lymph node fragment transfer or physiologic procedures such as lymphaticovenous anastomosis and vascularized lymph node transfer. Furthermore, the use of BioBridge offers patients an adjunct procedure that can enhance results beyond a physiologic procedure alone, even in late-stage secondary lymphedema, without incurring additional donor site morbidity as would an additional lymph node transfer[25]. Overall, while the specific indications for BioBridge are still under investigation, this technology has demonstrated efficacy across several lymphedema populations (i.e., primary therapy versus secondary therapy after previous physiologic procedure) by helping to improve lymphedema symptoms and engendering targeted, functional lymphangiogenesis. However, it should be noted that BioBridge therapy is thought to confer the greatest efficacy in patients with excess fluid volume, as it aims to divert fluid back into lymphatic circulation. Thus, for patients with severe, late-stage lymphedema and excess fibrofatty tissue, the use of this technology as a primary or standalone therapy may be limited, and they may prefer to benefit from surgical debulking. With regards to contraindications, those with allergic or anaphylactic reactions to the materials in the BioBridge scaffold should not undergo scaffold implantation, and most included studies suggest that this scaffold should not be implanted in infected fields[36]. Those with evidence of cellulitis/soft tissue infection in the affected extremity should first be treated with antibiotics prior to undergoing lymphedema surgery.

It is important to note that BioBridge represents a physiologic intervention that can be undertaken even in clinical settings without microsurgical/supermicrosurgical capacity. This is especially encouraging for the treatment of secondary lymphedema in low-resource settings when considering the data from Hadamitzky *et al*., demonstrating significant improvement in limb volume with BioBridge placement and autologous lymph node fragment transfer[40]. While vascularized lymph node transfer is a more advanced surgical technique, autologous lymph node fragment transfer with BioBridge placement is a relatively simple procedure that can be performed without a microscope or complex surgical dissection. Thus, tissue engineering approaches to secondary lymphedema treatment hold substantial promise in expanding surgical treatment of lymphedema to a wider population of patients in need.

Future directions

Nanofibrillar collagen biosynthetic scaffolds have evolved out of a need to improve outcomes in patients with acquired lymphedema. While current investigations have been largely observational, multi-center, prospective randomized controlled trials are necessary to truly evaluate the efficacy of these scaffolds as a viable treatment for secondary lymphedema. Currently, the clinical trial is underway comparing vascularized lymph node transfer with BioBridge placement to vascularized lymph node transfer alone. Further clinical trials should also investigate the preventive capacity of these scaffolds. There are many efforts underway (e.g., LYMPHA) investigating the utility of microsurgical lymphedema treatments undertaken in a preventative context[45]. Future work should investigate the efficacy of pre-emptive scaffold placement in patients undergoing lymph node dissection to forestall the development of lymphedema, especially given promising preclinical results with preventative scaffold placement in rodent models of lymphedema.

Additionally, 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 transfers[15].

As previously described, nanofibrillar collagen scaffolds represent a viable physiologic therapy for secondary lymphedema that is minimally invasive and does not require microsurgical technique. Further work should investigate the relative cost-effectiveness of using these scaffolds in secondary lymphedema patients to better understand their utility in high-volume lymphedema centers as well as their applicability to low-resource settings. Additionally, understanding the cost-effectiveness of these scaffolds can help inform reimbursement and coverage for these procedures, as acquired lymphedema remains a substantial survivorship issue amongst cancer patients[32].

In conclusion, this article reviewed novel tissue engineering efforts for the treatment of secondary lymphedema, with a particular focus on nanofibrillar collagen scaffolds. Overall, these scaffolds have demonstrated promise in augmenting lymphangiogenesis upon both preclinical and clinical testing, and they have been demonstrated to improve secondary lymphedema outcomes when used both preventatively and therapeutically.

DECLARATIONS

Authors' contributions

Contributed to conception and design, acquisition, analysis, interpretation of data, manuscript writing, and final approval of manuscript: Yesantharao PS, Nguyen DH

Availability of data and materials

Study articles and data are available at reasonable request of the corresponding author.

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Conflicts of interest

Dr. Dung H. Nguyen is the Principal Investigator of ongoing clinical trials of BioBridge in lymphedema patients. Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Plastic and Aesthetic Research

Technical Note

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Distal- to- proximal sequential ICG injection technique (DOPSIT) for lymphatic vessels mapping

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Abstract

Supermicrosurgical lymphaticovenular anastomosis (LVA) is the most sought-after procedure among lymphedema patients. However, the same enthusiasm is currently not shared among lymphedema surgeons due to the lackluster results of LVA. The common unfavorable experience with this famed procedure is at least partially caused by the difficulty in finding the lymph vessels. We share our time-tested indocyanine green-based lymph vessel mapping technique, which has helped us establish LVA as our procedure for all fluid-predominant lymphedema.

Keywords: ICG lymphography, ICG flow, linear patterns, lymphatic mapping, multipoint injection, multilevel injection, advanced lymphedema

INTRODUCTION

With recent technical breakthroughs, supermicrosurgical lymphaticovenular anastomosis (LVA) is no longer limited to early lymphedema[1-4]. However, performing LVA in late disease is frequently challenging due to difficult lymphographic identification of the functioning lymph vessels. Classically, indocyanine green (ICG) lymphographic mapping is performed with 2 to 3 injections of the fluorophore in hands and feet. The "linear" patterns observed immediately post-injection are identified as targets for LVA. In late

lymphedema, lymphatic stasis and unfavorable pressure gradients may prevent visualization of healthy lymph vessels even when they are present. Based on our observation, the classic ICG injection technique has resulted in many patients being unnecessarily declared as poor LVA candidates, due to the scant visualization of lymph vessels. In this article, we share our ICG lymphographic mapping technique[5], which is time-tested and has helped us achieve successful LVA reconstruction in many difficult cases.

TECHNIQUE

The procedure begins with intradermal injection of two to three dorsal web spaces of the ipsilateral hand/feet using 0.1 cc of 0.25% indocyanine green per injection point. This is followed by a gentle massage at the injected sites for 2 minutes. A near-infrared, fluorescence camera system is then used for visualizing the real-time spread of ICG. The course of the identified lymphatic vessels is then marked on the skin. Another row of ICG injections is given at the ankle/wrist level and the resultant change in lymphatic patterns is marked. This process is repeated at 15 cm (10 cm in upper limb) intervals along the extremity till the popliteal fossa/ cubital fossa is reached. Each level includes a row of multiple injection points, 3 to 4 cm apart, along the anterior and medial part of the limb circumference. The lymphatics pattern generated from these different injection levels is marked with different colors in Figure 1 to distinguish their origins. This distal-to-proximal sequential ICG injection technique (DOPSIT) is demonstrated step by step in Supplementary Video.

DISCUSSION

In our lymphedema clinic, we most commonly hear from our patients, "I want LVA. I don't want any other surgery!" The popularity of LVA stems from its capability to treat a bothersome, disabling condition with minimal invasiveness. Indeed, in comparison to vascularized lymph node/vessel transfers (VLNT/VLVT), LVA is conceptually benign and is free of the risk of causing donor-site lymphedema[3]. Interestingly, LVA's popularity among patients is not replicated among surgeons. In North America, VLNT remains the most commonly offered/performed lymphedema reconstruction. Why?

Many factors go into successful and efficacious LVA, including but not limited to patient selection, preoperative optimization, proficiency in supermicrosurgery, number of anastomoses, choice of anastomotic configuration, and postoperative care[6,7]. Among these, the ability to identify all available lymph vessels is crucial. After all, without the "L", there would be no LVA. LVA has been our go-to technique for all cases of fluid-predominant lymphedema. After overcoming our learning curve, we have found LVA to be technically straightforward, effective, and gratifying for both the patient and the surgeon. One of the keys to our procedural success is the ICG lymphographic mapping using DOPSIT. This technique allows us to identify more viable lymph vessels than achievable with the classic injection technique, leading to the creation of more functioning lymphatic drainage pathways in both upper and lower limbs.

In severe disease, unfavorable lymphatic pressure gradients can be such that, despite the use of DOPSIT, no lymph vessels are detectable. In this challenging scenario, the lymph vessels can usually be found by making incisions over veins mapped using an infrared vein finder. This technical trick takes advantage of the anatomic fact that superficial lymphatic anatomy loosely approximates that of superficial venous anatomy. In the unfortunate scenario of failure to image both the lymph vessels and the superficial veins, the lymph vessels can still be uncovered with the so-called "blind/anatomic" approach, based on a detailed knowledge of the superficial lymphatic system - how the lymph vessels are distinctly clustered in certain anatomic segments[5,8].

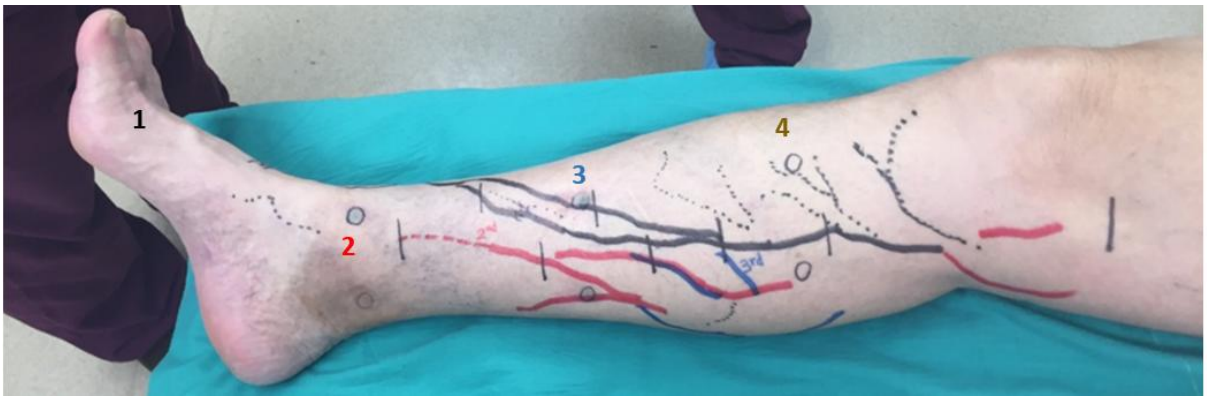

Figure 1. ICG lymphography-mapped lymphatics are shown in the lower extremity after sequential rows of injections (circles) were given on the anterior and medial surfaces. The injection row levels have been numbered from distal to proximal. The pattern in black originated from row 1 (webspace level), and the pattern in red originated from row 2 (ankle level). Part of the ICG injected at row 2 entered the same channel highlighted by the row 1 injection and lengthened it further proximally. The pattern arising from row 3 (distal calf) injection is marked with blue lines and is seen overlapping partially with the level 1 and level 2 patterns. The highest level of injection points at 4 (proximal leg) did not show any further linear patterns, and since this was close to the popliteal fossa, no further injections were necessary.

In patients with advanced lymphedema, the dermal backflow results from reflux of lymph/ICG from collectors into the precollectors (valved) and lymph capillaries (valveless). This reflux may not be apparent immediately after injection, but the poor flow gradient hinders the forward flow of ICG injected distal to such zones. This will be seen as interrupted linear pattern in ICG lymphography. To allow ICG to re-enter the lymphatic channels and resume antegrade flow, it is injected anatomically proximal to such an area of linear pattern interruption [Figure 2][9].

In keeping with the lymphosome theory, multiple, distal-level injection techniques have been described by some authors to include more lymhosomes[8,10-12]. However, within the length of a given lymphosome, there can be segments of unfavorable flow. Our technique allows the inclusion of all relevant lymphosomes as well as overcomes barriers to ICG antegrade flow within a lymphosome by injecting both distal and proximal to it.

CONCLUSION

The described distal- to- proximal sequential ICG injection technique (DOPSIT) enhances the intraoperative lymphatic mapping capability of ICG lymphography and facilitates successful LVA.

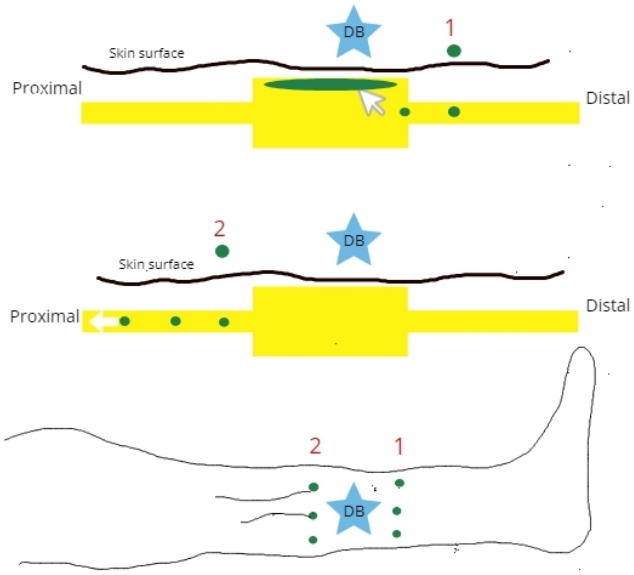

Figure 2. An illustration of a leg and its sagittal cross section showing the difference in the flow of injected ICG at levels 1 and 2, which are respectively distal and proximal to dermal backflow (DB)/zone on unfavorable pressure gradient. The green dots depict the ICG and the white arrows show the direction of ICG flow. A single collector channel in yellow is shown in each image for simplification, with widened central part representing the zone of unfavorable pressure gradient. Injection at level 2 bypasses this zone and ICG resumes antegrade flow.

DECLARATIONS

Authors' contributions

Created the technique and conceptualized this article: Chen WF
Designed the article and figures: Pandey SK

Availability of data and materials

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Conflicts of interest

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Plastic and Aesthetic Research

Review

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Robotic-assisted microsurgery for lymphedema treatment

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Abstract

The recent development of robotic-assisted microsurgery and supermicrosurgery has raised great expectations to support some of the most demanding microsurgical procedures, which are applied in lymphatic reconstructive surgery to restore lymphatic vascular integrity and treat lymphedema. Procedures such as the establishment of lymphovenous anastomosis (LVA), the harvest of lymph nodes from anatomic locations that reduce donor-side morbidity and the transplantation of the vascularized lymph node flaps (VLNT) present procedures necessitating extreme precision and dexterity in often difficult-to-reach areas, thus pushing the physical limitations of the performing microsurgeon. Despite being limited in number, recent preclinical and clinical studies of independent groups using different robotic systems demonstrate the feasibility of robotic technology to perform supermicrosurgical procedures successfully. The robotic assistance offers unparalleled precision, refining the surgical techniques and minimizing potential side effects, with clinical outcomes comparable to the conventional techniques. Although the relative disadvantages of robotic assistance mostly appear to be related to adequate training and the prolonged learning curve, the technology promises to revolutionize the field of supermicrosurgery and improve the clinical outcomes of lymphatic reconstructive surgery.

Keywords: Robotic microsurgery, robotic supermicrosurgery, lymphatic reconstruction, lymphatic surgery, lymphedema, lymphovenous, vascularized lymph node transfer, robotic-assisted surgery

INTRODUCTION

Lymphedema is defined as the insufficiency of the lymphatic system to efficiently drain interstitial fluid from the periphery, resulting in edema. It is classified as primary or secondary, depending on the cause of the lymphatic disorder; primary lymphedema is a rare genetic disorder, while secondary lymphedema may occur following infection, trauma or iatrogenic intervention[1]. Secondary lymphedema as a result of surgical oncology is one of the most common yet underestimated side effects of the oncologic treatment. It is estimated that approx. 20% of the patients receiving lymphadenectomy as part of their oncologic regime, e.g., breast cancer, other gynecological tumors, urological malignancies, melanomas and sarcomas, will develop lymphedema, with potentially increased risk for lower extremity lymphedema[2,3]. While the gold standard remains conservative decongestive therapy, lymphedema is increasingly treated surgically, as lymphatic reconstructive surgery aims to reestablish the lymphatic network integrity using microsurgical and supermicrosurgical techniques. Recent studies report improved outcomes when lymphedema is treated earlier, as the fibroadipose tissue alterations contribute to the irreversible character of the disease[4,5].

Lymphatic reconstructive surgery for lymphedema includes the installation of lymphovenous anastomosis (LVA) or transfer of vascularized lymphatic tissue (VLNT)[6]. While LVAs redirect lymph into the venous system, the transfer of vascularized lymph nodes supports lymphangiogenesis and allows lymph to drain through the venous system[7]. The efficacy of these surgical approaches in reducing the edema of the affected extremities and improving the quality of life for the treated patients has been assessed in a number of clinical studies, which have been summarized in comprehensive systematic reviews[8,9].

The progress in the development of novel surgical approaches has been supported by the improvement of the surgical armamentarium and the use of robots in surgery has pushed the boundaries of medical innovation. From the first reported use of the daVinci® Surgical Robotic System in a robotic-assisted cholecystectomy twenty years ago[10], the daVinci® technology has been implemented in many surgical specialties to accomplish highly complex minimally invasive interventions[11]. The three-dimensional stereoscopic vision, instruments with increased motion of freedom, scalable movements and elimination of tremor offered by the robotic technology found a number of applications in plastic and reconstructive surgery quickly[12]. Despite these advantages, experimental studies indicated the drawbacks of this technology in microsurgery due to the absence of dedicated, refined instruments of small size and subtle handing that this type of surgery requires[13]. The special and refined needs of reconstructive microsurgery led to the development of specialized robotic systems for microsurgery and supermicrosurgery, which have been found particularly useful in lymphatic reconstructive surgery[14,15].

In this review, we will address the use of robotic surgery in the field of lymphatic reconstructive surgery. We will provide an overview of the various robotic applications, their advantages and disadvantages, as well as the future directions in robotic-assisted supermicrosurgery.

ROBOTIC-ASSISTED PLASTIC AND RECONSTRUCTIVE SURGERY

Robotic technology has been introduced into the field of plastic and reconstructive surgery with a number of applications, ranging from flap harvest to nerve surgery and trans-oral robotic surgery[12].

In a constant effort to improve flap harvesting, robotic-assisted surgery was a promising tool. Decreasing scaring, attempting a less traumatic dissection and increasing the pedicle length have been the driving incentives. Muscle flap harvest has been attempted by different groups for isolated cases, suggesting the feasibility of the method[12]. In the particular case of the DIEP flap harvest for breast reconstruction, the usage of a robot was found to enable a minimally invasive intra-abdominal dissection of the entire pedicle

length, reducing the fascial incision to 1.5-3cm while achieving a pedicle length of 10-15cm[16]. Given its well-known abdominal donor site morbidity[17], this suggests an attractive approach to improve outcomes after DIEP flap harvest.

ROBOTIC-ASSISTED HARVEST OF VASCULARIZED LYMPHATIC TISSUE

Autologous lymph node transplantation has widely gained acceptance in lymphedema reconstructive surgery, particularly in advanced and primary lymphedema. In the process of refining the procedure, an effort was paid to decrease the donor site morbidity and thus reduce the risk of causing lymphedema at the harvesting site. Among the different options, the omentum presents an ideal donor for autologous vascularized lymph node transfer. It is abundant in lymphatic tissue, offers a broad surface area and reliable vascularity and eliminates the risk of donor-site lymphedema[18,19].

The use of the omentum was initially limited due to the concern of complications related to intra-abdominal manipulation and the need for laparotomy. The development of laparoscopic techniques clearly improved the harvest and significantly reduced the associated complications. Reduced blood loss, reduced post-operative pain, faster recovery and improved cosmesis are counting among the major benefits of this less invasive technique. But the visualization is still imperfect, restricting the ability of fine dissection. The inclusion of robotic harvest enabled a leap in the omentum flap harvest technique. The robotically assisted harvest offers an unparalleled visualization of the tissue, thus supporting very precise tissue dissection and pedicle preparation. What is more, the risk of damaging adjacent anatomical structures is minimized due to the tremor amortization and increased motion of freedom. The inclusion of additional imaging tools, such as fluorescent optics to visualize the blood and lymphatic vascular patterns, allows for improving the flap design and harvest[20,21].

Despite the longer operating times in comparison to the laparoscopically assisted surgery and the specialized training needed, the robotic harvest presents a promising approach in lymph node harvest for lymphatic reconstructive surgery.

ROBOTIC-ASSISTED MICROSURGERY AND SUPERMICROSURGERY IN LYMPHEDEMA

It is without a doubt that the development and establishment of the VLNT and LVA techniques have drastically changed lymphedema treatment, particularly given that no pharmacological treatment is still currently available and the conservative measurements cannot correct the underlying lymphatic vascular compromise. Many prospective and retrospective studies highlight the positive outcomes of lymphatic reconstructive surgery, namely volume and circumference reduction, improved quality of life and reduction of compression garment use[18,22]. Both techniques are extremely refined and technically demanding, with strong physical demand for the performing microsurgeon. A significant level of experience is necessary, along with the acquisition of challenging surgical skills[23]. Thus, technical improvements in the surgical armamentarium used are needed to improve surgical outcomes.

With the urge to constantly improve and refine surgical techniques, the development of robotic-assisted supermicrosurgery was introduced into lymphatic reconstructive surgery. Lymphatic microsurgeons are confronted with the anastomosis of vessels with a diameter between 0.3 to 0.8 mm for the reconstruction of lymphatic flow and the transplantation of pedicled lymph nodes in often hard-to-reach areas, e.g., the axilla. In particular, for the performance of LVAs, extremely fine nylon sutures (11-0 or 12-0) on a 50 μm needle are required, defining undoubtedly extremely technically demanding circumstances. Even for experienced surgeons with outstanding skills and experience, the surgical performance is still limited by the precision and dexterity of the human hands[12,24].

Robotic supermicrosurgery facilitates these procedures, helping microsurgeons overcome these limitations. Robotic assistance provides complete tremor amortization and motion scaling up to 20x. This leads to increased precision and unparalleled steadiness, particularly when handling or preparing extremely small and fragile lymphatic vessels or performing anastomosis with size mismatch or in deeper body cavities. The presence of flexible, free-moving robotic arms and seven degrees of freedom enables the deployment of the robot even in deeper and less accessible anatomic locations. While the microsurgery robots are compatible with existing operation microscopes, three-dimensional visualisations systems, also referred to as exoscopes, may contibute in a better spacial vision in light of the the absent "haptic" feedback. Additionally, the recent development of robotic systems without fixed joysticks[15] but with a remote console further improves the surgeon's ergonomic position and endurance performance.

Currently, there are two robotic microsurgery systems available. The robotic system MUSA® (MicroSure, Eindhoven, The Netherlands) developed in 2014 is the first available system of its kind[25]. It is equipped with dedicated supermicrosurgical instruments. However, it is mounted to the surgical table with fixed joysticks. Its feasibility for microsurgery has been demonstrated in both preclinical and clinical models[14,25]. The second available system is the Symani® Surgical System [Medical Microinstruments (MMI), Pisa, Italy] which was designed the second available system is the Symani® Surgical System (Medical Microinstruments (MMI), Wilmington, DE, USA) which was designed to provide movable manipulators istead of fixed handling joysticks [Figure 1]. In the system, the specialized microsurgical instruments are connected to flexible robotic arms, which are guided through freely movable forceps-like joysticks. The system also allows teleoperation, and the forceps-like joystick's similarity to conventional micro-instruments has been reported to enhance the robot-assisted experience[15].

The available but limited literature reporting the first experiences of the robotic system application in lymphatic reconstructive procedures[15,25], including the personal experience of the senior author of this manuscript, suggests the technical feasibility of the technique, with clinical outcomes comparable between robotic-assisted and conventional lymphatic surgery[26,27] [Table 1]. However, potential drawbacks of these initial applications of the new technology definitely exist and are analyzed below.

THE CHALLENGES OF ROBOTIC-ASSISTED (SUPER)MICROSURGERY

Despite the obvious advantages of using robotic-assisted supermicrosurgery, a number of limiting factors have to be acknowledged as well. The major obstacle in the broad integration of robotic technology in the surgical routine is the learning curve and the initially increased operating times. The published literature indicates increased anastomosis times using the robot versus the manual technique, even for very experienced microsurgeons. However, the learning curve was found to be steep, with the quick improvement in the operating times. The frequency of practice and level of microsurgical experience were found to support faster improvement and significantly decrease anastomosis time[27,28].

Furthermore, the absence of haptic feedback and the need for the performing surgeon to develop a "see-feel" concept during the performance of the anastomosis is a relative limiting factor. The use of adequate imaging support and training has been reported to significantly and rapidly improve the absence of sensorial feedback, especially among already experienced surgeons[15,29].

Lastly, the increased costs to purchase and maintain the robot, the expensive robotic consumables and instruments, as well as the need to have an appropriately educated operating room team to maintain time efficiency have to be taken into consideration and may limit the accessibility and adoption of the technology.

Table 1. Summary of clinical studies using robotic-assisted lymphatic surgery

Publication	Type of robot	Type of surgery	Total Nr of patients	Nr of patients with robotic anastomosis	Nr of robotic anastomosis	Time (min) for robotic anastomosis	Time (min) for manual anastomosis	Year of publication
van Mulken *et al.*[25]	MUSA	LVAs	20	8	14	25 ± 6 min and a range 16-33 min	9 ± 6 min and range 4-36 min	2020
van Mulken *et al.*[26]	MUSA	LVAs	20	8	14			2021
Lindenblatt *et al.*[15]	Symani	LVA & VLNT	5	5	10			2022
Barbon, Lindenblatt *et al.*[27]	Symani	LVA & VLNT	22	22	32	25.3 ± 12.3 min	14.1 ± 4.3 min	2022

LVA: Lymphovenous anastomosis; VLNT: vascularized lymph node transfer.

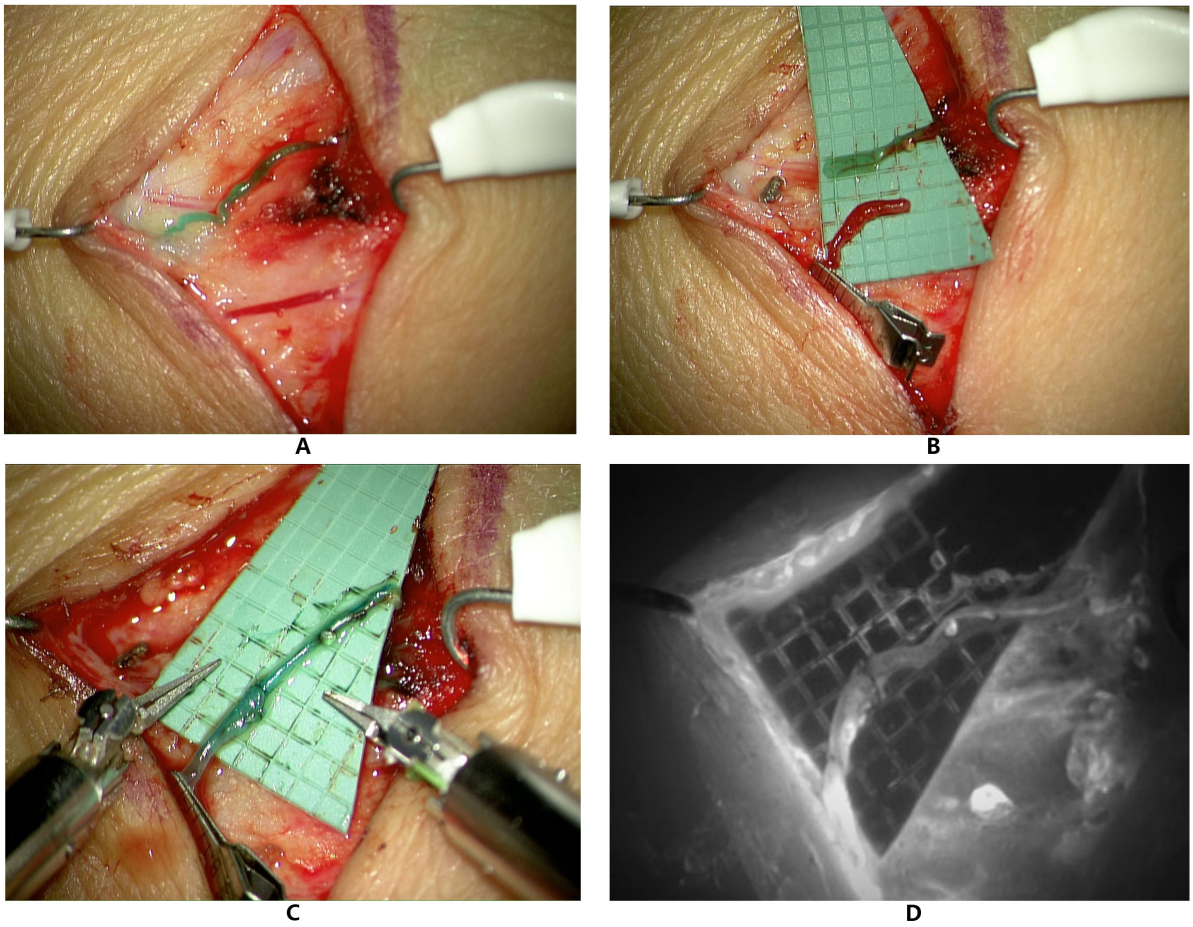

Figure 1. Presentation of a robotic-assisted lymphovenous anastomosis performed with the Symani Surgical System®. (A): 0.5 mm lymphatic vessel (above) and 0.5 mm vein (below) after intradermal injection of 0.2 mL Indocyanine green (ICG)/patent blue. (B): Proximal transection of the lymphatic and distal transection of the vein for end-to-end anastomosis. An intravascular stent (IVAS) was used for vessel stabilization during anastomosis. (C): Robot-assisted lymphovenous anastomosis with Nylon 11-0 showing good patency. (D): Fluorescent mode confirming lymphatic flow of ICG into the vein.

FUTURE PERSPECTIVES

As research continues, further improvement of the robotic systems available is expected, as well as the

development of new robots for specific indications. This progress is expected to enhance surgical precision and enable the expansion of surgical procedures.

The expansion of microsurgical instruments to improve the degree of articulation and meet different size demands will decisively influence the increase of robotic deployment. Additionally, the development of new instruments or miniaturized versions of existing ones will augment the surgeon's capabilities. Instruments to dissect vessels and tissue will be introduced. The inclusion of biosensors and improvement in the haptic feedback may restore one of the main drawbacks of robotic surgery, even if visual cues can mimic the perception of tactile feedback. This is particularly crucial in supermicrosurgery, as the surgeon is unable to sense the forces applied to the fragile lymphatic capillaries. Thus, the inclusion of haptic feedback could further improve surgical precision and atraumatic handling[26,29].

The optimal visualization of the operating field presents another topic of intense research that decisively influences supermicrosurgery. The development, refinement or integration of imaging modalities such as three-dimensional imaging, high-spectral imaging or near-infrared fluorescence imaging could facilitate the intraoperative anatomical navigation, support the functional assessment of anastomosis patency and partially compensate for the absence of haptic feedback[29,30].

Last but not least, the inclusion of artificial intelligence systems in robot-assisted systems promises to bring surgical techniques to a new level. The recording and analyzing of the surgical movements used in intelligent robots will result in the development of cognitive skills and a process of "self-learning", thus leading to semi-automated surgical applications. The possibilities for improving surgical techniques and training can be breathtaking[31].

CONCLUSION

Following the establishment of lymphatic reconstructive surgery as the only means currently available to at least partially restore lymphatic integrity, the effort is now placed on refining the techniques used, improving surgical outcomes and minimizing potential side effects.

Due to the extreme nature of lymphatic surgery, surgeons face technical and physical limitations. However, robotic-assisted supermicrosurgery enables the performance of this delicate surgery beyond the physical capabilities of the human hands, offering unprecedented dexterity, accuracy and endurance. In addition robotic systems will make access to the central part of the lymphatic sytsem, e.g., the thoracic duct more accessible[32].

The literature available so far demonstrates the feasibility of the technology and favorable clinical outcome, with a considerable but steep learning curve effect. Undoubtedly tremendous potential is available, empowering the growth and hopefully the accessibility of robotic-assisted supermicrosurgery, identifying novel applications for the patient`s needs and optimizing surgical outcomes.

DECLARATIONS

Authors' contributions

Review conception and design: Gousopoulos E, Grünherz L, Lindenblatt N
Manuscript preparation: Lindenblatt N
Critical revisions: Gousopoulos E, Grünherz L, Giovanoli P, Lindenblatt N

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Nicole Lindenblatt acts as a symposium speaker and clinical advisor for Medical Microinstruments. All other authors have no conflict of interest.

Ethical approval and consent to participate
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Consent for publication
Written consent to publish the intraoperative photos has been given by the patient.

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Recent progress in lymphovenous anastomosis

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Abstract

Breast cancer-related lymphedema (BCRL) is a debilitating disorder affecting an estimated 1 in 5 women and men treated for breast cancer. Fortunately, super microsurgical techniques have advanced in recent years and now provide better options for the treatment of lymphedema, allowing timely surgical intervention that can delay or even prevent lymphatic degeneration. Lymphovenous anastomosis (LVA), a physiologic procedure that restores lymphatic drainage by connecting functioning lymphatic vessels with nearby veins, has been shown to be both minimally invasive and highly effective. The authors describe innovative approaches to LVA that will help optimize outcomes for patients with BCRL.

Keywords: Lymphovenous anastomosis, lymphedema, super microsurgery

INTRODUCTION

Breast cancer-related lymphedema(BCRL) is a frequent complication of axillary lymph node excision with adjuvant therapy, and affects both women and men diagnosed with breast cancer[1,2]. As secondary lymphedema is a progressive disorder that results in irreversible damage to the lymphatic vessels and surrounding tissue[3], patients should be encouraged to seek surgical advice in an early phase, particularly when refractory to initiated compression therapy[4]. While surgical treatment for lymphedema previously focused on ablative procedures, current surgical techniques for the treatment of lymphedema aim to restore the drainage of lymphatic fluid from the affected limb. Lymphovenous anastomosis (LVA) consists of an anastomosis between a lymphatic vessel and a subcutaneous vein, and because it allows the lymphatic fluid

to drain into the systemic circulation, LVA has an immediate positive impact[5]. Furthermore, as LVA does not require harvesting of existing lymphatic tissue, the latter carrying an inherent risk of donor-site lymphedema, it is also a safe procedure[6]. Another advantage of LVA is that it requires only a small incision in the skin that can be performed under loco-regional anesthesia, resulting in a very low complication rate. Thanks to these advantages, LVA is particularly suitable as a first-line surgical option for the treatment of BCRL[7-9]. However, one must be aware that experience, together with specialized equipment, are prerequisites for a good patient outcome[10,11].

SURGICAL TECHNIQUE

The earliest series of LVAs in humans were described several decades ago[12,13], but the technique in current use was first developed by Koshima[14]. Supermicrosurgery refers to the handling of vessels with a diameter less than 1 mm, but the lymphatic vessels targeted in LVA are usually considerably smaller, between 0.20 and 0.80 mm in diameter. Several factors play a role in the outcome, including the incision location, the size and configuration of vessels, and the type of anastomosis.

An LVA skin incision is, on average, 2 cm in length and, despite directly interrupting superficial lymphatic vessels, does not provoke iatrogenic lymphedema. The location of the incision is based on the identification of lymphatics and veins during pre-operative assessment. Intra-operatively, the choice of suitable vessels can be challenging. Ideally, equally-sized vessels and/or vessels with favorable lymph-to-blood pressures should be used for the creation of the LVA. However, in case of a mismatch, several different approaches are available, ranging from venous-branch-plasty[15] and interposition[16] to funnelization[17] [Figure 1A]. The choice of a favorable recipient vein is also crucial[18]. It has been suggested that a relatively smaller subcutaneous vein should be selected for LVA when the lymphatic vessels are abnormally dilatated[5]. Particular importance should be paid to the prevention of blood reflux, for instance, by valvuloplasty[19], although[20] found no adverse effect on the outcome after blood reflux through anastomosis.

The efficacy of LVA is also determined by the quality of available lymphatics. 'Normal' or 'ectatic' lymph vessels are preferred when creating a functioning LVA[11,21], although the true histopathology of the vessel is rarely known intra-operatively. An intima-to-intima approach is essential to prevent post-operative occlusions[5]. Intraluminal insertion of a custom-made nylon stent can help to avoid picking up the back wall, as well as to prove the patency of the LVA[22] [Figure 1B].

The patency of the LVA after anastomosis can now be easily confirmed through washout by lymphatic fluid in the vein and/or by observing indocyanine green (ICG) in the vein[23][Figure 2]. Indeed, thanks to the improvement in operative microscopes in terms of magnification and built-in infrared cameras, intra-operative visualization of lymphatic vessels is now common practice. Any leak can also be easily traced with the ICG module and should be rectified in order to prevent thrombosis. Before closing the incision, the position of the LVA and the vessels should be checked in order to optimize the long-term patency of the anastomosis: traction or aberrant position of the new construction should be avoided.

Depending on the available vessels preoperatively, a variety of anastomotic configurations can be created with the aim of increasing maximal lymphatic drainage into the venous system[23-25]. However, in the large majority of cases, an end-to-end anastomosis will be performed. Other configurations, including end-to-side, side-to-end, and side-to-side, are sometimes required, depending on the venous pressure and anatomy[26].

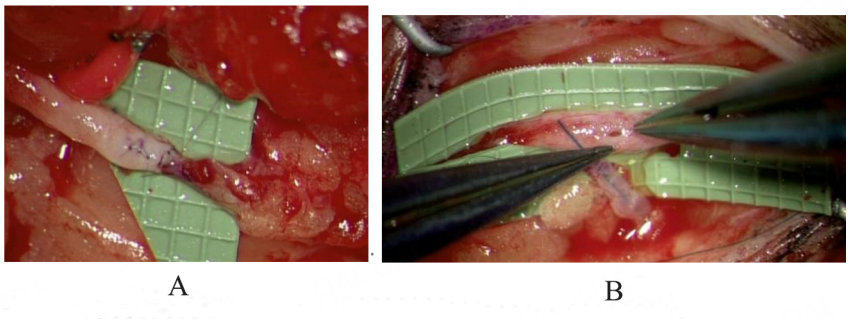

Figure 1. A: Funnelization of the vein; B: Intraluminal insertion of nylon stent in preparation for an end-to-side anastomosis.

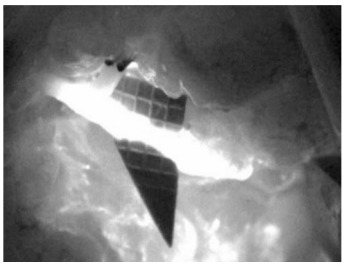

Figure 2. Peri-operative proof of patent anastomosis.

IMAGING AND EQUIPMENT

An already successful LVA procedure for lymphedema treatment can be further enhanced by the use of innovative technology and refined techniques[27]. While ICG lymphography is the gold standard for the identification of lymphatic vessels[28], deeper vessels (> 2 cm subcutaneously) cannot be visualized due to the limitations of current infrared cameras. The identification of lymphatics by ICG lymphography in patients with severe lymphedema is also limited due to the overlying dermal backflow. The implementation of super microsurgery for lymphedema treatment permitted the use of small vessels, an issue of particular importance in patients with BCRL who often present with swelling of the hand. Visualizing small lymph vessels in the distal region of the upper limb is paramount, as these vessels may allow anastomosis to low-pressure venules[14]. As LVA requires lymphatic vessels to be connected to nearby veins, the identification of suitable veins is obviously crucial.

The introduction of ultra-high-frequency ultrasound allows the detection of small-sized lymph vessels and veins in a non-invasive manner[29-31] [Figure 3]. While ultra-high frequency ultrasound has been revolutionary in the imaging of small-sized lymphatic vessels and veins, finding lymphatics with ultrasound in cases of severe lymphedema can nevertheless be challenging due to the limitations of coaptating contrast. Multispectral optoacoustic tomography (MSOT) is a 3D imaging modality based on the photoacoustic effect which allows exact spatial identification of (fluorescent) lymphatics and adjacent veins, thus overcoming these drawbacks[32] [Figure 4]. In a pilot study involving 11 patients, MSOT was found to accurately differentiate between distinct types of vessels including lymphatics, even in areas of dermal backflow, and provided images with high spatio-temporal resolution[33]. Of particular relevance to lymphatic surgery, we were able to successfully perform an LVA between an MSOT-identified lymphatic vessel and an adjacent vein[33]. In addition to identifying lymphatic vessels appropriate for LVA, photoacoustic imaging has also been used to confirm the post-operative patency of LVAs[34].

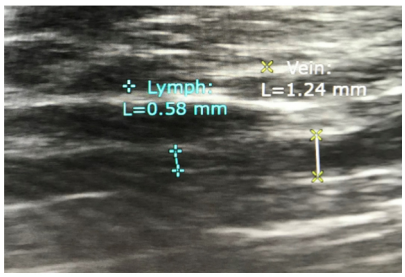

Figure 3. Visualization of lymphatic vessel and vein following ultra-high frequency ultrasound.

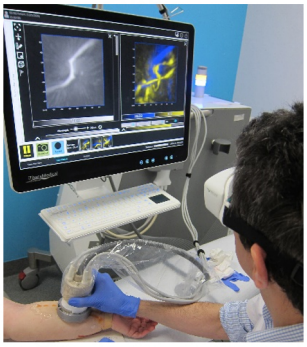

Figure 4. Visualization of lymphatic vessel (yellow) and vein (blue) in real-time following Multispectral optoacoustic tomography (MSOT).

The widespread application of super microsurgery, with its inherent focus on small-diameter vessels (0.1-0.3 mm), has also increased the demand for suitably-sized instruments [Figure 5] and needles[11] [Figure 6]. As all needles unavoidably cause tissue damage, with the extent directly related to needle size, fine needles are required for small and thin-walled lymphatics. For larger vessels, various 50 micron needles (suture size 11.0) are available and adequate. We recently reported on the use of a new 30 micron needle (suture size 12.0) in 20 LVAs in 10 patients with lymphedema of the limb[35]. Lymphatic vessels and veins had diameters of 0.2 to 0.4 mm and 0.3 to 0.8 mm, respectively. In total, 18 end-to-end and 2 end-to-side anastomoses were successfully performed.

Today, remarkable technological developments are underway, such as dedicated robots that have been successfully used for supermicrosurgical treatment of BCRL[36,37]. Furthermore, microscope-integrated laser tomography, which allows high-resolution assessment of the condition of the lymphatic lumen, is showing consideable promise[38].

UPPER EXTREMITY LYMPHEDEMA AND LYMPHORRHEA

Substantial evidence from a multitude of studies and reviews performed worldwide supports the efficacy of LVA for lymphedema of lower and upper extremities[39-42]. While immediate benefits include volume reduction of the affected limb, longer-term advantages include a decreased need for conservative therapy and compression garments, as well as a reduced frequency of infection[39,43,44].

LVA is typically used in the early stages of BCRL when a functional lymphatic system can still be identified. Early-stage lymphedema refers to excess volume caused by the accumulation of interstitial fluid. More advanced lymphedema is characterized by increased tissue fibrosis, hypertrophy of adipose tissue, and

Figure 5. Dedicated instrument: forceps.

Figure 6. Needles ranging from 50 microns.

sclerosis of the lymphatic vessels, which are irreversible. While LVA is efficient in early-stage lymphedema, even late-stage lymphedema, typically treated by debulking procedures[45] or combined techniques[46], is increasingly being treated using LVA[47,48]. Alternatively, lymphatic vessel transplantation can reconstruct interrupted lymphatic pathways after axillary lymph node resection in patients with breast cancer[49].

In addition to arm lymphedema, breast lymphedema (BLE) is also a major sequela of breast cancer treatments[50]. Although an estimated one-third of all breast cancer patients develop BLE after breast-conserving surgery with axillary lymph node intervention, its management remains poorly described. LVA is reportedly effective for extremity lymphedema and also has proven efficacy in BLE[51,52]. While compression therapy is a cornerstone of the treatment of extremity lymphedema, in BLE, the complexity of breast shape causes significant difficulties. Given that patients with BLE mostly complain of (lymphatic) congestion, a newly created lymph-to-venous bypass will give immediate relief. As men may also develop BLE following breast cancer treatment, LVA can also be successfully performed in this group[53].

Axillary lymph node dissection in breast cancer treatment may also result in lymphorrhea. While lymphatic discharge generally ceases spontaneously, intractable leakage may result in a lymphocele or fistula and discomfort for the patient. Sclerotherapy or macroscopic ligation of the injured lymphatic vessels carries a risk of subsequent aggravating (clinical) lymphedema. Therefore, the anastomosis of a damaged lymph vessel to a nearby intact lymph vessel or vein is a physiological approach to restoring lymphatic drainage[54]. We have previously described the successful treatment of axillary lymphorrhea in a series of patients treated by LVA for intractable lymphorrhea[55].

DISCUSSION

Lymphedema surgery has evolved rapidly in the last decades, largely thanks to the introduction of super microsurgery and the application of ICG imaging. LVA is a physiological approach to lymphedema and is now well established as an effective and minimally-invasive surgical treatment for lymphedema without risk for complications[8,9]. LVA is safe and has an immediate post-operative therapeutic effect compared to other

techniques including vascularized lymph node/vessel transfer. Consequently, LVA can now be considered the first-line surgical treatment for lymphedema, including BCRL. However, several remaining challenges need to be recognized.

Supermicrosurgery is technically difficult and a steep learning curve is inevitable. While major challenges such as vessel number and/or size mismatch or difficult vessel position may be encountered preoperatively, technological advances in equipment including microscopes and robotics allow LVAs to be performed with greater confidence.

How many anastomoses should be performed in order to obtain maximal lymphatic drainage is still a matter of debate[39,56]. And which factor is most important for success, the quantity or the quality (of vessels), also remains to be unequivocally established. On average, at least 3 LVAs are performed per patient, but factors including lymphedema stage and surgeon skill should also be taken into account[57]. Everyday practice, though, is determined by the number of vessels available for anastomoses and/or the reimbursement rules imposed by authorities or insurance companies. The exact location of a skin incision is also crucial for a good clinical result: the incision site is selected primarily on the basis of the ICG pattern, but for technical reasons, lymphatics and veins should preferably be in close proximity. Therefore, it is of the utmost importance that the surgeon has access to several (innovative) technologies/devices that facilitate the identification of vessels. This will be particularly beneficial in the case of patients with dermal backflow patterns and in patients with lymphedema of the hand, which is often an indication of degenerated lymphatic status. In addition to the indisputable role of near-infrared cameras, nowadays, ultrasound is also a prerequisite for good pre-operative assessment. More specifically, ultra-high frequency ultrasound can accurately detect (histologically confirmed) functional lymphatic vessels, even in advanced cases[58]. Lymphoscintigraphy is a reliable tool in the visualization of lymphatic function but well-known disadvantages, such as the two-dimensional view and the lack of projection onto anatomical landmarks, can be overcome with the use of lympho-SPECT/CT, which provides integrated information on lymphatic pathways[59]. However, as with magnetic resonance imaging, these technologies do not provide real-time information, which makes them less suitable for pre-operative planning.

Another concern is the long-term patency of an anastomosis. Efforts to prove patency should be made during the intervention. Furthermore, post-operative patency can be confirmed by means of ICG lymphography, lymphoscintigraphy, lympho SPECT/CT, or photoacoustic lymphangiography[59]. According to one report, over 70% of patients had at least one patent anastomosis 12 months after intervention[60]. Notwithstanding the data on functioning LVAs, there is still no consensus in the literature as to which tool should be used to assess the post-operative clinical effect of LVAs. It should be stressed that many variables need to be taken into account when assessing the overall outcome after LVA, among which are the number of patent anastomoses, lymphedema staging, patient characteristics, the surgeon's experience, and accessible equipment.

LVA is now an established treatment option for lymphedema in various parts of the body, but is also being increasingly used to treat a broad range of lymphatic diseases varying from lymphorrhea, a complication of lymph node excision, to generalized lymphatic anomalies mostly encountered in pediatric patients[61]. However, the question of whether prophylactic LVA after lymphadenectomy actually avoids the morbidity associated with lymphedema needs to be proven in high-quality studies with a long follow-up period[62-64]. New technologies that focus on lymphangiogenesis also appear promising and may contribute to the treatment of lymphedema in the near future[65,66].

CONCLUSION

Thanks to major innovations and refinements in existing technologies and techniques, the outcome of LVA has improved considerably in recent years. LVA is now an effective and safe procedure and thus has the potential to become the first-line surgical treatment for lymphedema, greatly benefiting patients experiencing BCRL.

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Authors' contributions

Made substantial contributions to the paper: Giacalone G, Belva F

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All patients gave consent for participation and publication.

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Plastic and Aesthetic Research

Review

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Immediate lymphatic reconstruction for the prevention of breast cancer-related lymphedema: an experience highlighting the importance of lymphatic anatomy

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Abstract

Immediate lymphatic reconstruction (ILR) has become increasingly utilized for the prevention of breast cancer-related lymphedema (BCRL). A growing body of evidence has demonstrated the long-term efficacy of ILR in reducing the rate of BCRL. While certain risk factors for BCRL are well-recognized, such as axillary lymph node dissection, regional lymph node radiation, and elevated body mass index, other potential risk factors such as age and taxane-based chemotherapeutics remain under discussion. Our experience with ILR has highlighted an additional potential risk factor for BCRL. Lymphatic anatomy, specifically compensatory lymphatic channels that bypass the axilla, may play a largely underrecognized role in determining which patients will develop BCRL after ILR. Foundational anatomic knowledge has primarily been based on cadaveric studies that predate the twentieth century. Modern approaches to lymphatic anatomical mapping using indocyanine green lymphography have helped to elucidate baseline lymphatic anatomy and compensatory channels, and certain variations within these channels may act as anatomic risk factors. Therefore, the purpose of this review was to highlight ways in which variations in lymphatic anatomy can inform the application and improve the accessibility of this procedure. As ILR continues to advance and evolve, anatomical mapping of the lymphatic system is valuable to both the patient and lymphatic microsurgeon and is a critical area of future study.

Keywords: Lymphatic anatomy, immediate lymphatic reconstruction, lymphedema

INTRODUCTION

A significant survivorship issue following breast cancer treatment is breast cancer-related lymphedema (BCRL). BCRL arises due to the accumulation of lymphatic fluid in the upper extremity as a result of damage to the lymphatic system during axillary lymph node dissection (ALND)[1]. The fluid accumulation can result in disfiguring edema, erythema, pain, tightness, heaviness, and diminished function of the affected extremity[2,3]. If left untreated, BCRL is typically progressive and can be complicated by life-threatening infections. In addition to distressing physical symptoms, patients may face psychosocial burdens secondary to BCRL[4,5,6]. Additionally, patients with BCRL face considerable out-of-pocket costs irrespective of treatment modality[7,8].

The incidence of BCRL following axillary lymph node dissection is reported to be between 21% to 34%[9-14]. Variation in reported incidence may be due to the lack of standardization in methods of assessment and diagnostic criteria. Notably, the incidence of lymphedema is disproportionately higher among Black and Hispanic patient populations, highlighting a healthcare disparity among breast cancer survivors[15]. Breast cancer mortality rates have declined due to advancements in diagnostic modalities and clinical management[16]. Therefore, the rates of BCRL can be expected to increase in the coming decades and there remains an unmet need for physicians and researchers dedicated to the prevention and treatment of this disease[17].

The pathophysiology of BCRL occurs through three stages: fluid accumulation, fibrosis, and fatty tissue deposition. In the initial stages, interstitial fluid stasis takes place and proliferation of inflammatory cells ensues[18]. This inflammatory response leads to lymphatic vessel deterioration, fibrosis, and inhibition of lymphangiogenesis[19-22]. Lastly, subcutaneous adipose tissue is deposited[23,24]. Notably, multiple genes have been implicated in the development of BCRL, including *HGF* and *GJC2* genes[25-28]. This knowledge has been utilized clinically by recommending genetic testing for patients for earlier detection of lymphedema, though further research is warranted[29].

As the underlying inciting event of BCRL development is the disruption of lymphatic vessels during oncologic surgery, our team has focused on the operative prevention of BCRL. The purpose of this review is to highlight ways in which variations in lymphatic anatomy can inform the application and improve the accessibility of the surgical prevention of lymphedema. In order to adequately discuss surgical prevention, it is important to first understand identifiable preoperative risk factors.

RISK FACTORS FOR DEVELOPING BCRL

The single greatest risk factor is ALND. Patients who undergo ALND are at a substantially higher risk of developing BCRL, with a relative risk of 3.47 in comparison to those who do not require ALND for oncologic treatment[11,30,31]. Findings from Yusof *et al.* determined that ten or more excised lymph nodes was associated with a three-fold increased risk of BCRL, due to more extensive damage to the lymphatic vessels[32]. Furthermore, patients with a larger burden of oncologic disease within the lymph nodes may be at higher risk of BCRL development, as the invasion of cancer cells within the lymph nodes may overcrowd and disrupt normal lymphatic architecture, thereby impairing lymphatic flow[30,33].

Regional lymph node radiation (RLNR) substantially increases a patient's risk of BCRL in a delayed manner, as it can take months or years for radiation-related fibrosis to develop[34,35]. The development of fibrosis within the lymph node can compress and distort the lymphatic tissue, resulting in increased fluid accumulation in the distal lymphatics[36,37]. RLNR targeted at supraclavicular or axillary lymph nodes presents the greatest risk of BCRL, whereas the risk after chest wall radiotherapy appears to be lower[37].

Body mass index (BMI) is recognized as the primary modifiable risk factor linked to the development of BCRL[30,38-40]. A higher BMI has been positively correlated with the development of BCRL, with obese patients having a greater risk of developing lymphedema compared to those who are overweight or within the normal range[39]. This correlation may be explained by underlying biochemical changes to the lymphatic system in patients with higher BMI, including inflammatory processes and direct injury to lymphatic endothelial cells, which likely induce baseline lymphatic disruption[41].

There are other important risk factors that remain controversial. Multiple studies have reported an association between taxane-based chemotherapeutic administration and BCRL development[42-46], while other studies have not supported this finding[47]. Cariati *et al.* demonstrated that the use of adjuvant taxane-based chemotherapy conferred a threefold increase in the risk of BCRL development[45]. In a large prospective study, Swaroop *et al.* noted that adjuvant docetaxol increased the risk of mild swelling though taxane-based chemotherapy was not a risk factor for BCRL development[47]. Fewer studies have focused on examining the effects of neoadjuvant taxane-based chemotherapy on the development of BCRL[48-50]. Johnson *et al.* demonstrated that patients who received neoadjuvant taxane-based chemotherapy had a reduction in lymphatic contractile function and demonstrated a possible association with the presence of peripheral neuropathy in those who received neoadjuvant taxane-based chemotherapy[48].

Multiple prior studies have noted an association between increasing age and BCRL[51-53]. Shang *et al.* demonstrated that aging results in loss of muscle cells, impairment of lymphatic contractile function, and increased production of inflammatory cytokines[54]. However, other studies offer contradictory findings, with some reporting that the incidence of BCRL is higher in younger women[55-57].

There is uncertainty as to how factors pertaining to oncologic breast surgery, such as the extent of breast surgery and reconstruction, may modify individual risk of BCRL. A previous investigation reported that modified radical mastectomy appeared to be an independent risk factor for BCRL[58]. Other studies have indicated that the rate of BCRL was higher in those who underwent a total mastectomy compared to those who underwent partial mastectomy[59]. Additionally, patients undergoing multiple surgeries including both mastectomy and lumpectomy on the same breast are likely at higher risk of BCRL than those having only one procedure alone[32]. In addition, multiple studies have examined the relationship between breast reconstruction and BCRL development. In a meta-analysis, Siotos *et al.* determined that breast reconstruction was associated with a lower risk of lymphedema compared to mastectomy alone[60]. In a matched cohort study of over 400 patients, Basta *et al.* reported that immediate breast reconstruction did seem to influence the risk of BCRL development[61]. Though the influence of breast reconstruction on the risk of BCRL development is not fully understood, breast reconstruction does not appear to adversely affect the risk of BCRL[62].

IMMEDIATE LYMPHATIC RECONSTRUCTION

Lymphovenous bypass (LVB), as described by Yukio Yamada in 1969 as a surgical treatment for chronic lymphedema, was the first successful surgical technique developed to restore lymphatic flow in an animal model[63]. In this study, a successful anastomosis of the thoracic duct into the venous system was created,

thereby restoring a novel afferent route for lymphatic fluid. In 2009, Boccardo *et al.* applied this innovation for the prevention of BCRL by rerouting arm lymphatics to an axillary vein tributary at the time of ALND[64]. This procedure, originally termed Lymphatic Microsurgical Preventative Healing Approach (LYMPHA)[64,65], has more recently been referred to as immediate lymphatic reconstruction[66]. A growing body of evidence has demonstrated promising results of ILR for the prevention of BCRL, including a recent meta-analysis which reported a BCRL incidence of 5.7% in patients who underwent ILR compared to 34% in those who underwent ALND alone[13].

An overview of the steps of immediate lymphatic reconstruction is outlined in Figure 1. Immediately prior to ALND, a lymphatic-specific dye is injected intradermally for lymphatic channel identification. In order to ensure comprehensive visualization of lymphatic channels, we perform intradermal injections of 0.25cc of 2% fluorescein isothiocyanate (FITC) mixed with albumin at the 1st and 4th dorsal hand web spaces and at the radial and ulnar aspects of the volar wrist crease. Additionally, 1cc of isosulfan blue is injected intradermally over the course of the cephalic vein, identified by ultrasound, in the lateral upper arm. The anatomic location of these injections can vary, with some opting for upper arm injections as originally described[67,68]. Once the ALND is complete, the dye allows for visualization of disrupted lymphatic channels within the axilla and the channels can then be prepared for the LVB.

Various dyes have been utilized for identification of lymphatic channels, including isosulfan blue, indocyanine green (ICG), and FITC[67]. Isosulfan blue dye was initially used for ILR, but this dye is also frequently utilized for the oncologic mapping of sentinel lymph nodes; therefore, this presented challenges in distinguishing sentinel lymph nodes from peripheral arm lymphatics. This necessitated the adoption of novel dyes for lymphatic channel identification, such as ICG, which remains a favorable option as it is not consistently used during the oncologic portion of the procedure. However, the use of ICG is limited by the inability to visualize the dye without a near-infrared camera and can compromise the surgeon's view of the surrounding structures under the surgical microscope. Additionally, some oncologic surgeons will utilize ICG for breast sentinel lymph node biopsy, though this is institution dependent. Some groups have utilized FITC as an effective alternative, given the ability of FITC to be visualized with a fluorescence filter applied to the microscope that does not limit the visibility of surrounding anatomical structures[69]. Therefore, both lymphatic channel visualization and microsurgical reconstruction can be carried out without interference. Notably, each of these techniques allows for visualization of superficial structures 1-2 cm below the skin and therefore, deep lymphatic channels are not currently able to be readily identified during ILR.

While each dye has distinct advantages and disadvantages, further research is necessary to develop standardized methods for lymphatic channel identification[70]. For example, increasing dye uptake in lymphatic vessels and improved visualization of deep lymphatic channels are notable obstacles in the application of newer dyes. Conjugating a fluorophore to a larger compound, such as to dextran, albumin, or polyethylene glycol (PEG), may have potential utilization, as any particle too small (< 5 nm) or too large (> 100 nm) precludes dye uptake into the lymphatic channels[71]. Prior investigations determined that the optimal size for lymphatic uptake is 10-100 nm; therefore, these dyes may aid in optimizing lymphatic uptake. Furthermore, near-infrared (NIR) dyes and upconverting nanoparticles (UCNPs) are other potential methods to enhance lymphatic visualization[72].

Following the identification of the transected lymphatic channels, a target vein for the lymphovenous bypass is identified. There are multiple recipient venous candidates in the axilla, including the accessory vein (thoracoepigastric vein), lateral thoracic vein, medial pectoral vein, circumflex scapular vein, thoracodorsal vein, or other unnamed adjacent venous tributaries [Figure 2][67,73]. The accessory vein, which is the most

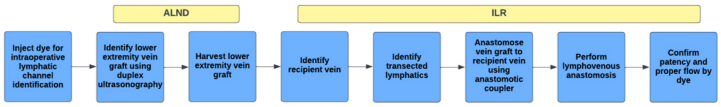

Figure 1. Comprehensive workflow of immediate lymphatic reconstruction (ILR) following axillary lymph node dissection (ALND).

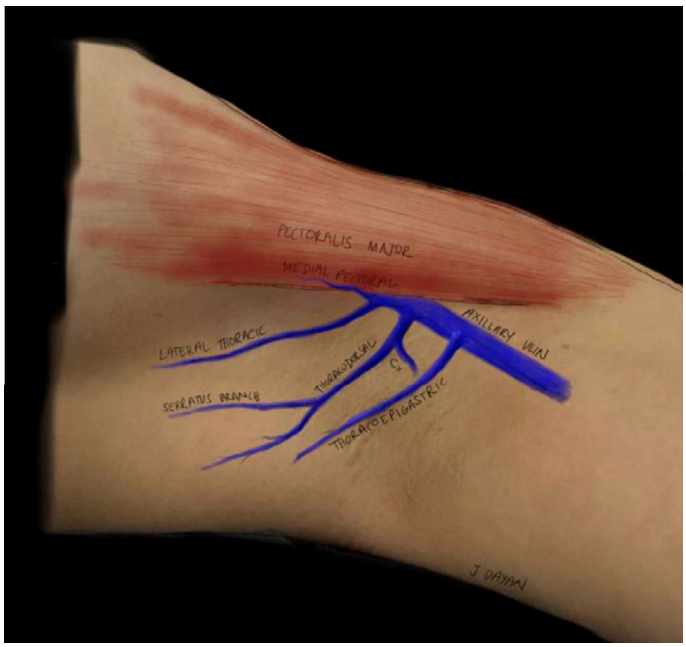

Figure 2. Potential recipient vein options in the axilla for immediate lymphatic reconstruction (reused with permission, Coriddi *et al.*, 2020, Plastic and Reconstructive Surgery Global Open[67]).

popular for ILR, is found coursing through the level 1 axillary lymph nodes, originating perpendicular from the axillary vein, 2 cm anterior to the thoracodorsal vessels. Due to its proximity to arm lymphatic channels, it has become an ideal candidate for the procedure[67]. Unfortunately, this proximity to the axillary lymph nodes also places this vein at risk for transection and removal during axillary lymph node excision. In this case, any of the previously mentioned veins can be used as an alternative[74,75].

The recipient vein requires adequate length, which we have found to be ideally ≥ 5cm, as it must be long enough to reach the arm lymphatic vessels while avoiding undue tension on the anastomosis. The presence of at least one venous valve is vital for preventing venous back-bleeding through the site of the anastomosis. Significant back-bleeding can overwhelm the lymphatic system, given the pressure differential across the anastomosis, thereby preventing afferent lymphatic flow. Furthermore, the size of the recipient vein is a critical consideration as the lymphatic channels are significantly smaller than that of their venous counterparts. To help alleviate this size discrepancy, multiple lymphatic channels can be intussuscepted into the vein, or if the lymphatic vessels are large enough, an end-to-end anastomosis can be performed with a small vein[67,76]. Utilization of venous branches of the recipient vein has also become an effective method to optimize the size-matching of the lymphatic channel to the recipient vein[67]. Moreover, each branch point is likely to contain a valve, thereby further preventing the backflow of venous blood[77]. Of note, unlike lymphovenous bypasses for chronic lymphedema performed in the distal extremity where preoperative ultrasound can assist in identifying reflux-free veins[74,75], this is not possible pre-operatively in preventative cases as the veins are deeper and their availability and physiology may be altered following

lymphadenectomy. Even with careful consideration and selection of the recipient vein, venous back-bleeding and inadequate recipient vein length are two technical challenges that impede the success of ILR and lead to aborting procedures intraoperatively. Recently, our team has instituted routine use of a lower extremity vein graft to overcome these venous-related complications[78]. In this technique, a 5 cm target vein is identified by ultrasound as a superficial secondary or tertiary branch of the greater saphenous vein in the medial lower leg, caudal to the medial epicondyle of the knee. This segment is ideally selected to ensure the presence of at least two branches or one venous valve, which can be visualized on ultrasonography. The vein is then harvested and anastomosed to the axillary vein tributary, maintaining the orientation of the vein graft in order to preserve the proper directionality of the venous valve. Since utilizing a lower extremity vein graft during ILR, our intraoperative aborted case rate was reduced from 14% to 0%, thereby suggesting the promising effects and potential utility of this innovation to mitigate venous-related complications[78]. Furthermore, the harvest of the lower extremity vein graft was performed synchronously with the ALND and therefore did not increase the intraoperative time of the overall operation[78].

Of note, additional preventative surgical approaches to reducing the risk of lymphedema have been proposed, including peripheral supermicrosurgical anastomoses and prophylactic lymph node transplantations and lymphatic flaps[79-83]. Prophylactic peripheral lymphovenous bypasses offer an interesting approach which would essentially eliminate the effect of adjuvant radiotherapy which is usually targeted to the nodal region. The challenge of this prophylactic approach is identifying anatomically which lymphatic channels should be bypassed. Prophylactic lymph node transplantations and lymphatic flaps offer a promising approach. However, the surgeon must carefully balance the morbidity of the donor site with the relative risk reduction of lymphedema development[83,84].

LYMPHATIC ANATOMY

Despite continued evidence demonstrating the effectiveness of ILR for the prevention of BCRL, there are several barriers that may hinder the progress and advancement of this approach within the field of lymphatic surgery. Firstly, ILR remains a technically demanding procedure that is not frequently covered by health insurance[85]. Additionally, there are a limited number of lymphatic centers and surgeons formally trained in lymphatic microsurgery, and therefore patients are often required to travel long distances to undergo ILR[86]. While the incidence of BCRL after ALND and RLND approaches 25-30%, around 70% of patients do not ever develop lymphedema. Although the occurrence of BRCL may be moderate, counseling all patients regarding the risk of lymphedema after oncologic surgery is necessary for proper patient management. In addition, discussing the benefits of ILR and obtaining thorough informed consent enhances patient autonomy and understanding of medical information[87]. Importantly, identifying the individuals with the highest risk for BCRL development will allow us to overcome resource constraints and deliver this procedure to those who need it the most.

We believe that a better understanding of individual variations in lymphatic anatomy will help identify those patients in greatest need for ILR. To date, there is no modern comprehensive compendium or map of normal lymphatic anatomy and most of our current foundational knowledge has been obtained from cadaveric dissections that predate the twentieth century[88]. However, more recent efforts have been made to further the anatomic knowledge of the lymphatic system. In 2016, Suami *et al.* described the lymphosome concept [Figure 3], which is defined as predictable areas of the body in which the lymphatics will reliably drain to a designated group of lymph nodes[89,90]. This concept has advanced our understanding of lymphatic anatomy and allowed for more accurate predictions regarding the location of major lymphatic channels. A detailed appreciation of lymphatic anatomy based on the lymphosome concept may help guide lymphatic surgeons in selecting which lymphatic channels to bypass when multiple transected channels are identified

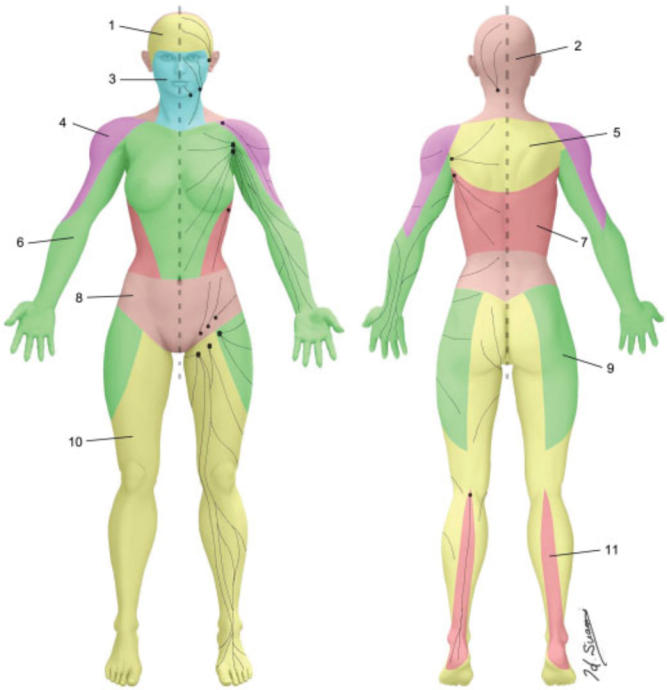

Figure 3. Major lymphosomes of the body (reused with permission, Suami *et al.* 2018, Seminars in Plastic Surgery[90]).

intraoperatively and knowledge of lymphatic anatomy in relation to venous vasculature may facilitate lymphovenous bypass[91].

Based on delineated lymphosomes, in our experience with ILR, we have noted that different regions of the upper extremity drain to distinct areas of the axilla. We previously investigated lymphosomes of the upper extremity using two distinct dyes, FITC and isosulfan blue, in order to differentiate medial and lateral upper arm lymphosomes[92]. In this study, we demonstrated that the lateral upper arm drained via a lymphatic channel that did not course through the axilla in the vast majority of patients[92]. This pathway was distinct from those of the medial upper arm, which reliably were identified as draining to the axilla. Given its extra-axillary drainage, the lateral upper arm channel had previously been described as one of the few compensatory routes of lymphatic drainage following ALND, which was further supported by our study[92]. The lateral upper arm channel, along with other compensatory drainage routes that bypass the axilla, are postulated to be protective against BCRL and may help to explain why only a percentage of patients undergoing the same oncologic treatments ultimately go on to develop BCRL. This finding has focused our group on lymphatic anatomy as we believe characterization of baseline anatomy and compensatory channels will help to predict which patients will develop BCRL after ALND.

A surgical prevention program cannot exist without a comprehensive surveillance protocol involving a multidisciplinary preoperative assessment. As part of our program's preoperative assessment, we routinely perform ICG lymphography prior to ALND and ILR in order to visualize and map baseline superficial lymphatic anatomy. Over time, our group became increasingly focused on the visualization of compensatory lymphatic channels on ICG and this informed our ICG injection sites such that we implemented targeted ICG injection sites to capture these channels[93]. Early in our ICG experience, we performed two anterior ICG injections in the wrist crease and two posterior injections at the first and fourth webspace of the hand. However, we later refined our injection technique to include an additional injection

over the cephalic vein, which allowed us to reliably visualize the lateral upper arm channel[94]. Additionally, we have more recently added a peri-olecranon injection to visualize another compensatory channel: the tricipital or Caplan's pathway[95-99].

Though we have observed significant variation in baseline lymphatic anatomy between individuals, we have noticed distinct trends in both the main channels and compensatory lymphatic channels [Figure 4]. In 102 preoperative ICG lymphographies performed, we observed that the main pathways arising from the hand and forearm (posterior radial, posterior ulnar, anterior radial, and anterior ulnar) often demonstrate a functional connection to one of two channels in the upper arm: the medial and lateral upper arm channels[100]. We also noticed variations in the connectivity of the lateral upper arm channel to the forearm channels, specifically long and short bundle phenotypes [Figure 5][93]. The long bundle lateral upper arm channel is defined as having a functional connection with a forearm channel, most commonly, the posterior radial channel. In the short bundle phenotype, the lateral upper arm channel lacks a functional connection to the forearm channels and is only visualized following the targeted injection over the cephalic vein. Upon postoperative surveillance of 60 patients who underwent ALND, the short bundle lateral upper arm pathway appeared to act as an anatomic risk factor for BCRL[101]. We hypothesize that these findings were due to the short bundle phenotype resulting in a watershed region of lymphatic drainage between the forearm and upper arm. We have also observed analogous anatomic phenotypes in the tricipital pathway [Figure 6]. We believe that future investigations focusing on the anatomical variability of this and other compensatory channels such as the tricipital pathway, will help patients at the greatest risk for BCRL development[99].

FUTURE DIRECTIONS

This knowledge can be applied clinically at various levels of care in both the preoperative and postoperative settings. For the lymphatic surgeon, this information may inform which patients would benefit most from the ILR procedure. Ideally, every patient undergoing ALND would have access to ILR for the prevention of lymphedema despite their anatomical phenotype, as the morbidity of the procedure is quite low. However, the relative inaccessibility to lymphatic surgery and inconsistent healthcare coverage for ILR hinders patients' ability to access and undergo ILR. Preoperative mapping of lymphatic anatomy using ICG lymphography can be accomplished in an outpatient clinical setting and does not require a lymphatic surgeon. Therefore, this is a feasible way to identify patients at the greatest risk for lymphedema development and for whom ILR would be most beneficial.

Moreover, a better understanding of lymphatic anatomy may inform which lymphatic channels should be prioritized for bypass or identified with an additional dye, the channels in closer proximity to the axillary vein. This knowledge would be important not only to the lymphatic surgeon, but also to members of the tumor board. For example, oncologists may choose to consider anatomical risk when determining a patient's neoadjuvant chemotherapy regimen and avoid taxane-based regimens altogether when possible. Postoperatively, patients with high-risk anatomy can follow a more rigorous lymphedema surveillance protocol or wear compression garments prophylactically[102]. Additionally, understanding compensatory lymphatic channels can help guide both physical therapists and patients in performing manual lymphatic drainage[103]. Finally, anatomical knowledge can possibly inform radiotherapy planning and field design in efforts to protect collateral drainage pathways from radiation exposure[104].

Finally, non-surgical methods for the prevention of lymphedema continue to be investigated. The use of pharmaceuticals that promote lymphangiogensis has been developed as potential treatment for lymphedema[105]. These drugs could potentially be applied to lymphedema prevention by enabling collateral

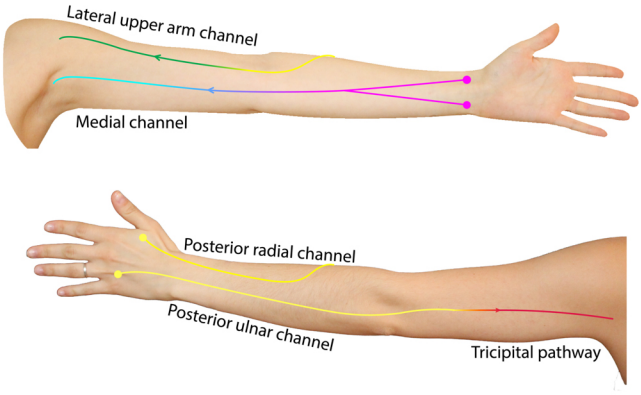

Figure 4. Schematic demonstrating the most frequently observed baseline lymphatic anatomy as visualized on preoperative ICG lymphography; colored circles represent webspace and wrist crease ICG injection sites.

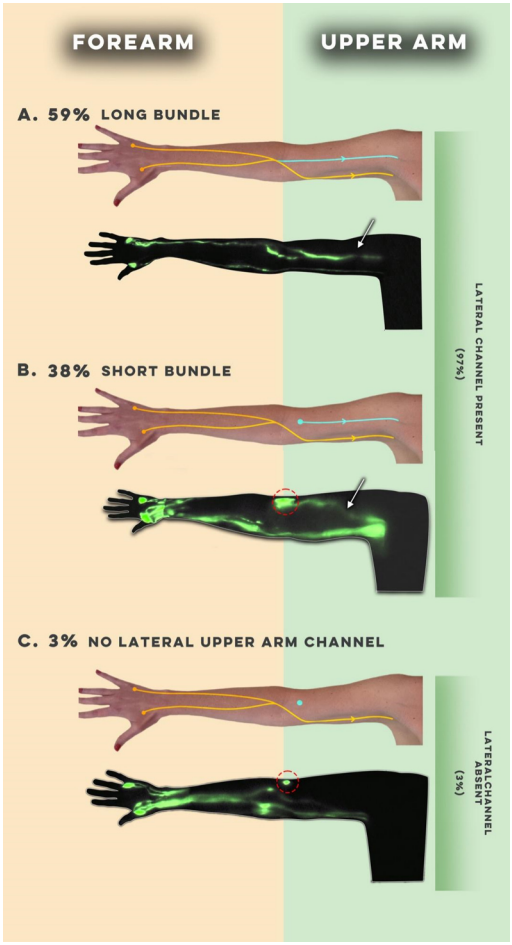

Figure 5. Long and short bundle phenotypes of the lateral upper arm lymphatic channel (reused with permission, Granoff *et al.* 2022, Plastic and Reconstructive Surgery[101]).

growth of lymphatic vessels, thereby allowing for continued lymphatic flow after ALND. Further investigation into methods of pharmacological treatment and prevention for lymphedema via

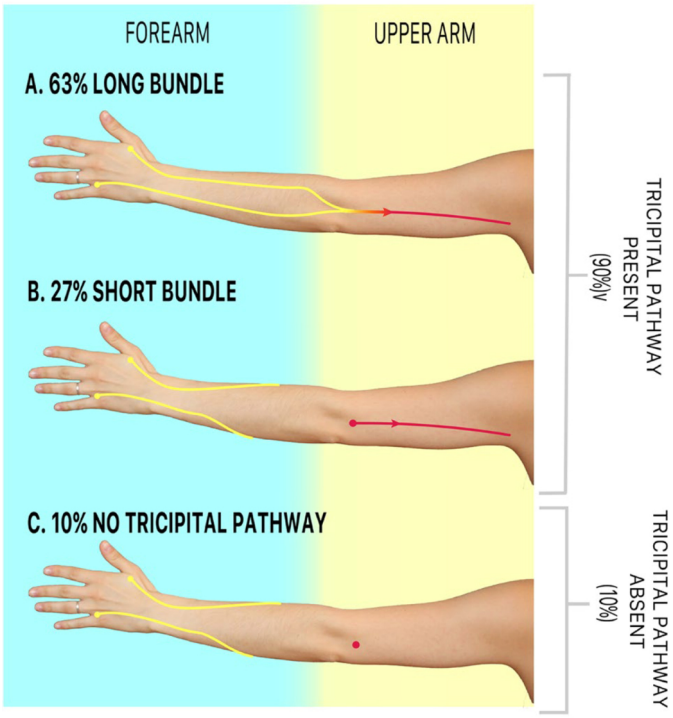

Figure 6. Long and short bundle phenotypes of the tricipital lymphatic channel (reused with permission, Friedman *et al.* 2022, Breast Cancer Research and Treatment[99]).

lymphangiogenic cytokine delivery, anti-inflammatory agents, as well as anti-fibrotic agents could aid in the non-surgical prevention and treatment of BCRL[105].

CONCLUSION

The development of breast cancer-related lymphedema following breast cancer treatment is multifactorial and surgical prevention with ILR can reduce the rate of BCRL development[13]. Although our understanding of risk factors has evolved, currently established risk factors do not fully account for the variation in BCRL development at the individual level[106]. A deeper appreciation of lymphatic anatomy will help to further our understanding of the pathologic changes that occur in BCRL and will help to explain why only a subset of patients develop BCRL after oncologic treatment and ILR. Therefore, there is high utility and value in anatomical mapping of the lymphatic system for both the patient and surgeon.

DECLARATION

Authors' Contributions

Made substantial contributions to the completion or design of the work: Friedman R, Kinney JR, Bahadur A, Singhal D

Performed data acquisition, analysis, and interpretation of data for the work: Friedman R, Kinney JR, Bahadur A, Singhal D.

Helped with drafting or revision of the manuscript for important intellectual content: Friedman R, Kinney JR, Bahadur A, Singhal D.

Provided final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Friedman R, Kinney JR, Bahadur A, Singhal D.

Availability of data and materials

Not applicable.

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Conflict of Interest

None.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Consent was obtained for the acquisition of intraoperative patient photographs for research purposes.

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Plastic and Aesthetic Research

Review

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Combination of lymphovenous anastomosis and lymph node transfer for breast cancer-related lymphedema

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Abstract

With the remarkable advancement of microsurgery, surgical treatment for lymphedema has been increasing, and its good results are well established. However, surgical treatment for advanced-stage lymphedema is still a challenging task. We reviewed several methods of combining lymphovenous anastomosis (LVA) and vascularized lymph node transfer (VLNT) in breast cancer-related lymphedema (BCRL) patients. Representative VLNT flap options for BCRL patients include the omental flap, superficial circumflex iliac perforator (SCIP) flap, and deep inferior epigastric artery (DIEA) flap combined with inguinal lymph nodes performed simultaneously with breast reconstruction. The surgical outcome, technical details, and donor site morbidities of each surgical option were reviewed. While all three options show significant surgical benefits, each has its clear advantages and disadvantages. The decision on the surgical method may vary according to the needs of each patient and the clinical situation.

Keywords: Breast cancer, lymphedema, advanced stage BCRL, omental flap, DIEP flap, SCIP flap, lymphovenous anastomosis, vascularized lymph node transfer

INTRODUCTION

With the advancement of microsurgical and supermicrosurgical techniques, new surgical methods for breast cancer-related lymphedema (BCRL) have been introduced. Since the introduction of supermicrosurgery-based lymphovenous anastomosis (LVA) and microsurgery-based vascularized lymph node transfer (VLNT), surgeons worldwide have utilized these techniques with promising results[1-3].

Furthermore, new imaging modalities, including lymphoscintigraphy, indocyanine green (ICG) lymphography, high-frequency ultrasonography, and magnetic resonance (MR) lymphangiography, have been applied to the field of lymphedema, allowing more accurate and sensitive detection of lymphatic vessels and lymphatic fluid collection[4-7]. While LVA has previously been performed predominantly in early-stage lymphedema patients, based on these advanced images, the indications for LVA have been widened to include advanced lymphedema patients as well[8,9].

However, some researchers have postulated that LVA alone may not be effective in chronic lymphedema patients[10,11], particularly patients in the late 2 and 3 stages of The International Society of Lymphology (ISL) lymphedema stage. As previously shown in pathophysiological studies, chronic inflammation and lymphatic fluid stasis cause deterioration of the pumping mechanism of the lymphatic vessels along with programmed cell death of lymphatic endothelial cells[12]. Together, they cause tissue fibrosis and progressive pathological changes in the lymphatic lumen until the lymphatic vessel becomes sclerotic and nonfunctioning. In these cases, providing a bypass through LVA at the distal lymphatic system where there is insufficient lymphatic flow may not be effective in the long run.

In these advanced BCRL patients, providing healthy lymphatic vessels and lymph nodes (lymphatic complex) through VLNT has effectively reduced arm volume and improved the patient's quality of life[3,13,14]. Compared to lower extremity lymphedema patients, BCRL patients have the advantage of having an anatomical recipient candidate for lymph node transfer, the axilla. Therefore, in theory, utilizing both of these methods with very different fundamental mechanisms can maximize the outcome for these patients. More recently, the combination of LVA and VLNT has been introduced to combine the effects of these procedures in treating BCRL patients[15-17]. This paper will discuss our protocol and techniques for performing combined LVA and VLNT in BCRL patients.

FLAP OPTIONS, PATIENT SELECTION, AND OPERATIVE DETAILS

Decision-making of surgical methods in late-stage lymphedema

Aside from radical debulking procedures, there are three main options for advanced BCRL: LVA, VLNT, and suction-assisted lipectomy(SAL). While technical details and indications of each procedure vary between different surgical centers, selecting the most suitable surgical method or a combination of techniques to maximize the outcome and patient satisfaction is the common goal for all surgeons.

Our protocol for lymph node donor selection

At our institution, we primarily use three donor sites for VLNT: right gastroepiploic artery-based omental flap, deep inferior epigastric perforators (DIEP) flap with the superficial inferior epigastric artery (SIEA) or superficial circumflex iliac artery (SCIA) based lymph node flap, and superficial circumflex iliac artery perforator (SCIP) flap [Figure 1].

The donor selection depends mainly on two factors: the need for breast reconstruction and the contracture level of the axilla [Figure 2]. If the patient wants simultaneous breast reconstruction, the DIEP flap harvested with groin lymph node is our preferred choice. Patients who do not need or desire breast

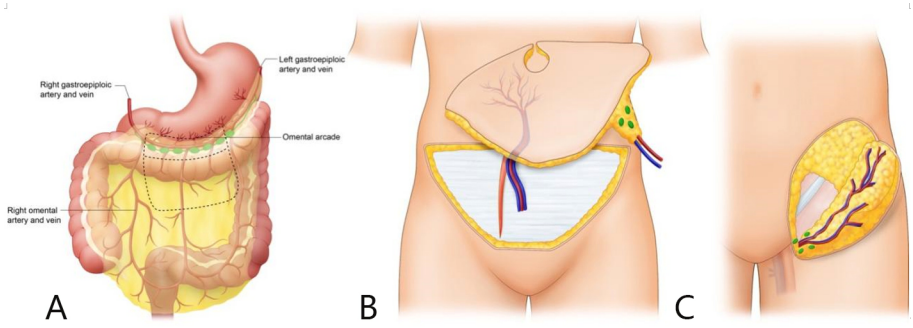

Figure 1. (A) omental lymph node flap based on the right gastroepiploic artery; (B) DIEP and SIEA or SCIA-based lymph node flap. Either contralateral or ipsilateral lymph nodes can be used; (C) SCIP flap. The lateral portion of the flap is elevated superficial to Scarpa's fascia, while the medial flap is elevated deeper to incorporate superficial inguinal lymph nodes. DIEP: deep inferior epigastric perforators; SIEA: superficial inferior epigastric artery; SCIA: superficial circumflex iliac artery; SCIP: superficial circumflex iliac perforator.

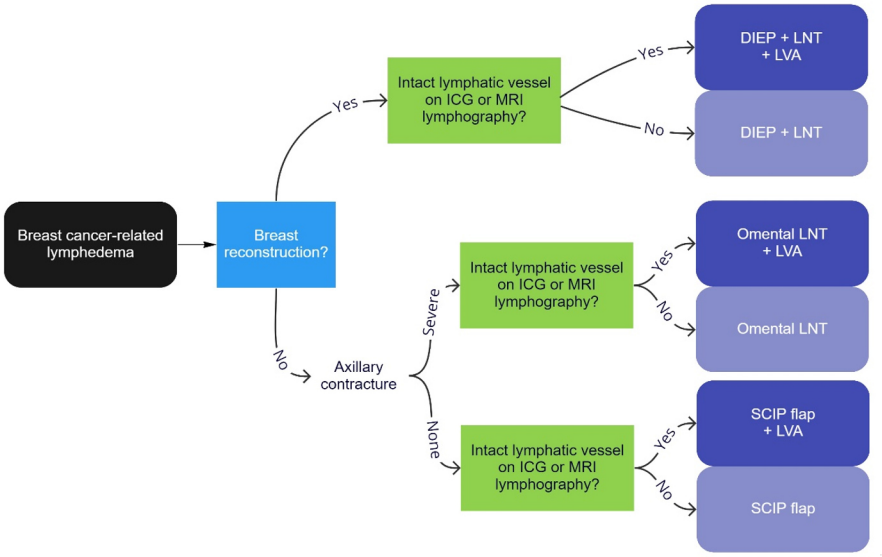

Figure 2. Flow chart of the operative plan decision-making. The flap selection depends on whether the patient needs breast reconstruction and whether the axilla is severely contracted or not. In addition, in patients with intact and functional lymphatic vessels on preoperative imaging, LVA is concurrently performed. ICG: indocyanine green; DIEP: deep inferior epigastric perforators; LNT: lymph node transfer; LVA: lymphovenous anastomosis; SCIP: superficial circumflex iliac perforator.

reconstruction can benefit from either the omental flap or the SCIP flap. In patients with severely scarred axilla, the soft tissue of the omental flap can provide the volume and cushion in the axilla. On the other hand, if no additional bulk is needed, the thin SCIP flap can deliver the benefits of lymph node transfer without altering the contour of the axilla or the limb. The lymph node flap is anastomosed to the thoracodorsal artery or a branch after the axilla's scar release. If intact and functional lymphatic vessels are identified on preoperative imaging, LVA is also performed at two to three sites, usually in the forearm region.

In all patients, ICG lymphography and MR lymphangiography are performed to identify intact and functional lymphatic vessels. In patients with lymphatic ducts suitable for LVA, LVA is performed. In patients undergoing breast reconstruction, CT angiography is performed to identify perforators, pedicle paths, and the location of supra-inguinal lymph nodes. In patients undergoing omental LNT, abdomen-pelvis CT is performed only if the patient has a history of abdominal operation. In patients undergoing SCIP flap, the use of ultrasound can help in the identification of SCIA and nearby lymph nodes.

These three donor sites are primarily used due to minimal donor-site complications and reduced operation time. Other studies have proposed that LVA and VLNT be performed in a staged or staggered fashion due to the long operation time. However, the aforementioned donor sites allow lymph node harvest to be performed simultaneously with LVA since the operative fields do not overlap[18]. As a result, the addition of LVA does not significantly elongate the operation time compared to VLNT alone.

Omental flap

The omental flap's biggest advantage is the low possibility of iatrogenic lymphedema. Compared to supraclavicular, submental, or groin flaps that can cause iatrogenic lymphedema or chyle leak, iatrogenic lymphedema has not been reported after the omental flap harvest[19]. However, some disadvantages are the need for intra-abdominal surgery, its associated complications, and possibly conspicuous abdominal scars. Additionally, harvesting lymph nodes in a relatively unfamiliar area can be a hurdle for plastic surgeons. At our institution, we overcome these pitfalls by cooperating with general surgeons specializing in laparoscopic gastrointestinal surgery. After harvesting the flap through a single port in the umbilicus, the flap is inset in the scar-released axilla [Figure 3].

Another benefit of the omental flap is its abundance of lymph nodes. Along the omental arcade, numerous lymph nodes exist. In their cadaveric study of ten adults without gastric disease, Borchard *et al.* reported an average of 14.9 ± 14.1 lymph nodes along the greater curvature[20]. This contrasts with 6.2 ± 1.3 lymph nodes found in 10 × 5 cm groin flaps in another cadaveric study by Cheng *et al.*[21].

Combined breast reconstruction with DIEP and lymph node transfer

Early reports have shown the benefit of immediate breast reconstruction in reducing the occurrence of BCRL[22]. However, the lymphedema-reducing benefit of autologous tissue-based breast reconstruction without concurrent lymph node transfer has been debated[22-24]. On the other hand, simultaneous VLNT and breast reconstruction have shown promising results[25-28].

Therefore, in BCRL patients seeking delayed breast reconstruction, combined breast reconstruction using DIEP flap and SIEA-based lymph node flap can be an excellent option to restore the breast and improve BCRL symptoms.

Similar to omental harvest, LVA can be performed in the arm while DIEP and lymph node flap is harvested in the abdomen to reduce operation time. While DIEA is used as the feeding vessel for the perforator flap, SCIA is used as the feeding vessel for the groin lymph nodes. DIEA is anastomosed to the internal mammary artery (IMA), and SIEA/SCIA is anastomosed to the thoracodorsal artery. SCIA and the lymph node can be harvested either ipsilateral or contralateral to the DIEA[29]. In our experience, using the contralateral SIEA minimizes kinking of the DIEA pedicle. If the inset proves difficult, the SIEA/SCIA-based lymph node can be separated from the DIEP flap for easier anastomosis and inset.

SCIP flap

In patients who do not want delayed breast reconstruction and are at increased risk of complications from abdominal surgery (e.g., previous surgery, peritonitis, *etc.*), SCIA-based VLNT flap is another possible option. The main advantages of SCIP flap are inconspicuous scar, well-known anatomy of the vasculature and the lymphatic drainage, and the ability to provide a large skin paddle when needed[30].

SCIP flap has limited donor site morbidity and is a familiar free flap for most microsurgeons. One major disadvantage of the SCIP flap is the possibility of iatrogenic lymphedema, which will be discussed in the

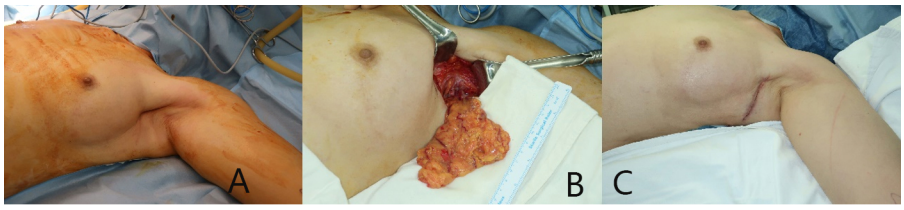

Figure 3. (A) Left BCRL patient with severe contracture of the axilla; (B) Omental lymph node flap after anastomosis to a branch of the thoracodorsal artery. In severely scarred axilla, extra omental tissue is harvested as shown and inset into the axilla; (C) Postoperative axilla. BCRL: breast cancer-related lymphedema.

next section.

To incorporate only the superficial groin lymph nodes and to minimize the bulkiness of the flap, we start the lateral elevation of the flap superficial to Scarpa's fascia. As the dissection approaches the femoral vessels, dissection continues deep to the Scarpa's fascia to harvest the lymph nodes superficial to the femoral vessels. Reverse lymphatic mapping using Technetium (deep lymph nodes) and ICG (superficial lymph nodes) is performed to accurately identify the superficial lymph nodes to be incorporated into the flap [Figure 4][30]. These nodes are usually located "within a 3 cm radius of a point 3cm inferior and perpendicular to a point 1/3 the distance from the pubic tubercle to the anterior superior iliac spine"[30].

Donor site morbidity

As with all operations, combined LVA and VLNT have their risks. While complications associated with LVA are minor and easily manageable, donor site morbidity after VLNT can perplex the patients and the surgeons. The potential morbidities of each of the mentioned donors are as follows.

Omental flap

Omental flap harvest can be performed through a conventional laparotomy, multiport laparoscopic approach, a single port approach, or a robotic approach[31,32]. In a retrospective comparative study of 177 patients, gastroepiploic lymph node flap harvest was performed through laparoscopic (126) or open approach (51)[33]. In the laparoscopic approach group, there was 1 case of acute pancreatitis and 2 cases of ileus. Complication rates were higher in the open approach group with 3 cases of ileus, 1 case of small bowel obstruction, 2 superficial surgical site infection, and 1 wound dehiscence. Furthermore, postoperative pain was significantly less in the laparoscopic, with the additional benefit of a shorter hospital stay. At our institution, the omental flap is harvested through a multiport laparoscopic or single-port laparoscopic approach to minimize complications, decrease scarring, and improve patient recovery [Figure 5].

SIEA or SCIA-based lymph node flaps

A possible detrimental complication in harvesting groin lymph nodes is iatrogenic lymphedema of the lower limb. To reduce the risk, reverse lymphatic mapping using Technetium and ICG is necessary[30]. Groin lymph nodes are composed of deep and superficial nodes, where the deep nodes manage the lymphatic flow from the leg. The flap must be elevated to incorporate the superficial node while preserving the deep nodes [Figure 4]. Several studies have reported such complications[34]. While rare, it is very difficult to manage and should be avoided at all costs through careful dissection and reverse lymphatic mapping.

OUTCOMES

Proper postoperative management is crucial in maximizing the benefits while reducing complications of these operations. In all patients undergoing LVA, a compression garment is applied immediately after the

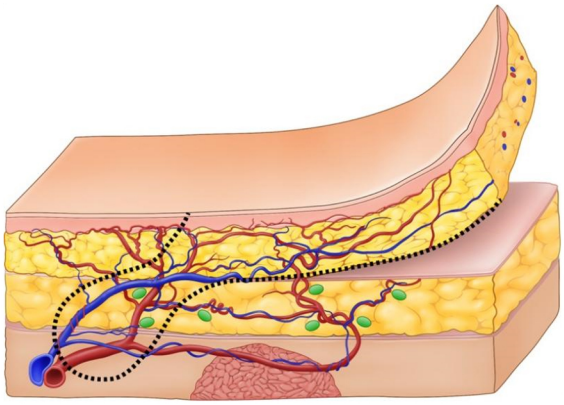

Figure 4. Superficial lymph nodes should be accurately harvested with thin flap elevation in order to minimize iatrogenic lymphedema risk.

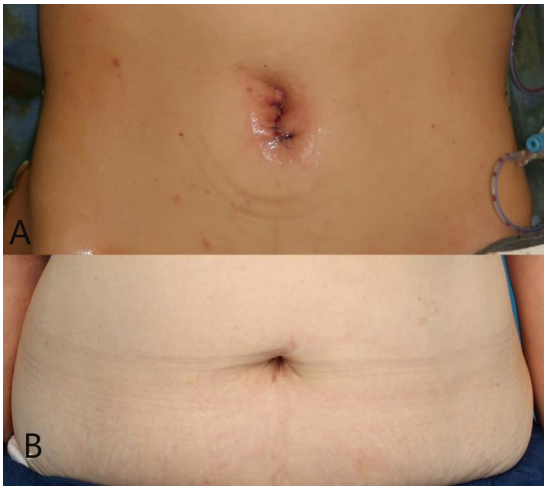

Figure 5. (A) Immediate postoperative photograph of the umbilicus after single-port laparoscopic harvest of the omental flap; (B) 12-month photograph of the umbilicus.

operation to maintain the positive pressure gradient from the lymphatic duct to the anastomosed vein. In patients undergoing breast reconstruction with DIEP and LNT, the patient is encouraged to maintain absolute bed rest for three days. After this period, the patient is allowed for light mobilization to minimize the potential of anastomosis-related complications. In patients undergoing omental LNT, the patient is closely monitored for any abdominal discomfort and pain with daily abdomen x-rays. In patients undergoing SCIP flaps, the routine postoperative free-flap protocol involves minimal ward ambulation, intravenous Prostaglandin E1 injection, and a low-residue diet for three days.

Di Taranto *et al*. reported a significant reduction in lower limb circumference and tonicity in both VLNT and VLNT and LVA groups at 1-year follow-up[15]. However, there was no significant difference between the two groups, possibly due to the short follow-up. Garza *et al*. also reported similar improvements in volume and quality of life as reported by the Lymphedema Life Impact Scale (LLIS)[17]. Their long-term study on both upper and lower extremities analyzed limb volume changes for combined VLNT and LVA procedures.

Interestingly, limb volume change showed V-shaped improvements where the volume reduction effect diminished during postoperative six months through 12 months and then improved dramatically at 24 months follow-up. This can be explained by the initial benefit of LVA immediately postoperatively due to the diversion of the excess lymphatic fluid through the bypass. The effects of VLNT were evident at 24 months of follow-up after sufficient lymphangiogenesis.

It is important to note that both limb volume reduction and LLIS scores were best at 2~3-year follow-ups, even more so than at 3-month postoperative follow-ups, where the benefit of LVA would be in effect. This study provides evidence that combined LVA and VLNT may provide better outcomes than each operation on its own.

DISCUSSION

While the exact mechanism behind the synergistic effects of LVA and VLNT has not been elucidated, several possible explanations exist. First, the initial volume reduction induced by LVA can improve patient compliance. In a study by Yang *et al.*, liposuction allows chronic patients to apply compression garments more easily, improving patients' compliance with complete decongestive therapy[35].

Secondly, LVA's physiological changes can improve the effectiveness of VLNT. Histological evidence shows decreased hyperkeratosis, local inflammation, and dermal fibrosis[36]. As Rustad and Chang pointed out, LVA can reduce local tissue inflammation and promote better lymphangiogenesis from the VLNT[37].

Di Taranto *et al.* previously compared VLNT alone with LVA and VLNT in patients with secondary lower limb lymphedemas[15]. In all the patients, suction-assisted lipectomy (SAL) was also performed two weeks after the initial lymphedema operation. Both groups showed a significant reduction in limb volume and skin tonicity. Although not statistically significant due to the small sample size (*P*-value of 0.08), the addition of LVA showed greater volume reduction above the knee.

In their preliminary report of 12 patients who underwent simultaneous supraclavicular VLNT and LVA for lower limb lymphedemas, Chung *et al.* showed a significant reduction in both mean limb circumferences and lower extremity lymphedema index[38]. These findings can also be applied to BCRL patients.

Most BCRL patients have undergone axillary lymph node dissection, which causes fibrosis of the axilla. Postmastectomy radiotherapy (PMRT) can further aggravate this fibrosis. In addition to worsening lymphedema by constricting the drainage[39], fibrosis can cause neurologic symptoms such as tingling sensations and neuropathic pain for the patients. While its definitive effect is still debated, releasing the scar tissue and providing new fresh tissue (VLNT) can provide physiological benefits[11,17,40].

Furthermore, LVA and VLNT have different mechanisms for improving lymphedema. LVA forms a shunt between a functioning lymphatic vessel and a vein, allowing drainage of lymphatic fluid into the venous system[41]. On the other hand, VLNT's mechanism is thought to be multifactorial. VLNT acts as a "pump" for lymphatic fluid from the limb to drain through the VLNT after lymphangiogenesis occurs into the surrounding tissue[42]. Because of the difference in the underlying mechanism, LVA's effect is evident almost immediately after the operation, while VLNT shows a delayed effect after successful lymphangiogenesis into the surrounding tissue. By combining these two techniques, synergistic benefits can be gained while overcoming one of the drawbacks of VLNT, the absence of immediate effect, which can deter patient compliance.

Another question to consider is the future roles of old debulking surgeries, such as the Charles procedure, in more advanced BCRL patients. As mentioned previously, performing SAL in conjunction with other methods, such as LVA and VLNT, can improve patient compliance by reducing the volume immediately after the operation[16]. Reducing the volume can ease the elastic stocking application process and motivate patients to comply with CDT. While radical procedures have been considered the last resort for severe cases, they may also be performed in combination with LVA and VLNT either simultaneously or in stages as technology and techniques advance.

As emphasized in this study, patients may have different clinical situations when considering LVA combined with VLNTs for patients in advanced BCRL. Patients may or may not want breast reconstruction, and each patient's degree of axillary fibrosis and contracture can differ. In addition, the availability of laparoscopic or robotic surgery for omental flap harvest in the institution performing the surgery may vary. Considering these various clinical situations, the optimal surgical method should consider the patient's lymphedema pattern, severity, and clinical needs.

CONCLUSION

A further randomized clinical trial is needed to compare the benefits and disadvantages of combined procedures. However, if combined procedures can be performed without increasing overall operation time and complication rates, current evidence does not seem to direct the surgeons away from these combined procedures.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Park Jh, Myung Y

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable. Informed consent was obtained from the patients involved in this manuscript.

Consent for publication

Written informed consent for the publication of the images has been obtained.

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Diagrams with describing words (including, flow chart, coordinate diagram, bar chart, line chart, and scatter diagram, *etc.*) should be editable in word, excel or powerpoint format. Non-English information should be avoided;
Labels, numbers, letters, arrows, and symbols in figure should be clear, of uniform size, and contrast with the background;
Symbols, arrows, numbers, or letters used to identify parts of the illustrations must be identified and explained in the legend;
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All non-standard abbreviations should be explained in the legend;
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Tables should be cited in numeric order and placed after the paragraph where it is first cited;
The table caption should be placed above the table and labeled sequentially (e.g., Table 1, Table 2);
Tables should be provided in editable form like DOC or DOCX format (picture is not allowed);
Abbreviations and symbols used in table should be explained in footnote;
Explanatory matter should also be placed in footnotes;
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2.4.7 Abbreviations

Abbreviations should be defined upon first appearance in the abstract, main text, and in figure or table captions and used consistently thereafter. Non-standard abbreviations are not allowed unless they appear at least three times in the text. Commonly-used abbreviations, such as DNA, RNA, ATP, *etc*., can be used directly without definition. Abbreviations in titles and keywords should be avoided, except for the ones which are widely used.

2.4.8 Italics

General italic words like *vs*., *et al., etc*., *in vivo*, *in vitro*; *t* test, *F* test, *U* test; related coefficient as *r*, sample number as *n*, and probability as *P*; names of genes; names of bacteria and biology species in Latin.

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SI Units should be used. Imperial, US customary and other units should be converted to SI units whenever possible. There is a space between the number and the unit (i.e., 23 mL). Hour, minute, second should be written as h, min, s.

2.4.10 Numbers

Numbers appearing at the beginning of sentences should be expressed in English. When there are two or more numbers in a paragraph, they should be expressed as Arabic numerals; when there is only one number in a paragraph, number < 10 should be expressed in English and number > 10 should be expressed as Arabic numerals. 12345678 should be written as 12,345,678.

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Equations should be editable and not appear in a picture format. Authors are advised to use either the Microsoft Equation Editor or the MathType for display and inline equations.

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3. Research and Publication Ethics

3.1 Manuscript Structure

All studies involving human subjects must be in accordance with the Helsinki Declaration and seek approval to conduct the study from an independent local, regional, or national review body (e.g., ethics committee, institutional review board, *etc.*). Such approval, including the names of the ethics committee, institutional review board, etc., must be listed in a declaration statement of Ethical Approval and Consent to Participate in the manuscript. If the study is judged exempt from ethics approval, related information (e.g., name of the ethics committee granting the exemption and the reason for the exemption) must be listed. Further documentation on ethics should also be prepared, as Editors may request more detailed information. Manuscripts with suspected ethical problems will be investigated

according to COPE Guidelines.

3.1.1 Front Matter

For all studies involving human subjects, informed consent to participate in the studies must be obtained from participants, or their parents or legal guardians for children under 16. Statements regarding consent to participate should be included in a declaration statement of Ethical Approval and Consent to Participate in the manuscript. If informed consent is not required, the name of the ethics committee granting the exemption and the reason for the exemption must be listed. If any ethical violation is found at any stage of publication, the issue will be investigated seriously based on COPE Guidelines.

3.1.2 Consent for Publication

All articles published by OAE are freely available on the Internet. All manuscripts that include individual participants' data in any form (i.e., details, images, videos, *etc*.) will not be published without Consent for Publication obtained from that person(s), or for children, their parents or legal guardians. If the person has died, Consent for Publication must be obtained from the next of kin. Authors must add a declaration statement of Consent for Publication in the manuscript, specifying written informed consent for publication has been obtained.

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A case report is considered the diagnosis, treatment and post-treatment follow-up of a single patient. A case series is considered a group of case reports involving patients who were all given similar treatments. A clinical dataset is a list of well-defined variables collected during ongoing patient care or as part of a clinical trial program. It includes electronic health records, administrative data, patient registries, and clinical trial data.

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Given the specificity of details provided in a case report, case series or clinical dataset, authors are required to obtain consent for the publication of the case(s) from patients, or their guardians if they are not adults or lack capacity to provide informed consent, or next of kin if deceased. A statement confirming consent for publication has been obtained must be included in the manuscript. Authors should share this with the journal Editorial Office if requested.

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Researchers must confirm they have obtained ethical approval from ethical review boards to perform the study, as well as permission from the dataset owner to use the information in databases for the purposes of the research they are performing. If permission to use information from a database is not required (e.g., it is publicly available and unrestricted re-use is permitted under an open license), a statement explaining this must be included in the manuscript. For studies which ethics approval has been waived, authors must state clearly in the manuscript and provide brief details of the waive policy. The statement should include details of the policies under which the waive was granted.

Authors must keep data anonymized. If participants' details are not to be anonymized, authors must ensure that written informed consent, including consent for publication, was obtained from each participant, and consent statement must be included in the manuscript.

3.1.5 Ethical Approval and Informed Consent for Survey Studies

Researchers must ensure the participant's right to confidentiality has been considered, and they must inform all participants about the aims of the research and if there are any possible risks, and how the collecting data is being stored. The voluntary consent to participate of participants should be recorded and any legal requirements on data protection should be adhered to. Same with all research studies, ethics approval from IRB/local ethics committee for survey studies must be obtained before performing study. If ethics approval for certain survey study is not required, authors must include a statement to explain this clearly in the manuscript.

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9. Editorial Process

9.1 Initial check

9.1.1 Initial manuscript check

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Disseminate high-quality scientific achievements; promote the innovation and development of relevant disciplines.

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OAE is committed to publishing valuable scientific achievements, enriching the academic research and promoting the innovation of scientific research in relevant disciplines via scientific, standard, and professional publishing processes.

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