Demystifying vascularized lymph node transfers and lymphatico-venous anastomoses

Yasser Almadani[1], Peter Davison[1], Johnny Ionut Efanov[2], George Kokosis[3], Joshua Vorstenbosch[1]

[1]Division of Plastic and Reconstructive Surgery, McGill University Health Centre, Montreal, Canada; [2]Division of Plastic and Reconstructive Surgery, Centre Hospitalier de l'Université de Montréal, Montreal, Canada; [3]Division of Plastic and Reconstructive Surgery, Department of Surgery, Rush University Medical Center, Chicago, IL, USA

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Correspondence to: Joshua Vorstenbosch, MD, PhD, FRCSC. Division of Plastic and Reconstructive Surgery, McGill University Health Centre, Royal Victoria Hospital, 1001 Boul Decarie, Room D02.7007, Montreal, Quebec H4A 3J1, Canada. Email: joshua.vorstenbosch@mcgill.ca.

Abstract: Lymphedema continues to be a widely prevalent condition with no definitive cure. It affects a wide range of patients across different ages and backgrounds. The significant burden of this chronic and debilitating condition necessitates more research and comprehensive healthcare coverage for affected patients. In developed countries, cancer survivors are disproportionality affected by this condition. Risk factors including lymph node dissections and radiation render many cancer patients more susceptible to the development of lymphedema. Part of the challenge with lymphedema care, is that it exits on a broad spectrum with significant variability of symptoms. Advances and broader availability of various imaging modalities continue to foster progress in lymphedema surgery. The conservative management of lymphedema remains the primary initial management option. However, lymphedema surgeries can provide significant hope and may pave the way for significant improvements in the quality-of-life for many patients afflicted by this progressive and enfeebling condition. Reductive and physiologic procedures are becoming an important part of the armamentarium of the modern plastic and reconstructive surgeon. Recent advances in physiologic lymphedema surgeries are accelerating their transition from experimental surgeries to broadly adopted and widely accepted procedures that can lead to major successes in the fight against this condition. Prophylactic lymphedema surgery also presents a promising choice for many patients and can help prevent lymphedema development in high-risk patients.

Keywords: Lymphedema surgery; vascularized lymph node transfers (VLNTs); lymphatico-venous anastomoses (LVAs)

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Introduction and epidemiology

Lymphedema (LE) is a chronic, progressive disease of the lymphatic system that exists on a wide spectrum of presentations (1,2). Globally it is estimated that LE affects up to 1 in 30 people, with wide variability in its estimated prevalence and etiologies amongst developing and developed countries (3). Epidemiologic studies estimate that the prevalence of LE in North America ranges anywhere between 1/1,000 to 1/36 (4,5). In developed countries, LE is predominantly a sequela of surgical oncologic resection, posing a significant additional burden on a stressed patient population (6-8). It is estimated that breast cancer-related lymphedema (BCRL) develops in approximately 21% of breast cancer survivors (3,9,10), while the excision of melanomas or gynecological cancers confers a significantly lower risk of LE development compared to BCRL, estimated to be around 13% and 10%, respectively (7,11-13). This could be related to associated axillary lymph node dissections (LND), as it is estimated that 31–49% of patients who undergo axillary LND for breast cancer management go on to develop LE (14,15). Even minimal lymphatic injury in the form of sentinel lymph node biopsy is thought to be associated with LE development in 5–7% of patients (16,17).

Types of LEs

Primary LE is mostly related to a variety of genetic etiologies leading to developmental deficiencies of the lymphatic system (18). Primary LE is commonly subdivided into: (I) congenital LE, present at birth or identified within 2 years of birth comprising 10–25% of primary LE cases; (II) LE praecox, which is the most common type of primary LE representing 65–80% of primary cases, which is observed almost exclusively in young women occurring around the age of puberty; or (III) lymphedema tarda, which begins after 35 years of age and is thought to represent less than 10% of primary LE cases (19-21).

Secondary LE results from the disruption of a normally developed lymphatic system. This may lead to an obstruction of lymphatic channels and an imbalance between the production of lymphatic fluid and its outflow from affected body regions. A variety of etiologies have been associated with the development of secondary LE including: surgical resections of tumors, radiation, trauma, recurrent infection, chronic venous insufficiency, obesity and filarial infections, especially by *Wuchereria bancrofti*—the most common etiology worldwide with over 51 million people infected in 2018 as estimated by the World Health Organization (WHO) (22-24).

However, unlike in primary LE, the overall structure of the lymphatic system is preserved in secondary LE despite its impaired function (25). This helps in conceptually differentiating secondary from primary LE where anatomic defects of the lymphatic system are detected at various structural levels. Ultimately, this may lead to less favorable surgical outcomes for primary LE compared to early-stage secondary LE (25). In many instances in primary LE, the progression of lymphatic damage can hamper the efficacy of surgical treatment as significant delays are thought to increase the risk of surgical failure (26). The same principles are thought to apply to late stages of secondary LE where fibrosis has ensued and the lymphatic vessels have lost their ability to transfer lymphatic fluid, thus commencing the vicious cycle of impaired lymphatic drainage and accumulation of interstitial fluids and altered immune response leading to chronic inflammation (27).

Pathophysiology

LE is a frequently overlooked condition that involves complex micro and macro-level processes. Amongst the key functions of the lymphatic system is maintaining balanced tissue levels of fluids. The lymphatic system plays a vital role in returning and transporting back the capillary ultrafiltrate and filtered plasma proteins as well as emulsified fat to the bloodstream. By doing so, lymphatic vessels complete the extravascular circulation of fluid and protein and maintain overall volume homeostasis (28). This is a continuous dynamic process where filtration and absorptive forces lead to a “steady state” (29). The lymphatic system also plays an integral role in the immune system and circulatory system where it aids in lipid transport (30,31).

LE is characterized by increases in extremity volume caused by the accumulation of tissue fluid, the proliferation of cells, and excessive production of collagen as a consequence of impaired lymphatic drainage. As a result, bacterial colonization is enhanced due to the favorable conditions created by disrupted lymphatic fluid. It is estimated that the lymphatic system can transport between 20 to over 200 mL during 24 hours per limb (32). As expected, if this ability is lost, significant stasis of intercellular water, proteins, fat, and migrating immune cells occurs ultimately leading to scarring and loss of contractility of the lymphatic system (33,34).

As a consequence of the disrupted steady state and ensuring stasis, more than 50% of LE patients develop bacterial dermato-lymphangio-adenitis (DLA) (35). Generally, there are two lymphatic drainage pathways within each extremity; the superficial subdermal network and the deeper subfascial network (36). In cases of obstruction, where one pathway is disrupted, the remaining patent pathway attempts to compensate for the other pathway by increasing its efforts for drainage. However, it is reported that the subdermal pathway is more efficient and as a result, patients do not usually develop LE as a result of an obstruction of the subfascial system (37). Recent data suggest that lymph nodes also communicate with the venous system through lymphatic venous communications that can drain lymph fluid from the surrounding tissue into the node, ultimately draining into the local venous vascular system highlighting the correlation between chronic unchecked venous stasis and the development of LE (38,39).

Burden of LE

LE is a condition that has been shown to significantly affect patients' lives. Overall, LE is associated with significant physical and psychological sequalae including pain, decreased strength, reduced function, and decreased self-confidence (40,41). The increasing limb circumference appears to be a significant stressor for LE patients and a decrease in limb circumference was associated with higher patient satisfaction overall (42).

Given the heterogeneity and varying presentations of LE, the precise impact of this chronic condition may be challenging to capture. Validated questionnaires indicate that LE patients score worse in domains such as: anxiety, mood, well-being, self-control, general health, and overall vitality (43). LYMQOL has emerged as a simple and useful tool for use in clinical practice and scientific contexts for evaluating the quality of life (QoL) of LE patients (44). Other QoL outcomes measures include the upper limb LE 27 scale (ULL27), the short form 36 questionnaire (SF-36), the Lymphedema Functioning, Disability and Health Questionnaire (Lymph-ICF), and Lymphedema Life Impact Scale (LLIS) of the limbs. QoL following physiologic surgical treatment for LE was a reported outcome in 32 studies. The outcomes of lymphatico-venous anastomoses (LVAs) were qualified in 18 studies, and 14 studies examined the QoL outcomes of vascularized lymph node transfers (VLNTs). All of those studies concluded that physiologic LE surgeries led to an improvement in QoL ranging between 50–100% (45).

Risk factors

The national LE network defines people at risk for LE as "*individuals who have not yet displayed signs and symptoms consistent with a diagnosis of lymphedema but have a known insufficiency of their lymphatic system*" (46). Many studies examined various risk factors that contribute to the development of LE. Common risk factors include obesity, radiation, surgical procedures involving lymph nodes, infections and genetic factors (47-52). Prospective data suggest that patients with a BMI of >30 kg/m^2 had a three times higher risk of developing BCRL as compared to patients with a BMI of <25 kg/m^2 (53).

There is a strong association between lymphadenectomy and the development of LE. It is estimated that the rate of lower extremity LE development ranges from 7.6% to 35.1% after inguinal sentinel lymph node biopsy, and from 48.8% to 82.5% after inguinal LND. This compares to a 4.4% to 14.6% rate of LE development in the upper extremity following axillary LND for melanoma excisions (54). BCRL incidence after axillary LND ranged from 4.1% to 21.4% (55,56).

Radiation is another widely accepted risk factor contributing to the development of LE, especially in the context of oncologic tumor resection or lymphadenectomy (57). As previously highlighted, the disrupted steady state in the lymphatic channels resulting from the radiation-induced fibrosis leads to stasis and predisposes LE patients to recurrent infections. LE patients who developed early infections had an increased risk of LE development (58). Radiation is usually administered as adjuvant therapy after surgery and the radiation effect on the lymphatic vessels is synergistic with the effects of surgical disruption. As an example, LE incidence rates after axillary LND and adjuvant radiation increased on average to 33.4% (59).

Genetic factors may also play a role in LE development (60). Various genetic mutations are being examined and this is an area of ongoing discovery (61,62). LE is a recognized feature of several syndromes, including Klippel-Trenaunay, Parkes-Weber and Proteus syndromes (63,64). Patients with systemic lymphatic abnormalities can be classified based on their clinical presentation into one of two categories: a generalized lymphatic dysplasia (GLD) for which four genes are currently known to be causal, *CCBE1*, *FAT4*, *PIEZO1*, and *EPHB4*, and a multi-segmental lymphatic dysplasia with systemic involvement which is considered to be due to somatic mutations (65).

Among the many fascinating facets of LE research is current gaps in our understating of lymphatic anatomy. Detailed knowledge of the lymphatic draining channels may help identify more susceptible patients who may benefit from prophylactic procedures (66). Accessory lymphatic pathways can be helpful in understating the varying severity of LE presentation (67).

The tricipital, or Caplan's, lymphatic pathway has been described in cadavers and described as a potential compensatory pathway for lymphatic drainage of the upper extremity, which can drain directly to the scapular lymph nodes and not the axillary lymph node groups. The significance of the presence of these accessory pathways or lack thereof will require long-term follow-up studies. These studies can help determine the individual risk of LE after axillary nodal dissection (68).

Table 1 International Society of Lymphology Staging System for Lymphedema

Stage	Description
0 (latent LE)	Lymphatic system injury disrupting its function, but LE has not yet developed
I (spontaneously reversible LE)	Beginning of pitting edema and swelling that can be managed with the use of compression garments
II (spontaneously irreversible LE)	Progression to non-pitting edema. Fibrosis starts to occur as the limbs harden and increase in size. At this point, compression garments are less effective
III (lymphostatic elephantiasis)	Irreversible swelling as tissues become heavily fibrosed and unresponsive to treatment. Skin has become significantly thickened

LE, lymphedema.

Table 2 Staging system for lymphedema from Mihara *et al.* (70)

Type	Description
Normal type (step 0)	Lymphatic vessels are normal and functional
Ectasis type (step 1)	Lymphatic pressure is increased leading to the dilation of lymphatic vessels
Contraction type (step 2)	Lymphatic vessels wall thickening
Sclerosis type (step 3)	Lumen of lymphatic vessels is narrowed as a result of fibrosis. Significant fibrosis leading to the loss of function of the lymphatic vessels

Table 3 MD Anderson classification of lymphedema based on indocyanine green lymphangiography [from Chang *et al.* (71)]

Stage	Description
1	Many unobstructed lymphatic vessels are observed with minimal dermal backflow in localized areas
2	Moderate number of lymphatic vessels can be seen with segmental dermal backflow
3	Few unobstructed lymphatic vessels can be seen and significant dermal backflow can be observed throughout the entire arm
4	No patent lymphatic vessels can be seen. Severe dermal backflow observed in the extremity

Staging

LE exists on a spectrum which further emphasizes the importance of a coherent and widely understood classification system. The International Society of Lymphology (ISL) classification system is widely adopted and stages LE based on the progression of the disease (*Table 1*) (69).

Despite its broad use and applicability, the ISL classification is not universally adopted, and other classification systems are also widely accepted (*Tables 2,3*).

Diagnostic modalities in LE

LE remains a clinical diagnosis as it is diagnosed by history and physical examination. Oftentimes, it is a diagnosis of exclusion and patients have usually other reasons for extremity swelling (deep venous thrombosis, venous insufficiency, congestive heart failure, kidney failure) ruled out before they are referred to a LE specialist. However, modern imaging techniques of the lymphatic vascular system including X-ray contrast lymphography, lymphoscintigraphy, near-infrared lymphography, computed tomography angiography and magnetic resonance imaging (MRI) continue to shape our understating of LE and can help guide surgical planning (72,73).

Imaging modalities are also foundational to classifying LE, as in the MD Anderson classification of lymphedema [MD Anderson Cancer Center (MDACC)] based on the indocyanine green (ICG) lymphangiography staging system (*Table 3*). ICG lymphography can facilitate the clear visualization of superficial lymph flows in real time without radiation exposure (74).

Color-duplex ultrasound can also be utilized as a diagnostic and pre-surgical planning modality and can be a safe, and relatively inexpensive imaging modality (75). Color-duplex ultrasound is increasingly becoming the standard approach in preoperative planning for LVAs as it allows for the visualization of both lymphatic collectors and venules (76).

The utility of specialized imaging is not limited to diagnosing and staging LE. Recent studies highlight the utility of reverse lymphatic mapping in intraoperatively guiding surgeons to avoid lymph nodes within a regional lymph node basin that drains the donor extremity and consequently reduces the risk of causing iatrogenic donor site LE (77,78). single-photon emission computerized tomography (SPECT)/computerized tomography (CT) offers unique planning capabilities over lymphoscintigraphy for detailed preoperative planning. The use of presurgical SPECT/CT reverse lymphatic mapping and intraoperative gamma probe guidance resulted in no clinical cases of iatrogenic donor lower extremity LE in a small-size (56 patients) study (78).

Contrast magnetic resonance (MR) lymphangiography can aid in visualizing the precise morphological status of lymphatic vessels and lymph nodes in the affected limb. It can illustrate the functional status of lymph flow transportation in lymphatic and the nodes by real-time observation. MR lymphangiography is also minimally invasive and combines morphological and functional examination in a single acquisition (79).

MR lymphangiography can also reliability provide key ratios such as the fluid-fat ratio/grade that can guide management options. MR lymphangiography can facilitate the identification of LE-afflicted limbs with advanced fibrofatty proliferation that may not respond well to conservative management or physiologic LE surgeries, such as vascularized lymph node transplant and LVA. In these circumstances, liposuction can be a viable option in combination with compression therapy. On the other hand, a limb with a higher fluid component may respond better to decongestive therapy, vascularized lymph node transplant, or LVA (80). However, ideal timing and patient selection remain important factors that should also be considered.

Lymphoscintigraphy is another reliable imaging modality to evaluate LE and evaluate outcomes of interventions. It entails an intradermal injection of radiolabeled colloid in the distal aspect of the limb followed by imaging of the lymphatic channels (81).

Management of LE

The management of LE remains a multidisciplinary challenge for many healthcare professionals across multiple specialties. With the increasing involvement of microsurgeons, many emerging surgical approaches are continuing to be further refined and are being increasingly adopted as part of the surgical armamentarium to manage LE.

Timing

There is a growing consensus that the surgical treatment of LE is more effective in the early stages, before the occurrence of extensive fibrosis (71,82). The early detection of LE symptoms is key to achieving better surgical outcomes. With significant data on LE predisposing risk factors, it is imperative to identify patients predisposed to LE development during the early stages of LE. Close communication between all health care professionals involved including medical oncologists, oncologic surgeons, LE specialists, physicians specializing in LE and reconstructive surgeons is therefore crucial to detect early symptoms of LE in cancer survivors. This close cooperation can identify predisposed patients and facilitate their path to surgical treatment during the initial stages of LE, thus preventing disease progression and potentially improving outcomes.

Conservative management

The management of LE can be broadly dichotomized into two categories: conservative (non-surgical) and surgical. Complete decongestive therapy (CDT) is widely accepted as the first-line treatment for LE management and demonstrates excellent outcomes in the management of skin care (83). CDT comprises of two treatment phases and four components which include: skin care, manual lymphatic drainage (MLD), compression therapy, and exercises. The initial phase aims to achieve maximal reduction of limb volume, through utilizing skin care, MLD, multilayer wrapping, and daily exercises. The second phase aims to conserve and optimize the results obtained in the initial phase and includes fitting of elastic garments, exercises, skincare, and MLD when necessary (69). CDT remains a cornerstone in limb volume reduction and symptom control and has been demonstrated to improve QoL outcomes in LE patients (84,85).

Manual lymph drainage by a specialized physiotherapist can enhance the absorption of fluids by the lymphatic capillaries, ultimately increasing the volume of fluid returning to the venous system. Some data suggest that MLD can provide some additional benefits in early LE, However, in moderate to severe LE, MLD may not provide additional benefits when combined with CDT (86). A recent meta-analysis of 12 randomized controlled trials (RCTs) corroborates this finding and suggests that MLD may not significantly reduce or prevent LE in patients after breast cancer surgery (87). Similar conclusions were reached for intermittent pneumatic compression devices, where a number of RCTs suggested that these devices may not provide additional benefits when used in combination with the routine management of LE.

Overall, the conservative management of LE with CDT, can achieve a 45–70% reduction in LE volume (88). Recent prospective data indicate that CDT led a statistically significant reduction in excess volume up to 66.5% and 71.5% for upper limb and lower limb LE respectively. Another study examined the effect of CDT on 299 patients with upper or lower limb LE, primary and secondary type, where CDT was applied for about 15.7 days and led to a 59.1% volume reduction for the upper limb and 67.7% for the lower limb (89). Morgan *et al.* demonstrated a reduction greater than 50% among 78 BCRL patients presenting with grade I and II LE who followed CDT for 1 month (5 days per week) (90).

Across the different phases of CDT, frequent fittings are crucial to maintain the gains and continue the progress made. Despite its time-consuming nature, long-term adherence and commitment to CDT remains an important and effective approach in LE management. It is reported that 56% of women who were diagnosed with BCRL indicated that LE affected them financially and that costs increased with LE severity. BCRL also reported that the cost of compression garments formed a large proportion of these costs (91). This highlights the importance of comprehensive coverage by insurance providers to alleviate some of this financial burden on LE patients and ultimately health care system cost-savings of up to $21,483 as a result of decreasing episodes of cellulitis and subsequent hospitalizations (92). Unfortunately, with variable cost coverage by many insurance providers, many LE patients pay significant amounts out-of-pocket per year for LE care. Studies indicate that LE patients with moderate to severe LE pay over Aus$1,400 for LE care per year (91).

Surgical management

The main goals of various surgical treatments for LE are to re-establish channels for lymphatic flow, counter its deleterious effect on limb volume, alleviate some of the associated emotional distress and decrease the high burden of daily self-care procedures such as skin care and compression garment use. Those surgical options can be broadly classified as: reductive, physiologic and prophylactic procedures. Imaging modalities can be leveraged towards guiding this decision-making process. Identifying fat-to-fluid ratios utilizing MR lymphangiography may favor the consideration of a reductive versus a physiologic procedure as previously discussed. If minimal fat and fibrosis were observed, a physiologic procedure may be considered. ICG lymphangiography can help decide if sufficient patent lymphatic channels for LVA can be visualized or if only diffuse stardust pattern ICG uptake is observed, a vascularized lymph transfer may be a more reasonable option.

Reductive procedures

Historically, the Charles procedure has been described and involves the excisional debulking of affected tissues in severe LE patients, including the skin and soft tissues and the use of skin grafting (93). However, this approach has been plagued with significant wound-healing challenges and suboptimal aesthetic results (94,95). More recently, liposuction of excess adipose deposition has been gaining popularity (96-98). Liposuction techniques for LE are continuously evolving with some authors achieving a reduction of limb volume to normal (99). Even in patients who did not undergo any other surgical intervention for LE, an average of 20–23% reduction in volume using liposuction can be expected from removing the fibrofatty tissue generated from sustained lymphatic fluid stasis (100). One of the key advantages of liposuction lies in its inherent ability to eliminate the hypertrophied fibrotic adipose tissue accumulated in limbs as a result of LE and sustain the results for a long duration of time (101).

Generally, reductive procedures such as liposuction can be effective even in advanced and severe LE cases (ISL stages II and especially stage III) (102). They can be especially helpful in cases of significant fibrosis and fatty deposition. Liposuction can be an important and effective adjunct to the use of compression therapy as studies indicate that when comparing the combined use of liposuction and compression therapy to therapy alone in stage II patients, this led to a 115% reduction in volume compared to 54% of patients who had isolated compression therapy (99). This has been especially significant in BCRL where liposuction and compression therapy combined reduced arm edema volume by 50% more than compression therapy alone (103). The effects of liposuction were not only limited to volumetric reduction, but also decreased the incidence of cellulitis episodes per year (104).

As in many other contexts, liposuction is considered safe with quick recovery within 48 hours (105). However, it is not without risks as some authors suggest it may damage existing lymphatic channels and further complicate LE symptoms (104,106,107). Some authors advocate the use of sterile made-to-measure compression garments intraoperatively to minimize postoperative swelling (108). Tumescent fluid infiltration is also recommended to minimize blood loss intraoperatively (109). The continued use of compression garments is considered essential to maintaining the results of liposuction (99). Liposuction can be beneficial as a reductive procedure when the patients are found to have significant fatty deposition as it can effectively reduce limb volume in LE (106).

Liposuction can also be combined with LE physiologic surgeries. Performing liposuction after a physiologic procedure such as LVA, has been demonstrated to improve the reduction in lower limb volume without damaging existing lymphatic vessels (110). On the other hand, liposuction followed by another physiologic procedure known as VLNT at 11 and 22 months achieved 75% and 90% long-term volume reductions in two patients with upper extremity LE (111). The reverse sequence of has also demonstrated encouraging results, where liposuction, was performed as a second stage 6–8 months after VLNT (112). The main rationale in performing liposuction first in these studies was to remove some of solid fibrotic tissue that accumulated due to LE that may not be addressed by VLNT. This staged approach also allows for the postoperative swelling to subside. The gradual reduction in swelling post-liposuction could take about 6 to 12 months to reach a "steady state". VLNT can be performed after reaching this stage.

Physiologic procedures

Physiological procedures aim to restore and reconstruct the physiologic drainage of the lymphatic system. Numerous strategies have been described to achieve this elusive goal including direct repair of lymphatics, LVA, and VLNT. These procedures are most effective in the management of the earlier stages of LE (113).

Vascularized lymph node transfer

VLNT involves the harvest and transfer of functional lymph nodes from a healthy donor site to a limb affected by LE (114,115). The precise mechanisms through which VLNT are thought to be effective remain a subject of debate. Two theories are commonly postulated. The first suggests that newly transplanted LNs act as a new area of low pressure, preferentially draining lymphatic fluid and transferring it to the venous system analogous to a vacuum-like pump. The second theory suggests that VLNT may stimulate lymphangiogenesis through endothelial growth factor-C secretion from the transplanted lymph nodes thereby creating new channels for lymph drainage (116,117).

VLNT can be offered to patients optimized with conservative therapy who are compliant with daily wearing of a compression garment of adequate compression class for at least 3 months (118). Advanced stage LE (MDACC stage III/IV) can also be an indication for VLNT. No acute cellulitis or local malignant recurrence is also considered a prerequisite. Harvesting from previously dissected LNs or radiated areas should be avoided due to potential scarring of vessels and lymph nodes. Patients with advanced LE may benefit from adjunctive liposuction or a later debulking procedure once the fibrosis softens.

The optimal donor site remains a persistent question and as a result, many donor sites continue to be utilized with success and surgeon preference appears to be a guiding factor (38,119). Common donor sites include: the submental region, supraclavicular region, inguinal region, thoracodorsal axis, and omentum. Recipient site location considerations are also important where proximal scars, constriction points, bulkiness, and final aesthetic appearance should be considered. Some of the common recipient sites for the upper and lower extremities are summarized in (*Table 4*) (120,121). The distribution of the dermal backflow on ICG can aid in the decision for VLNT flap placement (122). When dermal backflow indicates a predominantly affected upper arm or thigh, proximal anatomical (orthotopic) VLNT can be performed. However, when the dermal backflow is found to be mainly concentrated distally in a gravity dependent distribution, distal non-anatomical (heterotopic) VLNT can be performed to the forearm or lower leg. ICG also plays a vital role in identifying obstructed lymphatic vessels, where a LVA can be performed at the same time of VLNT if suitable targets for LVA are identified.

Among the most notable donor sites for VLNTs are

Table 4 Common recipient sites for vascularized lymph node flap transfer

Recipient sites	Site	Recipient artery	Recipient vein
Upper extremity	Axilla	Subscapular; circumflex scapular; thoracodorsal; lateral thoracic; circumflex humeral	Comitant
	Elbow	Inferior ulnar collateral; anterior ulnar recurrent	Comitant; basilic
	Wrist	Dorsal branch of radial; ulnar	Comitant; cephalic
Lower extremity	Groin	Superficial inferior epigastric; superficial circumflex iliac; deep inferior epigastric	Comitant
	Knee	Medial sural; descending genicular	Comitant; great saphenous
	Ankle	Anterior tibial; posterior tibial	Comitant; greater or lesser saphenous

the gastroepiploic lymph node flaps either laparoscopically or utilizing an open approach (123). Manrique *et al.* demonstrated that a minimally invasive approach utilizing laparoscopy for harvesting gastroepiploic lymph node flaps can be efficient, cause less postoperative pain and lead to higher patient satisfaction (123).

VLNT is not without risks, and paramount amongst those risks is donor site morbidity. In an effort to minimize the donor site risk of developing LE, intraabdominal harvested VLNT has been proposed (124). The omentum is emerging as an appealing ideal donor for VLNT; however, its utilization has been historically limited by concerns related to the need for laparotomy (125,126). Laparoscopic techniques for omental flap harvest have further popularized its use and more recently robotic harvest has been introduced offering a shorter hospital stay, less estimated blood loss, and decreased postoperative complications in intra-abdominal procedures utilizing the surgical robot (127-130).

Compared to conservative management alone, there is a growing body of evidence confirming the encouraging outcomes of VLNT (122,131). Studies indicate an average volume reduction of 47% as a result of VLNT (132). Prospective data also confirm these findings indicating that at 24 months postoperatively, there were significant reductions in limb volume of up to 45% coupled with a statistically significant decrease in cellulitis episodes and an in the LLIS score (133).

VLNT have been reported to significantly reduce the number of episodes of cellulitis with lower donor site risks (124). Postoperatively, at our institution after VLNT procedures for the upper extremity, patients are typically instructed to limit shoulder abduction to 45 degrees and avoid lifting more than 5 lbs. For lower extremity VLNTs, patients are instructed to avoid weight-bearing on the operated extremity for 2 weeks. Compression stockings and wrapping can be resumed 1 week postoperatively for upper extremity VLNTs and after 2 weeks for lower extremity VLNTs. MLD and massages can also be resumed 2 weeks postoperatively for both. Patients can expect follow-ups and measurements at 1 week, 3 months, 6 months, 1 year and then annually after VLNTs.

Lymphatico-venous anastomosis

LVA is another physiological approach that is gaining popularity. The introduction of super microsurgical techniques have allowed LVA to continuously evolve (134,135). This physiologic approach involves an anastomosis connecting the distal lymphatic vessels ranging from 0.3 to 0.8 mm in diameter to veins proximal to the obstruction (136). ICG lymphangiography can be utilized to accurately identify functional lymphatic channels along with blue dye and can also evaluate the patency of the anastomoses intraoperatively (137). As a physiologic LE surgery, LVAs are thought to be most effective at the early stages of LE before the fibrotic destruction of lymphatic vessels (134,138).

Recent studies highlighted that LVA can prevent the progression of LE when compared to conservative therapy alone (139). Furthermore, Mihara *et al.* (136) evaluated cellulitis episodes in a cohort of 95 patients and found a statistically significant decrease in the episodes of cellulitis in patients with upper or lower limb LE before and after LVAs. Furthermore, studies have demonstrated an approximately 35 to 50 percent reduction in either extremity circumference or volume with mean follow-up periods greater than 1 year with LVAs (135,140,141). Chang *et al.* in a prospective analysis of 100 consecutive cases reported that 96% of patients reported a subjective improvement in their symptoms, and the mean volume reduction at 12 months was 42%. A smaller subset of patients was followed for 3 years, and their mean volume reduction remained at 38%, indicating sustained long-term improvements. As expected, the authors showed that LVAs produced superior results in patients with early-stage LE compared with patients with more advanced LE.

Debate remains active surrounding the ideal number of anastomoses to be performed to achieve maximal effectiveness in LVA (142). Koshima *et al.* initially advocated performing as many anastomoses as possible reaching up to 10 LVAs for the upper extremity (140). Mihara *et al.* reported a positive correlation between volume reduction and number of LVAs (143). However, these results may be confounded by the heterogeneity of patient populations as more LVAs can be feasible in patients with early-stage LE. As LVA techniques continue to evolve, favorable results are reported with significantly less anastomoses. Campisi *et al.* reported performing an average of 2.1 (±1.2) LVAs in stage III and IV LE of the lower extremities and achieving a 41.8% reduction in limb circumference at 14.5 months follow-up (144). The authors postulate that the preserved efficacy despite the decreased number of anastomoses performed relates to LVAs ability to disrupt the cycle of lymphatic hypertension, smooth muscle cell degeneration within lymphatic channels and that one well-executed LVA may be sufficient to break the vicious cycle. This coincides with the increasing adoption of a more minimally invasive approach in performing LVAs under local anesthesia with as few as 2 LVAs reported to lead to satisfactory results (145).

Due to the lack of RCTs comparing outcomes of LVA versus VLNT, the decision between VLNT versus LVA depends largely on patient factors, with most patients opting to undergo LVA due to better cosmesis, however, LVA requires available patent lymphatics for the anastomosis to be performed and if that is not present, the patient may still be a candidate for a VLNT (146).

Long-term patient compliance is a strong predictor of success as the attainment of satisfactory outcomes post-physiologic LE surgeries requires continued adherence to CDT. Patients are counseled that regardless of the success of the above-mentioned procedures, they may need to continue with therapy as a lifelong approach. Postoperatively, at our institution patients are instructed to avoid pressure on the incisions, and avoid lifting heavy objects (>5 lbs) for 2 weeks. Patients will not have LE therapy appointments during the early postoperative period (first 2 weeks) but will be instructed to resume compression therapy and massages around 2 weeks postoperatively. During the initial physiotherapy sessions, it is emphasized that no direct pressure or massages should be attempted over incisions. At 3–4 weeks postoperatively, activity related restrictions can be lifted. Patients can expect a follow-up pattern similar to previously described for VLNTs.

In light of currently available data, it is reasonable to offer patients with no or minimal fibrotic skin changes, and no or small amounts of fibrotic tissue a trial of physiological techniques (LVA or VLNT) as a first option in the affected limb. Subsequent reductive techniques such as liposuction can be offered as a second option to further reduce volume by removing fibrofatty tissue more effectively.

Prophylactic procedures

As long-term survival for many cancer patients continues to improve, the risk of LE continues to persist. Despite significant breakthroughs in microsurgical approaches for LE surgery, none has been demonstrated to be definitively curative. As a result, the concepts of lymphatic microsurgical preventive healing approach (LYMPHA) or immediate lymphatic reconstruction (ILR) are gaining traction and popularity. Historically, physiologic LE surgeries have been reserved for patients who have already been diagnosed with LE. However, a growing number of studies demonstrate encouraging results and suggest that preventive LE surgery may be effective in preventing LE onset across multiple solid malignancies including breast cancer, melanoma and gynecologic cancers (147-150).

ILR was introduced by Boccardo *et al.* in their seminal study published in 2009 (148). At the 4-year follow-up mark, 4% of their high-risk patients who underwent axillary LND, and radiotherapy developed LE as a result of the utilization of ILR (151). Similarly, Feldman *et al.* reported a 12.5% LE rate after axillary LND after ILR at a mean follow-up of 6 months, compared with their historical rate of 30.6% (147). Retrospective data from Cook *et al.* were also encouraging, with a rate of LE in their series reported to be 9.1% after the adoption of ILR, which was also an improvement from their historical rates of LE (152). Another retrospective review, demonstrated the effectiveness of ILR in high-risk patients with an overall LE incidence rate of 3.1% (150). Johnson *et al.* highlighted the effectiveness of ILR in a high-risk patient cohort with an overall LE rate of 3.1%. However, the retrospective nature of these studies, the variation in the criteria used to diagnose LE, the heterogeneity of measurement modalities used, and varying follow-up periods are significant limitations. Furthermore, prophylactic approaches are not broadly adopted partially because patients who undergo LND do not always develop LE.

As more data on ILR is becoming available, an increasing number of meta-analyses are reporting pooled outcomes for this emerging approach. A recent systematic review concluded that the weighted proportion of patients who developed LE after ILR was 6.6%, and found to be significantly lower than those without lymphatic reconstruction at 30.5% (153). This was corroborated by a recent meta-analysis concluding that only 2.7% of patients developed LE after ALND with ILR (154). These encouraging improvements in LE incidence, coupled with the high risk of developing the permanent and disabling consequences of LE, have resulted in an increased interest in ILR.

Proponents of ILR also highlight its relatively short procedural time—despite its technical complexity—and cost effectiveness. The cost-effectiveness of ILR after axillary LND ± radiation was evaluated and found to be the most cost-effective surgical option compared with axillary LND ± radiation without ILR for node-positive breast cancer patients (150). Furthermore, from a cost-utility perspective, the added costs of ILR were deemed to be justified (155).

Recent data from Coriddi *et al.* were also encouraging and indicate a transient LE rate in their high-risk cohort of patients to be 12.5%. As more studies publish their results, early experiences with ILR indicate that it can be a feasible, safe, and effective approach for the primary prevention of BCRL (156). The benefits of ILR may not be limited to the prevention of BCRL, as Morotti *et al.* described ILR for 12 lower extremities following inguinal LND and reported a LE rate of 8.3% (157). Decreases in LE incidence were also reported with ILR post-intrapelvic LND and inguinal LND (149,158). While these results are promising, studies with longer term follow-up and a larger number of patients are needed to draw definitive conclusions. Studies focused on tailored ILR procedures for specific patient populations and comorbidities may better elucidate the benefits of ILR in preventing LE in cancer patients.

ILR as a concept is not limited to BCRL, as Cakmakoglu *et al.* demonstrated in their prospective cohort of 22 upper and lower extremity melanoma patients involving axillary and inguinal LNDs, respectively. They demonstrate the technical feasibility of performing successful LVAs (1.8 LVAs average per patient) post-axillary or inguinal LND in the context of melanoma excision (149). However, key concerns regarding the potential systematic spreading of residual disease must be carefully weighed and addressed especially in the context of occult LN disease. This study included patients that were deemed to have a systemic pathology with significant LN disease (bulky and palpable LNs) and the surgical excisions were intended to improve QoL and not intended to be curative or aimed at improving oncological outcomes. This question regarding the oncologic safety of ILR post-cutaneous malignancy excision and LND will require further prospective studies could potentially be addressed by the upcoming LYMbR trial (Prophylactic LYMphatic Reconstruction to Prevent Lymphedema After Node Dissection for Cutaneous Malignancies; NCT05136079) (159).

After ILR procedures with LVAs patients are encouraged to avoid direct pressure and scrubbing over incisions and avoid lifting substantial weights (>5 lbs) in the first 2 weeks postoperatively. Close communication with physiotherapy is essential to communicate activity related restrictions in the first 2 weeks postoperatively. Most restrictions can be lifted after 3–4 weeks. In contrast to delayed LE reconstruction, patients undergoing ILR do no need to be on compression therapy or massages after undergoing ILR.

Despite significant data highlighting the potential of prophylactic lymphatic procedures, recent outcome studies further highlight the need for further long-term prospective data. Levy *et al.* shed some light on the 4-year outcomes of LYMPHA (160). In their retrospective review, they conclude that LYMPHA may not prevent LE development in patients undergoing axillary LND. However, they acknowledge a number of limitations related to the retrospective nature of their study and small sample size (45 patients). They also acknowledge the need for further long-term studies. This is contrasted by the findings from Herremans *et al.* in their 5-year retrospective review of 132 patients (161). In their study the diagnosis of LE was made by certified LE therapists in contrast to other LYMPHA studies. They conclude that patients who underwent LYMPHA at the time of axillary LND were significantly less likely to develop LE. Another study included a total of 380 patients with a median follow up time of 15 months concluded that the LYMPHA cohort had a significantly lower rate of LE both in univariate and multivariate analysis (162).

Despite the demonstrated effectiveness of various physiologic procedures in LE management, 48% of US-based healthcare insurance providers had a statement of coverage on LVA or VLNT, in which reimbursement was almost universally denied. Liposuction and debulking procedures were included in 43% and 22% of policies, respectively. However, over 75% of insurance providers imposed strict criteria for liposuction in LE management (163).

This can be a significant barrier to treatment for many LE patients and may ultimately lead significant financial toxicity as a result of these healthcare insurance policies.

Conclusions

The growing interest in LE surgery will continue to push the boundaries and will propel many new novel ideas closer to broader adoption. All the increased interest and accumulated experience offer unique opportunities to broaden the base of knowledge pertaining to LE surgery as large multi-center trials remain limited. There remains a need to evaluate lymphatic surgery in different patient cohorts with different co-morbidities, and its cost-effectiveness in various settings, and we await with eager anticipation the results of the many RCTs currently underway including the Memorial Sloan Kettering Cancer Center RCT (NCT0424134) and the Stanford University RCT (NCT05366699) on ILR post-ALND (164,165).

The overall consensus on the importance of multidisciplinary care for LE will remain a cornerstone in LE management. Patient-centered outcomes will continue to guide the cross-examination of LE surgery and more prospective data will help to advance the efficacy of these surgical techniques and hopefully help to reduce the substantial burden that LE imposes on patients.

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