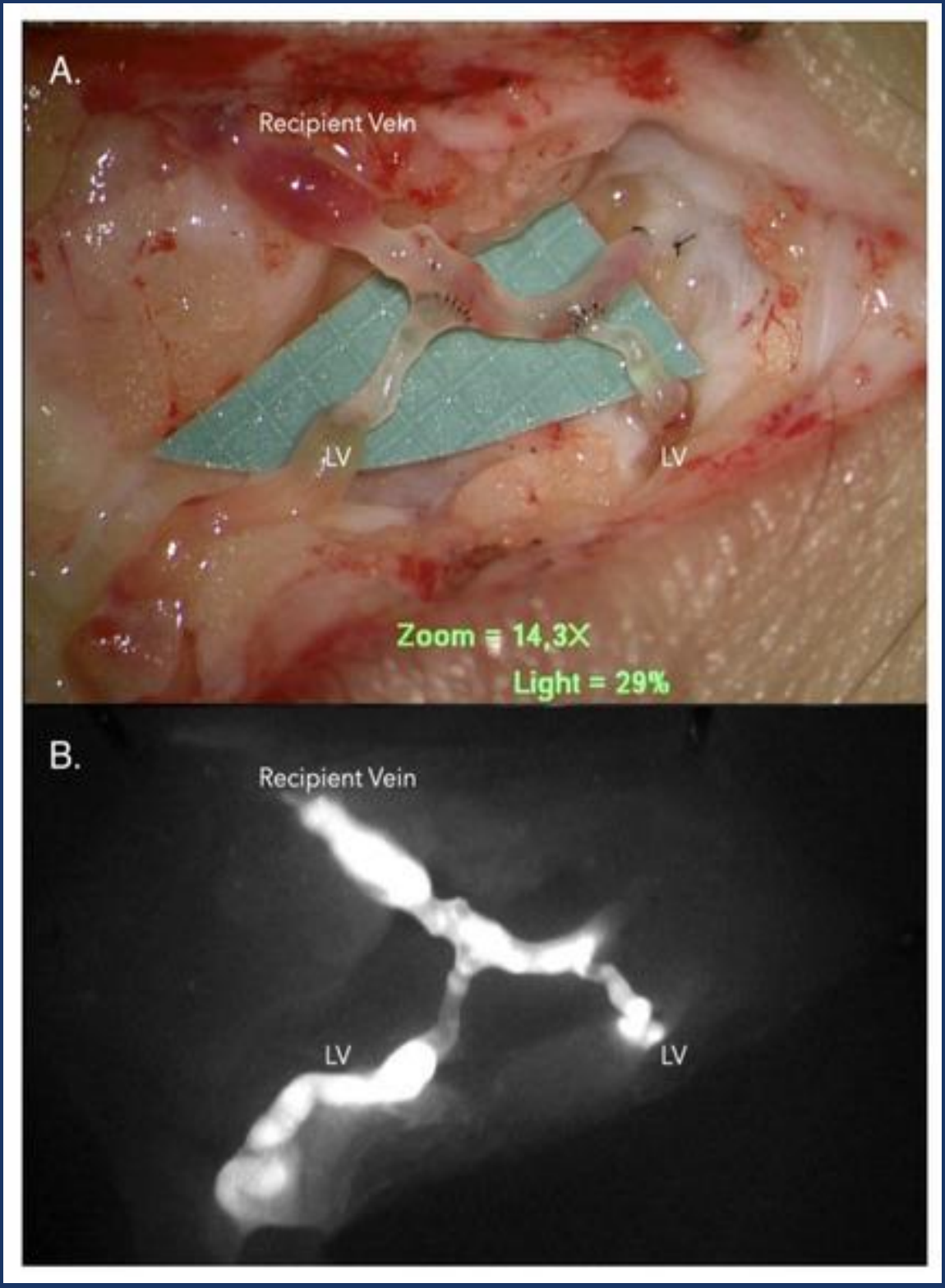
Recent advances in management of lymphedema



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Introduction

Lymphedema is a chronic condition characterised by accumulation of protein-rich interstitial fluid within subcutaneous tissue and skin as a result of dysfunction of the lymphatic system with no definitive cure. It is estimated to affect 90 to 250 million people worldwide. [1,2,3]

Here we are reviewing recent advances in management of lymphedema in relation to investigations, non-operative and operative modalities, outcome measures and future directions.

Primary lymphedema results from genetic or developmental anomalies. 28 known genes might harbor causal mutations for primary lymphedema, but they account for <30% of the cases. VEGF-C (vascular endothelial growth factor C)/VEGFR3 (vascular endothelial growth factor receptor-3) play an important role in normal development of lymphatic system and many of the mutations are related to them. By identifying these genes researchers are trying to develop a targeted molecular therapy. [4]

Secondary lymphedema results from obesity, trauma, infection, malignancy, or radiation to the lymphatic system. The majority of cases are caused by filarial infection. In developed countries, the leading causes of lymphedema are related to oncologic therapy for breast cancers, gynecologic malignancies, melanoma, sarcoma, and urologic and prostate cancer or due to tumor infiltration into the lymphatic system itself. [2,3]

Once the disease commences its progression is with fluctuations and significant physical, functional and psychological morbidity, affecting a person's quality of life. It has significant financial implication for patients and a burden on healthcare systems. [1]

In the last decade due to explosion of research we now have a better understanding of normal lymphatic structure (concept of lymphosome) and physiology. Along with parallel advances in super microsurgery and investigative modalities, treatment options have increased. [4,5]

Lymphedema Staging

The most widely used staging system is the International Society of Lymphology (ISL). [1,2]

Table 1 -

Stage	Symptoms
0	Subclinical lymphoedema without oedema but evidence of impaired lymphatic function. This can exist months or years before overt oedema occurs
1	Reversible pitting oedema. No palpable fibrosis
2a	Pitting oedema that is not reduced by elevation
2b	Non-pitting oedema secondary to pronounced fibrosis
3	Lymphostatic elephantiasis. Progressive fibrosis, acanthosis (hyperpigmentation), hyperkeratosis and papillomatosis (warty growths)

Investigations

Investigation modalities aid early detection to slow the progression of disease and to increase effectiveness of treatments. Commonly used objective criteria to define lymphedema is a 10% increase in limb volume from baseline. Volumetric methods are water displacement, perometry (Figure 1), and circumferential measurements using a measuring tape. In filarial endemic countries patients with lymphedema need undergo Alere strip test to detect filarial antigen in blood. Imaging techniques which directly visualize the lymphatic pathways are lymphoscintigraphy, ICG lymphography and MR lymphography (Table -2, 3). [1,2,4,5,6]

Figure 1

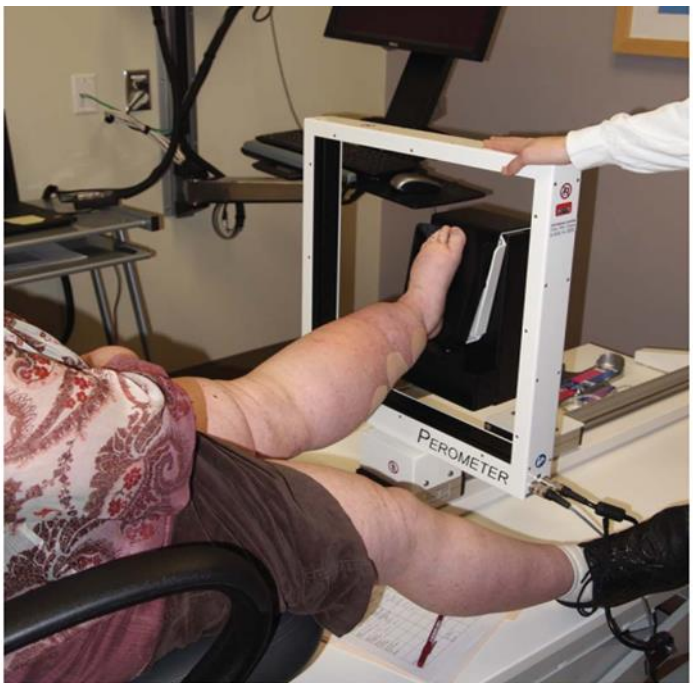


Table 2 - Overview of the main diagnostic strategies

Diagnostic method	Strengths	Limitations
Circumferential measurements	• Cheap; • Easily accessible; • High portability; • Non-invasive.	• Unable to detect lymphedema in subclinical settings; • Low intra- and inter-rater reproducibility; • Time consuming; • Left-right dominance, muscle atrophy, fibrous tissue deposition, or weight gain may affect the measurement.
Water displacement	• Current gold-standard method; • Evaluation of hand volume changes; • Cheap.	• Unable to detect lymphedema in subclinical settings; • Cumbersome; • Low portability; • Time consuming; • Not indicated in case of wounds/skin infections
Perometry	• Detection of subclinical forms; • Rapid, accurate and precise.	• Changes in fat or muscle composition can affect arm volume; • Low portability; • Expensive equipment.
Bioimpedance spectroscopy	• Detection of subclinical forms; • Rapid and easy to use; • High inter- and intra-rater reproducibility; • Selective measurement of water content.	• Not yet well established in clinical practice; • False negative results in late stage BCRL and segmental/superficial swelling; • Low portability.
Tissue dielectric constant	• Early diagnosis; • Applicable in almost any body site.	• Lack of full characterization of differences between Lymphedematous and non-lymphedematous tissue
Ultrasonography	• Cheap; • Easily accessible; • Analysis of physical properties and structural alterations of tissue in real time.	• Difficulties in achieving deep tissue penetration; • Operator'dependent; • No interpretation guidelines.
Magnetic resonance imaging	• Early diagnosis; • Evaluation of lymphatic function; • Assessment of morphologic tissue changes.	• Expensive; • Time consuming; • Possible adverse events to contrast agents; • Contraindications: claustrophobia and metal implants/devices. • Low portability
Lymphoscintigraphy	• Early detection of lymphatic impairment; • Direct visualization of the lymphatic system.	• Lack of standardized procedures and radiopharmaceuticals; • Need for consistent criteria to interpret the results; • Prolonged times.
3D photogrammetry	• Evaluation of hand volume changes; • Safe and non-invasive; • Portable; • Cheap	• Requires trained technicians; • Requires access to a 3D camera system.

Table 3 -

Clinical Imaging for Lymphedema. Modified From Polomska and Proulx

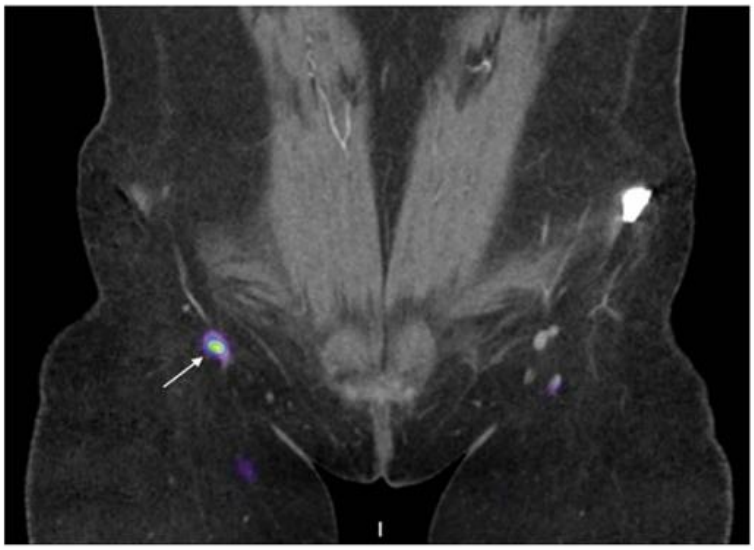
Technique	Lymphatic application	Resolution	Depth limitation
Contrast lymphography	Central/visceral lymphatic visualization	≈1 mm	No limit
Radionuclide lymphoscintigraphy	Imaging of collecting lymphatic vessels and dermal backflow; quantitative assessment of lymphatic function	≈1.5 mm	No limit
Near infrared lymphography	Imaging of collecting lymphatic vessels and dermal backflow; quantitative assessment of lymphatic function	μm range	1.5 cm
MR lymphography	Central/visceral lymphatic visualization; functional and morphological evaluation of lymphatic vessel status	0.5–2 mm	No limit
CT	Assessment of lymphatic vessel status	50–200 μm	No limit
SPECT	Assessment of lymphatic vessel status	1–2 cm	No limit

Lymphoscintigraphy and Single-Photon Emission Computerized Tomography/ Computed Tomography

Lymphoscintigraphy is performed using Tc99m-labeled filtered sulfur colloid injected intradermally. This helped to categorize primary lymphedema. But recent studies have shown patients with primary lower extremity lymphedema often have pathways for lymph fluid to reach the venous circulation other than through the inguinal nodes. lymphoscintigraphy provides poor spatial and temporal resolution and lacks standardization; it has high reported sensitivity (96%) and specificity (100%) for the diagnosis of lymphedema. But it has protocol variability and does not provide substantial anatomic information. [1, 4,7]

More recently Radioisotope lymphoscintigraphy allows for the global serial assessment of lymphatic physiologic function, and of the draining lymph nodes, it can be combined with computed tomography (single-photon emission computed tomography/computed tomography) for 3-dimensional localization of lymph nodes for reverse lymphatic mapping for vascularized lymph node transplantation (Figure 2). [8]

Figure 2



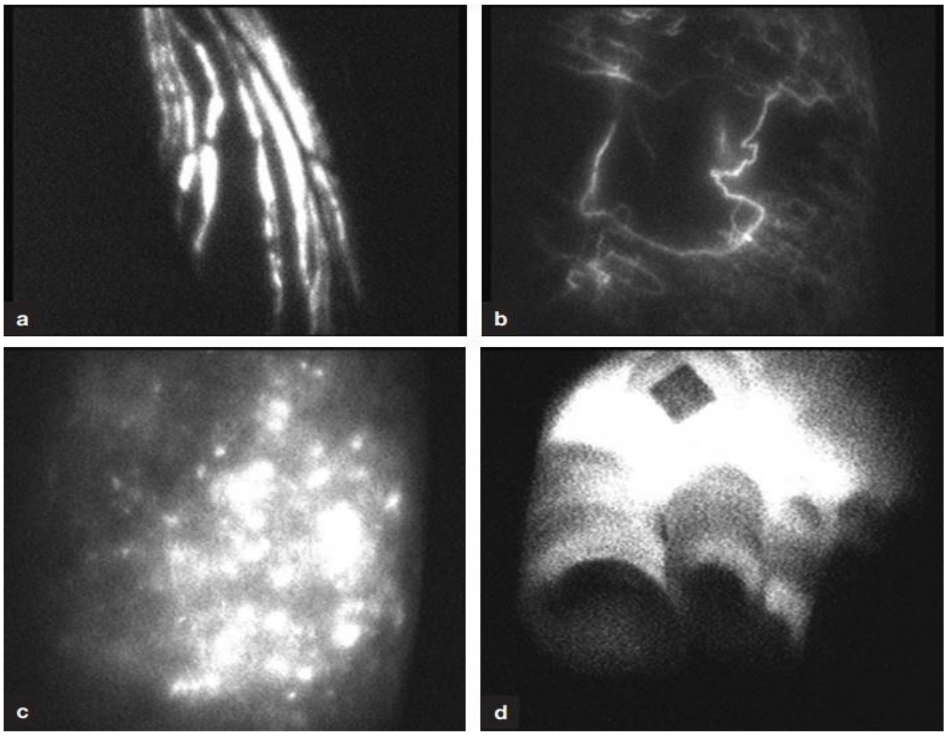
Single-photon emission computed tomography/computed tomography of the abdomen/pelvis for reverse lymphatic mapping for free deep inferior epigastric artery perforator flap breast reconstruction with a chimeric vascularized groin lymph node flap. On the right side the superficial inguinal lymph nodes are contrast-enhanced (*arrow*) and therefore must be preserved to avoid the risk of iatrogenic right lower extremity lymphedema.

Near-Infrared Lymphography

Indocyanine green (ICG) fluorescence lymphangiography is quickly becoming a standard staging modality used to evaluate candidacy for surgical intervention and planning. This technique uses near-infrared fluorescence (NIRF) imaging to provide real-time, detailed imaging of lymphatic flow by injecting ICG intradermally to visualize the uptake and transit of the dye. It has been shown to have both higher sensitivity and specificity than lymphoscintigraphy. ICG can reveal the condition of lymphatic vessels, their contractility, valvular competence and its diffusion pattern can assist in grading the severity of lymphedema. A linear pattern of ICG flow along the extremity is considered normal, whereas a "splash" pattern or "stardust" pattern indicates reflux of dye from deeper lymphatic transport channels back into the subdermal lymphatic plexus as a result of occlusion of the more proximal lymphatic channels (Figure 3,4) ICG lymphangiography can be performed in the clinic setting as a diagnostic tool, as well as in the operating room where it is used to define the location of those lymphatic channels requiring surgical intervention. [1,2,4]

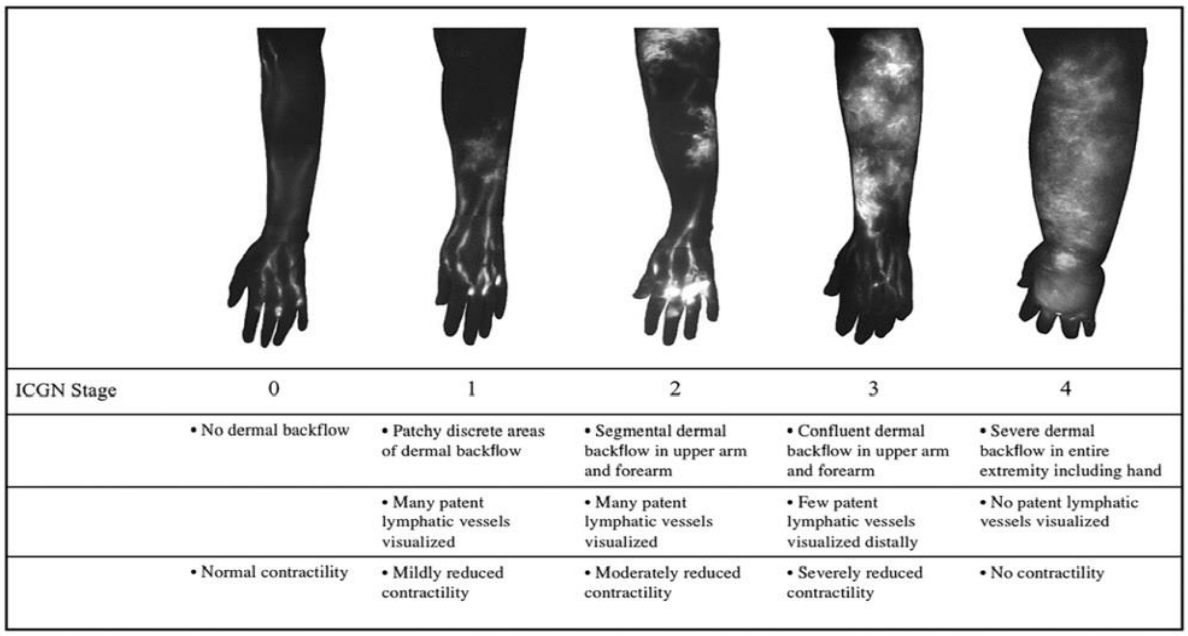
Increasingly used for surgical triage like decision to resort to lymphaticovenular anastomosis and for the presurgical identification of lymphatic vasculature. ICG can be employed to assess lymphatic flow in the context of free flap transplants and vascularized lymph node transfer (VLNT). It has also been proposed as a diagnostic method to guide and personalize the conservative management techniques in lymphedema, through the identification of compensatory drainage pathways (Mascagni or Caplan pathways). [4,9]

Figure 3



Indocyanine green lymphangiography images showing (a) linear, (b) splash, (c) stardust and (d) diffuse patterns.

Figure 4



ICGN Stage	0	1	2	3	4
	• No dermal backflow	• Patchy discrete areas of dermal backflow	• Segmental dermal backflow in upper arm and forearm	• Confluent dermal backflow in upper arm and forearm	• Severe dermal backflow in entire extremity including hand
		• Many patent lymphatic vessels visualized	• Many patent lymphatic vessels visualized	• Few patent lymphatic vessels visualized distally	• No patent lymphatic vessels visualized
	• Normal contractility	• Mildly reduced contractility	• Moderately reduced contractility	• Severely reduced contractility	• No contractility

The Indocyanine Green Staging Scale, modified from Chang et al.[38] This scale evaluates the physiologic function of the lymphatic vessels within the limb, including the distribution and severity of dermal backflow, visualization of patent lymphatic vessels, and lymphatic vessel contractility.

Magnetic resonance lymphangiography (MRL)

Conventional imaging through ICG and lymphoscintigraphy is not suitable to differentiate fat hypertrophy from liquid edema. More recently MRL has been developed to provide much higher resolution imaging of the lymphatic system, it has added benefit of characterizing the soft tissues such as fat and the degree of oedema and fibrosis, can differentiate between the venous and lymphatics. It aids evaluating the anatomical and functional status of a patient's lymphatics, including soft-tissue quality and the presence of nodal basins in the targeted limb, including the caliber, location, and distribution of lymphatic vessels and veins in the vicinity; presence of significant soft-tissue fibrosis and nonfunctional lymphatics would often preclude a patient from any physiologic procedure. Hence it helps in operative planning and patient selection. MRL has yet to gain widespread acceptance and use. [1,2,10,11]

Non operative treatment of lymphedema

First line intervention of lymphedema includes conservative measures, such as complex decongestive therapy (CDT). CDT is a multidisciplinary treatment approach consisting of an intensive volume reduction phase (therapist directed), followed by a maintenance phase to stabilize the limb volume (patient directed) along with patient education for risk reduction. CDT can be an effective treatment for lymphedema in all stages of the disease. Limitations include the need for strong patient compliance, the need of life-long compression garment use, and the high cost associated with prolonged adjunctive therapy, such as skin care and laser treatment. [1,2,12,13]

Table 4

Phases of CDT

Intensive reduction phase	Maintenance phase
Low-stretch bandage (or adjustable compression garment)	Compression garment
MLD	Exercises
Sequential gradient pump	Skin care and risk precautions
Exercises	MLD (if required)
Skin care and risk precautions	Sequential gradient pump (if required)

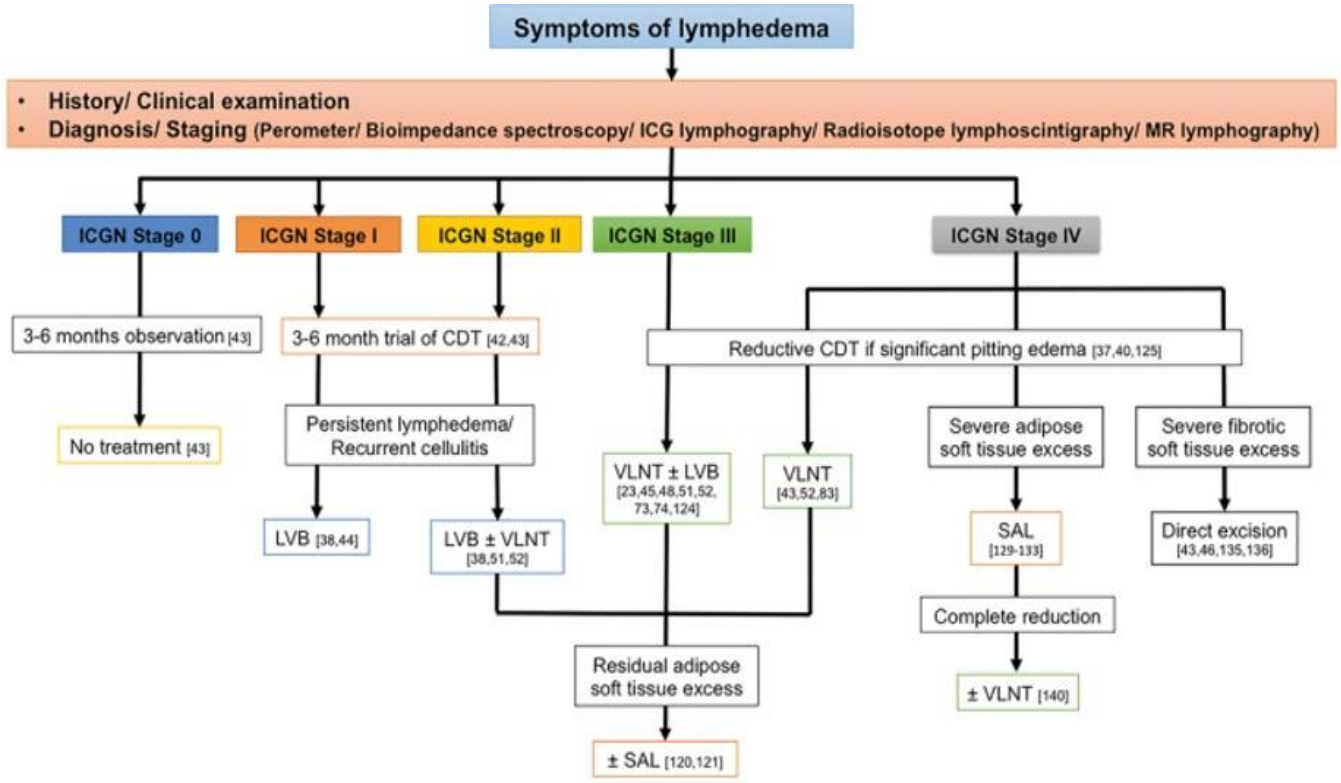
Abbreviations: CDT, complex decongestive therapy; MLD, manual lymph drainage.

Surgical advances

Surgical procedures are divided into -

Non-physiologic - suction assisted lipectomy (SAL) or surgical excision like Charles / Radical reduction procedure with perforator preservation. They aim to reduce the volume of the affected limb as well as reduce the lymphatic burden. ***Physiologic procedures -*** vascularized lymph node transfer (VLNT) and lympho-venous anastomosis (LVA), nodovenous shunt, lympholymphatic bypass, and vascularized lymph vessel transfer. [1,6]

Figure 5 - Algorithm for surgical management



An evidence-based surgical algorithm for patients presenting with symptoms of lymphedema. Patients are evaluated by history and clinical examination, including investigations such as volume or limb circumference measurements, bioimpedance spectroscopy, indocyanine green lymphography, radioisotope lymphoscintigraphy, or magnetic resonance lymphography. In this algorithm, treatment decisions are made according to the ICGN Staging Scale[36] (Table 1). For stage 0, where the patient is symptomatic but imaging does not reveal dermal backflow, a period of observation is appropriate, and a trial of complete decongestive therapy is instituted in patients that develop symptoms (stage I). *ICGN*, indocyanine green; *MR*, magnetic resonance; *CDT*, complete (or complex) decongestive therapy; *LVB*, lymphovenous bypass; *VLNT*, vascularized lymph node transplant; *SAL*, suction-assisted lipectomy.

Debulking procedures

SAL has replaced traditional operations which had unacceptable scarring and morbidity. Indicated in late stage lymphoedema patients with significant volume excess as a result of hypertrophied adipose tissue. It provides minimal physiologic improvement of the lymphatic system; patients must continue wearing compression garments lifelong to prevent recurrence. Preoperative optimization with CDT is done until there is minimal/ no pitting edema; then, custom compression garments are measured using the unaffected extremity as a template and are applied intraoperatively. Power assisted devices are beneficial where the soft tissues are fibrous. For patients with large-volume advanced fibrotic disease, SAL is ineffective and excisional techniques are required. These include staged direct excision (modified Homan procedure) and, in extreme cases, excision and skin grafting (Charles procedure), reduction with perforator preservation. [1,2,6,8,12,13,14]

Physiological procedure

Nodo-venous shunt (Figure 6,7)- commonly performed for lower extremity lymphedema. A lymph node with good lymph flow is anastomosed end-to-side with great saphenous vein. It is followed by debulking surgery after 5-7 days. [15]

Figure 6 & 7

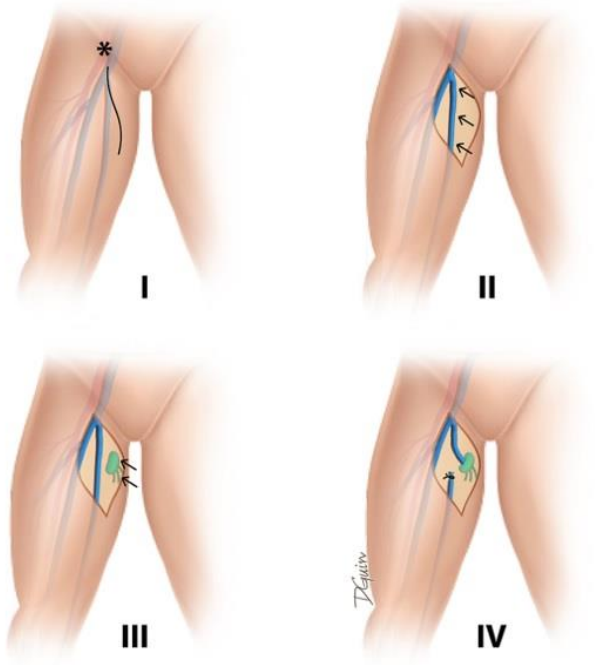


Illustration of the surgical steps of nodovenous anastomosis.

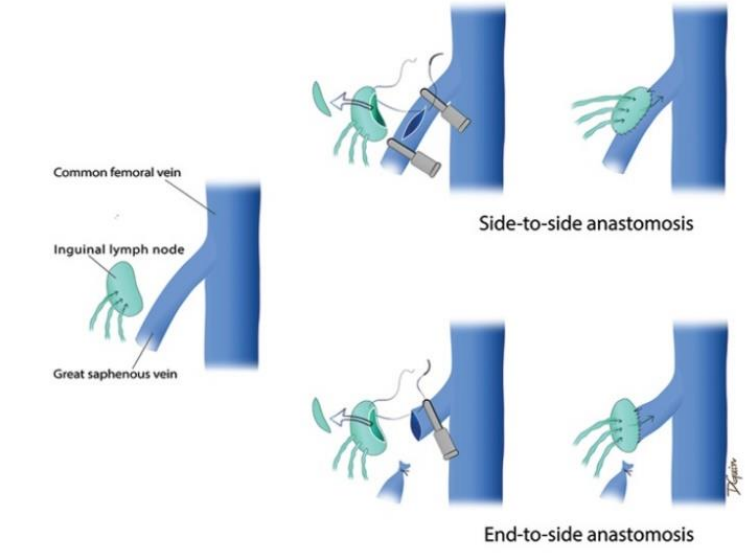


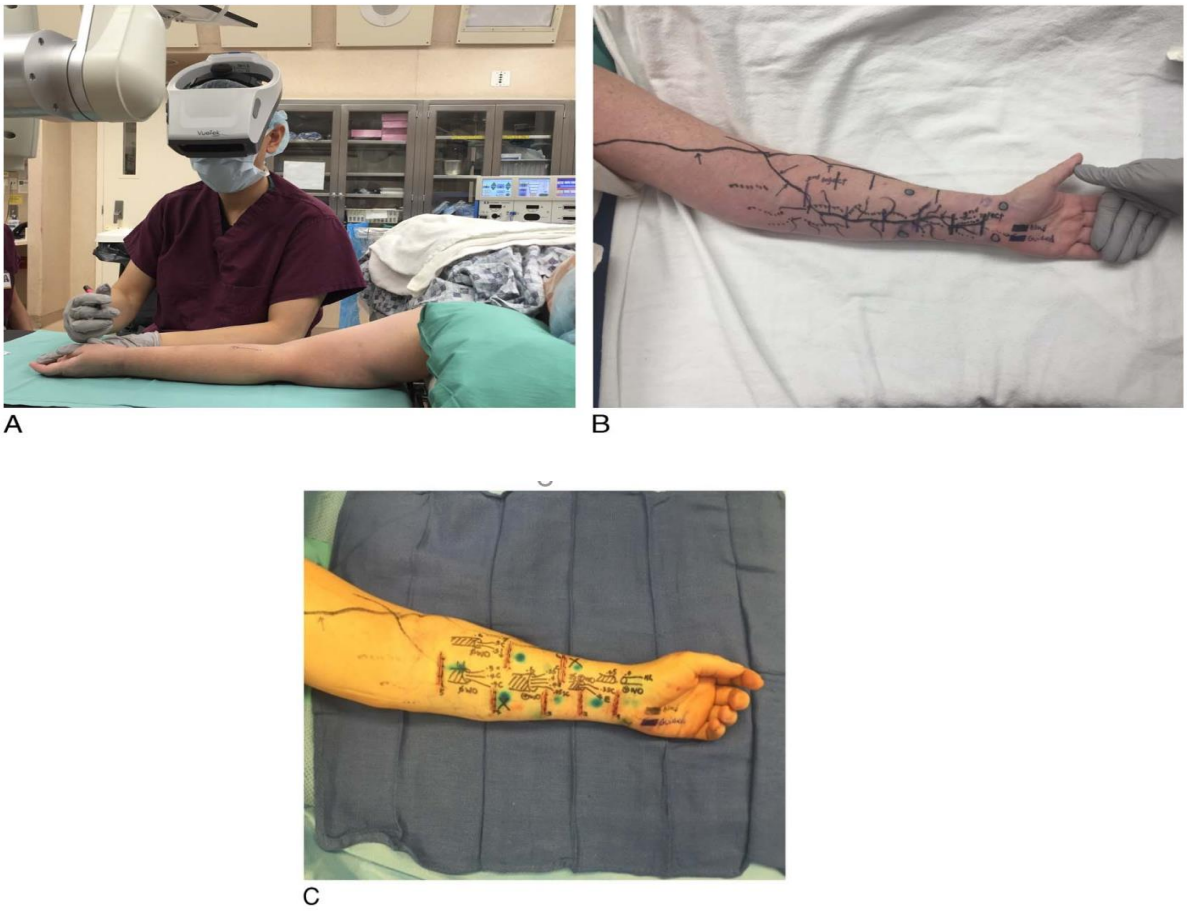
Illustration of side-to-side and end-to-side anastomosis of the saphenous vein to the inguinal lymph node.

Lympho-venous anastomosis

Koshima et al (2000) were the first to report using supermicrosurgery to anastomose tiny subdermal lymphatics and venules. prerequisite being some functional lymph channels, hence effective in earlier stages of lymphedema. [8, 13]

Using intradermal injection of ICG discrete obstructed lymphatic vessels distal to areas of dermal backflow, ranging in caliber from 0.3 to 0.8 mm, are identified and targeted for super-microsurgical anastomosis to adjacent small venules mapped using a near-infrared vein finder. Isosulfan blue can also be injected just distal to each of the incisions to further aid in lymphatic vessel identification. [14]

Figure 8

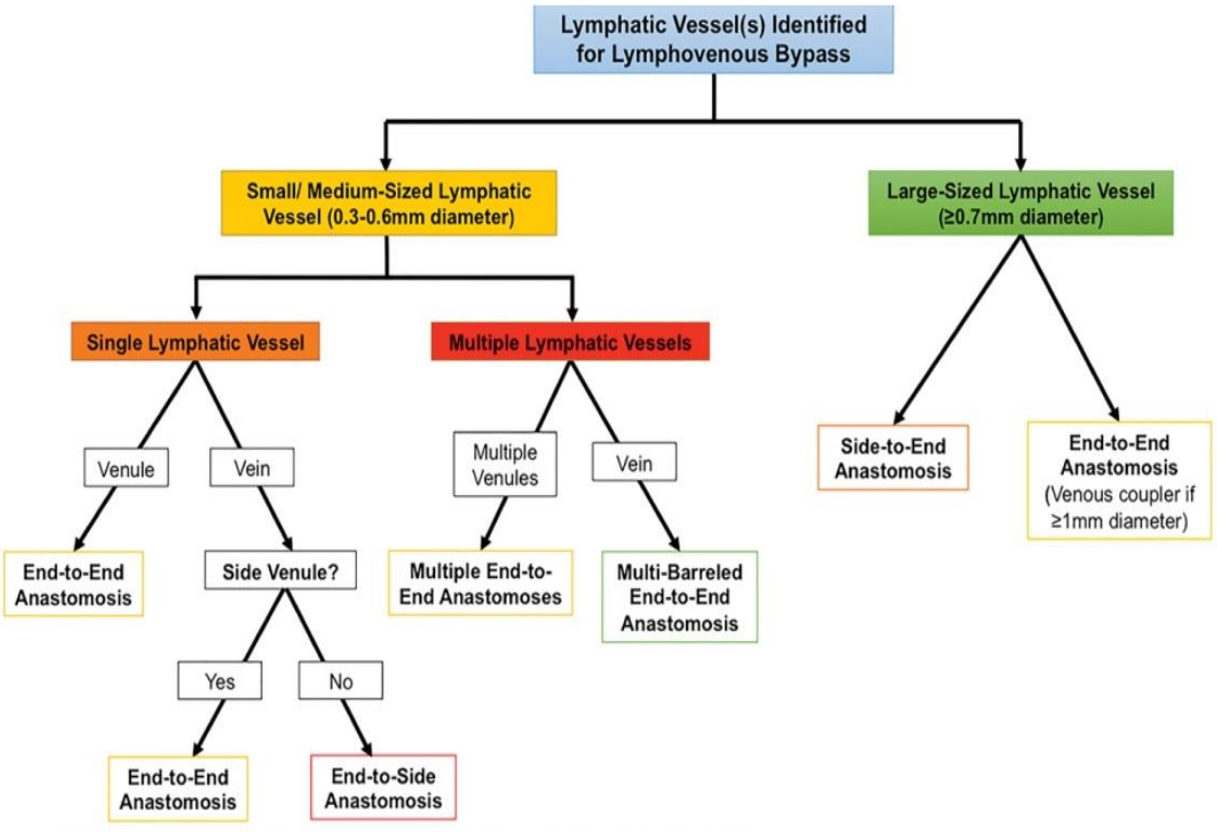


Head-mounted near-infrared vein finder was used to localized superficial veins adjacent to the lymphatic vessels mapped using ICG lymphography (A). The solid lines represented lymphatic vessels seen on ICG lymphography. The dotted lines were veins visualized using the near-infrared vein finder (B). Incisions were preferentially made at where both the lymphatic vessel and vein were present. Anatomically based incisions (following the anatomic course of cephalic vein, top 2 incisions) can also yield successful LVA construction, albeit with a lower efficiency (C).

Post anastomotic patency is confirmed by the presence of washout, “Backflow” sign also confirms patency, but indicates retrograde vein-to-lymphatic flow and is unfavorable. Microscope equipped with an ICG module patency can demonstrate flow of the ICG signal past the anastomosis. The procedure is performed in a distal-to-proximal fashion, end point is reached when the lymphatic vessels found are excessively damaged for LVA construction. [14]

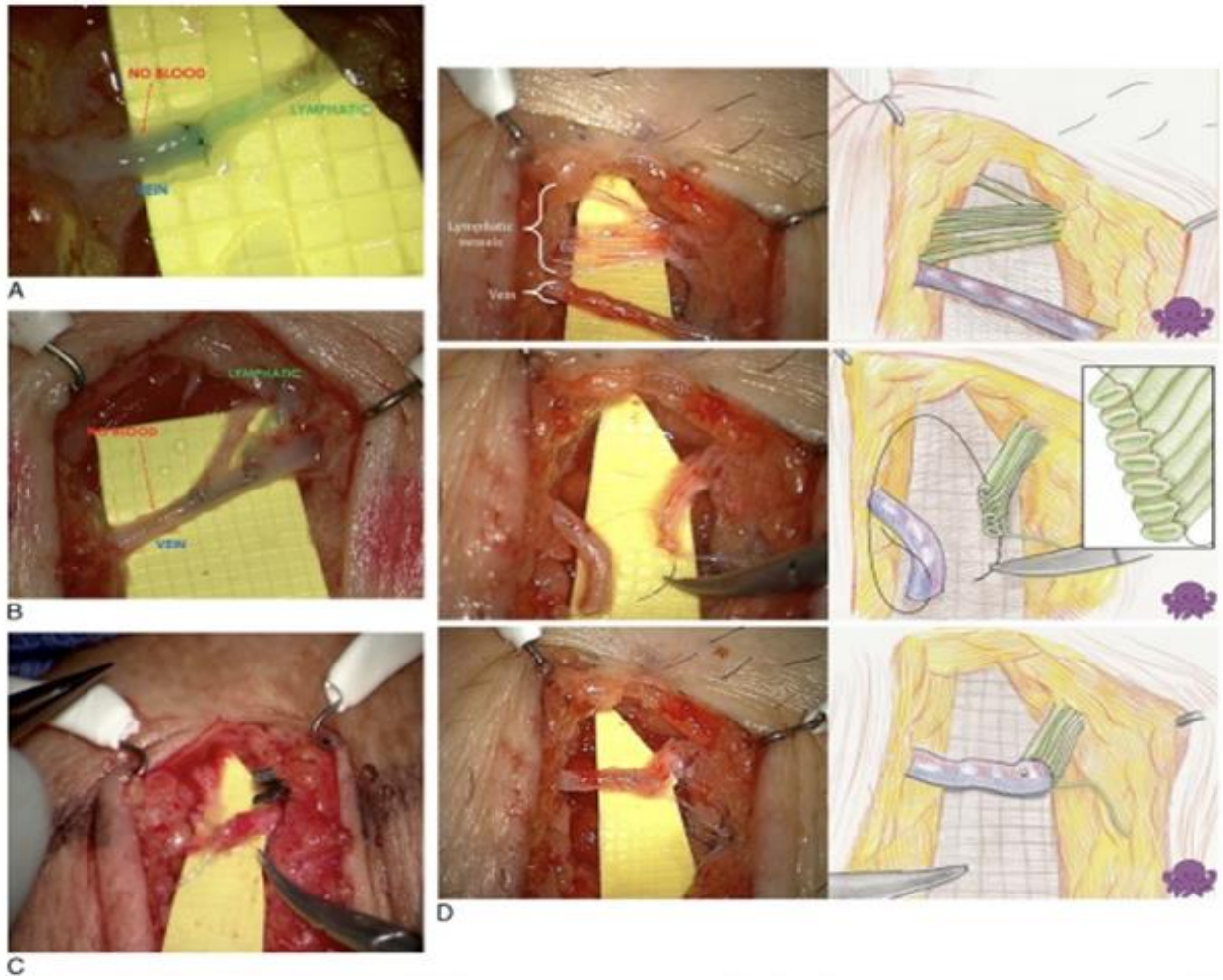
This procedure requires specialist surgical techniques, instruments and 11-0 to 12-0 nylon suture, and a high-powered surgical (magnification ranging 20x and more) microscope. Once the vessels have been identified, LVA is done (end-to-end, end-to-side, lambda shaped, octopus fashion) using super-microsurgical techniques depending on the size discrepancy between the vein and the lymphatic vessels. As many LVAs as possible can be done to improve lymph flow. The complication rate of LVA is low. These procedures can be performed under local anesthesia with minimal length of stay. Results are not as good for lower extremity lymphedema due to large size and constantly dependent nature as opposed to the upper extremity. [14,16]

Figure 9



Algorithmic approach for lymphovenous bypass anastomosis techniques.

Figure 10



Standard end-to-end anastomosis (A), double end-to-side anastomosis (B), and the octopus anastomosis (C, D). "Washout" sign can be clearly seen by the absence of blood in the vein and the simultaneous presence of the green/blue-stained lymphatic fluid in the vein (A, B). Four-to-one octopus LVA with a U-shape stitch that "intussuscepted" all 4 lymphatic vessels into a single vein (C). Cartoon illustration of the transadventitial suturing that bundles the lymphatic vessels together in the octopus technique (D). Figure 2D is reprinted from Chen W, Yamamoto T, Fisher M, et al. The "octopus" lymphaticovenular anastomosis: evolving beyond the standard supermicrosurgical technique, *Journal of Reconstructive Microsurgery*, 2015; Vol. 31(6), pp 450–445. Copyright by Thieme Medical Publishers, New York. Reprinted with permission.

Vascularized lymph node transfer (VLNT)

Vascularized lymph node transfer involves microvascular transfer of lymph nodes harvested from a donor site as a free flap to the affected limb. It can be either to an anatomic (orthotopic) or non-anatomical (heterotopic) location. VLNT procedures are indicated in advanced presentation lymphedema to import new lymphatic function. [1,8]

Exact mechanism of action remains unknown, there are two leading theories for how VLNT improves lymphatic drainage. The first theory suggests that the VLNT stimulates lymphangiogenesis by releasing growth factors, mainly VEGF. The second proposed mechanism is that the transferred lymph node acts as a "sponge" or "pump", wicking lymph fluid from the surrounding interstitial space, and projecting it into the efferent venous circulation. The high-pressure afferent arterial flow to the lymph node flap creates a local pressure gradient that transports adjacent lymphatic fluid towards the transplanted node. The fluid is subsequently absorbed into the low-pressure efferent venous anastomosis, thereby reducing lymphedema. [2,6,8,13]

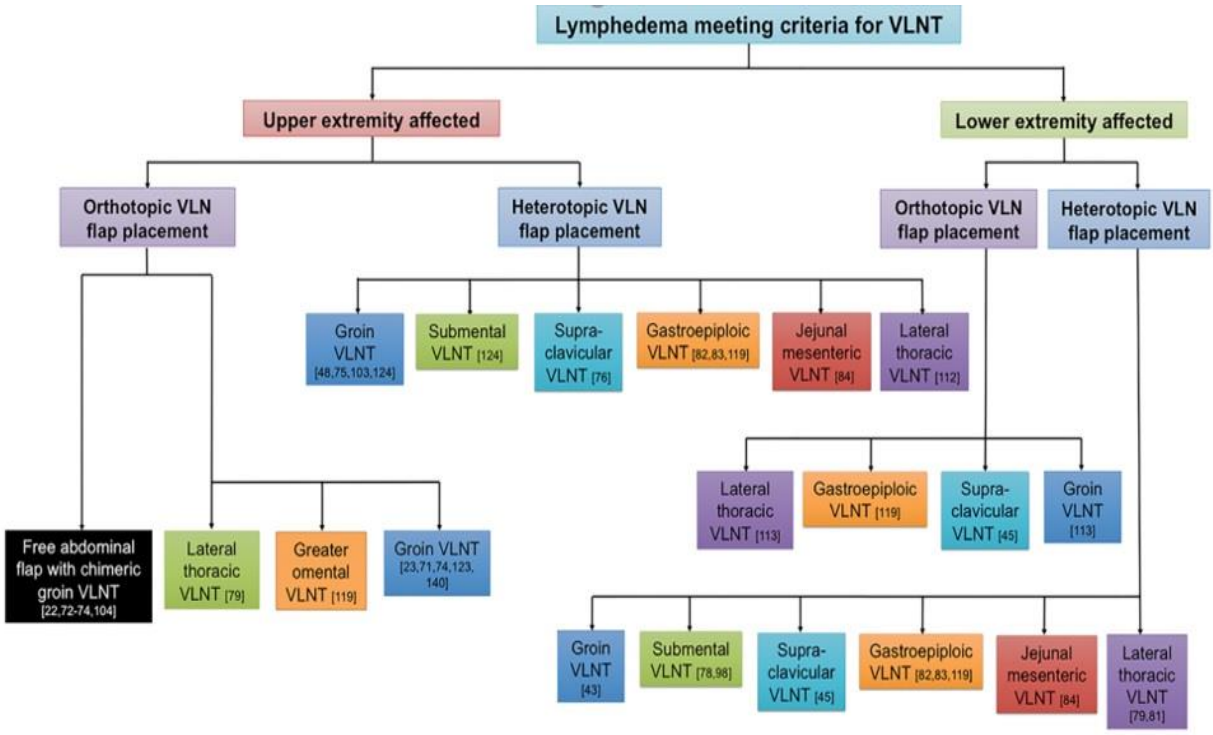
Donor sites – these flaps may be harvested from within the superficial inguinal (groin), lateral thoracic, supraclavicular, or submental regional lymph node basins. To avoid any risk of iatrogenic donor extremity lymphedema or visible donor site scars, intra-abdominal lymph node flap options like omental (gastroepiploic) vascularized lymphatic flap, which may be harvested laparoscopically. [16]

Recipient site - Choice flap inset site is based on - severity of lymphedema, scar tissue, and prior radiation and aesthetic appearance. VLN flap is placed distally to facilitate the pumping and absorption function of the stagnant lymph and because lymph is usually pooled in the most dependent location. Furthermore, distal locations are usually away from radiation site and when insetting the flap in the ankle, there is no need to sacrifice a large artery to use it as the recipient vessel. [2,6]

In patients undergoing postmastectomy breast reconstruction, VLNT may be performed by transferring a deep inferior epigastric artery perforator flap with a chimeric groin lymph node transplant. [16] VLNT from the inguinal or axillary regions must be performed under reverse lymphatic mapping guidance to reduce the risk of iatrogenic donor extremity lymphedema VLNT has been shown to reduce limb size, improved subjective feelings of heaviness and pain, and decrease episodes of cellulitis in multiple level 3 and level

4 studies. [6,13] Complication rates of donor-site seroma, lymphocele, infection, delayed wound closure, and donor-site lymphedema make VNLT a higher risk surgery than LVA.

Figure 11

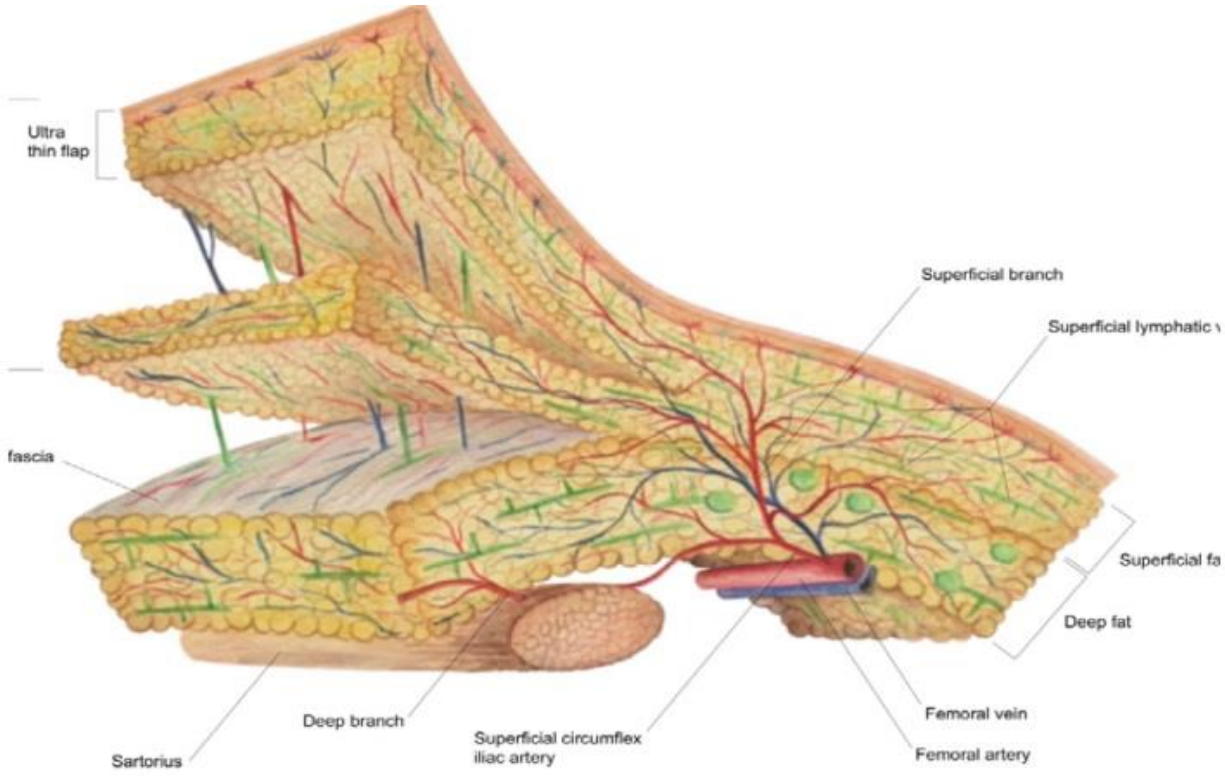


An evidence-based decision aid for the vascularized lymph node flap transplant procedure relative to donor- and recipient-site locations. Choice of flap is individualized based on clinical findings and staging imaging, body habitus, and availability and quality of donor sites. Free abdominal flap with chimeric vascularized groin lymph node flap transfer is indicated in postmastectomy breast reconstruction for patients in whom the abdominal donor site is suitable; otherwise, total breast reconstruction can be combined with either an orthotopic or heterotopic lymph node transplant procedure as indicated. Where the entire extremity is affected, dual-level transfer may be indicated; the intraabdominal donor site is well-suited for this requirement to reduce donor-site morbidity. *VLNT*, vascularized lymph node transplant.

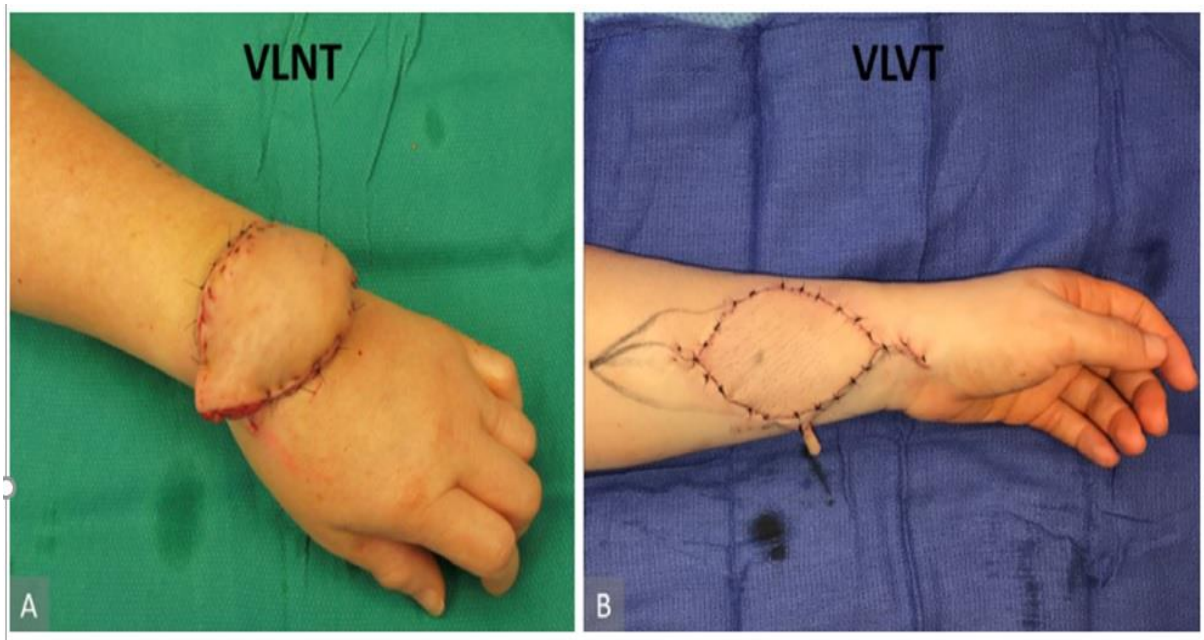
Vascularized lymph vessel transfer (VLVT)

To avoid the bulk of VLNT the concept of lymph vessel-only vascularized transfer based on first dorsal metatarsal artery (FDMA) or superficial circumflex iliac artery perforator flap (SCIP) is introduced. (Figure -12,13) Mechanism of flap take is similar to VLNT. Functioning smooth muscles lining the healthy lymphatic vessels contract helping to transport accumulated lymph fluid into the venous system. [17]

Figure 12 & 13



The SCIP-based VLVT flap was typically harvested immediately superficial to the Scarpa's fascia to preserve the lymph nodes that are anatomically situated deep to the Scarpa's fascia. This creates a thin flap that facilitates flap inset. In obese patients, the above technique would produce a thick flap. In these patients, we harvested the flap along a non-anatomic, artificially created plane created at 3-5 mm under the dermis. SCIP, superficial iliac artery perforator; VLVT, vascularized lymph vessel transfer.



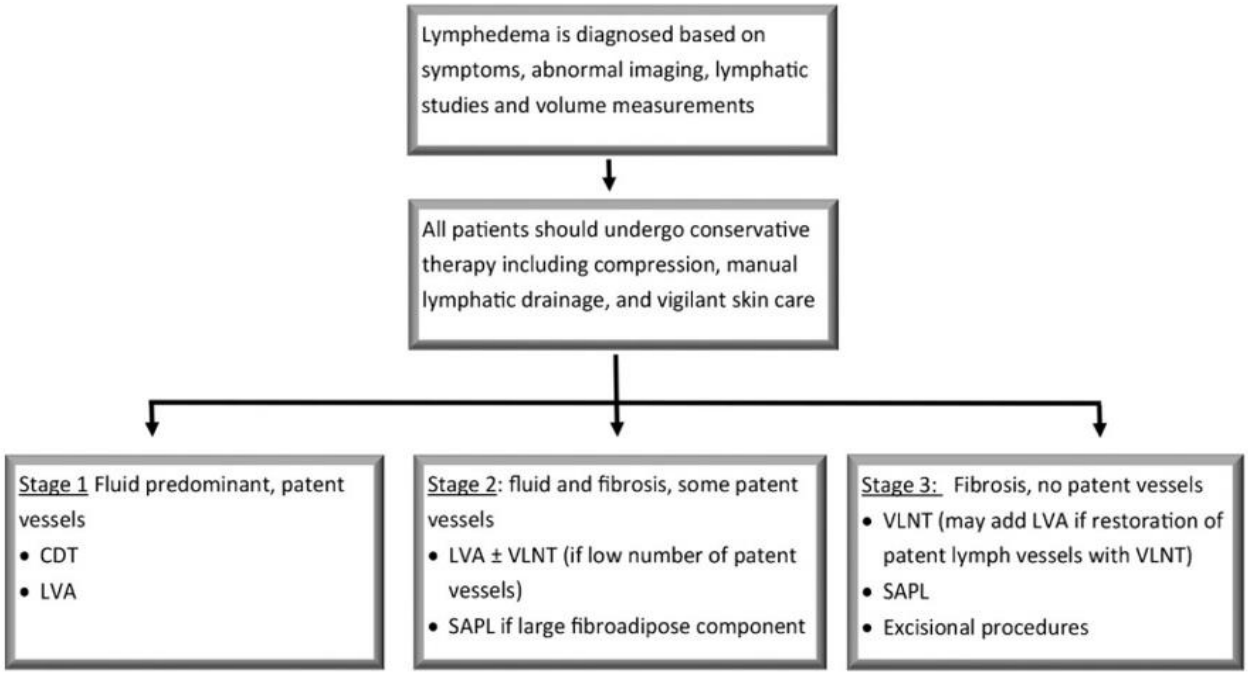
Comparison of lymph node flap inset and lymph vessel flap inset. Contour deformity was not avoidable due to the associated tissue bulk in a lymph node flap. In this case, we could not complete the flap inset due to venous congestion from pedicle compression with complete flap inset (panel A). The thin lymph vessel flap in combination with recipient site skin excision facilitated inset that did not disrupt anatomic contour (panel B).

Table 5

Options for surgical therapy of lymphedema

Technique	Advantages	Disadvantages	Comments
Lymphovenous anastomosis	• Minimally invasive surgery with the use of ICG	• Less effective for lower extremity lymphedema	• Performed in early stage lymphedema
	• Can be performed prophylactically at time of lymph node dissection	• Requires a patent lymphatic vessel for anastomosis	
Lymph node transfer	• Procedure not limited by recipient site lymphatic patency	• Risk of donor site complications (e.g., seroma, lymphedema)	• Can be performed at all stages, but most efficacious in early stage lymphedema
	• Variety of donor sites available		
	• Simultaneous breast reconstruction possible		
Liposuction	• Removes fibrofatty tissue unresolved by physiotherapy	• Requires continuous use of compressive garment therapy if performed alone	• Performed in all stages of lymphedema
	• High patient satisfaction		
Subcutaneous excision (e.g., Charles, Homans)	• Removes fibrofatty tissue unresolved by physiotherapy	• Risk of surgical site complications (e.g., infection, wound dehiscence)	• Performed at end stage lymphedema
	• Effective for severe lower extremity lymphedema (e.g., elephantiasis)	• Poor aesthetic outcome	

Figure 14



Lymphedema management summary. Stage refers to the ISL lymphedema staging system. CDT, complete decongestive therapy; LVA, lymphovenous anastomosis; VLNT, vascularized lymph node transfer; SAPL, suction-assisted protein lipectomy

Cancer related lymphedema

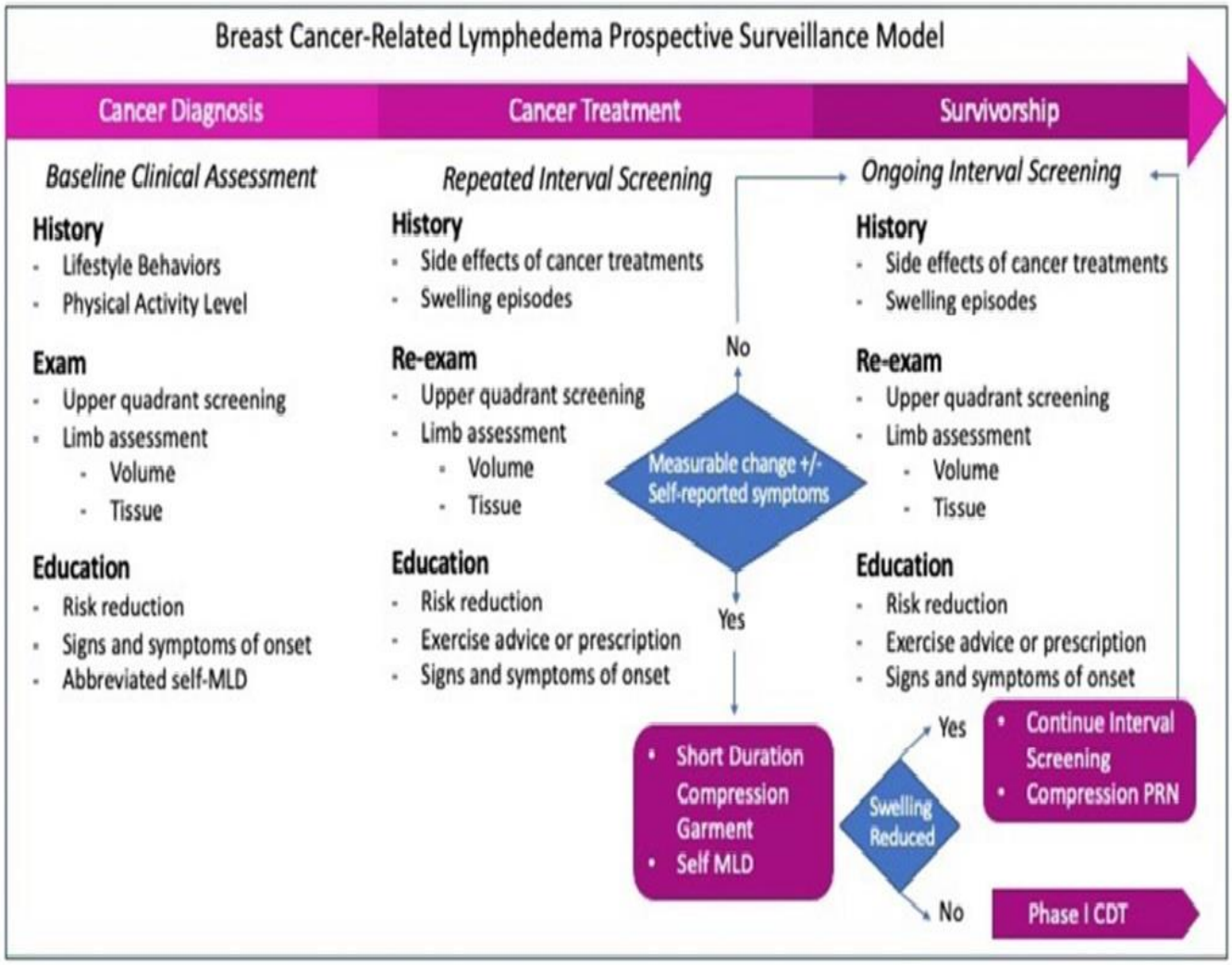
Lymphedema is a dreaded complication of cancer related treatment or the disease itself. Lymph node dissection or if combined with radiation increases risk of lymphedema. With the argument that cancer being a systemic disease on presentation itself, landmark clinical trials in surgical and radiation oncology especially have challenged the long-held notion of nodal clearance equates to improved survival. [6,16]

Breast cancer related lymphedema (BCRL) -patients undergoing axillary lymph node dissection definitely have more incidence of lymphedema compared with SLNB. Trials like American College of Surgeons Oncology Group (ACOSOG) Z0011 trial and The After Mapping of the Axilla: Radiotherapy or Surgery? (AMAROS) trial provide evidence for the systematic de-escalation of lymph node treatment. [16]

Melanoma related -Overall, the pooled incidences of lymphedema after melanoma surgery are reported as 4.1% after SLNB, 3% after axillary lymph node dissection (ALND), and 18% after inguinofemoral lymph node dissection. Multicenter Selective Lymphadenectomy Trial I (MSLT 1) - showed immediate/early lymph node dissection due to involved nodes/ positive SLNB had less lymphedema than those undergoing delayed lymph node dissection. MSLT-2 is an ongoing trial to compare lymphadenectomy with ultrasound surveillance. [16]

Risk assessment and surveillance– latency of lymphedema to emerge can be used to detect it early and delay its progression by standardized methodology for surveillance as shown below (figure – 15). [16]

Figure 15



Breast Cancer–Related Lymphedema Prospective Surveillance Model

Abbreviations: +/−, with or without; CDT, complete decongestive therapy; MLD, manual lymphatic drainage; PRN, as necessary.

Emerging strategies for surgical prevention of lymphedema

Surgical procedures designed to prevent lymphedema by minimizing damage to lymphatics or restoring drainage at the time of initial surgery include sentinel lymph node biopsy (SLNB), axillary reverse mapping (ARM), and lymphatic microsurgical preventive healing approach (LYMPHA). [6]

Axillary reverse mapping (ARM)

The lymphatics draining the proximal part of the arm are distinct from those of the breast. ARM seeks to preserve upper extremity lymphatics and nodes. The surgeon isolates the lymph nodes draining the breast with technetium and those draining the arm with blue dye. The Alliance A221702 trial is currently evaluating SLNB or ALND with and without ARM to formally evaluate the feasibility and utility of ARM. [6,16]

Lymphatic microsurgical preventive healing approach (LYMPHA)

This microsurgical technique is based on performing multiple lymphatic-venous anastomoses between lymphatics identified by ARM and axillary vein branches during axillary dissection in high-risk patients. It Restores lymphatic continuity at the time of nodal surgery by identifying disrupted lymphatic channels using reverse axillary mapping and reconnecting them to upstream lymphatic vessels or bypassing them to available veins. LYMPHA treated patients have shown a significantly lower risk of BCRL and other lymphatic complications like lymphorrhea and lymphocele. But further investigation is needed, as the added operative time and need for specialized microsurgical training must be considered if LYMPHA is to be widely adopted for all patients undergoing ALND. [6,16]

With increasing 10year survival of breast cancer patients there is increased BCRL causing impaired quality of life. Hence, we need tailored rehabilitation and treatment programs to minimize the impact of BCRL and is especially relevant in the current era of de-escalating axillary surgery. [18]

Quality of life (QOL) and Patient reported outcome measures (PROM)

Regardless of etiology, patients with lymphedema experience a variety of symptoms including swelling, pain, decreased range of motion, depression and anxiety. These symptoms substantially impact quality of life (QOL). Some patients have profoundly decreased QOL even without significant changes in extremity circumference therefore assessment of QOL is an important aspect of any study aiming to analyze outcomes following surgical treatment of lymphedema. So far studies have focused on objective changes in limb volume and there is little consensus on the use of PROMs. [19]

General QOL and PROM scores are short form 36 (SF-36). Validated lymphedema-specific questionnaires are -The lymph quality of life measure for limb lymphedema (LYMQOL), the upper limb lymphedema 27 scale (ULL27), lymphedema functioning, disability and health questionnaire (Lymph-ICF), and lymphedema life impact scale (LLIS). Over time proportion of studies utilizing validated tools has increased. [19]

Future directions

Targeted therapy

VEGF-C is the most important lymphangiogenic factor, which is a ligand VEGFR3. Loss of VEGFC/VEGFR3 signaling leads to blockade of lymphatic development, growth, and regeneration. Therefore, VEGFC is an important therapeutic target to induce lymphatic regeneration in lymphedema. [20]

In a study conducted by Dániel Szőke et al in-mouse models demonstrated that administration of a single low-dose of VEGFC mRNA-lipid nanoparticles induced durable, organ-specific lymphatic growth and functional lymphatic network. It also reversed experimentally induced secondary lymphedema by restoring lymphatic function without inducing any obvious adverse events. [20]

Stem cell therapy

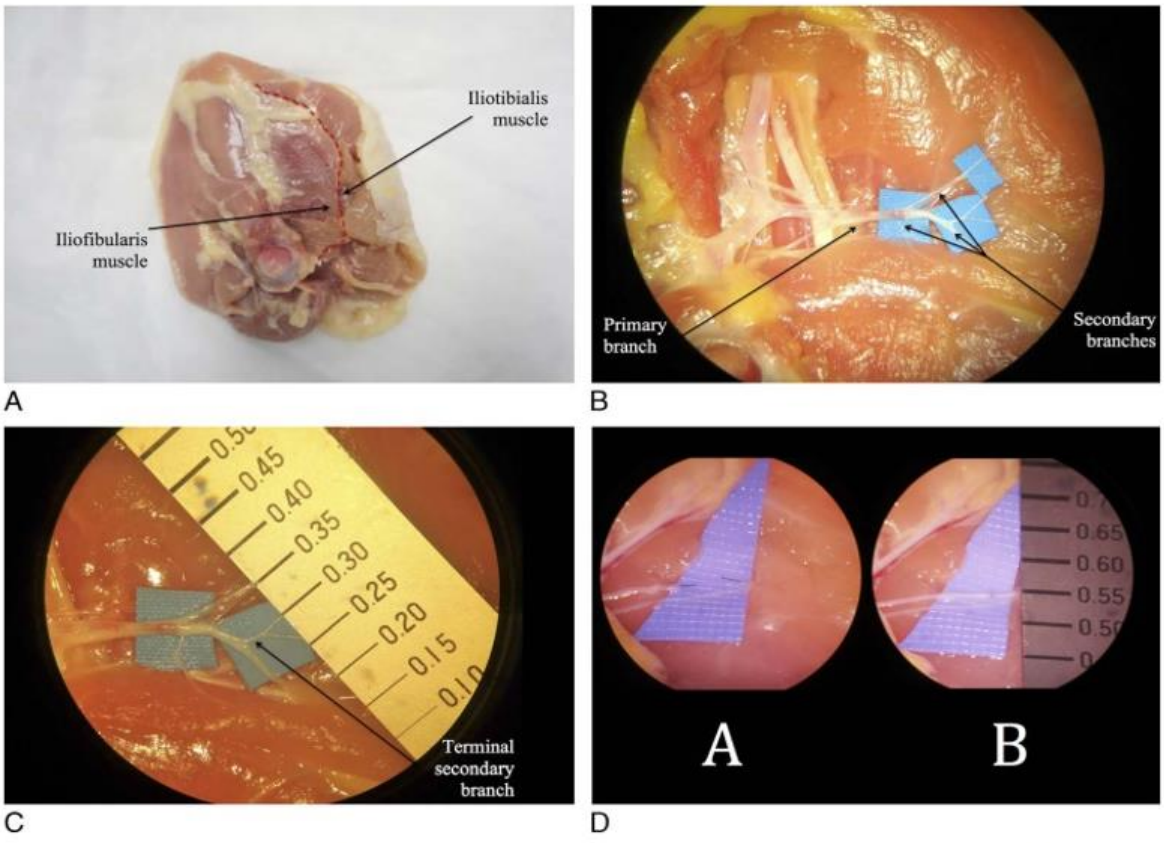
It represents a potential future alternative to direct therapeutic administration of growth, factors in lymphedema. The potential beneficial mechanism of stem cell therapy has not been firmly established for lymphedema, yet it is established that these mesenchymal cells have the capacity to differentiate into cells with lymphatic endothelial properties in vitro. These cells acquire both the phenotype and molecular expression profile of lymphatic endothelial cells and, in a preclinical lymphedema model, seem to improve lymphatic drainage after injection. [4]

Getting started for residents as well as experienced surgeons interested in super microsurgery

LVA remains much less commonly performed than the VLNT due to surgeons - unfamiliarity with super microsurgery, inexperience with LVA-related techniques. Lymphaticovenular anastomosis is supermicrosurgical because the lymphatic vessels and veins involved are frequently in the range of 0.2 to 0.6 mm so rigorous training is needed. A 0.1 mm error in suture placement would result in failed anastomosis in an LVA with 0.3 mm lymph vessel. [14]

Simulation training using the chicken thigh model for supermicrosurgical training is easy and economical to use (Figure-16). Its ischiatic neurovascular bundle and associated branches offer vessels in the range of 0.2 to 2.3 mm, we can tailor the training based on our skill level. Under the simulation environment, the surgeon can get accustomed with the higher magnification, handling of these instruments,12–0 suture with 50-micron needle, and various anastomotic configurations. [14]

Figure 16



Store-bought chicken thighs can be used to train LVA supermicrosurgeons. It is important to buy ones with bones, as the ischiatic neurovascular bundle is intimately associated with the bone. The redline indicates the areolar plane between muscles where the neurovascular bundle can be found with minimal dissection (A). The ischiatic neurovascular bundle and its associated branches are seen here under 10× magnification. The secondary and tertiary branches are usually adequate for supermicrosurgical training, while the main trunk and the primary branches are suitable for regular microsurgical training (B). In our study, 0.2-mm and 0.3-mm vessels could be found in all chicken thighs (C). A 7–0 nylon can be used as a vascular stent to prevent the vessel lumen from collapsing. Shown here is a 0.55-mm vessel anastomosed with 12–0 Nylon using the 7–0 nylon stent training technique (D).

Tables

Figures

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Abbreviations

1. VEGF-C	-	vascular endothelial growth factor C
2. VEGFR3	-	vascular endothelial growth factor receptor-3
3. ISL	-	International society of lymphology
4. ICG	-	Indo Cyanine Green
5. MRL	-	Magnetic resonance lymphangiography
6. NIRF	-	near-infrared fluorescence
7. VLNT	-	vascularized lymph node transfer
8. CDT	-	complex decongestive therapy
9. SAL	-	suction assisted lipectomy
10. LVA	-	lympho-venous anastomosis
11. VLN	-	Vascularized lymph node
12. FDMA	-	first dorsal metatarsal artery
13. SCIP	-	superficial circumflex iliac artery perforator
14. VLVT	-	Vascularized lymph vessel transfer
15. BCRL	-	Breast cancer related lymphedema
16. ACOSOG	-	American College of Surgeons Oncology Group
17. AMAROS	-	After Mapping of the Axilla: Radiotherapy or Surgery
18. ALND	-	axillary lymph node dissection
19. MSLT I	-	Multicenter Selective Lymphadenectomy Trial I
20. MSLT II	-	Multicenter Selective Lymphadenectomy Trial II
21. SLNB	-	sentinel lymph node biopsy
22. ARM	-	axillary reverse mapping
23. LYMPHA	-	lymphatic microsurgical preventive healing approach
24. QOL	-	Quality of life
25. PROM	-	Patient reported outcome measure
26. SF-36	-	Short form 36 questionnaires
27. LYMQOL	-	The lymph quality of life measure for limb lymphedema
28. ULL27	-	the upper limb lymphedema 27 scale
29. Lymph-ICF questionnaire	-	lymphedema functioning, disability and health
30. LLIS	-	lymphedema life impact scale
31. mRNA	-	Messenger Ribonucleic acid

Recognise the early signs – listen to your limb