

Lymphedema: Surgical and Medical Therapy

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Background: Secondary lymphedema is a dreaded complication that sometimes occurs after treatment of malignancies. Management of lymphedema has historically focused on conservative measures, including physical therapy and compression garments. More recently, surgery has been used for the treatment of secondary lymphedema.

Methods: This article represents the experience and treatment approaches of 5 surgeons experienced in lymphatic surgery and includes a literature review in support of the techniques and algorithms presented.

Results: This review provides the reader with current thoughts and practices by experienced clinicians who routinely treat lymphedema patients.

Conclusion: The medical and surgical treatments of lymphedema are safe and effective techniques to improve symptoms and improve quality of life in properly selected patients. (*Plast. Reconstr. Surg.* 138: 209S, 2016.)

Lymphedema is a disease process that is characterized by insufficient drainage of interstitial fluid mostly involving the extremities. In the developed world, secondary lymphedema is the most common type of lymphedema and may be caused by trauma, infection, or most commonly by oncologic therapy. It can be a dreaded and not uncommon complication from the treatment of various cancers, particularly breast cancer, gynecologic cancers, melanomas, and other skin cancers and urologic cancers. Cancer-related lymphedema affects cancer survivors on a daily basis and is a constant reminder of the cancer that they have fought to overcome. Patients often complain of pain, heaviness, swelling, inability to find proper fitting clothing, and in some cases frequent infections. We are just now beginning to better understand the disease process, its diagnosis, and treatment options of secondary cancer-related lymphedema.

EVALUATION OF THE LYMPHATIC SYSTEM

The lymphatic system is a complex network of lymph vessels, lymphatic organs, and lymph nodes. The field of lymphatic imaging continues to evolve rapidly, and technological advances,

combined with the development of new contrast agents, continue to improve diagnostic accuracy. Direct lymphangiography, a once practiced and now almost extinct method of visualizing the lymphatic channels from an extremity, is done using oil-based iodine contrast agents that are directly injected into the lymphatics.¹ Today, several other evaluation tools facilitate the diagnosis of lymphedema and assist in surgical planning. Radionuclide lymphoscintigraphy has been the gold standard for many years and is readily available in many centers. It involves the injection of a filtered colloid, Technetium-99, subdermally into the limb.¹ The limb is then scanned. The Technetium is taken up by the lymphatics. Lymphoscintigraphy can assess the function of lymphatic channels and drainage of lymph to nodal basins. It gives good information on the function of the lymphatic system and the function of the lymph node basins. Calculation of the transport index is

Disclosure: The authors have no financial interest in any of the products, devices, or drugs mentioned in this article. The authors received book royalties from Elsevier and CRC Press. No external funding supported this work. The authors have no conflicts of interest to declare.

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Received for publication March 28, 2016; accepted June 17, 2016.

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DOI: 10.1097/PRS.0000000000002683

useful to semiquantitatively ascertain the severity of lymphedema and provide insight into any anatomic abnormalities, such as areas of obstruction or a reduction in the number of visualized lymphatic channels.² It works by measuring the speed of uptake of the Technecium and how quickly it reaches the nodal basin. However, radionuclide-based imaging has the disadvantage of poor resolution, so it does not give good information on the anatomy of these lymphatic channels nor does it quantify changes in the limb other than those related to the lymphatic system. It only provides sets of static images at 1 period in time, is time consuming, and generally does not aid in surgical planning for lymphovenous anastomoses. It is also an uncomfortable investigation for the patient. Other modalities described below seem to be replacing lymphoscintigraphy for many patients. Still, it can be useful to determine if there are functional lymphatics in the affected extremity.

More recently, magnetic resonance lymphangiography (MRL) has been developed to provide superior high-resolution anatomic images of the lymphatic system and detailed characterization of the soft tissue changes associated with lymphedema.³ It is possible to get detailed limb circumference measurements from which limb volume can be calculated. To help distinguish lymphatic channels from veins, intravenous injection of ferumoxytol can be performed during MRL to isolate

the contrast enhancement of veins and eliminate these signals using novel techniques (Fig. 1).⁴ MRL is a good screening method to determine whether a patient has functioning lymphatics, the characteristics of the limb, and whether any nodal basins can be visualized. This can help guide the surgeon to choose the best possible procedure for the patient, as patients with significant fibrosis and minimal edema seen on MRL would likely not benefit from the physiologic type of procedures.

Another emerging imaging modality is indocyanine green (ICG) lymphangiography, which offers real-time visualization of lymphatic flow and is helpful in patients who cannot undergo MRL because of either contrast allergies or metal implants. Through the use of a near-infrared camera, the fluorescence of ICG activated by a laser light source can be seen and the subdermal lymphatic channels can be visualized. ICG lymphangiography can reveal the condition of lymphatic vessels in relation to the progression of lymphedema and identify suitable channels that may be amenable to lymphatic surgery (Fig. 2). Different patterns of diffusion of ICG can be used to grade the severity of lymphedema. The linear pattern is normal, whereas splash, stardust, and diffuse patterns indicate increasing severity of lymphedema and increased levels of fibrosis in the lymphatic channels (Fig. 2).⁵ In fact, ICG is indispensable as a means of intraoperative imaging and planning.

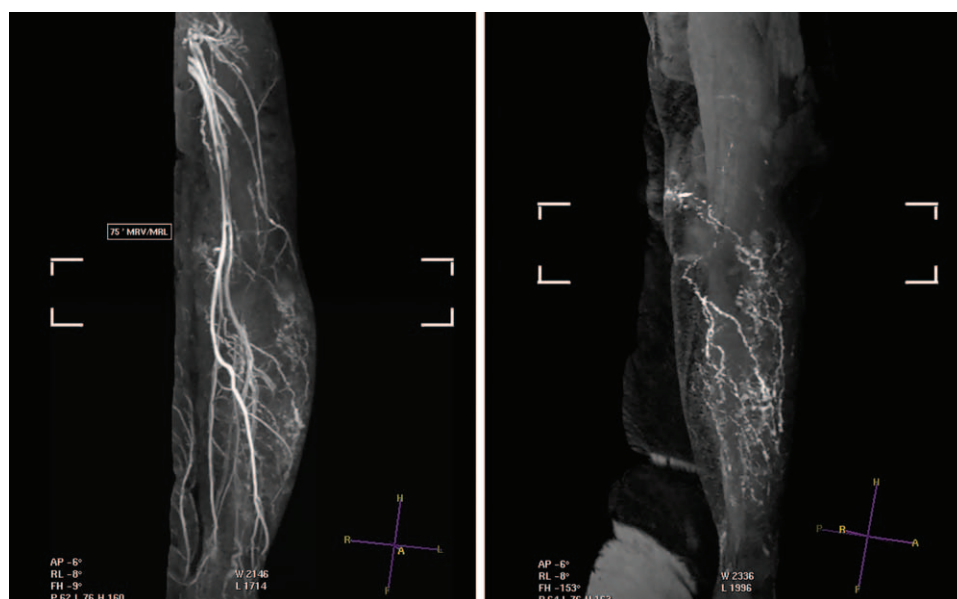


Fig. 1. (Left) Magnetic resonance venography without injection of intravenous ferumoxytol, demonstrating lymphatics and veins. (Right) Magnetic resonance lymphangiography of the same arm as (left) with injection of intravenous ferumoxytol, which allows suppression of the veins in the imaging study.

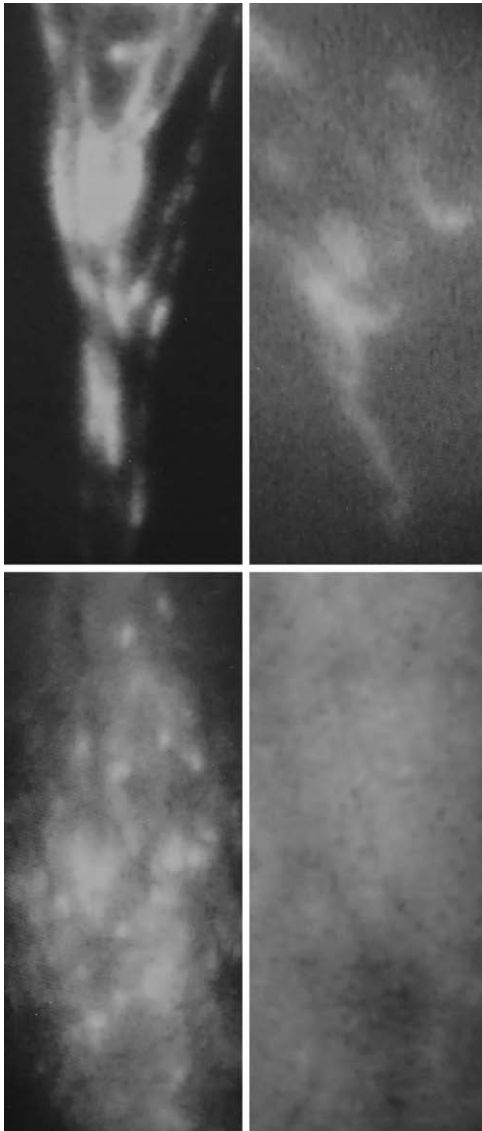


Fig. 2. Indocyanin green lymphangiography: (above, left) linear pattern; (above, right) splash pattern; (below, left) stardust pattern; (below, right) diffuse pattern.

A vascularized lymph node transfer (VLNT) can be done without ICG, whereas lymphaticovenular anastomosis (LVA) cannot.

MEDICAL AND NONSURGICAL MANAGEMENT

Complete Decongestive Therapy

Nonsurgical or conservative measures are generally considered first-line interventions for secondary lymphedema. Newly diagnosed patients are usually enrolled in physical therapy regimens that can use a combination of approaches, but complete decongestive therapy (CDT) has been the mainstay of initial management for lymphedema



Fig. 3. Mixed picture of lymphedema in the setting of venous insufficiency, obesity (body mass index, 31 kg/m²), and lymphedema.

patients. CDT (also known as complex physical therapy, comprehensive decongestive therapy, or decongestive lymphatic therapy) incorporates a multimodality approach, which includes manual lymphatic drainage, daily bandaging, exercise, and skin care.⁶

CDT is therapist directed. Lymphedema specialists meet patients typically 5 times per week for a total of 6 weeks of intensive care. Patients are transitioned from this phase 1 therapy that focuses on volume reduction to a phase 2 therapy that focuses on maintenance.

During phase 1, patients are taught to perform exercises, perform self-directed manual lymphatic drainage, and apply compression garments and wrapping. The lymphedema therapists perform manual lymphatic drainage, apply compression therapy, and take patients through a series of exercise to help prevent scar contractures and stiffness and improve posture.

Phase 2 is mostly patient-directed care. Both phases involve meticulous skin and nail care. This helps avoid minor trauma, which may lead to skin infections, such as erysipelas.⁷

There have been numerous studies that have evaluated the effectiveness of this labor and time intensive approach compared with compression bandages alone or physical exercise alone.^{6,8-11} Several studies have found no difference between CDT and less involved methods; most of these were underpowered. Three randomized controlled trials examined this question; the largest of which included 100 patients and followed up patients for 1 year.^{8,10,11} This study showed no significant difference in quality of life or volume reduction, despite a small volume difference (average = 107 mL) in favor of the CDT group.¹⁰

A more recent randomized trial including 1,000 patients examined outcomes of self-directed manual lymphatic drainage combined with physical exercise ($n = 500$) versus physical exercise alone ($n = 500$) and found that self-directed manual lymphatic drainage combined with physical exercise showed significant improvements in arm circumference, shoulder range of motion, and scar contracture.¹² No patients received any type of compression therapy in this study. It should be noted that lymphedema rates were significantly lower than what is generally quoted in the literature for both groups with only stage I lymphedema present in 1.6% and 7.8% at 1 year, respectively. Further research is needed to delineate the exact indications for compression and massage. We know several large-scale studies that are examining these questions and should provide answers soon; however, current evidence is contradictory.

Pharmacotherapy

In an effort to improve or cure lymphedema, several pharmaceuticals have been investigated; these include diuretics, coumarin, vitamin E, selenite, steroids, and nonsteroidal anti-inflammatory drugs. Diuretics have been anecdotally reported to be of benefit in early phases of the disease, but they are not effective for long-term management.¹³ Because of the multifactorial components with limb swelling, particularly with the lower extremity, diuretics may be useful in treatment of swelling attributed to venous stasis or congestive heart failure. However, isolated lymphedema is not generally treated with these medications. Coumarin, vitamin E, and pentoxifyline have all been evaluated with randomized controlled trials, and no evidence exists to suggest that they are useful in the treatment or prevention of lymphedema.¹⁴⁻¹⁷

Most clinicians treating lymphedema have observed at least a temporary beneficial effect of corticosteroids on lymphedema, usually administered for unrelated reasons. Kim et al¹⁸ and Park et al¹⁹ have investigated this and confirmed that stellate ganglion blocks with corticosteroids resulted in significant reduction in breast cancer-related extremity edema. However, no data exist to support a sustained effect beyond 1 month.

Nakamura et al²⁰ found in a murine model that Ketoprofen therapy reduces secondary lymphedema, yet direct tumor necrosis factor- α inhibition does not. Reducing inflammation while preserving tumor necrosis factor- α activity

seems to optimize the repair response. To date, no published human data exist to corroborate this beneficial effect seen in the animal model.

Stenting for Relative Venous Insufficiency

Lower extremity swelling has been a challenging problem for clinicians to manage and, more importantly, diagnose correctly. There are numerous causes of lower extremity swelling spanning the gamut from obesity to congestive heart failure to lymphedema, and often, there is more than 1 factor contributing to the finding of a swollen limb. In one study, only 75% of patients diagnosed with lymphedema, who were referred to a lymphedema specialist, actually had lymphedema. The remaining 25% had other diagnoses, including venous stasis, lipedema, obesity, injury, rheumatologic disease, and vascular malformations.²¹ It is not unusual to encounter a patient who presents with multiple factors contributing to their lymphedema, for example, cancer therapy, obesity, and venous insufficiency (Fig. 4). Raju et al²² evaluated 819 patients with lower extremity swelling and known venous outflow insufficiency that had lymphangiography performed; 219 had abnormal lymphangiography. With this heightened awareness of venous obstruction as a potential cause of secondary lymphedema, many practitioners are including evaluations of the venous system in the workup of lymphedema in either upper or lower extremity.²² Studies used to evaluate the venous system include venous duplex, venograms, and magnetic resonance venography.

Because venous insufficiency has been found as a potential cause of secondary lymphedema, ways of ameliorating the venous outflow problems have been investigated. Venous congestions can alter the interstitial fluid balance and contribute to lymphedema. Thus, improvement of venous insufficiency can help with lymphedema. Raju et al²³ looked at intravascular venous stents as a way to improve lower extremity venous outflow. The results showed improvement in all patients including those with abnormal lymphangiograms. The use of venous stents for upper extremity swelling has not been well studied. One of the concerns with venous stenting in the upper extremity is that stents placed in the axillary vein could become compressed or migrate with movement. For this reason, angioplasty has been used in this region exclusively (Fig. 5). Still, stenting and angioplasty of the venous system need further investigation before it should be considered part of the routine algorithm for lymphedema treatment.

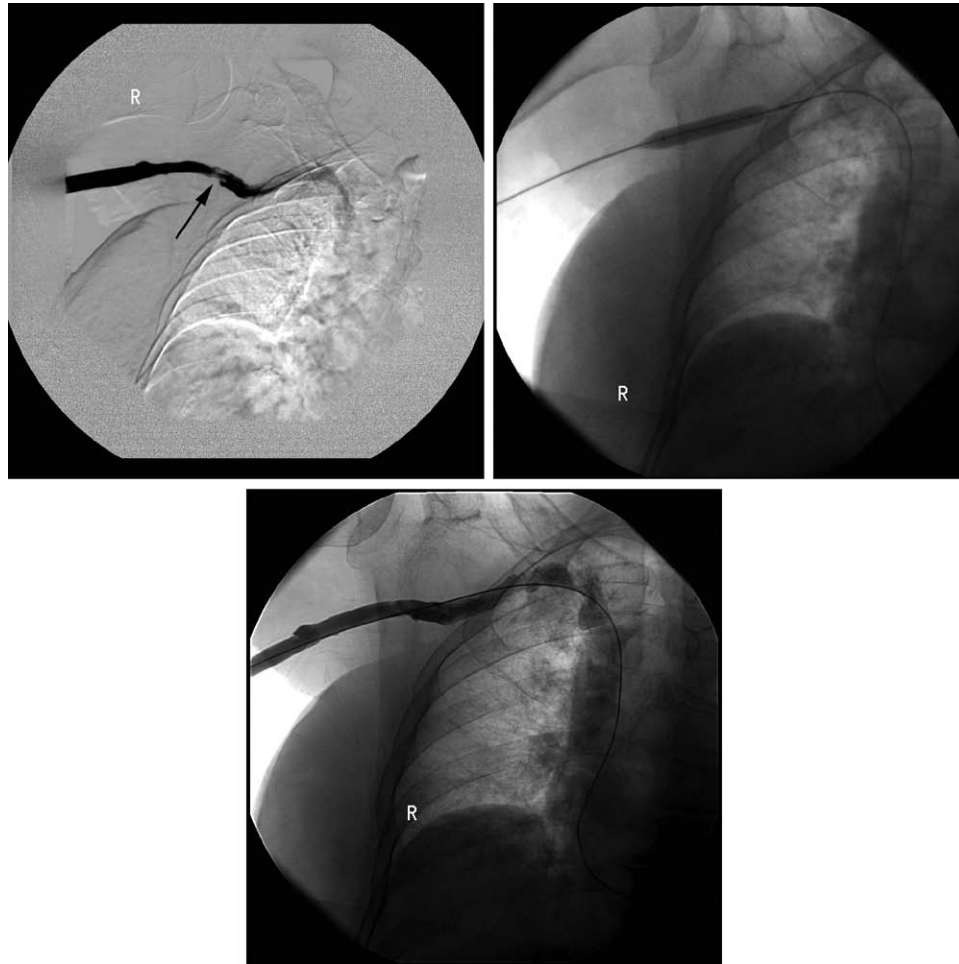


Fig. 4. (Above, left) Venogram demonstrating stenosis (black arrow) of the axillary vein and subclavian in a patient with lymphedema who has had axillary lymphnode surgery for breast cancer. (Above, right) Venogram, demonstrating angioplasty of stenosed axillary vein and subclavian vein. (Below) Postangioplasty venogram, demonstrating resolution of stenosis in axillary vein and subclavian vein.

New evidence is emerging that a relative, dynamic venous stenosis may contribute to lymphedema in postaxillary node dissection patients. Scar release and soft tissue augmentation of the scar bed may improve the edema in this subpopulation of patients.²⁴

PHYSIOLOGIC SURGICAL THERAPIES

Physiologic surgical procedures refer to those interventions that aim to augment clearance of excess lymphatic fluid through surgical means and include VLNT and LVA.

VLNT

Free tissue transfer of lymph nodes has been one of the most recent developments in the treatment of lymphedema. Orthotopically placed

lymph nodes may act as a sponge to absorb lymphatic fluid and direct it into the vascular network, and/or the transferred nodes may induce lymphangiogenesis.²⁵⁻²⁷ Although some researchers have experimented in animal models with grafting avascular whole nodes or lymph node fragments, their viability is highly variable.^{28,29} In general, it has been shown that preserving the vascular supply during transfer results in greater improvements of the edema and better lymphatic function.³⁰

The harvest of vascularized lymph nodes has been described using groin, thoracic, submental, and supraclavicular nodes, with the groin being the most popular. More recently, other options such as mesenteric lymph node transfer and the use of omentum have been reported.^{31,32} When harvesting the lymph nodes from the groin, it



Fig. 5. (Left) Right arm lymphedema 81% larger (based on volume calculations from circumferential measurements) than left arm secondary to treatment for breast cancer. (Right) Twelve-month follow-up. Reduction of 56% in excess volume after combined lymph node transfer and 4 lymphaticovenular anastomosis.

is advisable to harvest the laterally based nodes that drain the supraclavicular region supplied by the superficial circumflex iliac artery. This is important because the lymph nodes that drain the lower limb are located medially and centrally.^{33,34}

To minimize lymphatic impairment during nodal harvest, Althubaiti et al³⁵ advocate the use of supraclavicular nodes based off the transverse cervical artery and the transverse cervical vein. Similarly, Althubaiti et al³⁵ described the use of submental lymph nodes based off the submental branch of the facial artery, taking care to avoid injury to the marginal mandibular branch of the facial nerve. Finally, reverse lymphatic mapping techniques have been described and are now commonly used to avoid harvesting important sentinel nodes from the groin or the axilla to avoid secondary donor-site lymphedema. This mapping helps identify nodes that are draining the ipsilateral limb downstream from the node donor site. Subsequently, these nodes are avoided in the harvest theoretically, decreasing the chances of donor-site lymphedema.

Much like donor sites, the recipient sites also have variability. In treating upper extremity lymphedema, recipient sites have included the wrist, elbow, and axillary regions. As most upper extremity lymphedema results from previous surgery with or without radiation to the axilla, it is

important to perform wide excision of scar that may be enveloping nerves, muscles, and recipient vessels (e.g., thoracodorsal) both to ensure a healthy bed for lymphangiogenesis and to remove scar that would prevent bridging of lymphatics in the recipient bed. Becker et al³⁶ reported treating upper extremity lymphedema by transferring inguinal lymph nodes to the axillary region. The anterior recurrent ulnar artery and basilic vein or the radial artery and its venae comitantes have been used by Cheng et al³⁴ and Gharb et al³⁷ as recipient vessels at the elbow. Also, the radial artery at the level of the wrist has been used by Lin et al,³⁸ as recipient vessels for groin nodes based off the superficial circumflex iliac vessels.

For the lower extremity, the ankle and groin are the most common recipient sites. Similar to the axilla, the groin may often require extensive lysis or excision of scar from previous surgery and radiotherapy.²⁵ The superficial circumflex iliac vessels are identified superior to the inguinal ligament and used for anastomosis. The use of the ankle as a recipient site in the lower extremity follows along the logic that the gravitational forces keeping the lymphatic fluid from rising up to the groin are difficult to overcome.^{35,39} Instead, placement of the vascularized lymph nodes at the level of the ankle would take advantage of these forces to facilitate drainage into the flap at the level of

the ankle. The anterior tibialis or dorsalis pedis is used for recipient vessels, with careful attention to prevent excessive tension during flap inset, sometimes requiring skin grafting.

Aside from VLNT, women who are seeking simultaneous breast reconstruction and treatment of lymphedema may be excellent candidates for breast reconstruction using lower abdominal flaps harvested with attached inguinal lymph nodes. The thoracodorsal vessels are usually selected as recipient vessels allowing the positioning of the lymphatic tissue into the axillary space. Saaristo et al⁴⁰ reported 9 patients who received this treatment in which postoperative lymphoscintigraphy was improved in 5 of 6, limb circumference decreased in 7 of 9, and 3 of 9 patients no longer needed compression garments. Further studies need to be conducted, but this protocol offers an attractive option for delayed breast reconstruction patients with lymphedema.

Although the literature for vascularized lymph nodes is still in its early stages, results have been favorable with average excess volume reduction of 47% when compared with the unaffected limb.⁴¹ The indications for VLNT are still unclear, but some have advocated criteria based on total occlusion on lymphoscintigraphy, international society of lymphedema stage 2 with repeated episodes of cellulitis, no acute cellulitis, and more than 12 months of conservative therapy.³³ Although VLNT has been demonstrated to be generally safe, the complications include loss of flap, donor-site lymphedema, seroma, lymphocele, infection, and wound healing complications.

VLNT offers an exciting new horizon for the physiologic treatment of lymphedema. Furthermore, in many cases, combining both VLNT and LVA may optimize the chances for improvement of lymphedema as these 2 approaches work via different mechanisms (Fig. 5).

LVA

The concept of a lymphovenous shunt operation was first described by Jacobson and Suarez⁴² in 1962. Yamada⁴³ performed experiments using dogs and then applied this technique to the treatment of lower limb lymphedema in patients. O'Brien et al⁴⁴ used the same approach and reported their clinical experience in treating lymphedema in the 1970s.

In the last decades, improvement of microsurgical equipment allowed the development of supermicrosurgery techniques. These aim at the anastomosis of vessels at the capillary level with a diameter of 0.3 to 0.8 mm. The first report of

supermicrosurgery lymphovenous bypass is by Koshima et al.⁴⁵

LVAs are indicated when the patient still has functionality of the lymphatic system, which may be assessed and documented using ICG lymphography as defined as linear channels propelling dye from the distal extremity toward the trunk. Lymphoscintigraphy is also used by some in the evaluation of the lymphatic system; however, it lacks the resolution to demonstrate functioning subdermal lymphatics.

ICG lymphangiography and MRL allow us to locate the most functional lymphatic channels, which are then chosen for anastomoses. Such lymphatic channels are marked on the patient's skin just before surgery. [See Video, Supplemental Digital Content 1, which shows indocyanin green lymphangiography. The dye (ICG) is taken up by the lymphatics. It remains in the lymph channels (linear pattern). Dark veins can be seen traversing the lymphatics at the top of the picture, <http://links.lww.com/PRS/B810>.]

At the selected cutaneous sites and after injection of a small amount of local anesthetic with epinephrine to reduce bleeding, a 2- to 3-cm skin incision is made. Lymphatic channels are carefully dissected and subsequently anastomosed end-to-end or end-to-side to subdermal venules of similar caliber (usually between 0.3 and 0.8 mm in diameter), using 11-0 or 12-0 sutures. After performing the anastomosis, 0.1 to 0.2 mL of Patent V Blue dye is injected intradermally about 2 cm distal to the incision. The dye is absorbed generally into the functional lymphatic channels, and transport of lymph fluid can then be seen traversing



Video. Supplemental Digital Content 1 which shows indocyanin green lymphangiography. The dye (ICG) is taken up by the lymphatics. It remains in the lymph channels (linear pattern). Dark veins can be seen traversing the lymphatics at the top of the picture, <http://links.lww.com/PRS/B810>.

the anastomosis, thus verifying the patency of the anastomosis (Fig. 6). The objective of this procedure is to redirect the lymph to the venous stream directly, bypassing areas of obstruction, and without going through the thoracic duct. LVA can be performed under local anesthesia, but in most centers, it is performed using general anesthesia to ensure patient comfort and avoid any undesirable motion during this lengthy surgical procedure.

Preoperative assessment allows identification of potential candidates for reconstructive or reductive surgical techniques. It is crucial to individualize the treatment for every patient independent of the clinical stage or the duration. Many surgeons have adopted the Barcelona Lymphedema Algorithm for Surgical Treatment of Lymphedema or a modification thereof, which represents a

thoughtful and simple approach to the surgical management of lymphedema. The algorithm is as follows: patients are evaluated to determine if excess fluid is present by physical examination. Findings of pitting edema suggest that there is a significant component of fluid excess that would be amenable to a functional lymphatic surgery.

If there is no evidence of active lymphatic channels [ICG assessment is negative and lymphatic magnetic resonance imaging (MRL) is negative] with pitting lymphedema, intensive rehabilitation therapy is performed to reassess the possibility of a reductive surgical technique. LVA is not an option in this patient population, but VLNT may be considered.

If there is no evidence of active lymphatic channels [ICG assessment is negative and lymphatic magnetic resonance imaging (MRL) is negative] and the lymphedema is of an advanced stage with no pitting, a reductive technique, such as liposuction, according to the H. Brorson technique is performed.

If there is evidence of a functioning lymphatic system (ICG assessment is positive and/or MRL is positive) and pitting is present, a physiologic reconstructive technique is chosen. For example, if the axilla shows little sign of scarring, LVA is performed in the affected limb. However, if the axilla on physical examination has abundant fibrotic changes or signs of radiodermatitis, an autologous lymph node transfer (ALNT) into the axilla, after scar tissue release is performed, complemented by LVA in the affected limb distally. Many surgeons will prefer to place the ALNT into the affected limb distally, particularly if most of the lymphedematous changes are affecting primarily this region and limited scarring is evident in the axilla. Performing LVA first is another option. This represents a minimally invasive procedure with a short recovery and minimal postoperative restrictions. Selected patients (particularly with early stage) will experience significant symptom relief from LVA alone, sparing the additional morbidity of the lymph node transfer.⁴⁶ If the symptom relief is insufficient, an VLNT can be performed 3 to 6 months later.

If the patient has amastia and requests breast reconstruction, ALNT with nodes included in the abdominal perforator flap (deep inferior epigastric artery perforator or superficial inferior epigastric artery perforator flaps) may be the best option and can be combined with LVA distally on the affected limb. Masià et al⁴⁷ has found additional improvement in patient outcomes when transitioning from LVA surgery alone to the above outlined combined approach. In fact, the average excess limb

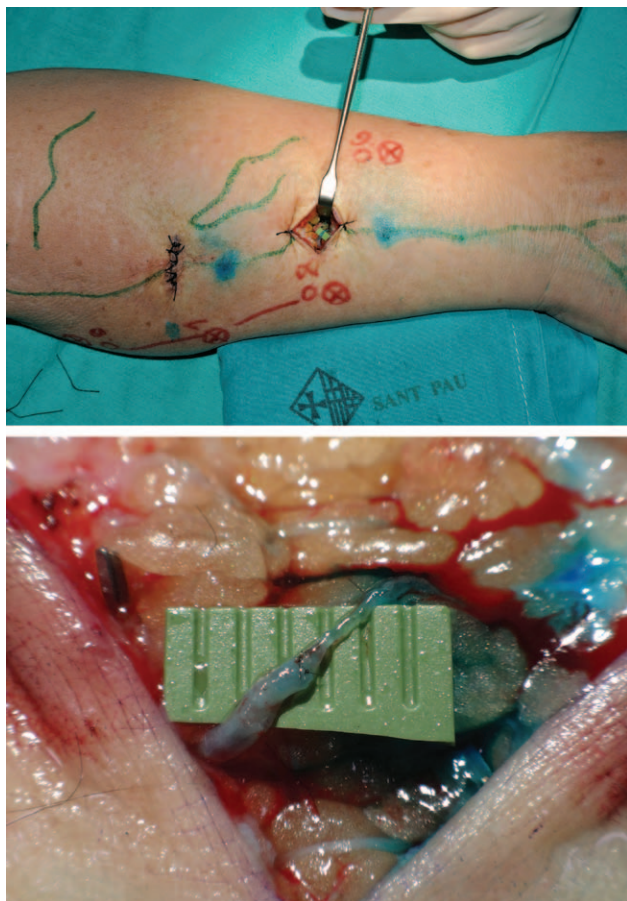


Fig. 6. (Above) Intraoperative view of the terminoterminal anastomosis between the distal stump of the lymphatic and the proximal stump of the venule. The green marks show the information given by the ICG lymphangiography, which show the location of the lymphatic channels. (Below) Patent V Blue dye is injected 2 cm distal to the incision to assess the patency of the anastomosis.

circumference reduction went from 40.72% with LVA alone to 69.2% when combining ALNT and LVA.

ABLATIVE SURGICAL THERAPIES

Ablative surgical procedures refer to those interventions that remove excess tissue between the deep fascial layer and the dermis and may include the dermis itself. Complete excision of the tissues above the deep fascia performed in a serial fashion with preservation of the overlying dermis or with sacrifice of the dermis and skin grafting is now generally reserved for the most severe cases. Liposuction as championed by Hakan Brorson has become the method of choice in patients in whom lymphatic fluid is controlled with compression garments and massage, but excess fat accounts for a significant volume difference compared with the unaffected limb. Long-term favorable results have been reported with this technique in appropriately selected patients.^{48,49}

CONCLUSIONS

The management of lymphedema is both complex and rapidly changing. As we learn more about the pathophysiology and progression of lymphedema, clinicians will be better able to provide treatment options for their patients. Going forward, treatment of lymphedema will likely involve a multimodality approach combining medical, noninvasive, and surgical therapies. Still, there is no current gold standard of care in these treatments, and we look forward to research aimed at providing insight to these questions.

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