



Overview of Lymphedema for Physicians and Other Clinicians: A Review of Fundamental Concepts

Oscar J. Manrique, MD, FACS; Samyd S. Bustos, MD; Pedro Ciudad, MD, PhD;
Kian Adabi, MD; Wei F. Chen, MD; Antonio J. Forte, MD, PhD, MS;
Andrea L. Cheville, MD; James W. Jakub, MD; Sarah A. McLaughlin, MD;
and Hung-Chi Chen, MD, PhD

Abstract

Lymphedema has historically been underrated in clinical practice, education, and scholarship to the detriment of many patients with this chronic, debilitating condition. The mechanical insufficiency of the lymphatic system causes the abnormal accumulation of protein-rich fluid in the interstitium, which triggers a cascade of adverse consequences such as fat deposition and fibrosis. As the condition progresses, patients present with extremity heaviness, itchiness, skin infections, and, in later stages, dermal fibrosis, skin papillomas, acanthosis, and other trophic skin changes. Correspondingly, lymphedema results in psychological morbidity, including anxiety, depression, social avoidance, and a decreased quality of life, encompassing emotional, functional, physical, and social domains. For this review, we conducted a literature search using PubMed and EMBASE and herein summarize the evidence related to the fundamental concepts of lymphedema. This article aims to raise awareness of this serious condition and outline and review the fundamental concepts of lymphedema.

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From the Division of Plastic and Reconstructive Surgery (O.J.M., S.S.B., K.A.), Department of Physical Medicine and Rehabilitation (A.L.C.), and Department of Surgery (J.W.J.), Mayo Clinic, Rochester, MN; Department of Plastic, Reconstructive and Burn Surgery, Arzobispo Loayza National Hospital, Lima, Peru (P.C.); Division of Plastic and Reconstructive Surgery, University of Iowa, Iowa City (W.F.C.); Division of Plastic Surgery (A.J.F.) and Department of Surgery (S.A.M.), Mayo Clinic, Jacksonville, FL; and Department of Plastic and Reconstructive Surgery, China Medical University Hospital, Taichung, Taiwan (H.-C.C.).

Lymphedema has historically been orphaned in clinical practice, education, and scholarship to the detriment of many patients worldwide. Past neglect still permeates today in spite of progress that has been made, and lymphedema can be effectively addressed to avoid morbid functional consequences. The advent of novel surgical management options, as well as tools allowing earlier diagnosis, has improved the lives of patients with this condition. However, lymphedema remains a chronic, incurable disease. Its damaging effects represent a staggering toll to all health-related quality of life domains, especially vocation capacity, physical function, and symptom burden.¹ Additionally, lymphedema is associated with significantly increased health care utilization.² Lacking formal training in lymphedema evaluation and management, many clinicians struggle with common difficulties and misunderstandings when evaluating edematous

patients—eg, distinguishing etiologic contributors, selecting diagnostic evaluations, and prioritizing management options. This article aims to offer guidance in these tasks and to outline the fundamental concepts of this condition. We conducted a systematic literature review using PubMed and EMBASE databases, limited to articles published in English between January 1, 1946, and December 30, 2018. The following key words and their combination were searched: *lymphedema*, *physiology*, *pathophysiology*, *diagnosis*, *treatment*, *surgery*, *therapy*, *clinical trial*, *practice guideline*, *review*, *comparative study*, *intervention study*, and *longitudinal study*.

CLASSIFICATION

Lymphedema is classified as primary or secondary. Primary lymphedema occurs in individuals with innate dysfunction, commonly agenesis or hypogenesis of their lymphatics. The role of genetics in lymphatic anomalies

is complex. Germline sequence variations associated with lymphedema have been identified in at least 23 human genes.³ Primary or hereditary lymphedema is characteristically subdivided into categories based on age at onset of symptoms.³ Nonne-Milroy disease—congenital hereditary lymphedema—is diagnosed in patients presenting at birth or within the first 2 years of life, has an autosomal-dominant inheritance, and can cause bilateral lower extremity lymphedema and intestinal lymphangiectasia and cholestasis.⁴ It is associated with an inactivation mutation of the vascular endothelial growth factor receptor 3 tyrosine kinase signaling pathway found in lymphatic vessels.^{5,6} Meige disease—familial lymphedema praecox—presents during puberty. Other clinical manifestations are cerebrovascular malformations, vertebral defects, hearing problems, and distichiasis.⁷ It is associated with sequence variations in the human forkhead box C2 (*FOXC2*) gene, a transcription factor in adipocyte metabolism, and has an autosomal-dominant inheritance.⁸ A late-onset type, lymphedema tarda, usually presents after age 35.⁹

Secondary lymphedema is more prevalent and develops when intact lymphatics become obstructed or sustain iatrogenic, infectious, inflammatory, surgical, or traumatic damage. Filarial infection in countries with developing economies remains the most prevalent cause of secondary lymphedema. In countries with developed economies, lymphatic resection and irradiation for staging or locoregional cancer control is the most common cause.¹⁰ However, the obesity pandemic has produced a rapidly expanding subgroup of patients with lymphedema in the setting of obesity who lack other sources of lymphatic compromise.^{11,12}

EPIDEMIOLOGICAL PROFILE

Three trends are dynamically reshaping lymphedema epidemiology. The first is the mass drug delivery program coordinated by the World Health Organization, which is attempting to eradicate filariasis and has already succeeded in some countries like Cambodia.¹³ The program has prevented a

ARTICLE HIGHLIGHTS

- Lymphedema is a chronic, progressive, and debilitating condition characterized by the accumulation of protein-rich fluid in the interstitium due to mechanical insufficiency of the lymphatic system, which generates a self-perpetuating cycle of inflammation, fat deposition, and fibrosis.
- Lymphedema is classified into primary and secondary forms: primary lymphedema is caused by innate abnormalities in the lymphatic system that may not always be clinically evident until later in life, and secondary lymphedema occurs when intact lymphatics become obstructed or sustain iatrogenic, traumatic, inflammatory, surgical, or infectious injury.
- Adequate work-up and objective tests to address diagnostic uncertainty regarding the etiologic contributors to edema are geared to identifying remediable systemic sources and obstruction of the lymphatic and venous drainage pathways.
- A multidisciplinary approach for the management of lymphedema is essential to restore function, reduce physical and psychological burden, and prevent the development of infection.
- Although there is currently no definite cure for lymphedema, the use of combined physiologic and excisional surgical approaches is permeating the surgical practice in order to address both the fluid and solid components of this condition.

minimum of 5.5 million cases between 2000 and 2012.¹³

Second, a radical shift has occurred over recent decades in the adoption of lymph node-sparing cancer operations. For example, sentinel lymph node biopsy (SLNB) procedures are now standard of care in the management of breast cancer and melanoma.^{14,15} Surgical treatment of gynecologic cancers follows this pattern, with increasing uptake of SLNB procedures in the primary treatment of endometrial and cervical cancer as reports attest their effectiveness and safety.¹⁶ High-level, randomized controlled trials support de-escalation of regional intervention maintaining equivalent regional control and survival.¹⁷ Further, clinical practice is shifting for many patients with lymph node-positive disease to avoiding both a full lymph node dissection and regional radiation therapy because this

combination is likely overtreatment in many patients and synergistic in their contributing to lymphedema risk when used in the same nodal basin.¹⁸

Third, the obesity pandemic has produced an expanding subgroup of patients with lymphedema in the setting of obesity who lack other sources of lymphatic compromise, leading to an increase in rates of generalized lower extremity and truncal lymphedema among individuals with a high comorbidity burden and often limited capacity to adhere to lymphedema treatments.¹²

Lymphedema affects between 90 and 250 million people worldwide.^{19,20} Globally, secondary lymphedema remains far more prevalent than primary lymphedema. Despite mass drug delivery programs, there are roughly 67.88 million cases of lymphatic filariasis, including 36.45 million microfilaria carriers, 19.43 million hydrocele cases, and 16.68 million cases of filarial lymphedema.²¹ A systematic review reported lymphedema incidences at 18%, 6%, and 22% following treatment for melanoma, lymph node–negative breast cancer, and lymph node–positive breast cancer, respectively.²² Estimated prevalence of primary lymphedema is 1.15 per 100,000 persons under the age of 20.⁴ Congenital lymphedemas comprise only 6.5% of all cases of primary lymphedema.²³

PEOPLE AT RISK AND RECOMMENDATIONS

People at risk for lymphedema are defined by the National Lymphedema Network 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.²⁴ This group includes, but is not limited to, anyone who has had lymph nodes removed or radiation therapy during treatment for cancer.^{25,26} In addition, individuals who have family members with hereditary lymphedema may also be at risk.²⁴

The National Lymphedema Network recommends 14 actions and precautions to screen for lymphedema in individuals at risk.²⁵ Regular follow-up visits should include limb measurements, assessment of posttreatment physical impairment, functional status, and subjective self-report of

symptoms.²⁵ Body weight should be maintained within normal standards, and any increase should prompt the patient to seek professional help to lose weight. Aerobic and weight (anaerobic) exercise tailored to the patient's individual needs with or without compression garments are recommended for individuals at risk for lymphedema; they should be started gradually, increased vigilantly, and stopped for pain, discomfort, or increased swelling.²⁴

Regarding patients with breast cancer, several actions may not significantly reduce their risk for breast cancer–related lymphedema (BCRL).^{27–29} Blood pressure readings, intravenous blood draws, intravenous access, and air travel were found not to significantly increase BCRL risk.²⁹ Association between BCRL and arm trauma, medical procedures, and arm use is still controversial.³⁰ Historical myths remain prevalent, such as advising arm restriction and limited activity, which probably lead to greater problems such as adhesive capsulitis of the shoulder.³¹ Current practice is to recommend activity and return to healthy active lifestyle, not inactivity and avoidance of usage.³²

LYMPHATIC ANATOMY AND PHYSIOLOGY

Lymphatic anatomy is matched to the requirements of its principal functions. The first of these, the sequestration of solid macromolecular interstitial debris, is directly related to the second, immune surveillance. The most distal elements of the lymphatic system scarcely distinguish between microbes and molecules, both being transported to lymph nodes for processing. [Figure 1](#) illustrates the relationship between lymph and blood capillaries. Lymph capillaries are larger than blood capillaries, with size differential estimates as high as 100%. Lymphatic endothelial cells are not contiguously adherent ([Figure 1](#)), and their edges separate, producing large openings allowing macromolecule ingress. Additionally, microfilaments effectively tether lymph capillary endothelial cells to the supportive architectural elements of the interstitium. When tissue turgor increases (due to edema), microfilaments become tense and pull

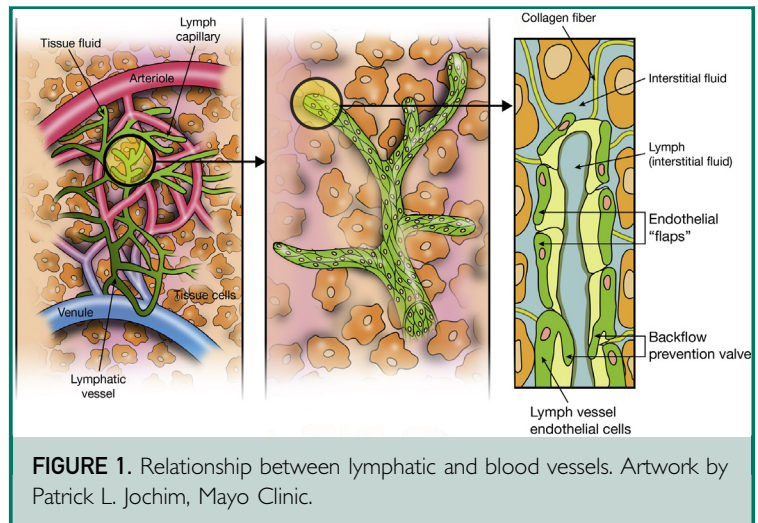
endothelial cells apart, thereby widening intercellular openings to encourage the entry of solid debris.³³

Unlike veins, the walls of the collecting vessels, which transport lymph proximally, are invested with smooth muscle permitting propulsion of lymph in peristaltic fashion. In addition to their intrinsic contractility, lymph collectors are highly responsive to mechanical stimuli in their immediate environment generated by arterial pulsations, muscle contractions, and skin distention.³⁴ Sympathetic stimuli activate myocytes in lymph collecting vessels, enabling the system to dramatically increase lymph flow in conditions of increased lymph production as occurs with exercise.³⁴

Lymph collectors terminate in lymph nodes, where debris filtration, identification of potentially harmful pathogens, and lymph viscosity regulation occur.³⁵ After transiting serial superficial nodes clustered throughout the body as 1 of the 6 lymph node beds (paired supraclavicular/cervical, axillary, and inguinal beds), the lymph is subsequently filtered through deep nodes to ultimately return to the venous systemic circulation at the right or left venous angle.

Nodes in the 6 superficial beds receive lymph generated by somatic tissues outside the visceral compartments. The territory drained by each superficial bed is referred to as its *lymphotome*,^{36,37} which is an area bounded by margins that demarcate where the direction of lymph flow changes as determined by valve orientation in the collecting vessels (Figure 2). Lymphotomes define the distribution where lymphedema may occur in the event of compromise of specific superficial nodes.

Because the inguinal lymph node beds drain to the iliac, pelvic, and periaortic nodes via a deep network of collecting vessels, perturbation of these elements, irrespective of side, has the potential to produce lymphedema in the lymphotomes of both superficial inguinal beds. Thus, following surgical treatment for gynecologic, prostate, or colon cancers that includes resection of deep nodes, secondary lymphedema may develop in the bilateral lower trunk, legs, and/or genitalia.



LYMPHATIC PATHOPHYSIOLOGY

When the lymphatic load exceeds the transport capacity of the lymphatic system, dynamic insufficiency of the lymphatic system occurs. In this scenario, the lymph vessels are intact but overloaded. This situation results in tissue fluid accumulation that is successfully treated with limb elevation or compression. Conversely, mechanical or low-volume insufficiency of the lymphatic system results in lymphedema. In this case, the transport capacity of the lymphatic

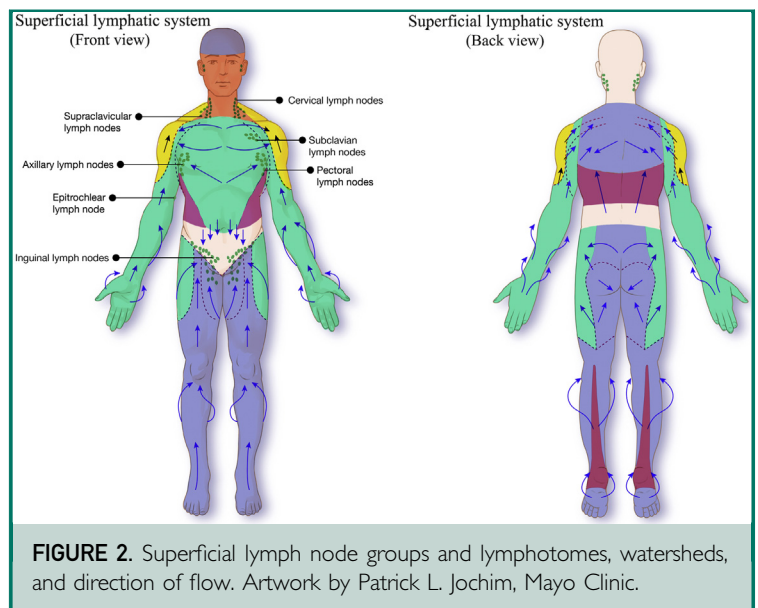


TABLE. Clinical Stages of Lymphedema

Clinical stage	Symptoms	Protein-rich fluid accumulation	Pitting edema	Nonpitting edema	Scar tissue formation	Hardening of dermal tissues	Skin papillomas
0 or Ia	Yes	No	No	No	No	No	No
I—Reversible lymphedema	Yes	Yes	Yes	No	No	No	No
Ila—Spontaneously irreversible initial lymphedema	Yes	Yes	Yes	No	Yes	No	No
Ilb—Spontaneously irreversible increasing lymphedema	Yes	Yes	No	Yes	Yes	No	No
III—Lymphostatic elephantiasis	Yes	Yes	No	Yes	Yes	Yes	Yes

system decreases below the physiologic level of the lymphatic loads of fluid. Mechanical insufficiency may be caused by hypogenesis or agenesis of lymphatic vessels, impaired lymph pump activity, increase in lymphatic permeability favoring protein influx from lumen to interstitial fluid, inflammatory response, lymphatic obstruction, or surgical removal of lymph nodes.³⁸ Edema formation does not occur until lymph flow is reduced by 50%, all other factor being equal.³⁸

In the absence of treatment, lymphedema progresses over time and more rapidly in lower extremities. Recently, a primary asymptomatic lymphatic insufficiency state was identified on indocyanine green (ICG) lymphography that may explain an increased likelihood of lymphedema after oncological treatment in patients with this condition compared with their healthy counterparts.³⁹ Lymphedematous progression is divided into 4 sequential stages⁴⁰ (Table). Stage 0 or Ia refers to symptoms, eg, heaviness, aching after activity, in the absence of objective swelling. Stage 0, also named *nonvisible* or *latent*, is a relatively recent addition and is based on several reports describing prodromal symptoms among breast cancer survivors prior to the onset of objective swelling and chronic lymphedema.⁴¹ Stage I, “spontaneously reversible” lymphedema, refers to measurable swelling that is comprised solely of protein-rich fluid. The affected body part can be restored to normal volume and

contour through elevation or compression. In contrast, Stage II, “spontaneously irreversible” lymphedema, is characterized by fibrosis in the interstitial space that will not resolve in the absence of fibrolytic, decongestive treatment. It is subdivided in stage IIa, initial lymphedema characterized by vanishing lymph transport capacity and pitting edema, and stage IIb, increasing lymphedema presenting with lymphostatic skin changes, worsening disability, and no visible pitting due to the progression of fibrosis and fat hypertrophy. The sole distinction between stage II and stage III, lymphostatic elephantiasis lymphedema, is the presence of dermal metaplasia. Papillomas, keratin deposition, and verrucous hyperplasia are common stigmata of stage III lymphedema. Figures 3 and 4 provide clinical images of patients with various clinical stages.

Chronic inflammation is presumed to initiate lymphedema progression. Macromolecular debris stimulates neutrophil and macrophage migration, which triggers fibroblast recruitment.^{42,43} Activated fibroblasts elaborate collagen, which becomes an extensive disorganized matrix of scar tissue that further entraps the lymphatics, impeding their physiologic activities.^{42,43} These pathophysiologic events establish a self-perpetuating cycle of inflammation, fat deposition, and fibrosis.^{42,43}

Accurate ascertainment of lymphedema stage relies predominantly on visual and tactile pattern recognition supplemented by



FIGURE 3. Patients with diverse clinical stages of upper extremity lymphedema A, Stage I. B, Stage IIa. C, Stage IIb. D, Stage III.



clinical examination. Distinctions between stages I and II are generally based on palpation, with a diagnosis of stage I being made if easy pitting is noted and no foci of rubbery, tense tissue. Subdermal fibrosis often occurs in specific anatomic locations that may prove high yield for initial palpation. The pericubital area and medial volar forearm tend to be preferentially affected in the upper extremity, as are the perimalleolar area and dorsum of the foot in the lower extremity. Thickening over the dorsal toes and interphalangeal joints is virtually pathognomonic for lymphedema because venous stasis tends to

spare the feet and is not associated with hypertrophic skin changes. Exaggerated skin folds are frequently appreciated at the base of the digits. The Stemmer sign—the inability to pinch a discrete skin fold overlying the dorsum of the second digit—has never been subjected to rigorous scrutiny as a diagnostic test. However, this inability may be a useful qualitative gauge of the extent to which scarring and dermal adherence to the underlying tissue has developed. Its presence indicates definitive progression to stage II, if not stage III, lymphedema. Stage III lymphedema is distinguished solely by the presence of skin changes: keratinization and papillomas.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of chronic swelling in the absence of lymphatic compromise includes lipedema, lymphedema syndromes (Klippel-Trenaunay, Noonan, and Turner syndromes), anasarca, organ failure, and venous insufficiency. Venous insufficiency is the most prevalent and challenging to distinguish because it can occur locally in the absence of other signs or symptoms and often co-occurs with lymphatic compromise. Dorsal foot involvement, soft tissue thickening, Stemmer sign, and characteristic skin changes suggest lymphatic compromise. In contrast, the presence of lipodermatosclerosis—an inverted champagne bottle contour—and hemosiderin staining of the skin implicate venous stasis. Identifying the principal contributor may inform prognosis, treatment components, risk of specific complications, and monitoring plan.

Work-up to address diagnostic uncertainty regarding the etiologic contributors to edema and their relative importance is geared to identifying remediable systemic sources and obstruction of the lymphatic and venous drainage pathways. Concern for organ failure can be addressed with serologic and function studies. Echocardiography may be useful to rule out cardiac failure. Systemic inflammation and endocrinopathies are also sufficiently common to warrant investigation in patients with regional swelling. Medications may be potent contributors to swelling, and newly

initiated drugs or recent dose escalations should be considered. Although not diagnostic, plethysmography—assessing transcutaneous oxygen pressures—may be an important guide to individualizing compression therapy.

EVALUATION AND DIAGNOSTIC TESTING

The onset of lymphedema is typically insidious.⁴⁴ Most patients who had lymph node dissection and/or radiation start experiencing limb swelling, tightness, heaviness, or aching pain within 6 months to 3 years of their procedure/treatment.⁴⁵ However, sudden onset of mild to moderate lymphedema without any warning or premonitory signs or symptoms has been reported.^{43,46}

It is fundamental to have baseline measurements of the ipsilateral and contralateral limbs, which is critical to establish the relationship between the two, and control for weight gain or loss. Similarly, follow-up strategies should be developed in order to screen for lymphedema. The ideal diagnostic test is a noninvasive, cost-effective, reliable examination with minimal interrater/intrarater variability.

Noninvasive Measurements

Limb volume (LV) or circumference measurements are used to clinically evaluate lymphedema. The most common way to clinically assess the function and structure of the lymphatic system is by simply using a tape measure.⁴⁷ In order to have a comparator, the measurements should be performed on both limbs by the same experienced individual on the basis of clearly distinct anatomic landmarks and at defined intervals. This process has been determined to be a reliable method for detecting and monitoring lymphedema.^{48,49}

Conversely, the clinician can measure LV with water displacement, perometry, or multifrequency bioimpedance measurements. These automated LV scanning methods eliminate interobserver variability but are more costly.⁴⁷ The criterion standard for volume assessment is water displacement; however, it does not delimit the affected area. Moreover, if the patient has

an infection or an open wound, it is technically unfeasible to perform it. Perometry uses an infrared optical electronic scanner to calculate LV and can detect smaller changes, but its cost prevents widespread use. Tissue tonometry evaluates tissue resistance against an applied compressive force. It gives an approximate idea of skin elasticity and subcutaneous tissue fibrosis.^{48,50} Bioimpedance spectroscopy assesses extracellular fluid by analyzing changes in water electrical conductance. It can also estimate increases in adipose tissue.⁵¹ It is more useful for detecting early-stage lymphedema, even before macroscopic changes are apparent or settled, but its utility decreases as more fibrotic edema develops, such as in later stages of lymphedema.^{52,53} Comparative evaluation of these LV measurement methods determined that use of a tape measure is effective, but the sensitivity of this technique leads to some uncertainty.⁵⁴

Imaging Measurements

Imaging techniques in lymphedema are paramount to diagnosis, treatment planning, and determination of posttreatment progression.⁵⁵ Lymphoscintigraphy involves intradermal injection of radiolabeled colloid and subsequent imaging of the lymphatic system. This technique allows for visualization of both lymphatic function and anatomy. Absent or delayed radiotracer transport, cutaneous flare, dermal backflow, and poorly visualized lymph nodes are some of the features seen in patients with lymphedema.⁵⁶ Moreover, quantitative analysis can reveal increased clearance time from the injection site and level of detectable radioactive residual. Even mild delays in tracer transport can be appreciated, making it particularly useful for functional outcome evaluation postoperatively.⁴⁷ The application of magnetic resonance angiography and magnetic resonance lymphangiography (MRL) to the diagnosis of lymphedema allowed for a higher level of resolution with fewer artifacts and no ionizing radiation.⁵⁷ Various contrast agents have been used, but paramagnetic gadobenate dimeglumine is the most common.⁵⁸ The technique has been found to be fast

and reliable with minimal complications. In addition, MRL generates 3-dimensional images comparing different types of tissues and compartments in the affected limb.^{57,59} Magnetic resonance lymphangiography is superior in visualizing the lymphatic system for both lymphatic and lymph node malformations because of its high resolution.

Another valuable modality is computed tomography, which also allows for simultaneous diagnosis of deep venous thrombosis, hematomas, cellulitis, and cysts. However, patients are exposed to radiation, and a relatively lower level of diagnostic and prognostic precision makes it not an ideal first-line option.⁶⁰ Duplex ultrasound elastography offers a simple, readily available noninvasive test to diagnose lymphedema based on tissue characteristics and velocity under sound waves.^{61,62}

The role of ICG and fluorescence imaging has rapidly increased in lymphedema diagnosis.⁶³ This technique involves the activation of molecules in tissue to generate high-resolution images. The short half-life of the ICG not only makes it safe for patients but also allows for repetitive application preoperatively, intraoperatively, and postoperatively.^{64,65} Similar to lymphoscintigraphy, both functional and anatomic analysis can be done. Compared with MRL, ICG imaging is superior in functional testing and easy performance; however, its resolution is relatively lower.

Ongoing research in the field continues to introduce new imaging modalities that are safe, reliable, and cost-effective. One newly emerging technology is 3-dimensional analysis with photogrammetry or surface scanners.⁶⁶ Devices such as VECTRA® 3D (Canfield Scientific, Inc), which use the principle of photogrammetry, have been reported to give volume measurements that correlate well with water displacement and limb circumference.⁶⁷

CONSERVATIVE MANAGEMENT

The current international standard for initial lymphedema treatment remains manual and is referred to as *complex* or *complete decongestive therapy*.^{68,69} Complex

decongestive therapy includes an intensive, reductive phase 1 and maintenance phase 2. Phase 1 includes manual lymphatic drainage, a massage technique developed to stimulate contractions of the smooth muscle in lymph collecting vessels; short stretch compression bandaging; repetitive limb movements to create internal pumping action; skin care; and instruction in self-management. Recommended treatment frequency is twice daily during phase 1 therapy, a labor-intensive schedule often challenged by resource and reimbursement limitations.⁷⁰ With twice daily treatments, most patients achieve maximal reductions of 50% to 70% over 10 to 14 days, at which point they are transitioned to phase 2 maintenance therapy.⁷¹

Compression garments worn during waking hours are the mainstay of phase 2 lymphedema maintenance therapy. Garments range widely in compression, extent of coverage, knit, and cost. Most patients with stage I lymphedema are adequately managed with less costly off-the-shelf garments available in diverse compression classes up to 3 (40 to 50 mm Hg). Patients with stage II and higher lymphedema, particularly of the lower extremities, generally derive greater benefit from custom garments. Custom garments may be sewn of circular knit fabric or custom loomed to generate flat knit garments. Both can be fabricated in any shape or size and made with sections of different compression classes. Custom garments are generally required for truncal, facial, or genital lymphedema. Dynamic partnerships with experienced lymphedema therapists able to match the complex array of available garments with the needs and preferences of patients are vital to tolerable and effective maintenance compression.

PRINCIPLES OF SURGICAL MANAGEMENT OF LYMPHEDEMA

Advances in our understanding of the lymphatic system as well as new technology and improved skill sets have resulted in an increasing number of surgical options for patients with lymphedema. Surgical

intervention is offered to patients in whom conservative treatment has failed. Nonoperative management remains the first-line approach and criterion standard, although it is labor intensive, requiring strict lifelong compliance and commitment.⁷² The goals are to improve function and cosmesis, reduce infection episodes, and prevent disease progression.⁷³ Patients in the earlier stages (I and II) are offered surgical treatment if they have been symptomatic for more than 12 months and have undergone at least 6 months of complex decongestive therapy without improvement. In the more severe stages (stage III), patients can be offered surgical treatment without failure of conservative treatment if they have been symptomatic for more than 12 months.¹⁹

The surgical management of lymphedema can be broadly divided into 2 categories: physiologic and excisional. Physiologic procedures utilize microsurgical techniques to restore lymphatic flow by either bypassing the lymph to the venous system from the diseased lymphatics or transferring lymph nodes from unaffected regions.^{74,75} Alternatively, reductive procedures remove the lymphedematous fibrotic tissue.^{74,76,77} Currently, there are no established guidelines for the type of procedure, patient selection, and timing of intervention. Generally, physiologic approaches are thought to lead to better outcomes in earlier stages because there is some remnant lymphatic flow and less fibrotic tissue; reductive approaches are thought to be best at addressing very advanced stages in which volume reduction could only be achieved by excision of the tissue.⁷⁴

PHYSIOLOGIC PROCEDURES

Lymphatic Bypass

Several direct methods to reestablish lymphatic function using a microsurgical technique have been described: direct lymphatic-venous anastomosis, lymphatic-lymphatic bypass, lymphatic-venous-lymphatic bypass, and lympholymphatic segmental reconstruction.⁷⁸⁻⁸⁷ Diseased lymphatics can be bypassed to either normal lymphatics or to local or distant veins.

Lymphatic-lymphatic bypass involves harvesting healthy lymphatic vessels as a composite graft; they are completely removed from the body and implanted into the affected region. The harvested lymphatic is buried in the subcutaneous tissue and microscopically anastomosed to recipient lymphatics. Typically, healthy vessels in the supraclavicular region are used for upper extremity lymphedema, and the contralateral groin region is used for lower extremity lymphedema.¹⁹ One study using this technique in 55 patients with lymphedema reported an 80% reduction in LV and 30% improvement in lymphatic flow as assessed by lymphoscintigraphy.⁸⁰ Drawbacks to the procedure include a long incision at the donor and receipt sites and increased risk of subsequent donor site lymphedema. The recipient region needs to have relatively viable lymphatics without elevated back pressure and recurrent infection.^{78,79}

Another surgical approach has been to bypass the lymphatic vessels and drain directly into the venous system. This is called *lymphovenous bypass* (LVB) or *lymphaticovenular anastomosis* (LVA), depending on the caliber of veins used. Attention must be given to form the anastomosis to minimize the effects of venous hypertension and reflux into the lymphatic system. In this regard, LVA has the advantage of lower intraluminal pressure within the conduit.⁸⁸ With both techniques, the vessels used can be less than 0.8 mm in diameter and require 11-0 sutures to perform the anastomosis, representing some of the greatest advances in supramicrosurgical techniques today.⁸⁹⁻⁹¹ Described anastomosis techniques include end-to-end, end-to-side, side-to-end, side-to-side, “lambda” technique, and “octopus” technique.⁹¹⁻⁹⁴ Results from these procedures vary based on patient population and surgeon-specific techniques, but recent systematic reviews report approximately one-third reduction in volume size and symptom relief in more than 50% of patients.⁹⁵ A long-term follow-up study with LVB found that 74% of patients were able to discontinue conservative treatment, and cellulitis episodes decreased by 58%.⁹⁶ A recent study reported that postoperative compression

following LVA can augment lymphatic flow, converting unfavorable retrograde flow to favorable anterograde flow without harming the anastomosis.⁹⁷

Vascularized Lymph Node Transfer

The transfer of lymph nodes from unaffected regions as vascularized free tissue transfer and placing them in the affected limb via microsurgical techniques is termed *vascularized lymph node transfer* (VLNT). This approach reconstitutes lymphatic flow in areas of previous lymph node dissection or allows for neolymphatic regeneration in nonanatomic areas such as the wrist or the ankle distally or the groin or axilla proximally.^{74,98-100} Evidence for their function in rat models was revealed with indocyanine drainage into the pedicle vein of injected lymph node flaps.¹⁰¹ Although the exact mechanism of VLNT function continues to be an active area in lymphedema research, the procedure has been gaining popularity, with increasing centers documenting favorable outcomes.^{73,74,99,100,102-104}

Various locations for the harvest of lymph nodes are readily used by microsurgeons. These sites include, but are not limited to, the groin, breast, and submental, supraclavicular, appendicular and ileocolic, and omental regions.^{103,104} Careful selection of the lymph node recipient site is important to minimize morbidity and risk of subsequent donor site lymphedema.¹⁰⁵ In this regard, the omental lymph nodes and their supplying branches from the gastroepiploic arteries and veins are gaining popularity.¹⁰⁶⁻¹⁰⁸ A 2017 study using the omental flap reported a limb circumference reduction rate of $43.7\% \pm 2.5\%$ over a 9.7-month follow-up period with no episodes of infection postoperatively.¹⁰⁶

Vascularized Lymph Vessel Transfer

Despite the high success of VLNT and LVA, both surgical options are not exempt from limitations. An LVA is contraindicated in advanced stages in which lymph vessels are severely damaged and sclerotic, whereas VLNT carries the no less serious risk of donor site iatrogenic lymphedema. Koshima et al¹⁰⁹ developed a vascularized lymph

vessel transfer based on the first dorsal metatarsal artery. This concept is built on the hypothesis that functional lymphoadiposal flaps incorporate normal functioning lymphatic vessels with intact smooth muscle cells into the diseased tissue and help reestablish normal lymph drainage function. This study found that 37.5% patients had an excellent response (no need for compression therapy), 50% had a good response (improvement with compression), and 12.5% had no improvement. Major advantages of these methods are less invasiveness with small incisions, more rapid flap elevation, and low complication rate. Temporary hypersensitivity on donor sites has been described.¹⁰⁹ This concept raises the question of whether harvesting lymph nodes is necessary to treat lymphedema.¹¹⁰

Preventive Procedures at Primary Surgical Intervention in Patients With Breast Cancer

With increasing evidence of favorable outcomes with physiologic approaches, some investigators have shifted focus to risk reduction with prophylactic lymphedema procedures in patients with breast cancer in an attempt to prevent BCRL. Axillary reverse mapping with or without LVB is gaining popularity. It involves injecting blue dye into the arm to visualize the lymphatic drainage from the arm. During SLNB, an attempt is made to protect these lymphatics, thus preserving the lymphatic flow draining from the arm. If an axillary lymph node dissection is performed, a microscopic anastomosis, known as a *lymphatic microsurgical preventive healing approach*, is performed between the blue-dyed lymphatics draining the arm and a branch of the axillary vein, with the goal of maintaining lymphatic drainage from the arm back to the central circulation. Although a recently published systematic review reported that prophylactic LVA significantly reduced lymphedema incidence (risk ratio, 0.33) when compared with patients receiving no prophylactic treatment ($P < .01$),¹¹¹ the level of evidence remains low because most published studies are retrospective, single-institution trials with

limited follow-up. The early success of the lymphatic microsurgical preventive healing approach raises a further question regarding the appropriate timing for surgical treatment of lymphedema. If patients improve with prophylactic LVA, do patients with a diagnosis of chronic lymphedema require a trial of conservative therapy before considering surgical treatment options?

EXCISIONAL PROCEDURES

Some of the earliest surgical approaches were excisional procedures that involved debulking of deposited and hypertrophied adipose tissue that results from this long-term disease.¹¹²⁻¹¹⁴ Most of these procedures are now of historical interest only. Direct excision procedures may result in substantial morbidity, including pain, delayed wound healing, infections, and joint contractures. Patients may also have significant scars, poor cosmesis, or even worsening lymphedema requiring amputation.^{112,115}

More recently, with a better understanding of vascularization of the skin and utilizing the microvascular principles of skin perforators, a limb radical excision with preservation of skin perforators, a technique known as *radical reduction with preservation of perforators*, is possible.^{116,117} This approach provides the effective reduction of lymphedematous tissue and restoration of limb function while minimizing the risk of poor cosmesis. The procedure is usually performed for upper extremity lymphedema, with studies reporting approximately 20% volume reduction in the forearm in patients with stage III lymphedema.^{116,117}

For cases of severe and refractory lymphedema, a more aggressive approach is taken with the Charles procedure, which involves complete removal of skin and subcutaneous tissue and placement of skin grafts from the resected specimen onto the underlying deep fascia. Various modifications of the Charles procedure have been described over the years using full-thickness grafts, split-thickness grafts, or allografts.^{113,118,119} Typically, these procedures are used for the lower extremity given their poor cosmesis.¹¹² Undoubtedly, although these procedures can be an effective

way of reducing bulk, a staged approach can also be used to minimize the morbidity or to address specific areas of tissue accumulation. Therefore, for patients with severe impairment due to their disease, these excisional procedures can be their best option for symptomatic relief.

Similar to the concept of liposuction in cosmetic surgery, suction-assisted lipectomy is also considered an excisional treatment in lymphedema. Aspirating lymphedematous tissue with a fenestrated metallic cannula connected to vacuum suction is emerging as a viable treatment option for carefully selected patients.^{74,102,120} Favorable outcomes and long-lasting results have been found, with reduction in LVs of about 50% that was maintained over a 4-year period. Compression garments postoperatively are almost always necessary to avoid reaccumulation of fluid and fatty tissue. Previous studies⁷⁶ have found that patients receiving suction-assisted lipectomy combined with compression therapy had significantly better results than those in a control group with compression only. Overall, the procedure has a low complication profile, including temporary paresthesia and minor delays in wound healing or infections. Moreover, it does not appear that suction-assisted lipectomy disrupts already impaired lymphatic vessels. Although there are no current guidelines for the use of suction-assisted lipectomy as a tool for this patient population, most surgeons require that patients have garment compression for at least 3 months.

COMBINATION THERAPY

Removal of the irreversibly damaged tissue seems to be essential in a holistic therapeutic approach. This step is particularly relevant for end-stage extremity lymphedema in which chronic inflammation leads ultimately to increased collagen deposition and extracellular matrix remodeling. Several surgeons have combined VLNT and LVA, but these procedures address the fluid component only. Excisional procedures, whether suction-assisted lipectomy, Charles procedure, or radical reduction with preservation of perforators, have been combined with physiologic

procedures (as 1-stage or 2-stage procedures) in a safe and reliable manner to provide a surgical approach that best addresses multiple components of lymphedema.¹²⁰⁻¹²³ However, there is still no consensus regarding timing between procedures.

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CONCLUSION

Early detection and education are key to managing lymphedema. Lifestyle restrictions based on myths or generalized misperceptions negatively impact patients' ability to go on living and enjoy life. Complex decongestive therapy remains the mainstay of treatment. Once lymphedema develops, surgical options for treatment are now available and can be offered to patients in whom conservative management has failed. A tailored approach with careful patient selection is the cornerstone for the current surgical management of patients with lymphedema. Aside from these general considerations, substantial variety exists in the surgical techniques utilized by surgeons. A better understanding of the nature of the disease and the different treatment options will allow the health care team to offer more comprehensive care to patients with lymphedema.

Abbreviations and Acronyms: BCRL = breast cancer–related lymphedema; ICG = indocyanine green; LV = limb volume; LVA = lymphaticovenular anastomosis; LVB = lymphovenous bypass; MRL = magnetic resonance lymphangiography; SLNB = sentinel lymph node biopsy; VLNT = vascularized lymph node transfer

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Correspondence: Address to Oscar J. Manrique, MD, FACS, Division of Plastic and Reconstructive Surgery, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (oscarj.manrique@gmail.com; Twitter: @manriqueoscarj).

ORCID

Oscar J. Manrique:  <https://orcid.org/0000-0002-6177-0709>; Andrea L. Cheville:  <https://orcid.org/0000-0001-7668-6115>

REFERENCES

1. Morgan PA, Franks PJ, Moffatt CJ. Health-related quality of life with lymphoedema: a review of the literature. *Int Wound J*. 2005;2(1):47-62.
2. Shih Y-CT, Xu Y, Cormier JN, et al. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. *J Clin Oncol*. 2009;27(12):2007-2014.
3. Brouillard P, Boon L, Vikkula M. Genetics of lymphatic anomalies. *J Clin Invest*. 2014;124(3):898-904.
4. Smeltzer DM, Stickler GB, Schinger A. Primary lymphedema in children and adolescents: a follow-up study and review. *Pediatrics*. 1985;76(2):206-218.
5. Irtum A, Karkkainen MJ, Devriendt K, Alitalo K, Vikkula M. Congenital hereditary lymphedema caused by a mutation that inactivates VEGFR3 tyrosine kinase. *Am J Hum Genet*. 2000;67(2):295-301.
6. Karkkainen MJ, Ferrell RE, Lawrence EC, et al. Missense mutations interfere with VEGFR-3 signalling in primary lymphoedema. *Nat Genet*. 2000;25(2):153-159.
7. Wheeler ES, Chan V, Wassman R, Rimo DL, Lesavoy MA. Familial lymphedema praecox: Meige's disease. *Plast Reconstr Surg*. 1981;67(3):362-364.
8. Yildirim-Toruner C, Subramanian K, El Manjra L, Chen E, Goldstein S, Vitale E. A novel frameshift mutation of FOXC2 gene in a family with hereditary lymphedema-distichiasis syndrome associated with renal disease and diabetes mellitus. *Am J Med Genet A*. 2004;131(3):281-286.
9. Connell F, Brice G, Jeffery S, Keeley V, Mortimer P, Mansour S. A new classification system for primary lymphatic dysplasias based on phenotype. *Clin Genet*. 2010;77(5):438-452.
10. Laredo J, Lee BB. Lymphedema. In: Mowatt-Larssen E, Desai SS, Dua A, Shortell CEK, eds. *Phlebology, Vein Surgery and Ultrasonography: Diagnosis and Management of Venous Disease*. Cham, Switzerland: Springer International Publishing; 2014:327-339.
11. Cederberg A, Grønning LM, Åhrén B, Taskén K, Carlsson P, Enerbäck S. FOXC2 is a winged helix gene that counteracts obesity, hypertriglyceridemia, and diet-induced insulin resistance. *Cell*. 2001;106(5):563-573.
12. Mehrara BJ, Greene AK. Lymphedema and obesity: is there a link? *Plast Reconstr Surg*. 2014;134(1):154e-160e.
13. Ramaiah KD, Ottesen EA. Progress and impact of 13 years of the global programme to eliminate lymphatic filariasis on reducing the burden of filarial disease. *PLoS Negl Trop Dis*. 2014;8(11):e3319.
14. Boland GM, Gershenwald JE. Sentinel lymph node biopsy in melanoma. *Cancer J*. 2012;18(2):185-191.
15. Morton DL, Thompson JF, Cochran AJ, et al; MSLT Group. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med*. 2014;370(7):599-609.
16. Smith B, Backes F. The role of sentinel lymph nodes in endometrial and cervical cancer. *J Surg Oncol*. 2015;112(7):753-760.
17. Pirillo MF, Liotta G, Andreotti M, et al. CMV infection in a cohort of HIV-exposed infants born to mothers receiving antiretroviral therapy during pregnancy and breastfeeding. *Med Microbiol Immunol*. 2017;206(1):23-29.
18. Nguyen AT, Suami H, Hanasono MM, Womack VA, Wong FC, Chang EI. Long-term outcomes of the minimally invasive free vascularized omental lymphatic flap for the treatment of lymphedema. *J Surg Oncol*. 2017;115(1):84-89.
19. Garza R III, Skoracki R, Hock K, Povoski SP. A comprehensive overview on the surgical management of secondary lymphedema of the upper and lower extremities related to prior oncologic therapies. *BMC Cancer*. 2017;17(1):468.
20. Chang DW, Suami H, Skoracki R. A prospective analysis of 100 consecutive lymphovenous bypass cases for treatment of extremity lymphedema. *Plast Reconstr Surg*. 2013;132(5):1305-1314.

21. Sivaprakasam R, Rajamanickam A, Gurusamy M, Bethunaickan R. An overview of lymphatic filariasis lymphedema. *Lymphology*. 2018;50(4):164-182.
22. Cormier JN, Askew RL, Mungovan KS, Xing Y, Ross MI, Armer JM. Lymphedema beyond breast cancer: a systematic review and meta-analysis of cancer-related secondary lymphedema. *Cancer*. 2010;116(22):5138-5149.
23. Brunner U. Natural history of primary lymphedema of the legs. *Pathol Microbiol (Basel)*. 1975;43(2-O):230-234.
24. NLN Medical Advisory Committee. Position statement of the National Lymphedema Network: exercise. 2013: <https://klosetraining.com/wp-content/uploads/2014/08/nlnexercise.pdf>. Accessed April 7, 2019.
25. NLN Medical Advisory Committee. Position statement of the National Lymphedema Network: lymphedema risk reduction practices. National Lymphedema Network website. 2012: http://klosetraining.com/wp-content/uploads/2015/05/NLN_practices.pdf. Accessed April 7, 2019.
26. Maguire A, Brogi E. Sentinel lymph nodes for breast carcinoma: an update on current practice. *Histopathology*. 2016; 68(1):152-167.
27. Ahn S, Port ER. Lymphedema precautions: time to abandon old practices? *J Clin Oncol*. 2016;34(7):655-658.
28. Asdourian MS, Skolny MN, Brunelle C, Seward CE, Salama L, Taghian AG. Precautions for breast cancer-related lymphoedema: risk from air travel, ipsilateral arm blood pressure measurements, skin puncture, extreme temperatures, and cellulitis. *Lancet Oncol*. 2016;17(9):e392-e405.
29. Ferguson CM, Swaroop MN, Horick N, et al. Impact of ipsilateral blood draws, injections, blood pressure measurements, and air travel on the risk of lymphedema for patients treated for breast cancer. *J Clin Oncol*. 2016;34(7):691-698.
30. Kilbreath SL, Refshauge KM, Beith JM, et al. Risk factors for lymphoedema in women with breast cancer: a large prospective cohort. *Breast*. 2016;28:29-36.
31. McLaughlin SA. Lymphedema: separating fact from fiction. *Oncology (Williston Park)*. 2012;26(3):242-249.
32. McLaughlin SA, DeSnyder SM, Klimberg S, et al. Considerations for clinicians in the diagnosis, prevention, and treatment of breast cancer-related lymphedema, recommendations from an expert panel: part 2: preventive and therapeutic options. *Ann Surg Oncol*. 2017;24(10):2827-2835.
33. Leak LV. The structure of lymphatic capillaries in lymph formation. *Fed Proc*. 1976;35(8):1863-1871.
34. Margaris KN, Black RA. Modelling the lymphatic system challenges and opportunities. *J R Soc Interface*. 2012;9:601-612.
35. Moore JE Jr, Bertram CD. Lymphatic system flows. *Annu Rev Fluid Mech*. 2018;50:459-482.
36. Bemas M, Witte M, Kriedeman B, Summers P, Witte C. Massage therapy in the treatment of lymphedema: rationale, results, and applications. *IEEE Eng Med Biol Mag*. 2005;24(2):58-68.
37. Suami H. Lymphosome concept: anatomical study of the lymphatic system. *J Surg Oncol*. 2017;115(1):13-17.
38. Scallan J, Huxley VH, Korthuis RJ. Pathophysiology of edema formation. In: *Capillary Fluid Exchange: Regulation, Functions, and Pathology*. San Rafael, CA: Morgan & Claypool Life Sciences; 2010:47-62.
39. Heineman JT, Chen WF. Indocyanine green lymphography to diagnose primary lymphedema and the incidental discovery of primary asymptomatic lymphatic insufficiency [abstract]. *Plast Reconstr Surg Glob Open*. 2018;6(9, suppl):55-56.
40. International Society of Lymphology Executive Committee. The diagnosis and treatment of peripheral lymphedema: 2016 consensus document of the International Society of Lymphology. *Lymphology*. 2016;49(4):170-184.
41. Soran A, Ozmen T, McGuire KP, et al. The importance of detection of subclinical lymphedema for the prevention of breast cancer-related clinical lymphedema after axillary lymph node dissection: a prospective observational study. *Lymphat Res Biol*. 2014;12(4):289-294.
42. Grada AA, Phillips TJ. Lymphedema: pathophysiology and clinical manifestations. *J Am Acad Dermatol*. 2017;77(6):1009-1020.
43. Mortimer PS. The pathophysiology of lymphedema. *Cancer*. 1998;83(12, suppl American):2798-2802.
44. Szuba A, Shin WS, Strauss HW, Rockson S. The third circulation: radionuclide lymphoscintigraphy in the evaluation of lymphedema. *J Nud Med*. 2003;44(1):43-57.
45. Akita S, Mitsukawa N, Rikihisa N, et al. Early diagnosis and risk factors for lymphedema following lymph node dissection for gynecologic cancer. *Plast Reconstr Surg*. 2013;131(2):283-290.
46. Kayiran O, De La Cruz C, Tane K, Soran A. Lymphedema: from diagnosis to treatment. *Turk J Surg*. 2017;33(2):51-57.
47. Padera TP, Meijer EF, Munn LL. The lymphatic system in disease processes and cancer progression. *Annu Rev Biomed Eng*. 2016;18:125-158.
48. NLN Medical Advisory Committee. The diagnosis and treatment of lymphedema: position statement of the National Lymphedema Network. Mylymph.com website. 2018: https://13gkfr50081srbm42cuf1bf-wpengine.netdna-ssl.com/wp-content/uploads/2016/02/2011_NLN_Position-Statement-of-NLN.pdf. Accessed September 4, 2019.
49. Dixon JB, Weiler MJ. Bridging the divide between pathogenesis and detection in lymphedema. *Semin Cell Dev Biol*. 2015;38:75-82.
50. Mayrovitz HN. Assessing lymphedema by tissue indentation force and local tissue water. *Lymphology*. 2009;42(2):88-98.
51. Buendia R, Essex T, Kilbreath SL, Czerniec S, Dylke E, Ward LC. Estimation of arm adipose tissue quotient using segmental bioimpedance spectroscopy. *Lymphat Res Biol*. 2018;16(4):377-384.
52. Cornish BH, Chapman M, Hirst C, et al. Early diagnosis of lymphedema using multiple frequency bioimpedance. *Lymphology*. 2001;34(1):2-11.
53. Qin ES, Bowen MJ, Chen WF. Diagnostic accuracy of bioimpedance spectroscopy in patients with lymphedema: a retrospective cohort analysis. *J Plast Reconstr Aesthet Surg*. 2018;71(7):1041-1050.
54. Bundred NJ, Stockton C, Keeley V, et al. Investigators of BEA/PLACE Studies. Comparison of multi-frequency bioimpedance with perometry for the early detection and intervention of lymphoedema after axillary node clearance for breast cancer. *Breast Cancer Res Treat*. 2015;151(1):121-129.
55. Rubenstein DA, Yin W, Frame MD. The lymphatic system. In: *Biofluid Mechanics: An Introduction to Fluid Mechanics, Microcirculation, and Microcirculation*. 2nd ed. Cambridge, MA: Academic Press; 2015:311-324.
56. Patel KM, Manrique O, Sosin M, Hashmi MA, Poysofson P, Henderson R. Lymphatic mapping and lymphedema surgery in the breast cancer patient. *Gland Surg*. 2015;4(3):244-256.
57. Liu N, Zhang Y. Magnetic resonance lymphangiography for the study of lymphatic system in lymphedema. *J Reconstr Microsurg*. 2016;32(1):66-71.
58. Liu N-F, Lu Q, Jiang Z-H, Wang C-G, Zhou J-G. Anatomic and functional evaluation of the lymphatics and lymph nodes in diagnosis of lymphatic circulation disorders with contrast magnetic resonance lymphangiography. *J Vasc Surg*. 2009;49(4):980-987.
59. Tepe S, Çapar AE, Ercocen AR. Magnetic resonance lymphangiography: clinical and radiological correlation. *Clinics Oncol*. 2017;2:1362.
60. Kim S-Y, Bae H, Ji HM. Computed tomography as an objective measurement tool for secondary lymphedema treated with extracorporeal shock wave therapy. *Ann Rehabil Med*. 2015; 39(3):488-493.
61. Erdogan Iyigun Z, Agacayak F, Ilgun AS, et al. The role of elastography in diagnosis and staging of breast cancer-related lymphedema. *Lymphat Res Biol*. 2019;17(3):334-339.
62. O'Donnell TF Jr, Rasmussen JC, Sevcik-Muraca EM. New diagnostic modalities in the evaluation of lymphedema. *J Vasc Surg Venous Lymphat Disord*. 2017;5(2):261-273.

63. Mihara M, Hara H, Araki J, et al. Indocyanine green (ICG) lymphography is superior to lymphoscintigraphy for diagnostic imaging of early lymphedema of the upper limbs. *PLoS One*. 2012;7(6):e38182.
64. Gurtner GC, Jones GE, Neligan PC, et al. Intraoperative laser angiography using the SPY system: review of the literature and recommendations for use. *Ann Surg Innov Res*. 2013;7(1):1.
65. Sood M, Glat P. Potential of the SPY intraoperative perfusion assessment system to reduce ischemic complications in immediate postmastectomy breast reconstruction. *Ann Surg Innov Res*. 2013;7(1):9.
66. Koban KC, Schenck TL, Giunta RE. Using mobile 3D scanning systems for objective evaluation of form, volume, and symmetry in plastic surgery: intraoperative scanning and lymphedema assessment. In: *Proceedings of the 7th International Conference on 3D Body Scanning Technologies*; November 30-December 1, 2016; Lugano, Switzerland.
67. Akita S, Tokumoto H, Mitsukawa N. Vectra 3D imaging for quantitative volumetric analysis of the upper limb: a feasibility study for tracking outcomes of lymphedema treatment [letter]. *Plast Reconstr Surg*. 2018;141(5):787e-788e.
68. Smile TD, Tendulkar R, Schwarz G, et al. A review of treatment for breast cancer-related lymphedema: paradigms for clinical practice. *Am J Clin Oncol*. 2018;41(2):178-190.
69. Bakar Y, Tuğral A. Lower extremity lymphedema management after gynecologic cancer surgery: a review of current management strategies. *Ann Vasc Surg*. 2017;44:442-450.
70. Feldman JL, Stout NL, Wanchai A, Stewart BR, Cormier JN, Armer JM. Intermittent pneumatic compression therapy: a systematic review. *Lymphology*. 2012;45(1):13-25.
71. Tidhar D, Hodgson P, Shay C, Towers A. A lymphedema self-management programme: report on 30 cases. *Physiother Can*. 2014;66(4):404-412.
72. Lee BB, Laredo J, Neville R. Current status of lymphatic reconstructive surgery for chronic lymphedema: it is still an uphill battle. *Int J Angiol*. 2011;20(2):73-80.
73. Chang DW, Masia J, Garza R III, Skoracki R, Neligan PC. Lymphedema: surgical and medical therapy. *Plast Reconstr Surg*. 2016;138(3, suppl):209S-218S.
74. Carl HM, Walia G, Bello R, et al. Systematic review of the surgical treatment of extremity lymphedema. *J Reconstr Microsurg*. 2017;33(6):412-425.
75. Karakousis CP. Surgical procedures and lymphedema of the upper and lower extremity. *J Surg Oncol*. 2006;93(2):87-91.
76. Boyages J, Kastanias K, Koelmeyer LA, et al. Liposuction for advanced lymphedema: a multidisciplinary approach for complete reduction of arm and leg swelling. *Ann Surg Oncol*. 2015;22(suppl 3):S1263-S1270.
77. Warren AG, Brorson H, Borud LJ, Slavin SA. Lymphedema: a comprehensive review. *Ann Plast Surg*. 2007;59(4):464-472.
78. Campisi C, Eretta C, Pertile D, et al. Microsurgery for treatment of peripheral lymphedema: long-term outcome and future perspectives. *Microsurgery*. 2007;27(4):333-338.
79. Krylov V, Milanov N, Abalmasov K. Microlymphatic surgery of secondary lymphoedema of the upper limb. *Ann Chir Gynaecol*. 1982;71(1):77-79.
80. Baumeister RG, Siuda S. Treatment of lymphedemas by microsurgical lymphatic grafting: what is proved? *Plast Reconstr Surg*. 1990;85(1):64-74.
81. Campisi C, Da Rin E, Bellini C, Bonioli E, Boccardo F. Pediatric lymphedema and correlated syndromes: role of microsurgery. *Microsurgery*. 2008;28(2):138-142.
82. Campisi C, Boccardo F, Zilli A, Macciò A, Napoli F. Long-term results after lymphatic-venous anastomoses for the treatment of obstructive lymphedema. *Microsurgery*. 2001;21(4):135-139.
83. Campisi C, Boccardo F, Alitta P, Tacchella M. Derivative lymphatic microsurgery: indications, techniques, and results. *Microsurgery*. 1995;16(7):463-468.
84. Campisi C, Boccardo F. Microsurgical techniques for lymphedema treatment: derivative lymphatic-venous microsurgery. *World J Surg*. 2004;28(6):609-613.
85. Olszewski WL. The treatment of lymphedema of the extremities with microsurgical lympho-venous anastomoses. *Int Angiol*. 1988;7(4):312-321.
86. Campisi C, Bellini C, Campisi C, Accogli S, Bonioli E, Boccardo F. Microsurgery for lymphedema: clinical research and long-term results. *Microsurgery*. 2010;30(4):256-260.
87. Baumeister RGH, Frick A. The microsurgical lymph vessel transplantation [in German]. *Handchir Mikrochir Plast Chir*. 2003;35(4):202-209.
88. Kanapathy M, Patel NM, Kalaskar DM, Mosahebi A, Mehrara BJ, Seifalian AM. Tissue-engineered lymphatic graft for the treatment of lymphedema. *J Surg Res*. 2014;192(2):544-554.
89. Koshima I, Nanba Y, Tsutsui T, Takahashi Y, Itoh S, Fujitsu M. Minimal invasive lymphaticovenular anastomosis under local anesthesia for leg lymphedema: is it effective for stage III and IV? *Ann Plast Surg*. 2004;53(3):261-266.
90. Winters H, Tieleman HJ, Hameeteman M, et al. The efficacy of lymphaticovenular anastomosis in breast cancer-related lymphedema. *Breast Cancer Res Treat*. 2017;165(2):321-327.
91. Chen WF. How to get started performing supermicrosurgical lymphaticovenular anastomosis to treat lymphedema. *Ann Plast Surg*. 2018;81(6S, suppl 1):S15-S20.
92. Yamamoto T, Yoshimatsu H, Yamamoto N, Narushima M, Iida T, Koshima I. Side-to-end lymphaticovenular anastomosis through temporary lymphatic expansion. *PLoS One*. 2013;8(3):e59523.
93. Chen WF, Yamamoto T, Fisher M, Liao J, Carr J. The "octopus" lymphaticovenular anastomosis: evolving beyond the standard supermicrosurgical technique. *J Reconstr Microsurg*. 2015;31(6):450-457.
94. Yamamoto T, Narushima M, Kikuchi K, et al. Lambda-shaped anastomosis with intravascular stenting method for safe and effective lymphaticovenular anastomosis. *Plast Reconstr Surg*. 2011;127(5):1987-1992.
95. Scaglioni MF, Fontein DBY, Arvanitakis M, Giovanoli P. Systematic review of lymphovenous anastomosis (LVA) for the treatment of lymphedema. *Microsurgery*. 2017;37(8):947-953.
96. O'Brien BM, Mellow CG, Khazanchi RK, Dvir E, Kumar V, Pederson WC. Long-term results after microlymphaticovenous anastomoses for the treatment of obstructive lymphedema. *Plast Reconstr Surg*. 1990;85(4):562-572.
97. Chen WF, Bowen M, Ding J. Immediate limb compression following supermicrosurgical lymphaticovenular anastomosis — is it helpful or harmful? *Int Microsurg J*. 2018;2(1):2-6.
98. Lin C-H, Ali R, Chen S-C, et al. Vascularized groin lymph node transfer using the wrist as a recipient site for management of postmastectomy upper extremity lymphedema. *Plast Reconstr Surg*. 2009;123(4):1265-1275.
99. Scaglioni MF, Arvanitakis M, Chen Y-C, Giovanoli P, Chia-Shen Yang J, Chang EI. Comprehensive review of vascularized lymph node transfers for lymphedema: outcomes and complications. *Microsurgery*. 2018;38(2):222-229.
100. Raju A, Chang DW. Vascularized lymph node transfer for treatment of lymphedema: a comprehensive literature review. *Ann Surg*. 2015;261(5):1013-1023.
101. Kwiecien GJ, Uygur S, Korn J, et al. Vascularized axillary lymph node transfer: a novel model in the rat. *Microsurgery*. 2015;35(8):662-667.
102. Kung TA, Champaneria MC, Maki JH, Neligan PC. Current concepts in the surgical management of lymphedema. *Plast Reconstr Surg*. 2017;139(4):1003e-1013e.
103. Ozturk CN, Ozturk C, Glasgow M, et al. Free vascularized lymph node transfer for treatment of lymphedema: a systematic evidence based review. *J Plast Reconstr Aesthet Surg*. 2016;69(9):1234-1247.

104. Ciudad P, Agko M, Perez Coca JJ, et al. Comparison of long-term clinical outcomes among different vascularized lymph node transfers: 6-year experience of a single center's approach to the treatment of lymphedema. *J Surg Oncol*. 2017;116(6):671-682.
105. Demiri E, Dionysiou D, Tsimponis A, et al. Donor-site lymphedema following lymph node transfer for breast cancer-related lymphedema: a systematic review of the literature. *Lymphat Res Biol*. 2018;16(1):2-8.
106. Ciudad P, Manrique OJ, Date S, et al. Double gastroepiploic vascularized lymph node transfers to middle and distal limb for the treatment of lymphedema. *Microsurgery*. 2017;37(7):771-779.
107. Chu Y-Y, Allen RJ Jr, Wu T-J, Cheng M-H. Greater omental lymph node flap for upper limb lymphedema with lymph nodes-depleted patient. *Plast Reconstr Surg Glob Open*. 2017;5(4):e1288.
108. Ciudad P, Date S, Lee M-H, et al. Robotic harvest of a right gastroepiploic lymph node flap. *Arch Plast Surg*. 2016;43(2):210-212.
109. Koshima I, Narushima M, Mihara M, et al. Lymphadiposal flaps and lymphaticovenular anastomoses for severe leg edema: functional reconstruction for lymph drainage system. *J Reconstr Microsurg*. 2016;32(1):50-55.
110. Chen WF, McNurlen M, Ding J, Bowen M. Vascularized lymph vessel transfer for extremity lymphedema - is transfer of lymph node still necessary? *IMJ*. 2019;3(3):1.
111. Jørgensen MG, Toyserkani NM, Sørensen JA. The effect of prophylactic lymphovenous anastomosis and shunts for preventing cancer-related lymphedema: a systematic review and meta-analysis. *Microsurgery*. 2018;38(5):576-585.
112. Miller TA. Charles procedure for lymphedema: a warning. *Am J Surg*. 1980;139(2):290-292.
113. Mavili ME, Naldoken S, Safak T. Modified Charles operation for primary fibrosclerotic lymphedema. *Lymphology*. 1994;27(1):14-20.
114. Savage RC. The surgical management of lymphedema. *Surg Gynecol Obstet*. 1985;160(3):283-290.
115. Tiwari A, Cheng K-S, Button M, Myint F, Hamilton G. Differential diagnosis, investigation, and current treatment of lower limb lymphedema. *Arch Surg*. 2003;138(2):152-161.
116. Salgado CJ, Mardini S, Spanio S, Tang W-R, Sassu P, Chen H-C. Radical reduction of lymphedema with preservation of perforators. *Ann Plast Surg*. 2007;59(2):173-179.
117. Salgado CJ, Sassu P, Gharb BB, Spanio di Spilimbergo S, Mardini S, Chen H-C. Radical reduction of upper extremity lymphedema with preservation of perforators. *Ann Plast Surg*. 2009;63(3):302-306.
118. Yeo MS-W, Lim SY, Kiranantawat K, Ciudad P, Chen H-C. A comparison of vascularized cervical lymph node transfer with and without modified Charles' procedure for the treatment of lower limb lymphedema [letter]. *Plast Reconstr Surg*. 2014;134(1):171e-172e.
119. Ciudad P, Agko M, Huang TCT, et al. Comprehensive multimodal surgical treatment of end-stage lower extremity lymphedema with toe management: The combined Charles', Homan's, and vascularized lymph node transfer (CHAHOVA) procedures. *J Surg Oncol*. 2019;119(4):430-438.
120. Agko M, Ciudad P, Chen H-C. Staged surgical treatment of extremity lymphedema with dual gastroepiploic vascularized lymph node transfers followed by suction-assisted lipectomy—a prospective study. *J Surg Oncol*. 2018;117(6):1148-1156.
121. Granzow JW, Soderberg JM, Dauphine C. A novel two-stage surgical approach to treat chronic lymphedema. *Breast J*. 2014;20(4):420-422.
122. Nicoli F, Constantinides J, Ciudad P, et al. Free lymph node flap transfer and laser-assisted liposuction: a combined technique for the treatment of moderate upper limb lymphedema. *Lasers Med Sci*. 2015;30(4):1377-1385.
123. Campisi CC, Ryan M, Boccardo F, Campisi C. Fibro-lipo-lymph-aspiration with a lymph vessel sparing procedure to treat advanced lymphedema after multiple lymphatic-venous anastomoses: the complete treatment protocol. *Ann Plast Surg*. 2017;78(2):184-190.