Lymphedema
A Comprehensive Review

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Background: Lymphedema is a chronic, debilitating condition that has traditionally been seen as refractory or incurable. Recent years have brought new advances in the study of lymphedema pathophysiology, as well as diagnostic and therapeutic tools that are changing this perspective.

Objective: To provide a systematic approach to evaluating and managing patients with lymphedema.

Methods: We performed MEDLINE searches of the English-language literature (1966 to March 2006) using the terms *lymphedema*, *breast cancer–associated lymphedema*, *lymphatic complications*, *lymphatic imaging*, *decongestive therapy*, and *surgical treatment of lymphedema.* Relevant bibliographies and International Society of Lymphology guidelines were also reviewed.

Results: In the United States, the populations primarily affected by lymphedema are patients undergoing treatment of malignancy, particularly women treated for breast cancer. A thorough evaluation of patients presenting with extremity swelling should include identification of prior surgical or radiation therapy for malignancy, as well as documentation of other risk factors for lymphedema, such as prior trauma to or infection of the affected limb. Physical examination should focus on differentiating signs of lymphedema from other causes of systemic or localized swelling. Lymphatic dysfunction can be visualized through lymphoscintigraphy; the diagnosis of lymphedema can also be confirmed through other imaging modalities, including CT or MRI. The mainstay of therapy in diagnosed cases of lymphedema involves compression garment use, as well as intensive bandaging and lymphatic massage. For patients who are unresponsive to conservative therapy, several surgical options with varied proven efficacies have been used in appropriate candidates, including excisional approaches, microsurgical lymphatic anastomoses, and circumferential suction-assisted lipectomy, an approach that has shown promise for long-term relief of symptoms.

Conclusions: The diagnosis of lymphedema requires careful attention to patient risk factors and specific findings on physical examination. Noninvasive diagnostic tools and lymphatic imaging can be helpful to confirm the diagnosis of lymphedema or to address a challenging clinical presentation. Initial treatment with decongestive lymphatic therapy can provide significant improvement in patient symptoms and volume reduction of edematous extremities. Selected patients who are unresponsive to conservative therapy can achieve similar outcomes with surgical intervention, most promisingly suction-assisted lipectomy.

Key Words: lymphedema, breast cancer, extremity swelling

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Lymphedema describes a progressive pathologic condition of the lymphatic system in which there is interstitial accumulation of protein-rich fluid and subsequent inflammation, adipose tissue hypertrophy, and fibrosis. The swelling and subsequent induration of the affected region can cause disfigurement, as well as decreased mobility and function. Although lymphedema has been described for centuries, recently more attention has been paid to the disease due to its presence as a relatively common complication of treatment of malignancy. It can be a difficult condition to treat and one that causes significant morbidity, both physical and psychologic, for patients. In addition, it is frequently underdiagnosed and undertreated, which can add to patients' frustration at their chronic and debilitating disease. However, new advances in the field, including expanded diagnostic and management options, are making strides towards improved care for affected patients.

Evidence Acquisition

We performed MEDLINE searches of the English-language literature (1966 to March 2006) using the terms lymphedema, *breast cancer–associated lymphedema*, *lymphatic complications*, *lymphatic imaging*, *decongestive lymphatic therapy*, and *surgical treatment of lymphedema*. An additional search was performed using the Medical Subject Heading term *lymphedema* and limiting publication type to randomized controlled trial OR clinical trial. Relevant bibliographies of literature were manually reviewed for additional resources. Published guidelines and resources from the International Society of Lymphology were also included for review.

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Evidence Synthesis

Pathogenesis

The underlying etiology in lymphedema is one of lymphatic transport dysfunction. Lymphatic vessels normally function to remove the net fluid efflux from capillaries that accumulates in the interstitium, thus maintaining steady interstitial pressure. Venous capillaries reabsorb 90% of the fluid in the interstitium, while the remaining fluid is transported to the blood by the lymphatics as lymph. Under normal conditions, the same amount is transported to the interstitium as is transported from it, a balance that is disrupted in lymphedema due to reduced lymph transport capacity, thus leading to fluid accumulation and swelling.

Lymph vessels also serve to remove macromolecules such as protein from the interstitium. As protein diffuses through arterial capillary walls, it is typically degraded by macrophages, thus allowing it to reenter the circulation through venous capillaries, or to be reabsorbed through lymphatic vessels.[1] In cases of absent, dysfunctional, or obstructed lymphatic systems, lymphatic stasis occurs, thus allowing for the buildup of protein and fluid within the interstitium. Classic theory posits that this increased protein concentration leads to increased tissue colloid osmotic pressure, which drives fluid into the interstitium and causes edema and the clinical manifestations of lymphedema.

Lymphedema is classified by the etiology of the patient's disease state, which is typically divided into primary and secondary causes. Primary lymphedema is used to describe patients who have a congenital abnormality or dysfunction in their lymphatic system, whereas secondary lymphedema results from disruption or obstruction of a normal lymphatic system due to disease or iatrogenic processes.

Primary lymphedema is subdivided into categories based on the age of onset of the patient's symptoms. The diagnosis of congenital hereditary lymphedema, or Milroy disease, is made in patients presenting at birth or within the first 2 years of life. Milroy disease demonstrates an autosomal-dominant pattern of inheritance and is seen to frequently affect the entire lower extremity and cause bilateral lymphedema of the legs, as well as intestinal lymphangiectasia and cholestasis.[2] Recent genetic studies have linked the disease to an inactivation mutation of the VEGFR (vascular endothelial growth factor receptor) −3 tyrosine kinase signaling pathway found in lymphatic vessels.[3,4] Familial lymphedema praecox, also termed *Meige disease*, typically presents during puberty and also demonstrates an autosomal-dominant inheritance pattern. It is associated with a variety of anomalies, including vertebral defects, cerebrovascular malformations, hearing loss, and distichiasis (double row of eyelashes).[5] Molecular genetic analyses of families with lymphedema-distichiasis have demonstrated over 30 different mutations in the human transcription factor *FOXC2* gene,[6] which has recently been shown to be involved in adipocyte metabolism.[7] Of the congenital lymphedemas, lymphedema tarda presents latest in life, with spontaneous onset appearing after age 35.

Worldwide, the most prevalent etiology of secondary lymphedema is filariasis secondary to infection with the nematode *Wuscheria banrofti*, which has been estimated to affect more than 90 million people.[8] Adult filarial worms lodge in the lymphatic systems, thus obstructing lymphatic vessels and disrupting lymphatic transport.

In the United States, nearly all cases of secondary lymphedema are related to malignancy or its therapy. Subsequent lymphatic dysfunction and edema have been well described after treatment of a variety of cancers, including breast cancer, melanoma, gynecologic cancers, lymphoma, and urologic cancers. Recent attention has been particularly paid to lymphedema following surgical and radiation treatment of women with breast cancer, which accounts for most of cases of upper-extremity lymphedema. Typical rates of lymphedema after mastectomy have been described between 24% and 49%,[9–13] with lower rates (4%–28%) reported after lumpectomy.[14,15]

The wide range in reported incidence rates stems largely from the varied measurement techniques and definitions used in studies evaluating rates of lymphedema, with some trials relying on patient self-reporting in cases of lymphedema and some delineating more rigorous definitions involving circumferential limb measurements. Additionally, treatment regimens vary significantly between studies. Given that axillary node dissection and radiation therapy to the axilla, mainstays of breast cancer treatment, have both been shown to increase the risk of edema,[14,16–19] studies involving populations largely managed with these therapies show higher rates of lymphedema. With the development of sentinel lymph node biopsy for the detection of locoregional breast cancer spread, however, more recent studies have shown significant reduction in the incidence of lymphedema as compared with traditional axillary node dissection.[20–24]

A number of other risk factors have been viewed as contributors to the development of lymphedema, including trauma, infection, and obesity. Sizeable weight gain and/or obesity have been shown to increase a woman's risk of lymphedema following treatment of breast cancer.[10,15,25,26] Large studies of women undergoing unilateral axillary node dissection have shown an increased risk of future development of lymphedema when trauma to the ipsilateral limb has occurred.[27] Further investigation into some theorized risks, however, particularly the avoidance of blood pressure measurements and venipuncture in limbs at risks for lymphedema due to prior surgical procedures, has shown some historical concerns to be unsubstantiated.[28]

Clinical Presentation

The clinical manifestations of lymphedema occur secondarily to the subcutaneous accumulation of edematous fluid and adipose tissue. An inflammatory response develops with chronic interstitial fluid accumulation. In addition to inflammation, slowed lymphatic flow has also been shown to incite lipogenesis and fat deposition and later leads to increased fibrocyte activation and connective tissue overgrowth.[29–31] Affected patients thus develop progressively firmer subcutaneous tissue as fibrosis ensues, in addition to hypertrophy of their adipose tissue. These pathologic changes manifest initially as swelling of the affected limb or region, described as soft and pitting, but later progress to a more indurated state.

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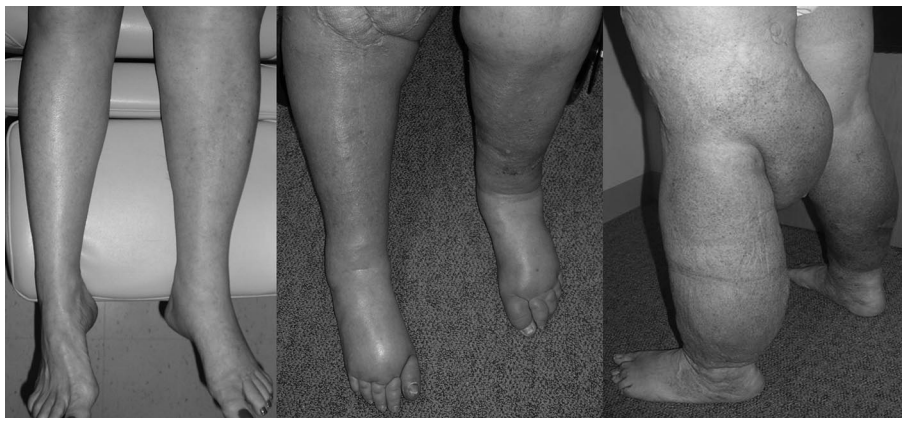

FIGURE 1. Mild (left), moderate (center), and severe (right) presentations of lymphedema.

Clinical classification of lymphedematous swelling has been defined by the International Society of Lymphology[32] using the following parameters (Fig. 1):

Stage 0. Latent or subclinical condition where swelling is not evident despite impaired lymph transport. It may exist months or years before overt edema occurs (stages I–III).

Stage I. Early accumulation of fluid relatively high in protein content (eg, in comparison with "venous" edema) that subsides with limb elevation. Pitting may occur.

Stage II. Pitting may or may not occur as tissue fibrosis develops. Limb elevation alone rarely reduces tissue swelling.

Stage III. Lymphostatic elephantiasis where pitting is absent. Trophic skin changes, such as acanthosis, fat deposits, and warty overgrowths, often develop.

Although the swelling alone does not typically cause severe discomfort, patients are prone to developing recurrent episodes of cellulitis due to increased microbial proliferation in the accumulated fluid. Lymphangitis is also common, which leads to further destruction of lymphatic vessels, thus worsening the edema. Other skin changes include hyperkeratosis, papillomatosis, and skin breakdown.[33]

A rare complication of chronic lymphedema is the development of cutaneous malignant tumors, such as lymphangiosarcoma, Kaposi sarcoma, or lymphoma.[34] Stewart Treves syndrome, which was first described in the subset of women who had developed significant lymphedema after radical mastectomy and were subsequently diagnosed with lymphangiosarcoma, has been reported in over 200 patients to date,[35–38] carrying with it a median survival time of only 19 months.[39]

Diagnosis

Diagnosis of lymphedema, particularly in more advanced stages, is typically made through clinical presentation and history (Table 1). Earlier stages, however, can be more difficult to differentiate from other common causes of limb edema. The differential diagnosis for lymphedema includes systemic causes of edema, such as cardiac failure, renal failure, and protein-losing conditions, and local etiologies, including lipedema, deep vein thrombosis, chronic venous insufficiency, myxedema, and cyclical or idiopathic edema. Physical examination features classically unique to lymphedema include peau d'orange changes of the skin, indicating cutaneous and subcutaneous fibrosis,[40] and a positive Stemmer sign (the inability to grasp the skin of the dorsum of the second digit of the feet).[41]

Documentation of lymphedema has typically been made through circumferential measurements or volumetric documentation comparing the patient's affected and unaffected limb. More recently, noninvasive methods that can be used during a patient's clinical examination have been studied in diagnosing lymphedema, including bioelectric impedance analysis,[42,43] tonometry,[44] and perometry.[45] Bioimpedance technologies are commonly used in body composition analysis and allow for more direct measure of differences in edema volume, versus simple measures of limb volumes that do not take specific tissue compartment changes into account.[46,47] The technique has been shown to be reliable and reproducible in the evaluation of lymphedema[48,49] and has demonstrated the capability of indicating subclinical lymphedema in women being followed after breast cancer therapies.[50]

TABLE 1. Relevant Historical and Physical Examination Findings in the Evaluation of Lymphedema

Reported risk factors
Prior surgical procedures, particularly nodal dissection
History of radiation therapy
History of trauma
History of infection
Travel to geographical region with endemic filiariasis
History of malignancy
Familial history of congenital lymphedema
Obesity
Associated symptoms
Recurrent cellulitis
Chronic skin breakdown
Clinical signs
Soft, pitting edema (early stage)
Fibrosis and induration (late stage)
Peau d'orange skin changes
Papillomatosis
Hyperkeratosis
Cellulitis
Positive Stemmer sign (lower extremity lymphedema)

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In cases in which clinical observation cannot definitively establish a diagnosis, various radiographic imaging modalities are typically used. Prior to the emergence of less invasive techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and lymphoscintigraphy, delineation of lymphatic dysfunction was made using the technique of direct lymphography, wherein dermal lymphatic vessels are surgically cannulated after intradermal injection of dye. This procedure, formerly reserved for patients planning to undergo lymphatic surgery, has been largely supplanted by lymphoscintigraphy. Lymphoscintigraphy, or isotopic lymphography, is a relatively noninvasive technique involving an intradermal injection of radiolabeled colloid in the distal aspect of the edematous limb and subsequent imaging of the lymphatic vasculature.[51,52] The study provides information regarding both lymphatic anatomy as well as lymphatic function. Typical abnormalities seen in patients with lymphedema include absent or delayed radiotracer transport, cutaneous flare, dermal diffusion or backflow, and poorly visualized lymphatic collectors and lymph nodes[53] (Fig. 2).

FIGURE 2. Abnormal lymphoscintigram demonstrating impaired lymphatic flow and dermal backflow after radiotracer injection.

Although lymphoscintigraphy is considered the gold standard for diagnosing lymphedema, other imaging studies may be indicated in certain clinical situations where the initial suspicion of lymphedema is lower. In patients in whom deep vein thrombosis or chronic vascular disease is considered as a potential cause for a patient's extremity swelling, duplex ultrasound should be performed. The onset of spontaneous lymphedema in an adult patient may indicate an underlying malignancy compressing lymphatic channels, which should be excluded through CT or MRI studies.

These alternative means of lymphatic visualization may also be useful for confirming diagnoses of lymphedema, particularly if access to nuclear medicine facilities providing ILS is unavailable. CT imaging has been shown to be highly sensitive (97%) and specific (100%) in confirming the diagnosis of lymphedema.[54] It is not used routinely, however, given the widespread access to MRI and the superior soft tissue imaging it provides.[55] Although more costly, MRI offers greater detail of lymphatic architecture,[56] without the radiation exposure, and has been shown to be equally sensitive and specific for the diagnosis of lymphedema. Classic signs of lymphedema seen in MRI include thickening of the skin, "honeycombing" of the subcutaneous tissue due to the presence of fibrotic tissue and fluid surrounding adipose accumulation, epifascial fluid lakes, and the absence of edema within muscular compartments.[57,58]

For all imaging studies, the decision to recommend radiologic evaluation to evaluate lymphatic function should be driven by uncertain clinical presentations and challenges. The majority of patients with lymphedema can be diagnosed through thorough history-taking and physical examination and can subsequently be advised on appropriate therapy without the need for additional confirmatory tests.

Treatment

Conservative Therapy

The mainstay of conservative therapy relies on the finding that reduction of pitting edema can be obtained by compression, which is often achieved using multilayer inelastic lymphedema bandaging[59] or controlled compression therapy, where the compression garment's size is reduced by regularly taking in the garment as the swelling decreases.[60] Both methods significantly reduce excess edema volume by as much as 31%[33] to 46%,[61] respectively.

More laborious conservative treatment includes decongestive lymphatic therapy (DLT), or complex physical therapy. This therapy has changed little over the last century,[60] relying on principles of skin hygiene, limb compression, and exercise. DLT typically involves massage or manual lymphatic drainage, compression bandaging, and exercise. These techniques operate on the principles of Foldi et al,[62] who further developed the idea of "complex decongestive therapy," and Vodder,[63] who posited that these methods would augment lymphatic contractility, increase lymphatic flow through cutaneous lymphatics, and reduce lymphatic fluid from affected extremities, thus reducing limb swelling. Results after DLT have shown generally positive results, with some randomized controlled studies showing as much as 40% to 60% mean decrease in excess volume in patients with pitting edema.[64–66]

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Others, however, have shown only minimal improvement,[67] and follow-up is often quite limited, at times to less than 6 months after the completion of therapy. Additionally, results from these studies have indicated that manual lymph drainage may not contribute substantially to the decrease of the edema volume over the effects of compression garments[65] or bandaging.[64] Noncontrolled clinical trials evaluating DLT have shown outcomes comparable to those from randomized trials.[68–72]

Significant patient-to-patient variability exists within outcomes from complex physical therapy, which has been attributed to differences in amount of fibrosis but has been difficult to conclusively prove or use to influence clinical practice.[73] There are also limitations to long-term use of the technique, including the required involvement of multiple health care providers, such as physicians, nurses, and trained therapists, as well as the intensive commitment of time and labor necessary on the part of the patient and his/her care providers. Patient discomfort or embarrassment in using compression garments or bandages may also limit patient compliance, which can negatively impact long-term outcome.[69] Critical to the initiation of complex physiotherapy is ensuring that patients understand that these therapies will only alleviate their symptoms and are not curative of their underlying lymphatic dysfunction, which means that they will likely need to actively participate in and adhere to their therapy indefinitely to maintain positive results.

External sequential pneumatic compression devices, which have been examined as an alternative to complex physiotherapy, have led to varied results in the treatment of chronic lymphedema. Positive outcomes from studies showing major improvements in edematous fluid volume shortly after use of the device[74–76] have been confirmed with longer follow-up in trials combining intermittent pneumatic compression with DLT.[77,78] However, several conflicting reports have demonstrated minimal or no significant reduction in excess volume with continued usage of the device over time.[79,80]

In addition to compressive and lymphatic drainage methods, use of numerous pharmacologic agents has been attempted in the treatment of lymphedema, most targeted to break down the protein accumulation in the edematous tissues.[81] Benzopyrones, thought to act by increasing proteolysis by macrophages,[82] are among the most commonly used drugs. Although randomized placebo-controlled crossover studies have shown significant effects on lymphedema with the use of benzopyrones,[83] others have shown no beneficial effect,[84] and their long-term use has been limited due to documented hepatotoxicity.[85] Diuretic agents have also been used in conjunction with physical therapy, although they are not typically recommended as they have only marginal benefit and can actually lead to increased fibrosis due to worsening protein accumulation.[86–88]

Nutritional supplements have also been evaluated for the treatment of lymphedema. A study of 12 patients with upper-extremity edema secondary to surgical and radiation treatment of breast cancer who received daily sodium selenite showed moderate, though nonsignificant, reduction of limb volume in 83% of patients,[89] outcomes which were mirrored in a study of patients with lymphedema secondary to oral and maxillofacial surgery.[90] Recent studies examining the role of vitamin E in combination with pentoxifylline have shown no benefit.[91]

Surgical Therapy

In selected patients for whom an adequate trial of conservative therapy has not proven effective, likely due to the presence of adipose tissue hypertrophy, surgical evaluation should be considered. Surgical treatment can be broadly divided into 3 main approaches: resection procedures, microsurgical interventions, and the use of suction-assisted lipectomy (liposuction).

A resection approach, or debulking, involves the surgical excision of subcutaneous tissue, which may or may not include excision of the overlying skin. Charles[92] first described his resection method in 1912, and variations on his technique of radical excision of the subcutaneous tissue and primary or delayed skin grafting are still used today. Debulking procedures are not designed to directly address lymphatic vessel dysfunction but instead serve to provide improved comfort by removing redundant skin and subcutaneous tissues. Therefore, as with all currently available therapies, the underlying pathology remains and limb edema may return. Patients may also develop complications of the skin from debulking procedures, including ulceration, cellulitis, papillomatosis, eczema, keloids, and lymphatic fistulas.[93]

Microsurgical techniques, which attempt to directly correct underlying lymphatic pathology, have become popular in several European and Asian countries, although use of the technique is rare in the United States. Approaches include the creation of anastomoses between lymphatic vessels and veins,[94] between lymph nodes and veins,[95] and between distal and proximal lymphatics.[96] Among others, Campisi and Boccardo[97] have shown good long-term results in a series of Italian patients undergoing microsurgical lymphaticovenous anastomoses for peripheral lymphedema, with a mean volume reduction of 69% and 87% reduction in the incidence of cellulitis, but outcomes are difficult to interpret, given that preoperative excess arm and leg volumes and whether compression garments were used is not presented. Lymphatic grafting in combination with postoperative elastic bandaging has shown a decrease in arm volume between 22% and 30%.[98] However, patients undergoing microsurgical lymphatic procedures are immediately prescribed continuous compression garment use postoperatively, which makes definitive conclusions regarding a direct benefit from the surgical procedure above the improvement from compression therapy difficult. Additionally, individual results have been inconsistent within and among studies, and there are no currently available means to study lymphatic vessel patency.

Alternatives to lymphatic anastomoses have also been tried, including the use of a free muscle flap transfer, which has shown promising results in case reports and small studies as a means of restoring lymphatic vessel function in cases of obstructive lymphedema,[99–101] results that are consistent with documented lymphatic regrowth across microsurgical flap reconstructions.[102]

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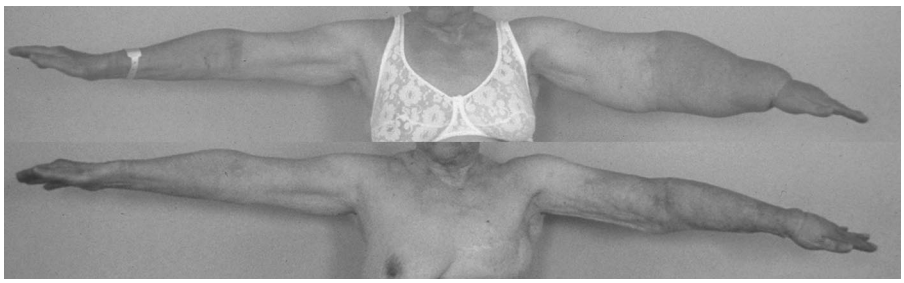

FIGURE 3. Preoperative (above) image of a 74-year-old woman with upper-extremity lymphedema secondary to surgical management of breast cancer. Results after circumferential liposuction (below) demonstrate sustained volume reduction 15 years postoperatively. (© Håkan Brorson 2006.)

The most recently developed technique for the surgical treatment of lymphedema has been the removal of subcutaneous fatty tissue through circumferential liposuction of the affected limb. Given the inflammation-induced adipose tissue deposition seen in lymphedema, liposuction performed with specialized suction-assisted lipectomy cannulas modified from the traditional cannulas used in cosmetic body contouring is a well- tailored approach that requires no excisional component, with only small, 3-mm incisions used in the procedure.[103] Results from the largest published case series,[61] done in women with upper-extremity lymphedema secondary to breast cancer therapy, show significant improvement in appearance and symptoms (Fig. 3). Patients in this study demonstrated postoperative mean edema volume reduction of 106% at 4 years' follow-up,[103] with results sustained now 10 years postoperatively (Brorson H, unpublished data). Recent use of this technique in patients with lower-extremity lymphedema has shown significant benefit in this population as well with regard to limb size and associated symptoms.[104] Postoperatively, patients undergoing suction-assisted lipectomy also require continuous treatment with compression garments, after it was noted that patients who discontinued their compressive therapy saw a rapid increase in limb edema.[61] However, given that liposuction is a significantly less invasive procedure with reduced complication rates as compared with excisional and microsurgical approaches, combination therapy with compression garment use may prove the optimal approach for sustained improvement in symptoms and disfigurement while minimizing risk and discomfort to the patient.

While surgical management has been used in patients with a wide range in severity of symptoms, patients with longstanding lymphedema dominated by fibrosis, particularly those with congenital lymphedema, are typically not appropriate surgical candidates and should continue trials of conservative therapy. Patients must also be counseled that these procedures, particularly the excisional and microsurgical approaches, can be lengthy operations, carrying with them associated risks of prolonged anesthesia and potential blood loss. Additionally, as is the case with all current therapies, none of the available surgical techniques completely address patients' underlying lymphatic dysfunction, although patients can achieve resolution of their symptoms and extremity swelling with sustained adherence to compression garment regimens postoperatively.

Whether conservative or surgical treatment has been used, the final common path of all lymphedema treatment approaches is the use of compression garments. When the excess edema volume has decreased such that a steady state has been achieved (ie, no pitting), new garments can be prescribed based on the most current limb measurements. In this way, the garments are renewed at least 4 times during the first year after initial garment prescription or surgical intervention. Garments are worn continuously, with treatment interrupted only briefly while the patient is showering.

Recommendations and Conclusions

Patients with lymphedema may present to a variety of medical providers, from the surgical or radiation oncologist to the vascular surgeon to the primary care physician. A careful history and assessment of risk factors for lymphedema can raise or lower the suspicion of lymphatic dysfunction. Physical examination findings can be quite helpful in distinguishing lymphedema from other causes of swollen extremities. In cases where the diagnosis is unclear, lymphoscintigraphy should be performed to confirm the presence or absence of lymphatic dysfunction. Additional imaging studies, including ultrasound, CT, or MRI, may be indicated when lymphoscintigraphy results are negative or in cases when suspected underlying pathology would be better determined

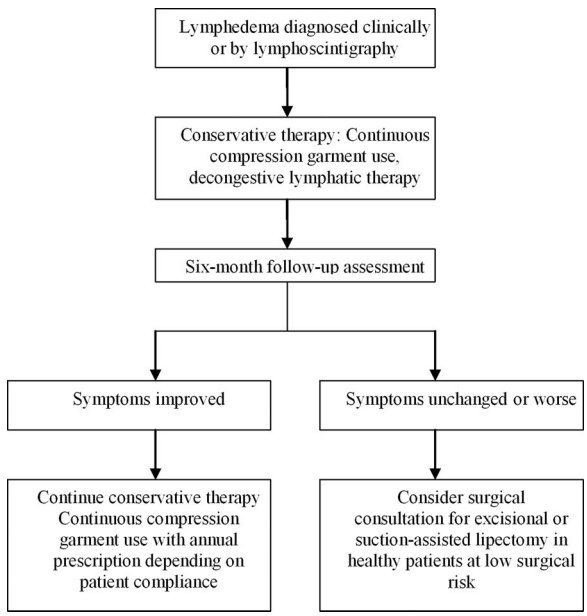

FIGURE 4. Algorithm for treatment of lymphedema.

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radiographically. After a diagnosis of lymphedema is made clinically or after lymphoscintigraphy, conservative therapy with continuous compression garment use should be initiated. Patients who achieve volume reduction of their affected limb and/or improvement in their associated symptoms should continue with conservative therapy and may elect to enter a less intensive maintenance phase involving only compression garment use. For patients who fail to respond to physical therapy and controlled compression, consultation regarding surgical intervention may be suggested in appropriate patients, which typically includes patients with less advanced disease who are otherwise healthy and low-risk surgical candidates (Fig. 4).

REFERENCES

1. Clodius L. Lymphatics, lymphodynamics, lymphedema: an update. *Plast Surg Outlook*. 1990;4:1.
2. Smeltzer DM, Stickler GB, Schirger A. Primary lymphedema in children and adolescents: a follow-up study and review. *Pediatrics*. 1985; 76:206.
3. Karkkainen MJ, Ferrell RE, Lawrence EC, et al. Missense mutations interfere with VEGFR-3 signalling in primary lymphoedema. *Nat Genet*. 2000;25:153.
4. Irrthum A, Karkkainen MJ, Devriendt K, et al. Congenital hereditary lymphedema caused by a mutation that inactivates VEGFR3 tyrosine kinase. *Am J Hum Genet*. 2000;67:295.
5. Wheeler ES, Chan V, Wassman R, et al. Familial lymphedema praecox: Meige's disease. *Plast Reconstr Surg*. 1981;67:362.
6. Yildirim-Toruner C, Subramanian K, El Manjra L, et al. 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;131:281.
7. Cederberg A, Gronning LM, Ahren B, et al. FOXC2 is a winged helix gene that counteracts obesity, hypertriglyceridemia, and diet-induced insulin resistance. *Cell*. 2001;106:563.
8. Szuba A, Shin WS, Strauss HW, et al. The third circulation: radionuclide lymphoscintigraphy in the evaluation of lymphedema. *J Nucl Med*. 2003;44:43.
9. Schunemann H, Willich N. [Lymphedema after breast carcinoma: a study of 5868 cases]. *Dtsch Med Wochenschr*. 1997;122:536.
10. Petrek JA, Senie RT, Peters M, et al. Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. *Cancer*. 2001;92:1368.
11. Querci della Rovere G, Ahmad I, Singh P, et al. An audit of the incidence of arm lymphoedema after prophylactic level I/II axillary dissection without division of the pectoralis minor muscle. *Ann R Coll Surg Engl*. 2003;85:158.
12. Ozaslan C, Kuru B. Lymphedema after treatment of breast cancer. *Am J Surg*. 2004;187:69.
13. Hinrichs CS, Watroba NL, Rezaishiraz H, et al. Lymphedema secondary to postmastectomy radiation: incidence and risk factors. *Ann Surg Oncol*. 2004;11:573.
14. Coen JJ, Taghian AG, Kachnic LA, et al. Risk of lymphedema after regional nodal irradiation with breast conservation therapy. *Int J Radiat Oncol Biol Phys*. 2003;55:1209.
15. Werner RS, McCormick B, Petrek J, et al. Arm edema in conservatively managed breast cancer: obesity is a major predictive factor. *Radiology*. 1991;180:177.
16. Schijven MP, Vingerhoets AJ, Rutten HJ, et al. Comparison of morbidity between axillary lymph node dissection and sentinel node biopsy. *Eur J Surg Oncol*. 2003;29:341.
17. Erickson VS, Pearson ML, Ganz PA, et al. Arm edema in breast cancer patients. *J Natl Cancer Inst*. 2001;93:96.
18. Borup Christensen S, Lundgren E. Sequelae of axillary dissection vs. axillary sampling with or without irradiation for breast cancer: a randomized trial. *Acta Chir Scand*. 1989;155:515.
19. Kissin MW, Querci della Rovere G, Easton D, et al. Risk of lymphoedema following the treatment of breast cancer. *Br J Surg*. 1986;73: 580.
20. Langer S, Guenther JM, Haigh PI, et al. Lymphatic mapping improves staging and reduces morbidity in women undergoing total mastectomy for breast carcinoma. *Am Surg*. 2004;70:881.
21. Armer J, Fu MR, Wainstock JM, et al. Lymphedema following breast cancer treatment, including sentinel lymph node biopsy. *Lymphology*. 2004;37:73.
22. Leidenius M, Leivonen M, Vironen J, et al. The consequences of long-time arm morbidity in node-negative breast cancer patients with sentinel node biopsy or axillary clearance. *J Surg Oncol*. 2005;92:23.
23. Purushotham AD, Upponi S, Klevesath MB, et al. Morbidity after sentinel lymph node biopsy in primary breast cancer: results from a randomized controlled trial. *J Clin Oncol*. 2005;23:4312.
24. Soran A, Aydin C, Harlak A, et al. Impact of sentinel lymph node biopsy on lymphedema following breast cancer treatment. *Breast J*. 2005;11:370.
25. Box RC, Reul-Hirche HM, Bullock-Saxton JE, et al. Physiotherapy after breast cancer surgery: results of a randomised controlled study to minimise lymphoedema. *Breast Cancer Res Treat*. 2002;75:51.
26. Kocak Z, Overgaard J. Risk factors of arm lymphedema in breast cancer patients. *Acta Oncol*. 2000;39:389.
27. van der Veen P, De Voogdt N, Lievens P, et al. Lymphedema development following breast cancer surgery with full axillary resection. *Lymphology*. 2004;37:206.
28. Greene AK, Borud L, Slavin SA. Blood pressure monitoring and venipuncture in the lymphedematous extremity. *Plast Reconstr Surg*. 2005;116:2058.
29. Smahel J. Adipose tissue in plastic surgery. *Ann Plast Surg*. 1986;16: 444.
30. Ryan TJ. Lymphatics and adipose tissue. *Clin Dermatol*. 1995;13:493.
31. Gaffney RM, Casley-Smith JR. Excess plasma proteins as a cause of chronic inflammation and lymphoedema: biochemical estimations. *J Pathol*. 1981;133:229.
32. The diagnosis and treatment of peripheral lymphedema: consensus document of the International Society of Lymphology. *Lymphology.* 2003;36:84.
33. Mortimer PS. Swollen lower limb-2: lymphoedema. *BMJ*. 2000;320: 1527.
34. Ruocco V, Schwartz RA, Ruocco E. Lymphedema: an immunologically vulnerable site for development of neoplasms. *J Am Acad Dermatol*. 2002;47:124.
35. Offori TW, Platt CC, Stephens M, et al. Angiosarcoma in congenital hereditary lymphoedema (Milroy's disease): diagnostic beacons and a review of the literature. *Clin Exp Dermatol*. 1993;18:174.
36. Kirchmann TT, Smoller BR, McGuire J. Cutaneous angiosarcoma as a second malignancy in a lymphedematous leg in a Hodgkin's disease survivor. *J Am Acad Dermatol*. 1994;31:861.
37. Sinclair SA, Sviland L, Natarajan S. Angiosarcoma arising in a chronically lymphoedematous leg. *Br J Dermatol*. 1998;138:692.
38. Azurdia RM, Guerin DM, Verbov JL. Chronic lymphoedema and angiosarcoma. *Clin Exp Dermatol*. 1999;24:270.
39. Woodward AH, Ivins JC, Soule EH. Lymphangiosarcoma arising in chronic lymphedematous extremities. *Cancer*. 1972;30:562.
40. Rockson SG. Lymphedema. *Am J Med*. 2001;110:288.
41. Stemmer R. [A clinical symptom for the early and differential diagnosis of lymphedema]. *Vasa*. 1976;5:261.
42. Ward LC. Bioelectrical impedance analysis: proven utility in lymphedema risk assessment and therapeutic monitoring. *Lymphat Res Biol*. 2006;4:51.
43. Cornish B. Bioimpedance analysis: scientific background. *Lymphat Res Biol*. 2006;4:47.
44. Bagheri S, Ohlin K, Olsson G, et al. Tissue tonometry before and after liposuction of arm lymphedema following breast cancer. *Lymphat Res Biol*. 2005;3:66.
45. Moseley A, Piller N, Carati C. Combined opto-electronic perometry and bioimpedance to measure objectively the effectiveness of a new treatment intervention for chronic secondary leg lymphedema. *Lymphology*. 2002;35:136.
46. Watanabe R, Miura A, Inoue K, et al. Evaluation of leg edema using a multifrequency impedance meter in patients with lymphatic obstruction. *Lymphology*. 1989;22:85.

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47. Mikes DM, Cha BA, Dym CL, et al. Bioelectrical impedance analysis revisited. *Lymphology*. 1999;32:157.
48. Hayes S, Cornish B, Newman B. Comparison of methods to diagnose lymphoedema among breast cancer survivors: 6-month follow-up. *Breast Cancer Res Treat*. 2005;89:221.
49. Ward LC, Bunce IH, Cornish BH, et al. Multi-frequency bioelectrical impedance augments the diagnosis and management of lymphoedema in post-mastectomy patients. *Eur J Clin Invest*. 1992;22:751.
50. Cornish BH, Chapman M, Thomas BJ, et al. Early diagnosis of lymphedema in postsurgery breast cancer patients. *Ann N Y Acad Sci*. 2000;904:571.
51. Weissleder H, Weissleder R. Lymphedema: evaluation of qualitative and quantitative lymphoscintigraphy in 238 patients. *Radiology*. 1988; 167:729.
52. McNeill GC, Witte MH, Witte CL, et al. Whole-body lymphangioscintigraphy: preferred method for initial assessment of the peripheral lymphatic system. *Radiology*. 1989;172:495.
53. Witte CL, Witte MH, Unger EC, et al. Advances in imaging of lymph flow disorders. *Radiographics*. 2000;20:1697.
54. Monnin-Delhom ED, Gallix BP, Achard C, et al. High resolution unenhanced computed tomography in patients with swollen legs. *Lymphology*. 2002;35:121.
55. Hudson TM, Hamlin DJ, Enneking WF, et al. Magnetic resonance imaging of bone and soft tissue tumors: early experience in 31 patients compared with computed tomography. *Skeletal Radiol*. 1985;13:134.
56. Case TC, Witte CL, Witte MH, et al. Magnetic resonance imaging in human lymphedema: comparison with lymphangioscintigraphy. *Magn Reson Imaging*. 1992;10:549.
57. Dimakakos PB, Stefanopoulos T, Antoniades P, et al. MRI and ultrasonographic findings in the investigation of lymphedema and lipedema. *Int Surg*. 1997;82:411.
58. Astrom KG, Abdsaleh S, Brenning GC, et al. MR imaging of primary, secondary, and mixed forms of lymphedema. *Acta Radiol*. 2001;42: 409.
59. Badger CM, Peacock JL, Mortimer PS. A randomized, controlled, parallel-group clinical trial comparing multilayer bandaging followed by hosiery versus hosiery alone in the treatment of patients with lymphedema of the limb. *Cancer*. 2000;88:2832.
60. Vodder E. [Vodder's lymph drainage: a new type of chirotherapy for esthetic prophylactic and curative purposes]. *Asthet Med (Berl)*. 1965; 14:190.
61. Brorson H, Svensson H. Liposuction combined with controlled compression therapy reduces arm lymphedema more effectively than controlled compression therapy alone. *Plast Reconstr Surg*. 1998;102: 1058.
62. Foldi E, Foldi M, Weissleder H. Conservative treatment of lymphoedema of the limbs. *Angiology*. 1985;36:171.
63. Vodder E. Lymphdrainage ad modem Vodder. *Aesthet Med*. 1965;14: 190.
64. McNeely ML, Magee DJ, Lees AW, et al. The addition of manual lymph drainage to compression therapy for breast cancer related lymphedema: a randomized controlled trial. *Breast Cancer Res Treat*. 2004;86:95.
65. Andersen L, Hojris I, Erlandsen M, et al. Treatment of breast-cancer-related lymphedema with or without manual lymphatic drainage: a randomized study. *Acta Oncol*. 2000;39:399.
66. Didem K, Ufuk YS, Serdar S, et al. The comparison of two different physiotherapy methods in treatment of lymphedema after breast surgery. *Breast Cancer Res Treat*. 2005;93:49.
67. Williams AF, Vadgama A, Franks PJ, et al. A randomized controlled crossover study of manual lymphatic drainage therapy in women with breast cancer-related lymphoedema. *Eur J Cancer Care (Engl)*. 2002; 11:254.
68. Hinrichs CS, Gibbs JF, Driscoll D, et al. The effectiveness of complete decongestive physiotherapy for the treatment of lymphedema following groin dissection for melanoma. *J Surg Oncol*. 2004;85:187.
69. Ko DS, Lerner R, Klose G, et al. Effective treatment of lymphedema of the extremities. *Arch Surg*. 1998;133:452.
70. Szuba A, Cooke JP, Yousuf S, et al. Decongestive lymphatic therapy for patients with cancer-related or primary lymphedema. *Am J Med*. 2000;109:296.
71. Daane S, Poltoratszy P, Rockwell WB. Postmastectomy lymphedema management: evolution of the complex decongestive therapy technique. *Ann Plast Surg*. 1998;40:128.
72. Mondry TE, Riffenburgh RH, Johnstone PA. Prospective trial of complete decongestive therapy for upper extremity lymphedema after breast cancer therapy. *Cancer J*. 2004;10:42.
73. Szuba A, Strauss W, Sirsikar SP, et al. Quantitative radionuclide lymphoscintigraphy predicts outcome of manual lymphatic therapy in breast cancer-related lymphedema of the upper extremity. *Nucl Med Commun*. 2002;23:1171.
74. Richmand DM, O'Donnell TF Jr, Zelikovski A. Sequential pneumatic compression for lymphedema: a controlled trial. *Arch Surg*. 1985;120: 1116.
75. Klein MJ, Alexander MA, Wright JM, et al. Treatment of adult lower extremity lymphedema with the Wright linear pump: statistical analysis of a clinical trial. *Arch Phys Med Rehabil*. 1988;69:202.
76. Miranda F Jr, Perez MC, Castiglioni ML, et al. Effect of sequential intermittent pneumatic compression on both leg lymphedema volume and on lymph transport as semi-quantitatively evaluated by lymphoscintigraphy. *Lymphology*. 2001;34:135.
77. Szuba A, Achalu R, Rockson SG. Decongestive lymphatic therapy for patients with breast carcinoma-associated lymphedema: a randomized, prospective study of a role for adjunctive intermittent pneumatic compression. *Cancer*. 2002;95:2260.
78. Zanolla R, Monzeglio C, Balzarini A, et al. Evaluation of the results of three different methods of postmastectomy lymphedema treatment. *J Surg Oncol*. 1984;26:210.
79. Dini D, Del Mastro L, Gozza A, et al. The role of pneumatic compression in the treatment of postmastectomy lymphedema: a randomized phase III study. *Ann Oncol*. 1998;9:187.
80. Johansson K, Lie E, Ekdahl C, et al. A randomized study comparing manual lymph drainage with sequential pneumatic compression for treatment of postoperative arm lymphedema. *Lymphology*. 1998;31:56.
81. Pain SJ, Purushotham AD. Lymphoedema following surgery for breast cancer. *Br J Surg*. 2000;87:1128.
82. Brennan MJ, Miller LT. Overview of treatment options and review of the current role and use of compression garments, intermittent pumps, and exercise in the management of lymphedema. *Cancer*. 1998;83: 2821.
83. Casley-Smith JR, Morgan RG, Piller NB. Treatment of lymphedema of the arms and legs with 5,6-benzo-α-pyrone. *N Engl J Med*. 1993;329: 1158.
84. Badger C, Seers K, Preston N, et al. Antibiotics/anti-inflammatories for reducing acute inflammatory episodes in lymphoedema of the limbs. *Cochrane Database Syst Rev.* 2004;CD003143.
85. Loprinzi CL, Sloan J, Kugler J. Coumarin-induced hepatotoxicity. *J Clin Oncol*. 1997;15:3167.
86. Petrek JA, Pressman PI, Smith RA. Lymphedema: current issues in research and management. *CA Cancer J Clin*. 2000;50:292.
87. Rockson SG, Miller LT, Senie R, et al, American Cancer Society Lymphedema Workshop. Workgroup III: diagnosis and management of lymphedema. *Cancer.* 1998;83:2882.
88. Paskett ED, Stark N. Lymphedema: knowledge, treatment, and impact among breast cancer survivors. *Breast J*. 2000;6:373.
89. Micke O, Bruns F, Mucke R, et al. Selenium in the treatment of radiation-associated secondary lymphedema. *Int J Radiat Oncol Biol Phys*. 2003;56:40.
90. Zimmermann T, Leonhardt H, Kersting S, et al. Reduction of postoperative lymphedema after oral tumor surgery with sodium selenite. *Biol Trace Elem Res*. 2005;106:193.
91. Gothard L, Cornes P, Earl J, et al. Double-blind placebo-controlled randomised trial of vitamin E and pentoxifylline in patients with chronic arm lymphoedema and fibrosis after surgery and radiotherapy for breast cancer. *Radiother Oncol*. 2004;73:133.
92. Charles H. Elephantiasis of the leg. In: Latham A, English T, eds. *A System of Treatment*. London: Churchill; 1912.
93. Gloviczki P. Principles of surgical treatment of chronic lymphoedema. *Int Angiol*. 1999;18:42.
94. O'Brien BM, Mellow CG, Khazanchi RK, et al. Long-term results after microlymphaticovenous anastomoses for the treatment of obstructive lymphedema. *Plast Reconstr Surg*. 1990;85:562.

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95. Olszewski WL. The treatment of lymphedema of the extremities with microsurgical lympho-venous anastomoses. *Int Angiol*. 1988;7:312.
96. Baumeister RG, Siuda S. Treatment of lymphedemas by microsurgical lymphatic grafting: what is proved? *Plast Reconstr Surg*. 1990;85:64.
97. Campisi C, Boccardo F. Microsurgical techniques for lymphedema treatment: derivative lymphatic-venous microsurgery. *World J Surg*. 2004;28:609.
98. Weiss M, Baumeister RG, Hahn K. Post-therapeutic lymphedema: scintigraphy before and after autologous lymph vessel transplantation: 8 years of long-term follow-up. *Clin Nucl Med*. 2002;27:788.
99. Classen DA, Irvine L. Free muscle flap transfer as a lymphatic bridge for upper extremity lymphedema. *J Reconstr Microsurg*. 2005;21:93.
100. Slavin SA, Van den Abbeele AD, Losken A, et al. Return of lymphatic function after flap transfer for acute lymphedema. *Ann Surg*. 1999;229:421.
101. Medgyesi S. A successful operation for lymphoedema using a myocutaneous flap as a "wick." *Br J Plast Surg*. 1983;36:64.
102. Slavin SA, Upton J, Kaplan WD, et al. An investigation of lymphatic function following free-tissue transfer. *Plast Reconstr Surg*. 1997;99:730.
103. Brorson H. Liposuction in arm lymphedema treatment. *Scan J Surg*. 2003;92:287.
104. Greene AK, Slavin SA, Borud L. Treatment of lower extremity lymphedema with suction-assisted lipectomy. *Plast Reconstr Surg*. 2006;118:118e.

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