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REVIEW ARTICLE

Breast Cancer-Related Lymphedema: A Review of Management and Innovative Surgical Techniques

Keeley D. Newsom[1], David Xiang[2], Alan Yang, MSc [2], Libby R. Copeland-Halperin, MD[3], *Anna Weiss, MD[2,4], *Justin M. Broyles, MD[2,5]

1. Indiana University School of Medicine, Indianapolis, IN
2. Harvard Medical School, Boston, MA
3. 1001 Fifth Avenue, New York, NY
4. Division of Surgical Oncology, Department of Surgery, University of Rochester, Rochester NY
5. Division of Plastic Surgery, Department of Surgery, Brigham and Women's Hospital, Boston, Massachusetts

*Anna_weiss@urmc.rochester.edu

#These authors contributed equally to this work

ABSTRACT

Lymphedema is one of the most feared complications of breast cancer treatment. The objective of this article is to review the basic workup, staging, and diagnostic criteria for lymphedema and to discuss non-surgical and surgical treatments, with a focus on breast-cancer related lymphedema. Non-surgical treatment consists of intensive physical therapy including manual lymphatic drainage via massage, daily compression wraps, and exercises to prevent scarring and increase mobility. Surgical intervention is considered when non-surgical treatment is ineffective or more recently as a preventive measure. Surgical interventions, used once lymphedema has developed, include 1) lympho-venous bypass, which is the anastomosis of lymphatic vessels distal to the site of dermal backflow to neighboring venules to shunt lymphatic drainage away from the area of lymphatic injury; 2) vascularized lymph node transplant, in which lymph nodes are harvested from a donor site with their supporting artery and vein and transferred to the affected recipient site; and 3) debulking procedures including liposuction and direct excision. Preventive surgical interventions include 1) lymphatic microsurgical preventive healing approach, known as LYMPHA, which also utilizes lympho-venous anastomoses but at the time of lymph node dissection to anastomose lymphatic channels transected during lymph node dissection with adjacent veins to preserve lymphatic drainage of the arm; and 2) axillary reverse mapping, which involves tracer or dye injection within the ipsilateral arm before axillary surgery so that the breast surgeons are able to delineate nodal drainage and therefore attempt to spare nodes specific to arm tissue provided they are not the sentinel lymph node. Patient selection is critical for these procedures, and requires a multi-disciplinary approach.

Introduction

Lymphedema is a chronic and progressive condition estimated to affect 3 million people in the United States and 90 to 250 million people worldwide, affecting women more than men.[1,2] Lymphedema is caused by the accumulation of protein-rich interstitial fluid due to mechanical or volume insufficiency within the lymphatic system.[3] Without treatment, this fluid build-up progresses to inflammation, edema, fat deposition, and fibrosis, resulting in further lymphatic damage.[4] The objective of this article is to review the basic workup, staging, and diagnostic criteria for lymphedema and to discuss non-surgical and surgical treatments, with a focus on breast-cancer related lymphedema.

Background

Lymphedema is classified as primary or secondary. Primary lymphedema is rare and associated with germline variations and congenital or hereditary lymphatic dysfunction.[5,6] Most primary lymphedema is present at birth or develops before puberty and patients often have other clinical manifestations, such as cholestasis, cerebrovascular malformations, vertebral defects, or hearing problems.[7] Secondary lymphedema is more prevalent and develops after lymphatics become obstructed or suffer infectious, inflammatory, traumatic or surgical or other iatrogenic injury. It can develop anytime months to years after the triggering event.[8] In developing countries, filarial infection (due to *Wuchereria bancrofti, Brugia malayi, or Brugia timori)* is the most prevalent cause of secondary lymphedema, while in developed countries iatrogenic causes (e.g. lymph node resection and/or radiation) are most common.[9] Prior reviews of cancer-related lymphedema reported an incidence of 18%, 6%, and 22% following treatment for melanoma, lymph node-negative breast cancer, and lymph node-positive breast cancer, respectively.[10–12] In addition to oncologic lymph node resection or radiation therapy, risk factors for lymphedema include a family history of lymphedema and obesity.[13] Independent risk factors for breast cancer-related lymphedema include cellulitis, low-level limb volume changes, and obesity.[14,15]

Lymphedema has a detrimental effect on patients' lives and is associated with several physical and psychiatric effects.[16] Patients with lymphedema are at greater risk for cellulitis in the affected limb (odds ratio 71.2) and can develop chronic pain and functional impairment in severe cases.[17] For example, patients with long-standing secondary lymphedema have also been shown to have higher risk of developing cutaneous angiosarcomas.[18] Due to pain and significant disability, patients with lymphedema are also at higher risk for depression, anxiety, and negative body image.[19]

In addition to psychosocial hardships, lymphedema carries a significant financial burden for patients and the healthcare system. On average, breast cancer survivors with lymphedema have higher medical costs (upwards of 1,000 USD per year difference in out-of-pocket expenses) compared with patients without lymphedema due to the increased need for doctor visits and physical therapy, as well as loss of income if they are unable to work.[20] Additionally, coverage of surgical treatments varies by insurance company and coverage policies are often elusive. In one study, less than half of insurance companies had a statement of coverage for more modern microsurgical techniques including lymphovenous bypass and vascularized lymph node transfer, and reimbursement for such procedures was almost universally denied. Debulking procedures were more commonly covered, though with strict inclusion criteria.[21] In contrast, non-surgical treatments were more likely to be covered.[22]

Workup and Staging

The definition of lymphedema varies in the literature and is often described subjectively. Several different imaging techniques can be used to more objectively evaluate lymphedema. One of the most common techniques is indocyanine green fluorescence, whereby a near-infrared fluorescent dye is injected intradermally to visualize superficial lymphatic networks.[23] However, this technique is limited by the superficial depth of penetration (about 1.5 cm) of near-infrared cameras into the tissue.[24] Gadolinium-enhanced magnetic resonance (MR) lymphography allows for three-dimensional visualization of lymphatic networks throughout an entire limb. It also provides information about soft tissue changes. It is challenging to distinguish veins and lymphatics with MR lymphangiography; however, this can be minimized by subtraction venography and/or concurrent use of other contrast agents to suppress the venous signal.[25] Tc-99 radioisotope lymphoscintigraphy, which involves intradermal injection of Technetium-99 Sulfur colloid, is a third modality. Sometimes paired with computed tomography, this technique is useful for assessing lymphatic function and individual lymph nodes, but is limited by low resolution and the inability to capture superficial lymphatics.[24]

Different lymphedema staging systems exist based on clinical presentation (e.g., limb

volume, edema), imaging (e.g., dermal backflow patterns), or both.[1,26–29] One commonly used clinical staging system is from the International Society of Lymphology (ISL). ISL stage 0 is subclinical lymphedema where lymph transport is impaired, but there is no swelling. In ISL stage 1 limb swelling improves with elevation, while in stage 2 there is pitting edema that does not resolve with limb elevation alone. In stage 3, pitting is absent due to fibrosis and the skin becomes thickened and hyperpigmented with fatty deposits.

In addition to clinical symptomatology, imaging findings can be used to establish or refine staging for lymphedema. In fact, staging systems that combine clinical and imaging findings are superior to clinical criteria alone.[30] For instance, indocyanine green lymphography can be used to classify the severity of lymphedema based on the presence and type of dermal backflow pattern. Dermal backflow represents the leakiness of the lymphatic channels. The pattern of backflow (e.g., linear, splash, stardust, or diffuse) and characteristics such as the number of patent lymphatic vessels visualized help to quantify the severity of lymphatic dysfunction.[31] A linear lymphatic backflow pattern consists of a linear fluorescent imaging pattern and represents more mild lymphedema. The splash and stardust patterns represent intermediate lymphedema; the splash pattern consists of dye scattered in tortuous lymphatic channels, while the stardust pattern depicts spotted fluorescent signals. Diffuse backflow, where dye is widely distributed without identifiable spots, indicates severe lymphedema.

Medical Treatments

Non-surgical treatment is the mainstay of lymphedema management. This consists of intensive physical therapy with compression and complete decongestive therapy (CDT). CDT involves an intensive followed by a maintenance stage.[32] The intensive stage consists of therapist-directed manual lymphatic drainage via massage, daily compression wraps, exercises to prevent scarring and stiffness, and meticulous skin and nail care to avoid complications such as cellulitis and erysipelas.[33] This regimen is time- and labor-intensive, requiring patients to attend up to 5 sessions per week for up to 6 weeks. The maintenance stage is life-long, requiring the patient to direct their own care using modalities from the intensive stage with the goal of maintaining limb volume. Patient outcomes for CDT are highly dependent on patient adherence.[34–40] More recently, CDT has been combined with pneumatic compression or extracorporeal shock therapy in an attempt to improve outcomes.[41,42]

There is limited evidence to support the use of pharmacotherapy to treat lymphedema. Studies evaluating steroid injections have demonstrated similar results to CDT. A randomized controlled trial demonstrated CDT and ultrasound-guided injection of the stellate ganglion yielded similar arm circumference measurements, patient satisfaction, and quality of life measures on short-term follow-up.[43] However, more long-term data is needed.

Recently, tacrolimus, an anti-T cell immunosuppressive drug that has already been FDA-approved as a topical agent in atopic dermatitis, has been shown to both prevent and treat lymphedema in mouse models.[44] Similarly, ketoprofen, a non-steroidal anti-inflammatory, has also been shown to improve lymphedema in animal models.[45] However, early human trials for ketoprofen only demonstrate reduction in skin thickness; limb volume remains unchanged when compared to placebo up to 4 months after treatment.[46] While diuretics may provide limited improvement early in the disease course in patients with heart failure or venous insufficiency, they have not proven effective for long-term management.[47] Investigations using Coumarin, vitamin E, and pentoxifylline have also failed to demonstrate improvement in lymphedema.[48,49]

Surgical Treatments

Surgical intervention is considered when non-surgical management is insufficient, ineffective, or in patients with recurrent infection.[50] In patients who present late in the disease course, a preoperative trial of CDT is warranted, as it can optimize conditions for surgery.[51] Untreated or uncontrolled malignancy, however, is a contraindication to surgical treatment.

Several surgical techniques have been described for the management of lymphedema, typically based on stage. In some patients, a relative, dynamic venous stenosis may contribute to lymphedema in the post-axillary lymph node dissection setting.[52] For these patients, scar release and lipofilling alone may improve lymphedema.[53] Physiologic techniques, such as lymphovenous bypass (LVB) or vascularized lymph node transfer (VLNT) may be preferred in other cases. For advanced disease (stage 3), liposuction-assisted or excisional debulking may be considered. While these techniques can reduce disease severity and improve symptoms, they do not cure lymphedema. Prevention, therefore, would be ideal and procedures like lymphatic microsurgical preventive healing approach (LYMPHA) are gaining popularity. A summary of surgical managements for

lymphedema can be found in **Table 1**, and comprise the remainder of this review.

TABLE 1: A summary of surgical treatments and surgical prophylactic procedures for breast-cancer related lymphedema. Abbreviations: LVB, lymphovenous bypass; VLNT, vascularized lymph node transfer; LYMPHA, lymphatic microsurgical preventative healing approach.

Surgical Intervention	Physiologic/ Excisional	Treatment/ Prophylactic	Intended Stage(s) to Treat	Microscope Required	Risk of Donor Site Lymphedema
Debulking	Excisional	Treatment	Stage 3 (late)	No	NA
LVB	Physiologic	Treatment	Stage 1 (early)	Yes	NA
VLNT	Physiologic	Treatment	Stage 1, 2, and 3	Yes	Yes
LYMPHA	Physiologic	Prophylactic	NA	Yes	NA

Lymphovenous Bypass

Lymphovenous bypass (LVB) is a lymphovenous anastomosis typically used in the treatment of early-stage lymphedema.[54–56] LVB leads to volume reduction in the affected limb and has been shown to improve Lymphedema Life Impact Scale scores when used in conjunction with vascularized lymph node transplantation to treat advanced-stage lymphedema.[57] During LVB, lymphatic vessels distal to the site of dermal backflow are anastomosed with neighboring venules to shunt lymphatic drainage away from the area of lymphatic injury. The success of LVB depends on selection of patent lymphatic vessels and reflux-free venules. The donor lymphatic vessel must be capable of carrying lymph, and the recipient vein must be compliant enough to bear the increased drainage without refluxing. Thus, the lymphatic vessel should have minimal sclerosis and the vein minimal fibrosis (e.g., due to radiation or post-surgical changes) to decrease risks of venous hypertension and reflux.

Fluorescent lymphography and non-invasive venous imaging can help with vessel selection and surgical planning. Moreover, the addition of non-invasive venous imaging can increase selection of reflux-free veins compared to fluorescent lymphography only.[58] The choice of anastomotic technique (i.e., end-to-end, end-to-side, side-to-end) depends on the vessel caliber and number of anastomoses (**Figure 1**).

Vascularized Lymph Node Transplant

Vascularized lymph node transplant (VLNT) is a treatment for patients with moderate to advanced lymphedema and is most commonly used in patients with disease that is resistant to physiotherapy, severe deformity, or patient preference.[59] Some have also advocated for using VLNT in patients with early-stage disease to help prevent complex or permanent consequences of lymphedema.[60]

In VLNT, lymph nodes are harvested from a donor site with their supporting artery and vein and transferred to the affected recipient site.[61] The goal of VLNT is to improve lymphatic flow by utilizing lymph nodes as low-pressure systems to collect lymphatic fluid and shift it into the venous system.[62] VLNT may also promote growth of new lymphatic channels through growth factors secreted by transplanted lymph nodes.[63]

Donor sites include the inguinal, axillary, supraclavicular, submental, thoracic, mesenteric jejunal, and omental nodal basins. Inguinal nodes are the most popular for upper extremity lymphedema and have a low complication profile.[64] In patients undergoing postmastectomy breast reconstruction, transferring a chimeric deep inferior epigastric artery perforator flap with inguinal lymph nodes is often used.[31] VLNT is generally well tolerated and risks are germane to each specific donor site. For axillary/inguinal sites, there is a slight risk of iatrogenic lymphedema (0-1.5%), though with the combination of reverse mapping, the risk of iatrogenic donor lower extremity lymphedema can be significantly reduced.[65–67]

Outcomes of VLNT are generally favorable with reductions in extracellular fluid ranging from 32% to 54% in limb volume reductions and decreasing the number of cellulitis episodes by 2.1 episodes per year.[68] VLNT has also been shown to improve patient-reported outcomes and improve limb function measures.[67–69] More recently, some have argued for simultaneous VLNT and LVB with studies demonstrating improved volume reduction and quality of life for both early and advanced secondary lymphedema.[57]

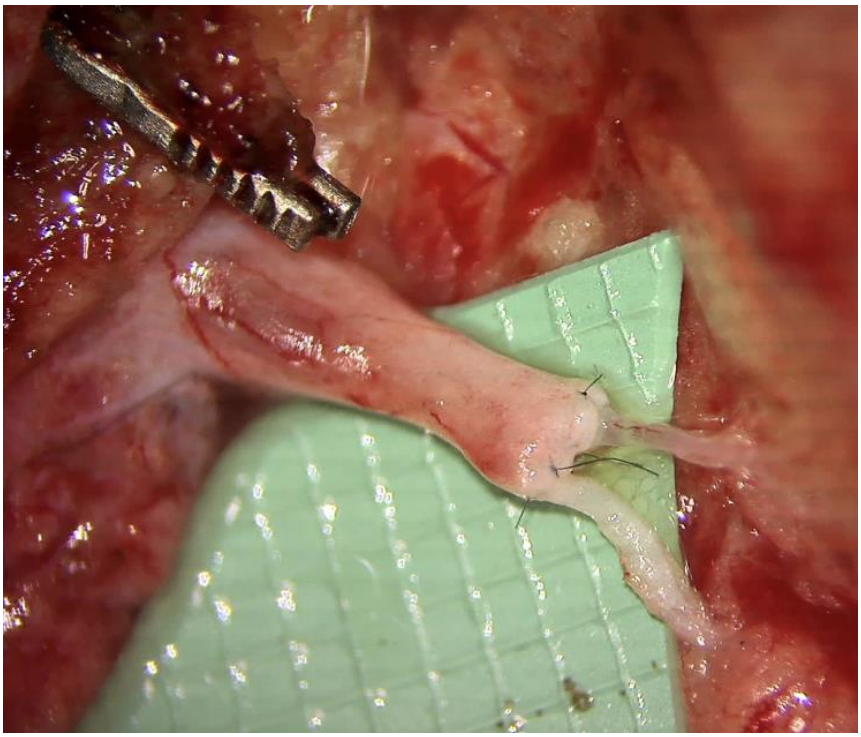

FIGURE 1: Intra-operative photograph of a lymphovenous bypass. Here two smaller lymphatic channels (right) are anastomosed to a vein (left) each in an end-to-end fashion.

Debulking Procedures

Suction-assisted:

Debulking procedures are considered for patients with advanced-stage lymphedema. In advanced lymphedema, the problem is no longer fluid accumulation, rather adipose tissue deposition (lipedema) and it cannot be reduced with CDT or microsurgical techniques alone. In these advanced stages limb volume can be reliably reduced through liposuction, which has been shown to decrease limb volume up to 15 years following intervention.[70,71] Following liposuction, patients must continue to wear compression garments consistently and indefinitely to prevent disease progression.[72] Risks of liposuction include hematoma, seroma, and further lymphatic damage.[73]

Those with excess limb edema greater than 1 liter in volume or an affected arm to healthy arm volume ratio of 1.3:1 benefit the most from suction-assisted liposuction. Liposuction is best suited for patients with lipedema superimposed upon lymphedema. Clinically, this can be distinguished by assessing for the presence of pitting edema. The former will demonstrate minimal residual pitting when pressure is release, while the latter will demonstrate pitting >5 mm after releasing pressure.[70] In individuals with >5mm of pitting, CDT and compression therapy are indicated prior to considering liposuction.

Direct Excision:

For those presenting late in the disease course, liposuction-assisted debulking may be ineffective. In these severe cases, direct excisional techniques may be employed. First described in 1912, the Charles procedure involves excising the skin and soft tissue of the affected limb to the level of the deep fascia followed by primary closure or skin grafting.[74] Excisional debulking has become less commonly performed due to high complication rates (e.g. wound healing problems, loss of limb function) and poor aesthetic outcome.

LYMPHA

Lymphatic microsurgical preventive healing approach (LYMPHA) is a prophylactic technique to prevent iatrogenic lymphedema in the setting of axillary lymph node dissection due to breast cancer. LYMPHA utilizes lympho-venous anastomoses (LVA) at the time of lymph node dissection to anastomose lymphatic channels transected during lymph node dissection with adjacent veins to preserve lymphatic drainage of the arm.[75] Several techniques have been described to identify candidate lymphatic channels, including use of isosulfan blue, methylene blue dye, or fluorescein isothiocyanate.[76–78]

First described in 2009 by Boccardo, *et. al.,* LYMPHA has been shown to decrease rates of lymphedema from 30% to as low as 4%.[75–77,79] In Boccardo, *et al.*'s original study, none of the 18

included patients who underwent LYMPHA developed lymphedema at 12-month follow-up.[75] On four-year follow up of 71 patients, 4% of LYMPHA patients developed lymphedema versus 30% observed in patients who underwent axillary node dissection without LYMPHA. While long-term follow-up data continues to emerge, LYMPHA is a promising technique for decreasing incidence of lymphedema in breast cancer patients who require axillary node dissection.[80] LYMPHA may also decrease the incidence of lymphedema in the setting of regional lymph node radiation.[81]

A large disadvantage for LYMPHA is that is requires the use of microsurgical techniques and instruments, thus limiting its use in resource-limited areas. However, simplified LYMPHA (S-LYMPHA), which avoids the use of microsurgery by implementing a sleeve technique, has been shown to be very effective in preventing lymphedema: patients who had undergone axillary lymph node dissection alone had a 6.3 times greater risk of developing lymphedema than those who had the same procedure in adjunct to S-LYMPHA.[82]

Exact indications for LYMPHA are still being defined, but those at higher risk of developing lymphedema will likely benefit most. These factors include a higher BMI (>30), older age, need for axillary lymph node dissection, and need for regional nodal irradiation.[76,80,81] As with LVB and VLNT, LYMPHA requires microsurgical expertise and specialized equipment.

ARM

Axillary reverse mapping (ARM) is another promising prophylactic technique used in adjunct with sentinel lymph node biopsies or axillary lymph node dissections. Using a technetium sulfur colloid injection to the affected breast and a blue dye injection within the ipsilateral arm, breast surgeons are able to delineate nodal drainage and therefore attempt to spare nodes specific to arm tissue provided they are not the sentinel lymph node. If the arm lymphatics must be divided, they are re-approximated loosely. This technique has had promising preliminary results, with lymphedema rates after the procedure as low as 1.7% at 12-month follow up.[83] Randomized controlled trial data is currently being collected to better assess this technique in the prevention of lymphedema (ClinicalTrials.gov Identifier: NCT03927027).

Limitations

While excisional and liposuction-assisted debulking have been used for the surgical management of lymphedema for decades, techniques such as LVB, VLNT, LYMPHA, and ARM are relatively novel and thus long-term outcome data are limited. Short-term outcomes are promising, but continuing to trend long-term outcome data for these innovative techniques is pivotal as lymphedema can develop even years after insult to lymph drainage.

Finally, while this review focuses on breast-cancer related lymphedema after surgical resection of ipsilateral lymph nodes, lymphedema may also affect the lower extremities. Lower extremity lymphedema is often caused by obstruction in the setting of parasitic infection, inflammation, or trauma. Excisional and liposuction-assisted techniques are again reliable techniques that can be used, though the limitations are similar to those discussed above. Of the novel techniques described in this review, LVB and VLNT have been used to successfully improve symptoms of lower extremity lymphedema.[31]

Conclusion

Lymphedema affects up to 250 million people worldwide and is likely under-reported in the literature due to variability in diagnostic criteria and reporting biases. This chronic and progressive disease can range in timing of onset and severity and can have a significant physical, psychologic, and financial impact on patients. Treatment options vary from non-surgical compressive therapy to surgical physiologic procedures and debulking procedures. More recently, LYMPHA has demonstrated favorable outcomes in preventing lymphedema in patients undergoing axillary lymph node dissection. However, inconsistent and incomplete insurance coverage can create barriers for patients seeking appropriate treatment. Patient selection for surgical intervention is critical and requires a multi-disciplinary approach.

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