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Surgical Treatment Options of Breast Cancer-Related Lymphedema

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Abstract
Purpose Lymphedema after cancer treatment is a progressive, debilitating condition that is becoming increasingly common as mortality rates decline. The purpose of this review is to summarize the evolution of treatment of lymphedema focusing on surgical management and outcomes.
Recent Findings With the development of supermicrosurgical techniques and advanced imaging technology, surgical treatment of lymphedema has evolved past reductive measures and sought to address the underlying pathophysiology. Particularly in breast cancer-related lymphedema, our group follows a novel algorithm to address both the autologous breast reconstruction with physiologic treatment of the affected extremity.
Summary Patients and physicians alike should be educated about the risk factors for developing lymphedema after cancer treatment, prompt and proper diagnosis, as well as conservative and surgical treatment options. While the optimal treatment algorithm remains to be elucidated, a multi-modality treatment approach has demonstrated promising outcomes in symptom improvement, volume reduction, and quality of life.

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Keywords Lymphedema · Vascularized lymph node transfer · Lymphovenous bypass · Lymphovenous anastomosis · Breast cancer-related lymphedema

Introduction

Lymphedema is a chronic, debilitating, and feared condition that results in swelling of the affected tissue [1]. While primary lymphedema is rare and thought to be associated with a mutation of vascular endothelial growth factor receptor 3 (VEGFR3) [2, 3], in developed countries, lymphedema is most commonly recognized by unilateral swelling of the ipsilateral extremity following treatment for cancer [4, 5•]. For example, it is estimated that there are over 3.5 million breast cancer survivors in the USA, and almost 1.45 million women suffer from breast cancer related lymphedema (BCRL), particularly those who are obese and undergo an axillary dissection, radiation treatment, and chemotherapy [6–8].

The severity and impact on a patient's quality of life (QOL) does not always correlate with objective metrics in limb circumference or volume. Patients with minimal swelling may still note significant heaviness, limited or diminished range of motion, increased woodiness and fibrosis, or suffer from recurrent infections and episodes of cellulitis. Furthermore, the outward signs of soft tissue swelling may not be directly related to the condition of the lymphatic channels within the extremity. With time, obstruction of the lymphatic drainage leads to protein rich fluid accumulating in the affected extremity, precipitating a progressive inflammatory process of sclerosis, fibrosis, and fat deposition [9, 10].

Complete decongestive therapy (CDT) is the mainstay of lymphedema management and consists of a therapistdirected approach including manual lymphatic drainage, bandaging, exercise, and skin care [11, 12]. Historically, surgical treatment of lymphedema has focused on volume reduction as in liposuction or excisional debulking without addressing the underlying dysfunctional lymphatic system [13]. However, with the advent of supermicrosurgical (anastomosis of blood or lymphatic vessels less than 0.8 mm) technique and a multi-modal algorithm, physiologic approaches to surgical treatment including lymphovenous bypass or anastomosis (LVA) and vascularized lymph node transfer (VLNT) have emerged as viable treatment options for oncologic-related lymphedema (Fig. 1) [14].

Evaluation and Surgical Planning

When considering secondary lymphedema, all patient evaluations begin with a thorough history and physical [15••], with specific attention to those findings that will influence surgical planning. For those who have not been engaged in a conservative treatment program, CDT is initiated prior to surgical intervention to optimize volume reduction and soft tissue quality. In mild lymphedema, this may be all that is needed [16]. Additional considerations are given to medical comorbidities, recurrent episodes of cellulitis and cancer treatment status. The degree of radiation injury or fibrosis as well as anticipated soft tissue defect will affect potential donor sites in patients in which VLNT is an option. For example, if a soft tissue deficit is anticipated, a larger vascularized lymph node (VLN) flap, such as the groin flap, will be favored over a thinner, commonly smaller surface area flap as with the submental flap. In the setting of combined autologous breast reconstruction (ABR) with VLNT, pre-operative imaging will guide surgical planning based on vascular patterns from the deep inferior epigastric perforator (DIEP) flap and functional lymph node mapping in the groin to limit the risks of iatrogenic lymphedema in the donor site.

A number of different modalities have been employed to objectively evaluate the affected and contralateral extremity including limb circumference measurements, volumetric perometer measurements, bioimpedence spectroscopy [17], magnetic resonance (MR)

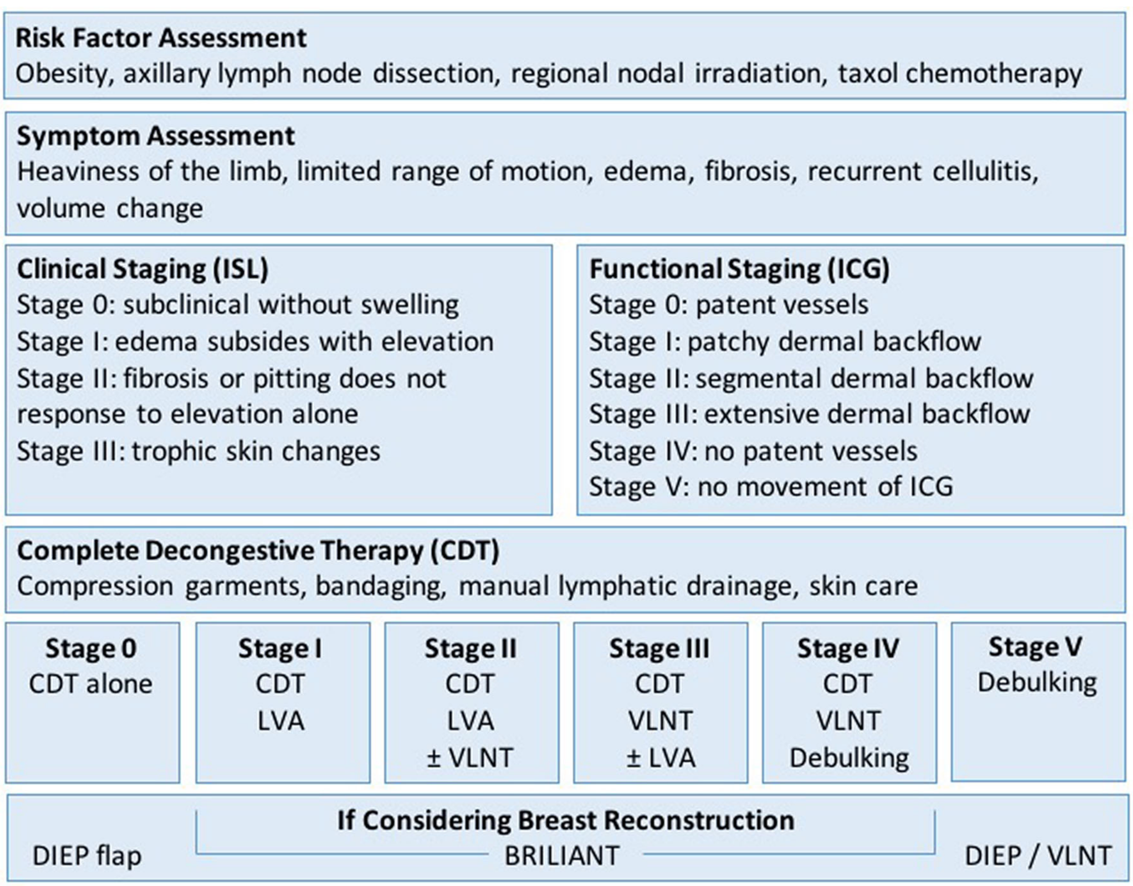

Fig. 1 Summary approach to breast cancer-related lymphedema. *CDT* complete decongestive therapy, *ISL* International lymphatic society, *ICG* indocyanine green, *LVA* lymphovenous anastomosis, *VLNT* vascularized lymph node transfer, *BRILIANT* breast reconstruction including lymphaticovenular anastomosis and inguinal to axillary node transfer

lymphangiography [18], and indocyanine green (ICG) lymphography [19]. A limb circumference difference of 2 cm is commonly used; however, a limb volume differential of 200 milliters or a 5% volume change can be used to identify early stage BCRL. The International Society of Lymphology (ISL) clinical staging ranges from 0 to 3 with stage 0 being considered sub-clinical without edema. Stages 1–3 demonstrate increasing presence of edema and impaired response to conservative treatment; stage 1 is characterized by early fluid accumulation and resolution with limb elevation while stage 2 typically shows pitting edema that does not resolve with elevation. In stage 3, the tissues are thickened and fibrotic [20].

Alternatively, the MD Anderson ICG staging [21], which allows visualization of lymphatic vessels and function (Fig. 1), ranges from I to V, with stage I demonstrating several patent vessels, minimal obstruction evidenced by "dermal backflow," and slightly impaired contractility; stage II–IV are characterized by decreasing vessel patency and contractility and increasing dermal backflow. Several patterns of dermal backflow can be visualized with ICG. A linear pattern is seen with normal uptake and functional lymphatic channels as is ICG stage 0–I. Any deviation from linear represents disrupted drainage and progressive backflow. A *splash* pattern demonstrates few linear channels with tortuous channels that appear as a paint splash on mapping of the extremity. A *stardust* pattern appears with scattered fluorescent pools and surrounding dim signal demonstrating interstitial leaking. In cases of severe fibrosis, a *diffuse* pattern may be seen with widely distributed dye throughout the extremity and no discernable patterns as in stage IV [22]. The rare condition of stage V lymphedema demonstrates no drainage of ICG [23]. Interestingly, there may be poor correlation between descriptive clinical staging schemes such as ISL and ICG physiological staging. An arm that is only mildly swollen may be on clinical exam may be ISL stage 1; however, ICG mapping may not show visible, functional lymphatic channels, but rather a stardust pattern, which is important for surgical planning. Our algorithm utilizes the clinical and imaging findings in our combined approach [15, 24].

Several refinements in pre-operative imaging have facilitated surgical planning and optimal outcomes. MR lymphography allows for visualization of the lymphatic channels and nodes for both assessment and planning. Lymphoscintigraphy with radioactive isotype gives an overall sense of functionality of the lymphatic channels [25]. When used with single photon emission computed tomography (SPECT/CT) scan, lymphoscintigraphy SPECT/CT are key in our approach to VLNT and intra-operative reverse lymph node mapping to identify the sentinel nodes in the groin or axilla and minimize the risk of iatrogenic lymphedema at the donor site [26]. With our preferred approach to BCRL combining a DIEP flap with the inguinal lymph node harvest described below, a CT angiogram may be performed to map out the vascular anatomy. In the setting of multi-modal physiologic surgery, the inclusion of simultaneous LVA is determined by ICG lymphangiography. This novel approach known as Breast Reconstruction Including Lymphaticovenular anastomosis and Inguinal to Axillary Node Transfer (BRILIANT), seeks to address the aberrant lymphatics through both mechanisms at the time of breast reconstruction (Fig. 1) [15, 24]. While ICG staging may be done in the clinic prior to surgery, our practice is to perform on table lymphatic mapping at the time of VLNT or BRILLANT procedure.

Physiologic Surgery

Lymphovenous Anastomosis

Advances in microsurgical techniques over the last several decades have led to surgical interventions that improve the drainage of excess lymphatic fluid. The first innovative procedure is an LVA or bypass which creates an anastomosis between the obstructed lymphatic channel and a recipient vein, effectively allowing fluid to shunt into the system circulation. With microscope magnification up to 40x, an anastomosis between a lymphatic vessel and an adjacent dermal venule of similar caliber, 0.3 to 0.9 mm diameter, can be performed using 11–0 or 12–0 nylon sutures. Koshima et al. pioneered supermicrosurgery techniques for anastomosing submillimeter lymphatic vessels in LVA [27•]. Refined imaging using ICG lymphatic mapping with either the photodynamic eye (PDE, Hamamatsu Inc, Japan) or Spy Phi (Stryker Inc, Kalamazoo, MI, USA) allows the identification of functional lymphatic vessels versus obstructed or fibrotic channels [21, 28••]. Areas of dermal backflow indicate obstruction and therefore discrete channels distal to these patches are ideal for LVA to a patent venule nearby. In general, only obstructed channels should be used for LVA whereas lymphatic vessels that appear patent and functional or reconstituted on imaging should not be violated.

Early retrospective reviews of LVA demonstrate both qualitative and quantitative improvements [16, 29]. The largest series of BCRL included 665 patients with average 7-year follow-up; 87% noted symptomatic improvement, 83% had significant volume improvement with a mean 67% reduction in volume, and 85% were able to discontinue conservative therapies [29]. Furthermore, the incidence of cellulitis in the affect limb was reduced in 87% of patients after LVA. Prospective studies are smaller, but equally promising. Outcomes of 100 consecutive LVA procedures demonstrate a 96% subjective response rate and an average limb volume reduction of 42% and maintained improvement up to two years postoperatively [21].

Immediate Lymphatic Reconstruction

Immediate lymphatic reconstruction (ILR) has recently been explored as a means to mitigate the significant morbidity associated with multi-modal cancer treatment. Microsurgical LVA in the ipsilateral axilla of patients undergoing radical mastectomy was first described nearly three decades ago [30]. Since this time, several case reports and smaller series have demonstrated variable results in preventing secondary lymphedema after oncologic treatment [31, 32]. Most promising has been the development of Lymphatic Microsurgical Preventive Healing Approach (LYMPHA) which preserves the upper arm lymphatics during lymph node dissection through reverse lymphatic mapping [33–35]. Immediate LVA to an axillary venous branch is performed, either in end-to-end or end-to-side configuration, at the time of oncologic surgery.

Recent meta-analysis demonstrated significantly less secondary lymphedema in patients treated with ILR or prophylactic LVA compared to reported rates in the literature based on anatomical location: 5% for axillary, 12% for ilio-inguinal, 7% for para-aortic and 0% for iliac lymph node dissection. Four studies included control groups which did not undergo ILR. Pooled analysis showed patients treated with prophylactic LVA had a relative risk of 0.33 (0.19, 0.56) for developing LVA compared to controls ($p < 0.0001$) [32]. One of the largest prospective series included ILR in 37 patients requiring axillary lymph node dissection. LYMPHA was performed on 27 and at 6 months follow up, rates of upper extremity lymphedema were significantly lower than in the 10 patients in which the procedure could not be performed (12.5% versus 50%, respectively) for lack of suitable vessels at the time of oncologic surgery [34].

Vascularized Lymph Node Transfer

For more advanced stages of lymphedema where lymphatic channels are no longer available or functional for bypass, an alternative physiologic option is VLNT or transferring unaffected lymph nodes from one location to the affect extremity [36]. While the exact mechanism is unknown, evidence suggests that the transferred lymph nodes not only stimulate neo-lymphangiogenesis, but that transferred lymphatic tissue also acts as a sponge to absorb lymphatic fluid as well [37]. Several donor sites exist for VLNT [36] including the inguinal [23, 38] submental [39], supraclavicular [40, 41], and lateral thoracic [42, 43] regions as well as intra-abdominal donor sites such as the omentum and jejunal mesentery [44–47].

In a review of VLNT outcomes, encompassing 24 studies and 271 lymph node transfers, Scaglioni et al. [48•] demonstrated beneficial improvement from all donor lymph node flaps except the lateral thoracic. The most commonly used inguinal groin flap showed subjective improvement in 70.4% patients ($n = 138$). While there was a greater benefit in the submental (100%, $n = 8$) and supraclavicular nodes (88.2%, $n = 15$), the overall number of these flaps was considerably smaller. However, more recent studies using both the submental and supraclavicular nodes have confirmed excellent outcomes that are reproducible. Of note, the authors identified only 3 cases (1.1%) of iatrogenic lymphedema affecting the donor limb. Intra-abdominal donors such as the omentum or mesentery carry the additional benefit of potential for minimally invasive harvest, obviated risk of donor lymphedema and the availability of two flaps based on the right or left gastroepiploic pedicles, as in bilateral or dual-level transfers [44, 49].

Upper extremity lymphedema responds better compared to lower extremity (74.2% versus 53.2%, respectively) [48•]. There is debate whether to place the vascularized lymph node flap proximally where the prior lymphadenectomy and likely radiation occurred versus distally on the extremity away from scarred and fibrotic surgical bed. Outcomes studies support either placement, with limb volume reduction observed with either proximal or distal VLNT [50]. Randomized comparison has yet to be performed and ultimately, this decision is left to the surgeon. Our general practice is to place the vascularized tissue in the proximal location, acknowledging the additional benefit of scar release concurrent with the new afferent and efferent collateral lymphatics connecting the transplanted nodes and the recipient site [37]. Proponents of distal VLNT favor the sponge mechanism of the nodal tissue in a more gravity dependent position [39]. Depending upon the distribution of disease involvement along the length of the affected limb, multi-level placement using split omental or mesenteric transfers may offer improved lymphatic drainage [45, 49].

Both LVA and VLNT have proven to be effective [14, 50, 51]. A recent systematic review of studies including objective measures of all forms of surgical intervention demonstrate that mean volume reduction for LVA was 33.1% (95% confidence interval [CI] 14.4–51.9%) and 26.4% (95% CI 7.98–60.8%) for VLNT [52•]. Traditionally, the surgical approach has been dictated by the severity of lymphedema in that early stages were treated with LVA while more advanced disease underwent VLNT. This makes head to head comparison of LVA with VLNT difficult and subject to selection bias [53]. Furthermore, the durability of reconstruction has come into question. For example, only 56.5% of patients

(15 of 23) treated with LVA had patent anastomoses at 12-month follow up [54].

A Combined Approach to BCRL

The BRILIANT approach to BCRL was recently implemented at the authors' institution demonstrating favorable results in early evaluation [15••, 24]. Thirty-three patients were treated with BRILIANT while 21 underwent DIEP with VLNT alone followed prospectively with 12 months follow-up. All patients in the BRILIANT group reported subjective symptom improvement compared to 81% in the DIEP + VLNT group ($p = 0.019$). Volumetric analysis demonstrated significant reduction at early time points, however, by 12 months there was no difference (60.4% versus 57.8%; $p = 0.43$). There have been no episodes of lymphedema at the donor site.

A recent systematic review of combined ABR with VLNT evaluated outcomes of 6 studies with a total of 103 patients. While the results are generally favorable, with the majority of patients reporting reduction of circumference, volume and symptoms, there is an obvious lack of consistent outcomes and follow-up reported across the various studies [55]. Both LVA and VLNT have shown to improve patient symptoms, volume and incidence of cellulitis among various studies, and have been described in a staged approach to lymphedema, none have reported simultaneous LVA and VLNT, therefore, like much of the field, clearly defined prospective outcome studies with adequate follow-up are needed.

The proposed synergistic mechanisms of the BRILIANT approach likely have a temporal benefit as well. An LVA has an immediate effect on the drainage of the affected arm while lymphangiogenesis from VLNT takes place over several months to a year. It is possible that redirecting the lymphatic flow to systemic circulation at the time of scar release and placement of the flap provides a more favorable short-term tissue environment. Furthermore, the development of new lymphatic channels may in turn take pressure off the more distal congested extremity and reduce the likelihood of delayed failure of the LVA [54, 56].

Conclusions

With significant advancements in microsurgical technique, physiologic surgery continues to expand as an effective treatment for oncologic-related lymphedema. In patients undergoing breast reconstruction, the optimal approach combines a simultaneous microvascular DIEP flap with chimeric inguinal VLNT and LVA if appropriate targets are identified. In patients developing lymphedema from treatment of other malignancies, we have also adopted a combined approach with VLNT and LVA using the full spectrum of donor sites. Although the incidence is not as common as BCRL, early results are encouraging. Surgical outcomes are uniformly better when performed earlier. Once fibrotic adipose tissue is established, debulking procedures such as liposuction or direct excision are warranted. Patient and physician education and early intervention remain critical elements of success in treatment and prevention of BCRL. The algorithm of the authors' current approach has evolved, providing an aesthetic, durable autologous breast reconstruction and maximizing the treatment for lymphedema in a single operation.

Compliance with Ethics Guidelines

Conflict of interest The authors have no commercial associations or financial disclosures that might pose or create a conflict of interest with information presented in this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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