Review Article on Lymphedema

Surgical management of lymphedema: a review of current literature

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Abstract: Lymphedema may be characterized by a progressive clinical course and limitations in improvement despite multi-modality treatment. In westernized countries, it most commonly presents as an undesirable complication of cancer treatment, particularly breast cancer. In the past several decades, surgical treatments for lymphedema have advanced, alongside developments in microsurgery. Lymphovenous anastomosis (LVA) and lymph node transplantation are physiological therapies that may reduce lymphedema through addressing its route cause. Ablative techniques such as liposuction and subcutaneous excision aid in resolving the accumulation of proteinaceous adipose and fibrotic tissue seen in advanced lymphedema. The goal of this review is to examine the outcomes and limitations of current surgical techniques used in lymphedema management.

Keywords: Lymphedema; lymph node transfer; lymphovenous anastomosis (LVA); liposuction

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Introduction

Lymphedema is a condition characterized by accumulation of protein-rich fluid in the interstitial space and consequent tissue swelling. Early stages may have physical findings and symptoms of painless pitting edema, discomfort, and heaviness of the limb, especially after continued use (1). However, as time passes without treatment, the condition progresses to fibrosis, thickening of the skin, and irreversible non-pitting edema. Patients experience a higher rate of chronic skin conditions as well, such as recurrent cellulitis, ulceration and impetigo (2). The etiology of lymphedema is classified as either primary or secondary. Primary lymphedema occurs due to a congenital anomaly or absence of the lymphatic system in certain populations. First symptoms of primary lymphedema usually occur between the ages of 10 to 25 years, with a reported prevalence of approximately 1/100,000 (3,4). Secondary lymphedema occurs due to an acquired impairment in lymphatic flow. Common etiologies include trauma, chronic infection, and malignancy (3). The most common cause, in westernized countries, is treatment of malignancy, particularly breast cancer (5). Studies have reported the incidence of upper extremity lymphedema following axillary lymph node dissection in the range of 7% to 45% depending on risk factors and supplemental use of adjuvant radiation therapy (6).

First line intervention of lymphedema includes conservative measures, such as complete decongestive therapy (CDT). CDT is a multidisciplinary treatment approach involving exercise, daily bandaging, manual drainage therapy and skin care. The intervention occurs as a 2 phase approach, with phase 1 focusing on reduction of lymphedema volume, and phase 2 focusing on maintenance of the reduced volume (7). CDT can be an effective treatment for lymphedema in all stages of the disease (8-10). However, limitations include the need for strong patient

compliance, the need of life-long compression garment use, and the high cost associated with prolonged adjunctive therapy, such as skin care and laser treatment (9-12).

Surgical treatment of lymphedema is suggested when conservative management fails, particularly early following the onset of the swelling. The field of lymphedema surgery is a constantly evolving field. Early techniques in management of lymphedema include ablative procedures such as the Homans or Charles procedures, which involve excision of the subcutaneous tissue beneath the affected skin and covering the defect with skin flaps or a full or split-thickness grafts (13,14). Advances in microsurgical techniques have allowed the advent of more physiologic and effective methods such as vascularized lymph node transplant (VLNT) or lymphovenous anastomosis (LVA). The purpose of this review is to provide an analysis of current techniques in lymphedema management, specifically related to their outcomes and limitations.

Methods

A review of peer-reviewed literature was performed on PubMed-MEDLINE to evaluate current strategies in surgical management of lymphedema. Initial query was performed using a combination of the terms "lymphedema," "surgery," "lymphovenous anastomosis", "lymph node transfer," and "liposuction". Additional queries were performed based on relevant references of the searched articles as well.

Physiological therapy

Surgical techniques of lymphedema management can broadly be divided into physiologic therapy and ablative therapy. Physiologic surgical techniques are microsurgical procedures that foster the physiologic drainage of lymphatic fluid through anastomosis of lymphatic vessels with the venous system, or the incorporation of a functional lymph node in the region of ablative treatment.

LVA

LVA was first described in the 1960s (15-17). Nielubowicz and Olszewski performed the procedure in 4 patients with secondary lower extremity lymphedema, and showed persistent limb circumference reduction over 1 to 9 month follow-up (16). In this technique, the surgeon forms an artificial connection between a patent lymphatic vessel and adjacent venules to redirect lymphatic flow, allowing the lymphatic fluid to bypass obstructed lymphatic vessels. The anastomosed vessels have diameters ranging from 0.1 to 0.8 mm, requiring supermicrosurgical technique (18,19). Recent use of indocyanine green (ICG) lymphography pre and intraoperatively to visualize patent lymphatic vessels has allowed for restoration of lymphatic flow using minimally invasive procedures, rendering LVA as an attractive option in early stage lymphedema (20,21).

Since its introduction, several studies have examined the outcomes of LVA (22-24). In a prospective study of 100 patients with secondary upper or lower extremity lymphedema, Chang *et al.* (2013) found a 61% reduction in upper extremity volume in patients with stage 1 or 2 lymphedema according to the MD Anderson lymphedema classification, compared to a 17% mean volume reduction in patients with stage 3 or 4 lymphedema (*Table 1*) (25). These results suggest that LVA is more effective in early stages of lymphedema, rather than at later stages when irreversible tissue fibrosis has occurred and lymphatic smooth muscle is dysfunctional. These authors also found that results were not as good for lower extremity lymphedema, with only 57% of patients reporting symptom improvement compared to 96% of patients who received LVA for the upper extremity. The large size and constantly dependent nature of lower extremities may make them less likely to improve in symptoms in comparison to the upper extremity (25). Given its efficacy in secondary lymphedema management, some have begun performing prophylactic LVA at the time of initial axillary dissection (26,27). In a meta-analysis Jørgensen *et al.* (2018) found that prophylactic LVA at the time lymphadenectomy reduced the risk of lymphedema by 77% compared to no prophylactic procedure ($P<0.0001$) (27).

Cheng *et al.* (2018) demonstrated the effectiveness of LVA in primary lymphedema as well (28). Although a sample size of 4, patients with congenital forms of lymphedema who received LVA experienced roughly 4 times/year fewer episodes of cellulitis, and self-reported increases in quality of life, appearance, symptoms, function, and mood (28). The author does suggest that other techniques such as VLNT may be more beneficial in primary lymphedema, as the congenital absence or occlusion of lymphatics in the case of primary lymphedema often preclude LVA as an option.

Despite the positive outcomes, there are still limitations to the technique. LVA relies on there being a patent lymphatic vessel, so its applicability may be limited in patients with congenital lymphedema or late stage

Table 1 Lymphedema classification systems in literature

Classification system	Stage	Characteristics
M.D. Anderson staging system	1	Abundant patent lymphatic vessels with minimal lymphatic dermal backflow on indocyanine green lymphangiography
	2	Moderate amount of patent lymphatic vessels with segmental lymphatic dermal backflow on lymphangiography
	3	Reduced number of patent lymphatic vessels with dermal backflow spanning entire arm on lymphangiography
	4	No visible patent lymphatic vessels with dermal backflow spanning entire arm and dorsum of hand on lymphangiography
Becker *et al.* (2006) staging system	I	Early edema with no or less than 2 infectious episodes, excess arm circumference not more than 30% of unaffected arm circumference
	II	Later stage edema, more than 2 infectious episodes, excess arm circumference between 30% an 50% of unaffected arm circumference
International Society of Lymphology staging system	0	Sub-clinical lymphedema with impaired lymph transport but no evidence of swelling
	I	Early accumulation of fluid high in protein content with swelling that reduces with limb elevation; pitting may be present
	II	Pitting edema with swelling that does not reduce with limb elevation
	III	Lymphostatic elephantiasis; non-pitting edema with skin changes (e.g., acanthosis, increase in thickness), fat deposition, and fibrosis

secondary lymphedema. Furthermore, there is still a lack of data regarding the long-term (greater than 5 years) patency of LVA, with most studies limited to a follow-up of 6 months to 2 years (28-30). Higher volume studies with prolonged follow-up are needed to fully understand the efficacy of LVA.

VLNT

VLNT is a relatively new technique in the treatment of lymphedema. It was first clinically described by Clodius *et al.* (1982), who transferred a pedicled groin flap with vascularized inguinal lymph nodes to the left lower extremity with partial success in reducing lymphedema (31). With advances in microsurgical techniques, VLNT has, since then, become a popular option of treatment particularly in cases of moderate to advanced lymphedema, where other treatment methods may not have been effective. The technique involves transfer of a vascularized lymph node and surrounding tissue to a region where a lymph node has been removed or lymph flow is impaired. A microsurgical anastomosis is created between recipient site blood supply and the flap, thereby maintaining vascularization of the lymph node. Common donor sites for the lymph nodes include omental, inguinal, mesenteric, lateral thoracic, axillary, gastroepiploic, and submental nodes (32,33). Common recipient sites include the axilla, elbow, wrist, groin, and ankle (34).

Although the exact mechanism through which VLNT works is unclear, there are 2 main theories. The first is that lymph node transfer induces lymphangiogenesis at the recipient site, leading to improved lymphatic flow and alleviation of lymphedema. This theory has been substantiated by animal and human studies that used lymphoscintigraphy to show formation of new lymphatic channels at the recipient site following VLNT (35,36). The second proposed mechanism is that the transferred lymph node acts as a "pump", wicking lymph fluid from the surrounding interstitial space, and projecting it into the efferent venous circulation (37,38). This is based on the observation that ICG dye injected in the tissue surrounding a transferred lymph node can be found in the afferent donor and recipient venules (39). Lin *et al.* (2009) reasoned that the high-pressure afferent arterial flow to the lymph node flap creates a local pressure gradient that transports adjacent lymphatic fluid towards the transplanted node (37). The fluid is subsequently absorbed into the low-pressure efferent venous anastomosis, thereby reducing lymphedema.

Reported outcomes of VLNT in literature have been promising. In a retrospective study of 24 patients suffering from post-mastectomy upper extremity lymphedema, Becker *et al.* (2006) reported decrease in limb circumference in 22 patients with return to normal size in 10 patients (40). Fifteen patients were able to discontinue physiotherapy permanently. All patients in this study were described as stage I or II lymphedema, indicating early to later stages of the condition (*Table 1*). Batista *et al.* (2017) performed a retrospective analysis on outcomes of lymph node transfers to 41 total legs of 38 patients with lower extremity lymphedema (41). Of the 23 legs for which lymph node transfer was the sole procedure performed as the treatment of lymphedema, 21 legs showed at least a minor degree of extremity volume reduction. Nine patients' legs demonstrated greater than 30% volume reduction when compared to the healthy, unaffected leg (41). Only 2 patients of the VLNT cohort experienced complete resolution of lymphedema, with a lower post-surgical volume in the affected lower extremity than the unaffected extremity. An advantage that VLNT has over LVA is that it can be performed in the absence of patent lymphatic vessels at the recipient site. Leppäpuska *et al.* (2019) reported outcomes of combined VLNT with liposuction in 21 patients with chronic non-pitting edema (average symptom duration =52 months) (42). After an 18 month follow-up, patients experienced an average of 87% volume reduction in the lymphedematous limb, and reported stabilization of the volume, even during a 7-day cessation of compressive garment therapy (42). Although the volume reduction cannot be attributed to VLNT alone, the findings suggest that VLNT can be an effective treatment in advanced lymphedema, when performed with adjunct ablative procedures.

In patients suffering of post-mastectomy lymphedema, VLNT can be combined with autologous breast repair, thereby reducing surgery time and improving aesthetic outcome. This approach was first described by Saaristo *et al.* (2012), who performed autologous breast repair with deep inferior epigastric artery perforator (DIEP) and muscle-sparing transverse rectus abdominus myocutaneous (ms-TRAM) flaps coupled with an accompanying inguinal lymph node (43). In a retrospective study of 27 patients, Akita *et al.* (2017) showed that patients who receive VLNT with autologous breast repair experience a larger reduction in extremity circumference compared to those who only receive VLNT (44). These findings suggest that autologous breast repair alone may have an independent or synergistic effect on lymphedema reduction.

A limitation of VLNT is the risk of donor site lymphedema. A systematic review by Demiri *et al.* (2018) showed that donor site lower extremity lymphedema occurred at an incidence of 1.6% in a population of 189 (45). Scaglioni *et al.* (2018) found a similar incidence of donor site lymphedema in patients whose inguinal lymph nodes were transferred, but a higher rate of 13.2% in patients whose donor site was the lateral thoracic node (46). Conversely, Maldonado *et al.* (2017) performed a prospective study of 100 supraclavicular VLNTs and had a donor site lymphedema rate of 0% over an average 11 month follow-up (47).

Reverse lymphatic mapping prior to surgery has been proposed as a technique to prevent donor site lymphedema following VLNT (48). This method allows the surgeon to visualize the donor site lymph nodes intraoperatively and actively avoid lymph nodes that drain the extremities, thereby lowering the risk of iatrogenic donor site lymphedema.

Ablative therapy

In advanced stages of lymphedema, where extensive interstitial tissue fibrosis has occurred, physiologic therapies may not provide sufficient volume reduction. "Rescue" procedures such as ablative surgical procedures can be used at this stage to improve aesthetic outcome, although they do not address the root cause of lymphedema. Commonly used ablative procedures include subcutaneous excisional procedures and suction-assisted lipectomy.

Excisional procedures

Therapeutic excisional techniques have been well described since 1912, particularly for the treatment of elephantiasis (49-51). One of the well-known procedures today is the Charles procedure, which involves radical circumferential excision of subcutaneous tissue followed by full thickness skin grafting. van der Walt *et al.* (2009) further modernized this technique to include negative pressure wound therapy and delayed skin grafting, in an effort to improve graft take and wound recovery (52). This is now known as the modified Charles procedure. Despite its long history of use, there have been no prospective studies investigating the outcomes of subcutaneous excision procedures with detailed long-term follow-up. Retrospective studies have reported positive outcomes in volume reduction, albeit with limited

sample sizes, and confounding results due to combination with other physiologic procedures (53,54). Subcutaneous excisional procedures are generally preserved only for advanced lymphedema due to its poor aesthetic outcome, risk of lymphedema recurrence, infection, wound break down, and in severe cases amputation (55).

Liposuction

Liposuction is a minimally-invasive, yet effective method of lymphedema treatment. The technique involves removal of subcutaneous adipose tissue from the lymphedematous limb using a suction-assisted lipectomy cannula. The target population are patients with chronic lymphedema whose pitting edema has been replaced by fatty deposits (56). Patient satisfaction with the technique is high, as patients are encouraged to return to their daily routine with a short recovery time (57,58). Furthermore, it can be performed as an adjunctive procedure to physiologic treatments such as LVA or VLNT to improve outcomes (59).

The use of liposuction for lymphedema was first popularized by Brorson and Svensson (1998) who examined the feasibility of combined liposuction and compression garment as a treatment for lymphedema (60). Their prospective study of 28 patients showed a 104% reduction in limb volume relative to the unaffected side with liposuction and postoperative compressive garments, compared to a 47% reduction for patients treated with compressive garments alone (60). More recent studies have shown similarly positive outcomes. In a prospective study of 105 patients, Hoffner *et al.* (2018) showed an average lymphedematous extremity volume reduction of 117% compared to the unaffected limb 5 years following liposuction and compressive garment treatment (61). Agko *et al.* (2018) demonstrated a limb circumference reduction of 96.4% following VLNT and liposuction, compared to 37.9% with VLNT alone, indicating effectiveness of combining liposuction with physiologic procedures (59). Decreased infection risk following combined therapy has been reported as well (59,62). The primary limitation of liposuction therapy is that patients must wear compressive garments indefinitely to maintain the reduced limb volume (63).

Proper follow-up of liposuction therapy for lymphedema involves a multidisciplinary approach to treatment, involving the surgeons, physiotherapists, and a compliant patient (64). Patients have reported increased quality of life following liposuction treatment, despite having to wear compressive garments long-term as part of their treatment (65,66). This suggests that the cosmetic and functional benefits of liposuction outweigh the burden caused by life-long compression therapy. The indications, advantages, and disadvantages of liposuction and each aforementioned surgical technique have been summarized in *Table 2*.

Combined surgical therapy

Recent reports of combined surgical therapy have demonstrated that performing physiological and ablative procedures together may have benefits beyond improved volume reduction (*Table 3*). Performing a physiological procedure such as VLNT or LVA in addition to liposuction has been shown to reduce the need for continuous compressive therapy following liposuction. Granzow *et al.* (2014) and Nicoli *et al.* (2015) both reported that performing a staged procedure of liposuction followed by VLNT allowed patients wear compressive garment less frequently and still maintain reduced arm volume and improved skin tonicity (62,67). Campisi *et al.* (2017) demonstrated that this is the case for LVA as well, as patients who received a combination of LVA with liposuction were able to maintain limb volume despite only wearing compression garment at night time (68). Eleven percent of the patient cohort were able to discontinue compressive garment use completely over 12 months post-operation (68). While physiological procedures are most effective in early stages of lymphedema, the addition of ablative therapy can render them effective therapeutic options for late stage lymphedema as well. In a retrospective study of 68 patients with International Society of Lymphology stage III lymphedema, Ciudad *et al.* (2019) reported that the combination of lymph node transfer with subcutaneous excisional procedures achieved significant limb circumference reduction and a decreased incidence of infectious episodes (*Table 1*) (69). Additionally, all patients in this study were able to discontinue compressive garment use 8 months after surgery (69).

Limitations

In this narrative review, we did not perform a statistical analysis of outcomes from the discussed studies. A meta-analysis of outcomes would allow for comparison of the efficacy of each technique, as well as a comparison between isolated and combined techniques. Furthermore, literature written in languages other than English were not included in this review.

Table 2 Options for surgical therapy of lymphedema

Technique	Advantages	Disadvantages	Comments
Lymphovenous anastomosis	• Minimally invasive surgery with the use of ICG • Can be performed prophylactically at time of lymph node dissection	• Less effective for lower extremity lymphedema • Requires a patent lymphatic vessel for anastomosis	• Performed in early stage lymphedema
Lymph node transfer	• Procedure not limited by recipient site lymphatic patency • Variety of donor sites available • Simultaneous breast reconstruction possible	• Risk of donor site complications (e.g., seroma, lymphedema)	• Can be performed at all stages, but most efficacious in early stage lymphedema
Liposuction	• Removes fibrofatty tissue unresolved by physiotherapy • High patient satisfaction	• Requires continuous use of compressive garment therapy if performed alone	• Performed in all stages of lymphedema
Subcutaneous excision (e.g., Charles, Homans)	• Removes fibrofatty tissue unresolved by physiotherapy • Effective for severe lower extremity lymphedema (e.g., elephantiasis)	• Risk of surgical site complications (e.g., infection, wound dehiscence) • Poor aesthetic outcome	• Performed at end stage lymphedema

ICG, indocyanine green.

Table 3 Reported combined therapies

Technique	Advantages over isolated procedure	Reporting studies
LVA/LNT + Liposuction	• Improved volume reduction • Improved aesthetic outcome • Reduced requirement of compressive garment therapy	• Leppäpuska *et al.* (2019) • Agko *et al.* (2018) • Campisi *et al.* (2017) • Nicoli *et al.* (2015) • Granzow *et al.* (2014)
LNT + subcutaneous excision (e.g., Charles, Homan procedures)	• Improved volume reduction • Improved utility in end-stage lymphedema • Reduced requirement of compressive garment therapy	• Ciudad *et al.* (2019)

LVA, lymphovenous anastomosis; LNT, lymph node transfer.

Conclusions

Surgical management of lymphedema has evolved in the past several decades, alongside advances in microsurgical techniques. The combination of microsurgical therapy such as VLNT and LVA with ablative procedures have provided patients with potentially improved functional outcomes and quality of life. Nonetheless, lymphedema remains to be a condition with progressive symptoms that surgeons and patients alike find difficult to manage. Further clinical studies with prospective design, larger patient numbers, and prolonged follow-up will help clarify treatment algorithms and improve outcomes.

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Footnote

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