

Controversies in Surgical Management of Lymphedema

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Summary: Surgical treatment of lymphedema has expanded in recent years. Lymphovenous bypass and vascularized lymph node transfer are both modern techniques to address the physiologic dysfunction associated with secondary lymphedema. While efficacy of both techniques has been demonstrated in numerous studies, there are several questions that remain. Here, the authors discuss the most pertinent controversies in our practice as well as the current state of surgical management of lymphedema. (*Plast Reconstr Surg Glob Open* 2020;8:e2671; doi: 10.1097/GOX.0000000000002671; Published online 25 March 2020.)

INTRODUCTION

The pathophysiology of lymphedema is heterogeneous. Primary lymphedema may develop as a result of abnormal lymph flow due to aplastic, hypoplastic, or hyperplastic lymphatic channels and/or lymphatic valvular dysfunction. More commonly, secondary lymphedema manifests as a sequela of injury to the lymphatic system by way of lymphadenectomy, radiation, or trauma, any of which may result in impedance of the lymphatic system. Currently, there is no curative treatment for lymphedema. Conservative management includes life-long compression garments, complex decongestive therapy, and often activity modification. Advances in microsurgical technique have led to lymphaticovenular anastomosis (LVA), also known as lymphovenous bypass (LVB), and vascularized lymph node transfer (VLNT) as possible treatment options to restore physiologic lymphatic drainage. Although these techniques have effect through different mechanisms, the primary objective is to restore alternative means of lymph drainage. With LVA, the fluid is re-directed to the venous system. Alternatively, VLNT replaces the damaged or excised lymph nodes, and is hypothesized to work by absorbing lymphatic fluid or stimulating lymphangiogenesis with new lymphatic channel formation.¹⁻³ While efficacy of both techniques has been demonstrated in numerous studies, there are several questions that remain. Here, the authors discuss the most pertinent controversies in our practice as well as the current state of surgical management of lymphedema.

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LVB and the Number of Optimal Anastomoses

The concept of surgical connection of an obstructed lymphatic channel with a vein to alleviate the flow blockage first emerged in the 1960s.^{4,5} A mechanical bypass of the diseased segment of the lymphatic system diverts the flow of the obstructed, high pressure lymph channel contents into the lower pressure, patent venous system proximal to the site of lymphatic blockage.⁶ This physiologic solution received renewed attention in 2000 after Koshima et al⁷ pioneered supermicrosurgery techniques for anastomosing vessels <0.8 mm in diameter. Since then, with vast improvements in technical experience, magnification technology, and precision instruments, interest in LVA continues to grow as a treatment strategy for lymphedema.^{6,8-12}

One of several points of debate surrounding LVA is the ideal number of anastomosis to be performed to achieve maximal effectiveness. In their initial published experience, Koshima's group described an average of 4 anastomoses per upper extremity, with as many as 10 LVAs when anatomy permitted.^{7,13} They believed that the number of anastomoses correlates positively with greater lymphovenous shunting and better outcomes.⁷ This rationale aligns with the experiences of others from the 1980's.^{9,14} Huang et al⁹ performed an average of 4.5 anastomoses in 87 patients with lower extremity lymphedema, and observed that the patients who experienced the greatest amount of circumferential reduction underwent the highest mean number of LVAs [(>5 cm, 5.4 LVAs), (3-5 cm, 3.8 LVAs), (1-3 cm, 3.4 LVAs)]. Thus, the group advocated maximizing the number of LVAs. Mihara et al¹⁵ similarly reported a positive correlation between volume reduction and number of LVAs. However, the greater number of LVAs feasible in patients with early stage lymphedema may confound the observed positive association between anastomotic number and postoperative improvement.^{9,11,15} In the authors' experience, patients presenting for surgical

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treatment of lymphedema rarely have >3 potential targets amenable to LVA.

In practice, Koshima et al⁷ did not observe proportionate improvement in outcome with increasing numbers of LVAs performed per patient. Their technique evolved over the next several years into a minimally invasive approach under local anesthesia, with as few as 1–2 LVA completed in <2 hours. Among 52 patients with Campisi stage III and IV lymphedema of the lower extremities in their 2004 series, an average of 2.1 (± 1.2) LVAs were performed with mean follow-up of 14.5 months, during which continued compression therapy was maintained.¹⁶ The authors observed a 41.8% ($\pm 31.2\%$) reduction in limb circumference, with an 82% effectiveness rate as defined by any circumference reduction.¹⁷ The authors' rationale for the maintained efficacy despite reduction in number of LVAs is that the benefits of LVA extend beyond the mechanics of lymph diversion. They theorized that the LVA interrupts the vicious cycle of lymphatic hypertension, smooth muscle cell degeneration within lymphatic channels, fibrosis, exacerbated lymphatic channel dysfunction, and one well-executed LVA may suffice to halt the entire process.¹⁸ The authors' experience reinforces these findings and have found excellent improvement in patients' lymphedema with as few as 1 LVA in an affected extremity.

In the absence of concrete evidence to support a critical threshold number of sufficient LVAs, heterogeneity in the approach to this matter persists. Potential confounding factors include lymphedema stage, upper versus lower extremity site, primary versus secondary etiology, surgeon experience and skill, vessel diameter, and anastomotic configurations beyond end-to-end, including end-to-side, side-to-end, side-to-side, and multi-luminal "octopus" anastomoses.^{19–22} While multisite single LVAs are common,^{11,15} multiple LVAs may also be undertaken via a single exploratory incision.¹⁶ Table 1 summarizes the number of LVAs performed per extremity in the largest published series dedicated to LVAs with consideration of some of the aforementioned variables, and describes outcomes using the reported subjective and/or objective measurement tools. In most studies, at least 3 LVAs per patient were performed.

Regardless of these unresolved controversies, there is consensus that the intrinsic contractility of the smooth muscle cells that comprise lymphatic channels is critical to the normal lymph flow.²⁹ Loss of this active pump mechanism observed in advanced, fibrotic stages of lymphedema is typically irreversible. Thus, it is intuitive that selection of functional lymphatic channels for LVA is paramount to the success of this procedure, and may explain the relatively diminished response obtained in patients with primary lymphedema and those with greatest disease severity.^{9,11,30} Garza and Chang³¹ favor the use of intradermal injection of indocyanine green for lymphography-guided visualization of the functional lymphatic channels that are linear in appearance. This strategy was associated with greater numbers of LVA performed when compared with previous attempts without the technology.¹¹ Hara et al³² have also advocated the selection of linear, splash, and stardust lymphography patterns representing normal, ectatic, and

contraction vessels rather than use of sclerotic, nonfunctional channels for LVA.

LVB Compared with VLNT

While both LVA and VLNT have proven to be effective in improving patients' lymphedema, considerable debate exists as to which technique is able to provide superior and more durable results. Historically, the authors' approach was dictated based on indocyanine green (ICG) lymphangiography. In general, our algorithm stratified patients who had patent lymphatic channels demonstrated on ICG imaging (stage 1 and 2) as candidates for LVA, while those with more severe disease (stage 3 and 4) underwent VLNT. Unfortunately, a direct comparison of outcomes between LVA and VLNT would include a selection bias as most patients undergoing a VLNT were more advanced stage and did not have lymphatic channels to undergo a bypass operation.

In a study comparing 4 limbs treated with LVA and 15 limbs treated with VLNT for primary lymphedema, Cheng et al³³ found that both the LVA and VLNT were effective in improving lymphedema but the VLNT group experienced a greater volume reduction (mean limb circumference reduction of 3.7 ± 2.9 cm and 1.9 ± 2.9 cm for VLNT and LVA, respectively; $P = 0.2$) and significantly more improvement in the Lymphedema Quality-of-Life score (from mean of 3.9 to mean of 6.4 and from mean of 3.0 to mean of 5.0 for VLNT and LVA, respectively; $P < 0.05$). However, the length of follow-up also needs to be taken into account in any study comparing the 2 modalities due to concern regarding the long-term patency of LVA. For example, in a study involving 12 patients with lymphedema treated with LVA, only 15 of 23 (56.5%) anastomoses were found to be patent after 12 months.³⁴ Despite the risks of thrombosis of the LVA, large cohort studies have demonstrated excellent success with both approaches, but well controlled data comparing LVA to VLNT is currently lacking.^{35,36}

Prophylactic Lymphedema Surgery

The significant impact that lymphedema has on quality of life after breast cancer treatment^{37,38} has led to the exploration of preventative measures, particularly, prophylactic lymphedema surgery. Microsurgical LVA on the ipsilateral limb of patients undergoing radical mastectomy was first described nearly 3 decades ago.³⁹ More recently, several small studies and case reports have demonstrated variable results in preventing the development of secondary lymphedema following oncologic treatment. Lymphatic microsurgical preventive healing approach (LYMPHA)^{40,41} is a technique that utilizes reverse mapping to identify and preserve upper arm lymphatics during axillary lymph node dissection. In addition, LVA to an axillary venous branch is performed at the time of oncologic surgery. Traditionally, these anastomoses were performed end to end or end to side; however, a more proximal location near the lymph node dissection is often associated with a larger size mismatch between the venous branches and primary lymphatics. To overcome this, several lymphatics can be sutured to the vein lumen using a U-shaped

Table 1. Summary Literature Highlighting Studies Examining Patients Who Have Undergone Lymphaticovenular Anastomosis (LVA) for Treatment of Primary or Secondary Lymphedema

Study	Patients	Extremities	Disease Site	Stage	Primary versus Secondary	Lymphedema		Outcome Assessment Tool	Objective Result	Objective %		
						Duration (mean)	No. LVA			Mean Follow-up	Cases Improved	Subjective (%)
Akita et al 2017 ²³	NR	29	Lower	Stardust pattern	Secondary	12 months	4.4	12.1 months	LEL index	4% decline	NR	58.6
Aljindan et al 2019 ²⁴	58	58	Upper and lower	Cheng grade I-II	Primary and secondary	43 months (median)	1	16.5 months	Circumference measurement	2.2%-3.2% decline	100%	100
Chang et al 2013 ¹¹	89	89	Upper	MDA lympho Stage I-IV	Secondary	42 months	NR	30.4 months	Volumetry	42% decline volume	NR	96
Chang et al 2013 ¹¹	7	11	Lower	MDA lympho Stage I-IV	Secondary	79 months	NR	18.2 months	Volumetry	differential 0%-33% decline volume	NR	57
Gennaro et al 2016 ²⁵	69	69	Upper and lower	ISL II-IV	Primary and secondary	69.6 months	5.3	"at least" 12 months	Circumference measurement	differential 50% decline volume	100% had improvement	81
Hara et al 2018 ²⁶	109	196	Upper and lower	ISL I-III Lympho I-V	Primary and secondary	89.2 months	3.3	9.1 months	Circumference measurement	differential 0.34%-1.83% decline volume	100% had improvement	NR
Huang et al 1985 ⁹	91	91	Lower	NR	Secondary	135.6 months	4.5	24 months	Circumference measurement	59.2% decline volume	100% had improvement	NR
Koshima et al 2007	12	12	Upper	11 "severe" 1 "moderate"	Secondary	42 months	4.1	26.4 months	Circumference measurement	differential 47.3% decline volume	92% had improvement	NR
Koshima et al 2003 ⁷	13	17	Lower	NR	Primary and secondary	80.4 months	NR	39.6 months	Circumference measurement	differential 55.6% decline volume	100% had improvement	NR
Koshima et al 2004 ¹⁷	52	NR	Lower	Campisi Stage III, IV	Secondary (primary NR)	63.6 months	2.1	14.5 months	Circumference measurement	differential 41.8% decline volume	82.5% had improvement	NR
Mihara et al 2014 ²⁷	95	NR	Upper and lower	ISL 0-III	Primary and secondary	NR	3 or more	27.3 months	No. cellulitis episodes	differential 1.46 episodes/year to 0.18	NR	NR
Mihara et al 2016 ¹²	84	162	Lower	ISL I-III Lympho I-V	Primary and secondary	NR	NR*	18.3 months	Lymphoscintigraphy, circumference measurement	episodes/year 58.9%-80% decline volume	47.7% had improvement	61.5
Seki et al 2015 ²⁸	30	30	Lower	LDB stage I-IV	Secondary	41-63 months	2	12 months	LEL, lymphoscintigraphy	differential depending on stage 0.03-24.4 reduction LEL	77% had improvement	NR
Yamamoto et al 2014 ³⁰	48	NR	Lower	ISL I-III	Primary and secondary	66 months (median)	1.6-1.8	6 months	LEL	10.9-16.5 LEL	NR	NR

* Not reported; however, increased numbers of ISL indicates International Society of Lymphology; LDB, lymphatic dermal back flow; LEL, lower extremity lymphedema index, combination of circumference measurement and body mass index; NR, not reported.

stitch.¹⁶ For most microsurgeons performing high volume lymphedema surgery, this approach is generally not recommended and an end-to-side anastomosis or perhaps a double barrel approach is more likely to have long-term patency and efficacy.

LYMPHA was attempted in 37 patients requiring axillary lymph node dissection and completed successfully in 27 with 6 months follow-up.⁴² Rates of upper extremity lymphedema were significantly lower in those with LYMPHA compared with those in whom the procedure could not be completed (12.5% versus 50%). Although there were no LYMPHA-related complications in their study, the procedure could not be completed in nearly a third of patients secondary to lack of suitable vessels for anastomosis. In their meta-analysis, Jørgensen et al⁴³ reported a pooled lymphedema rate significantly less than that reported in the literature for patients treated with prophylactic LVA based on location of the lymphadenectomy: 5% for axillary, 12% for ilio-inguinal, 7% for para-aortic, and 0% for iliac lymph node dissection. In quantitative analysis of 4 studies which included control groups, patients treated with prophylactic LVA had a relative risk of 0.33 (0.19, 0.56) for developing lymphedema compared with those not treated with LVA ($P < 0.0001$).⁴³ Although the clinical results of prophylactic LVA are encouraging, like much of the field, well-designed, prospective studies with clearly defined outcome measures and adequate follow-up are still needed.

Lymph Node Flap Placement

While VLNT has become accepted as an efficacious treatment for advanced lymphedema, the optimal recipient site location for the lymph node flap remains a subject of controversy. Proponents of VLNT to a proximal location on the affected limb cite the opportunity for radical release of scar resulting from prior regional lymphadenectomy and radiation. In the setting of postmastectomy breast reconstruction, this is most commonly performed by transferring a deep inferior epigastric artery perforator flap with a chimeric groin vascularized lymph node flap placed in the axilla.^{23,44–46} Surgeons that support distal extremity VLNT placement cite the ability for the fluid to be absorbed from the most gravity-dependent position of the limb.^{2,47–51}

Clinical and experimental studies regarding the mechanisms of action of VLNT seem to suggest that either proximal and distal flap placement should help to reduce lymphedema. These include lymphangiogenesis and the “bridging” mechanism, whereby new afferent and efferent lymphatic collateral pathways connect the transplanted LNs with lymphatic vessels in the recipient site to restore outflow^{52–55} and the “pumping” mechanism whereby new lymphaticovenous drainage is established within the transplanted LNs, driven by perfusion gradients between the arterial inflow and venous outflow.^{1–3,56,57} Clinical studies also support favorable limb volume reduction outcomes for both proximal^{46,58–60} and distal^{47,48,61,62} VLNT in both the upper and lower extremities, although a randomized, prospective study comparing the 2 techniques has not been published. Under certain circumstances, dual-level

transfer affords an opportunity to enhance the lymphatic drainage throughout the affected limb.^{63,64}

Donor Site Lymphedema

In counseling patients regarding VLNT for the treatment of lymphedema, the question of what the risk of causing lymphedema in the region drained by the transferred lymph nodes frequently arises. A systematic review by Demiri et al⁶⁵ sought to answer this question. Looking only at VLNT for breast cancer-related lymphedema, the authors identified 3 cases of donor site lymphedema out of 189 patients (1.6%) collected from 11 studies that met their inclusion criteria. In a separate review of VLNT outcomes, encompassing 24 studies and 271 lymph node transfers, Scaglioni et al³⁶ identified only the same 3 cases (1.1%) of iatrogenic lymphedema affecting the donor limb. An additional report by Lee et al⁶⁶ describes a fourth case of donor limb lymphedema not included in either review.

Specifically, Vignes et al⁶⁷ reported 2 cases of iatrogenic donor site lymphedema following groin lymph node transfer. These were made based on clinical diagnosis in which the donor limb was documented to have an increase of >2cm in limb circumference compared with the contralateral limb. Pons et al⁶⁸ reported 1 case of lower limb swelling after groin lymph node flap harvest in a series of 42 patients. The donor lower limb was found to have an increase in thigh circumference of 2cm at 24 months follow-up and lymphoscintigraphy of the affected limb demonstrated delayed drainage, although dermal backflow pattern was not found. Although not included in either review, there is 1 case of upper extremity lymphedema that resulted following harvest of a supraclavicular lymph node flap confirmed with compromised drainage on lymphoscintigraphy and an increase of over 1L in the ipsilateral arm.⁶⁶

Three of the 4 reported cases of iatrogenic lymphedema following VLNT come following groin lymph node harvest. It is not known whether groin lymph node harvest is inherently riskier than harvest from other potential donor sites (eg, supraclavicular, lateral thoracic, and intra-abdominal), or that more cases of donor site lymphedema have been reported following groin node harvest because it is a more common procedure than VLNT from other sites. One difficulty with estimating the risk of iatrogenic lymphedema following groin node transfer is that flap harvest techniques vary from surgeon to surgeon. For example, groin lymph node flaps have been described based on the superficial circumflex iliac artery (SCIA), superficial epigastric artery (SIEA), and the deep inferior epigastric artery. With regards to the reported cases of iatrogenic lymphedema following groin node transfer, Vignes et al⁶⁷ described harvesting an “abundant amount of tissue” and Pons et al⁶⁸ described harvesting “at least 3 lymph nodes” in the cases that resulted in donor limb lymphedema, leading Demiri et al⁶⁵ to recommend limiting the number of lymph nodes harvested.

It may be that clinically symptomatic iatrogenic donor limb lymphedema is rare, but lymphatic function is still compromised. A few studies have looked at the lymphatic

function in the donor limb following groin VLNT. Viitanen et al.⁶⁹ performed postoperative lymphoscintigraphy in 10 patients who underwent a SCIA-, or SCIA and SIEA-based groin lymph node flap transfer for BRCL. Minor changes in lymphatic flow were noted in 6 patients and the transport index (a sensitive and specific scoring system derived from lymphoscintigraphy findings) was abnormal in 2 patients. However, none of the patients complained of lymphedema symptoms in the donor limb nor was there a statistically significant difference in thigh circumference between the donor and non-donor limbs. In a follow-up study, the same group showed a smaller difference in limb volume between the donor limb and non-operated limb after modifying their groin lymph node flap harvest technique to only include the SCIA, no tissue medial to the femoral artery to avoid the sentinel lymph nodes, which are located medial and deep in the groin, and only 1 palpable lymph node, compared with their initial technique which involved harvesting tissue based on both the SCIA and SIEA with more than 1 palpable lymph node in the flap.⁷⁰ They found 2 out of 13 patients with abnormal transport index values on lymphoscintigraphy using the modified flap harvest technique compared to 1 out of 16 patients with an abnormal transport index using the earlier technique. Therefore, even with more conservative lymph node harvesting, it is possible to cause subclinical lymphatic dysfunction in the donor limb. In a recent study by Liu et al,⁷¹ postoperative limb circumference measurement and lymphoscintigraphy was performed in 30 consecutive patients undergoing VLNT for breast cancer-related lymphedema using groin lymph nodes supplied by the SCIA. With a mean follow-up of 13 months, there was no significant difference in limb circumferences between the contralateral and donor limbs, and while the mean transport indices were significantly different at 2.04 and 3.34, respectively, both were within the range of normal (<10) with no dermal backflow pattern observed on lymphoscintigraphy.

Based on the evidence available, it seems that symptomatic iatrogenic donor site lymphedema is a rare occurrence, although it may also be under-reported. Recommendations for minimizing the chances of iatrogenic lymphedema following VLNT include only harvesting a small number of lymph nodes and sparing the sentinel or major draining lymph nodes of the donor limb. For groin lymph node harvest, imaging and anatomic evidence suggests avoiding dissection medial to the femoral artery and inferior to the point where the superficial circumflex iliac vein joins the greater saphenous vein.^{69,70,71} Reverse lymphatic mapping techniques may help to reduce iatrogenic lymphedema by identifying donor limb lymphatic tissues that should be preserved. As described by Dayan et al,⁷² radioactive isotope (eg, technetium) is injected into the lower limb to map the draining lymphatic tissues that should be left undisturbed while ICG dye is injected in the upper abdomen/lateral groin to identify lymphatic tissues to be included with the groin lymph node flap. Others have described utilizing magnetic resonance angiography or SPECT-CT lymphoscintigraphy preoperatively to guide selective lymph node harvest and

spare the most functional lymph nodes for the donor limb.⁶⁵ The authors recommend performing preoperative lymphoscintigraphy on all patients who are planning to have a VLNT using the inguinal, lateral thoracic, or supraclavicular donor sites. Donor site lymphedema following harvest of the omentum or gastroepiploic nodes, jejunal mesenteric nodes, or submental lymph nodes has never been reported, but in the authors' opinion, there is no indication for obtaining preoperative imaging with the latter donor sites.

CONCLUSIONS

With many significant advances in super microsurgery, a surgical approach to lymphedema is increasingly common, though many controversies remain. Each of these—from optimal technique to prophylactic surgery to donor-site lymphedema—represents an area of ongoing investigation. The authors find that in our high-volume center, with both multi-disciplinary evaluation and multimodal approach, surgical treatment of lymphedema is patient-specific, safe, and efficacious.

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