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Lower extremity lymphedema and vascularized lymph node transfer recipient sites: a review of the current literature

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Abstract

Vascularized lymph node transfer is a surgical treatment for lower extremity lymphedema aimed at restoring physiological lymphatic flow. Much variation exists in determining the appropriate donor site from which to harvest lymph nodes as well as the optimal recipient site to anastomose the new lymph nodes. This article reviews the underlying principles of free vascularized lymph node transfer and discusses patient-specific, disease-specific and surgery-specific factors in considering recipient sites from the proximal, middle, and distal lower extremity. The clinical outcomes of published studies in lymphatic surgery for lower extremity lymphedema are presented. An omental flap to the middle lower extremity (mid-thigh, popliteal fossa, or medial calf) is then recommended due to the abundance of lymphatic tissue, proximity to pooled lymph fluid, and avoidance of added bulk or poor cosmesis of the distal lower extremity. However, additional clinical outcomes studies are needed and represent an area of further investigation.

Keywords: Lower extremity lymphedema, vascularized lymph node transfer, physiologic procedure, lymph node flap, lymphatic flap, lymph node donor, lymph node recipient, lymphangiogenesis

INTRODUCTION

Lymphedema is a heterogeneous group of conditions characterized by the loss of functional lymphatic channels leading to progressive limb swelling. It is a disease of significant morbidity leading to recurrent bouts of cellulitis - which often require inpatient hospitalizations for intravenous antibiotics, wound formation, activity restriction and aesthetic deformity. Primary lymphedema results from congenital lymphatic dysfunction and is subdivided by timing of disease onset. Secondary lymphedema is more common. In relatively lower-income countries, the most common etiology is filarial worm infection. In higher-income countries, the disease typically results from iatrogenic damage to the lymphatic system from oncologic surgery and radiation. Upper extremity lymphedema is seen after axillary lymphatic disruption frequently due to breast cancer care while lower extremity lymphedema commonly follows treatment of cancers affecting the groin and pelvis[1].

Several criteria have been proposed to diagnose lymphedema using a combination of patient history, clinical exam findings, and a variety of imaging modalities. Currently, the most widely used classification is the ISL staging system as proposed by the international society of lymphology. Once a patient has been diagnosed and appropriately staged, they are typically treated with a period of conservative management which includes regular evaluation and treatment by a lymphatic therapist with special training in complete decongestive therapy prior to being considered for surgical evaluation. Surgical therapies involve both physiologic and debulking techniques. Physiologic procedures include lymphovenous anastomosis (LVA) and vascularized lymph node transfer (VLNT), while debulking procedures include liposuction and direct excision. Multiple algorithms for surgical management have been proposed to guide the timing and selection of therapies but none are yet universally accepted. In general, physiologic procedures are believed to be most successful in earlier stages (ISL I-II) prior to the irreversible deposition of fibrous and fat tissue seen in advanced disease[2,3].

Lymphovenous anastomosis

Lymphovenous anastomosis is a physiologic procedure in which microsurgical techniques are used to re-establish lymphatic drainage by coapting lymphatic channels to nearby venules. Classically, this technique is indicated in early stage lymphedema[4,5]. More recent studies have shown a role in later stage lymphedema and even a synergistic effect with lymph node transfer[6]. As such, LVA can be an effective adjunct to VLNT in addressing the entire extremity. For the sake of this review, we will only discuss sites of lymph node transfer.

Donor sites of lymph node flaps

Experience with a variety of donor sites of vascularized lymphatic tissue has been reported in the literature for the treatment of both upper and lower extremity lymphedema. Described flaps include nodes from the submental, supraclavicular, thoracic, omental, and inguinal nodal basins[1,7]. Isolated and mixed series of each of these flaps have been published, reporting varying degrees of success in reducing symptoms and limb diameter. At this time, there is no clear "best" donor site for vascularized lymphatic tissue, and the merits of each flap continue to be debated.

The submental lymph node flap, based on the submental artery, includes both submental and submandibular lymphatic tissue with an overlying skin paddle. Previous anatomic studies suggest that this flap can be reliably harvested with 3-4 lymph nodes and a pedicle artery diameter and length of 1.3 mm and 6.4 cm, respectively[7]. Reported disadvantages of this flap include potential damage to the marginal mandibular nerve during flap elevation[7].

The supraclavicular lymph node flap is a thin flap based on the transverse cervical vessels. Its advantages include a relatively inconspicuous donor site and minimal excess tissue that reduce the need for subsequent flap thinning. The flap, however, is typically only harvested from the right neck as harvesting from the left neck carries the risk of damage to the thoracic duct[7]. Harvest from either neck can result in damage to the supraclavicular nerve, leading to superior chest wall numbness[7].

The thoracic lymph node flap is a larger flap that brings the level 1 axillary node based on either the thoracodorsal or lateral thoracic arteries. It typically includes more soft tissue bulk than other vascularized lymph node flaps, which could be advantageous in resurfacing larger defects[7]. However, its use is frequently limited due to the risk of causing iatrogenic upper extremity lymphedema[8]. Additionally, there are reported concerns regarding the reliability of the vascular pedicle as well as potential injury to the thoracodorsal nerve during harvest[7].

The omental lymph node flap offers potentially the largest amount of lymphatic tissue of all described flaps in use for VLNT. It includes large lymphatic chains along both the right and left gastroepiploic vessels[9,10]. It is typically elevated on the right gastroepiploic system but has also been described as a flow-through flap or being split into two flaps based on the right and left systems, respectively[9,10]. Its advantages include a large lymphatic basin and minimal risk for donor-site lymphedema. It can be harvested using laparoscopic or mini-open techniques, resulting in little donor site scarring[11-14]. Its disadvantages include the risks associated with intra-abdominal surgery and the lack of an available skin paddle[9,10]. Additionally, groups performing a high volume of this flap have reported concerns for significant venous hypertension and accordingly recommend anastomosis of the distal gastroepiploic venous stump for additional outflow[15].

The groin lymph node flap has been probably the most widely reported donor site for VLNT. The flap can be variably raised on either the superficial circumflex iliac artery or the medial branch of the common femoral artery, including up to 6.2 nodes. The flap typically includes a thin overlying skin paddle. Its reported advantages include a reliably large number of nodes and an inconspicuous donor site scar. However, it carries a risk of donor-site lymphedema, which limits its utility in the treatment of lower extremity lymphedema[8,16].

Reverse lymphatic mapping

Reverse lymphatic mapping is an imaging technology that aims to limit the risk of donor site lymphedema after harvest of vascularized lymphatic tissue. Using a combination of radioisotopes, a given nodal basin of interest can be investigated to differentiate nodes that drain an extremity versus those that drain the trunk. Using this information, flaps can be designed to harvest only those nodes that drain the trunk, thereby obviating the potential for iatrogenic lymphedema in the donor limb. As it was first described, the technique required nuclear medicine imaging pre-operatively which carried a significant cost burden. A subsequent modification using only a combination of indocyanine green and blue dye intra-operatively has been described which significantly reduces cost and the inconvenience of the original technique. In a series of 39 patients in which the two techniques were compared for design of a vascularized groin lymph node flap, the lower cost indocyanine green/blue dye technique showed no increase in donor site lymphedema[17].

RECIPIENT SITES

There is no consensus on the optimal recipient site for lower extremity VLNT. Successful reduction in limb circumference, decrease in infection incidence, and/or increase in patient reported quality of life have been achieved using proximal, mid, and distal lower extremity as recipient sites. A recent landmark systematic review and meta-analysis concluded that there is grade 1B evidence to support the efficacy of VLNT in

reducing the severity of upper and lower extremity lymphedema; however, this review did not include subgroup analysis comparing outcomes across the different recipient sites[2]. The only published review that specifically examined this distinction found that VLNT to the ankle was associated with greater reduction in limb volume and higher proportion of functioning lymph node flaps on post-operative imaging when compared to VLNT to the groin or proximal thigh[18]. Unfortunately, it was not completed as a formal systematic review or meta-analysis.

There have been, however, some studies published examining the outcomes between distal and proximal insets in the upper extremity. Chocron *et al.* performed a systematic review of lymph node transfer in breast cancer-related lymphedema comparing inset at the wrist to inset at the axilla. Their results showed no significant difference circumference reduction rate or excess volume reduction[19]. While including a large patient population, their analysis did not delineate changes in the arm *vs.* forearm. Cheng *et al.* showed some evidence that a distal inset is more likely to improve distal lymphedema. They found that there was a significant improvement in circumferential differentiation and circumferential reduction rate specifically below the elbow when lymph nodes are inset at the wrist *vs.* inset at the elbow[16]. Although their sample size was small, this may lend credence to directing recipient site based on the areas more severely affected by lymphedema.

Ultimately, the choice of recipient site must be individualized to each patient for the best outcome. There are a number of options that each possess advanatages and disadvantages that can help delineate surgical decision making [Table 1]. Multiple factors should be considered, including but not limited to the etiology, severity and location of lymphedema, availability of recipient vessels, prior surgery and/or radiation, the patient's concern for final aesthetic appearance, and the surgeon's experience with individual recipient sites[1,3].

Proximal lower extremity: groin & proximal thigh

Proximal recipient sites for VLNT to the lower extremity include the groin and the proximal thigh. Many recipient vessels have been described for this region, including branches of the external iliac (deep inferior epigastric, deep circumflex iliac) and the common femoral (superficial femoral, profunda femoris, superficial inferior epigastric, superficial circumflex iliac, lateral circumflex femoral)[20,21]. The pedicle to the profunda artery perforator has also been reported as a potential recipient[22].

The main advantage of this recipient site is that the dense scar and fibrosis from prior surgery and/or radiation are removed as part of the recipient bed preparation[3,4,23], which by itself may improve lymphatic and venous drainage. The transfer of a well-vascularized lymph node flap can then maintain the pliability of soft tissues in the region as well as aid in lymphatic drainage via lymphangiogenesis[24,25]. An early animal study demonstrated that transfer of lymph nodes to a lymph node-depleted area-such as the groin after pelvic lymphadenectomy and radiotherapy-restored lymphatic flow, but new transferred nodes did not induce lymphangiogenesis in normal uninjured areas[24,25]. Additional advantages include the ability to easily hide surgical scars with clothing and the relatively ample potential space to accommodate the lymph node flap without significant compression on the pedicle [Table 1][4]. Moon *et al.* showed a mean volume decrease of 13% when performing VLNT to the proximal thigh[26].

The main disadvantages of the proximal recipient site are that the heavy scar burden often makes the dissection challenging, tedious, and unpredictable[27]. In rare cases in which there is no recipient vessel to allow for a superficial placement of the lymph node flap, vein grafts may be required [Table 1][4].

Table 1. Summary of the characteristics of proximal, middle, and distal lower extremity recipient sites

Recipient site	Recipient vessel	Advantages	Disadvantages	Positioning
Proximal lower extremity groin proximal thigh	From external iliac - Deep inferior epigastric - Deep circumflex iliac From common femoral - Superficial femoral - Profunda femoris - Profunda artery perforator - Superficial inferior epigastric - Superficial circumflex iliac - Lateral circumflex femoral	- Excision of scar and fibrosis - Transfer of vascularized nodes to lymph node-depleted area - Ample space to inset lymph node flap (rare need for skin paddle or graft) - Well-hidden surgical scar	- Tedious, unpredictable dissection - Heavy scar burden	- Supine
Middle lower extremity mid-thigh popliteal fossa medial calf	- Lateral circumflex femoral - Medial sural - Descending genicular	- Sufficient space to inset for lymph node flap (decreased need for skin paddle or graft) - Faster healing compared to distal - No sacrifice of perfusion to the distal extremity	- Requires debulking of adjacent soft tissue to obviate skin paddle or graft	- Frog-leg
Distal lower extremity ankle	- Posterior tibial - Anterior tibial - Dorsalis pedis	- Most distant from radiation - Proximity to pooled lymph fluid	- Limited space to inset lymph node flap - Poor cosmesis due to the need for skin paddle or graft, bulk of the lymph node flap - Interference with footwear	- Supine

Distal lower extremity: ankle

The ankle is the recipient site of choice for the distal lower extremity. Options for recipient arteries include the posterior tibial, anterior tibial, and dorsalis pedis. Venous anastomosis can be performed to the venae comitantes of the above vessels and/or to branches of the greater saphenous vein[4]. Preference for superficial veins has been advocated based on anecdotal evidence that deep veins within the anterior and posterior compartments are often compressed, especially in limbs with higher stage and more long-standing lymphedema. However, an analysis of outcomes did not reveal statistically significant differences between the use of superficial versus deep veins, although the study was likely underpowered[28].

The main advantage of the distal recipient site is that it is spared from surgical or radiation-related injury, allowing the dissection to be straightforward. Some groups propose that distal, heterotopic placement of lymph node flaps has functional advantages. In a lymphedematous limb, especially the lower extremity, lymph fluid pools distally in the most dependent regions. Placement of the lymph node flap in this location allows proximal return of lymph via intra-nodal lymphovenous connections or anastomoses[27,29,30]. Indeed, in both animal and human clinical cases, indocyanine green (ICG) injected into the edge of the lymph node flap was later detected in the donor and recipient veins. This effect was also seen when the lymph node flap was placed in ICG-containing albumin solutions. In contrast, ICG injected into the edge of fasciocutaneous flaps without lymph nodes did not reach the pedicle vein even after prolonged imaging times.

With the flap inset distally at the ankle, gravity acts to pull excess lymph from proximal to distal where it can then be returned to the venous system via the lymph node flap [Table 1]. Importantly, this proximal to distal directionality is also observed in patients who underwent VLNT to the ankle at an average of 27 months prior, even while positioned supine[21]. Building upon this observation, Roka-Palkovits *et al.* developed a retrograde manual lymphatic drainage rehabilitation protocol wherein a sphygmomanometer is

used to massage the lymphedematous limb in the proximal-to-distal direction beginning 1 month after VLNT to the ankle[18]. Compared to a group of patients receiving only complete decongestive therapy, patients in this cohort experienced significantly greater decrease in limb circumference and increase in lymphedema-specific quality of life. Ciudad *et al.* were able to achieve a mean circumference reduction rate of 22.3% when performing VLNT to the ankle[31].

The main disadvantage of the distal recipient site is that there is limited laxity and space to accommodate the lymph node flap, necessitating a skin paddle or, more uncommonly, skin graft. This results in poor cosmesis and interference with footwear and compression garment [Table 1]. There is higher incidence of venous complications with VLNT to the ankle, even with the use of a skin paddle. Koide *et al.* reported a significant decrease in flap exploration and total complication rates with the use of delayed primary retention sutures, which are placed at the time of the lymph node transfer but can be loosened or tightened at the bedside in the immediate post-operative period[30]. Fortunately, with close flap monitoring, the majority of venous insufficiency cases can be salvaged and do not appear to compromise long-term functional outcomes of the procedure[28]. At 6-12 months post-operative, the skin paddle can often be removed in its entirety, after subsidence of edema and increased pliability of peri-lymph node flap tissues[1,16].

Middle lower extremity: mid-thigh, popliteal fossa, & medial calf

The mid-anterior thigh, popliteal fossa, and the medial calf have been described as recipient sites for VLNT to the mid lower extremity[9,10,27]. The most popular recipient vessels are the lateral circumflex femoral and the medial sural; the descending genicular is infrequently mentioned, and no detailed description of its surgical technique is provided in the literature.

Positioned in between the proximal and the distal recipient options, the mid lower extremity recipients blend many of the characteristics of their neighboring regions. For example, they are spared from the scar tissue and fibrosis of the groin and proximal thigh while having enough potential space to accommodate the lymph node flap without a skin paddle or graft-albeit with considerable debulking of the adjacent subcutaneous fat and medial gastrocnemius muscle. Because neither the lateral circumflex femoral nor the medial sural artery provides in-line flow to the distal extremity, there is no concern for distal perfusion. Lastly, its relative proximity to the pooled lymph fluid allows the transferred lymph nodes to fulfill their function as a lymphovenous shunt. Although not statistically significant, Manrique *et al.* showed a mean excess volume reduction of 23.3% when inset in mid-thigh *vs.* a reduction of 13.3% when inset at the ankle[10]. Furthermore, patient reported function scores; however, those who had mid extremity inset had significantly shorter hospital stay, faster return to daily activities and higher satisfaction with surgical scar and appearance [Table 1][10].

A notable modification to the VLNT technique features the use of omental lymph nodes as a flowthrough flap with the right gastroepiploic artery anastomosed to the proximal end of the divided medial sural artery and the left gastroepiploic artery anastomosed to the distal medial sural artery[9]. The flap is also supercharged by anastomosing the right gastroepiploic vein to one of the venae comitantes of the medial sural artery and the left gastroepiploic vein to the lesser saphenous vein. While this configuration theoretically minimizes the risk for venous hypertension by both reducing arterial inflow and augmenting venous outflow, long-term follow up data has not yet been reported.

Preferred protocol

At our high-volume institution, the author's preferred protocol begins with lymphoscintigraphy to assess the extent and severity of lymphedema in the affected limb. After the patient has been deemed an

appropriate candidate, the authors favor an omental flap to the middle lower extremity for the following reasons: abundance of lymphatic tissue, proximity to pooled lymph fluid, and avoidance of added bulk or poor cosmesis of the distal lower extremity.

Post-operatively, patients are monitored according to standard free tissue transfer protocols including frequent doppler checks and clinical perfusion assessment. For the first 48 hours after surgery, the patient is kept on strict bed rest with leg elevation and careful positioning to prevent pressure on the flap. If the vascularized nodes are transferred to the groin, hip flexion is limited to 90 degrees and the knee is splinted in extension. If a distal recipient site is chosen, the ankle is splinted in a neutral position and a dangle protocol is initiated after 48 hours. Patients are typically discharged to home 3-5 days after surgery. The first therapy visit takes place two weeks after surgery at which point range of motion restrictions are lifted. Manual lymphatic drainage (MLD) is initiated with care to avoid the flap and to remain one palm-width away from incisions. Wrapping is allowed distal to the transferred nodes only. At four weeks post-operatively, MLD is initiated throughout the extremity, including over the flap, and wrapping restrictions are lifted.

While this represents the authors' currently favored protocol, multiple suitable regimens likely exist, and a compelling case can be made for other lymph node transfers and multiple recipient options. Some recipient sites result in less morbidity and more acceptable scars[4]. Etiology and patient history should also be considered when determining optimal recipient site. For example, circumstances such as radiation, trauma, and prior surgery can eliminate options depending on the location, timing, or severity. Some recipient sites may be more effective in draining distal disease while proximal sites are more effective proximal in treating proximal disease[7,10]. Notably, no direct comparison data are available for analysis and represents a necessary area for future research.

CONCLUSION

Early data support the practice of vascularized lymph node transfer in carefully selected patients with lower extremity lymphedema. Many questions remain unanswered, including the ideal recipient location for the lymph node flap. A compelling case can be made for each of the three options, but no direct comparison data are available for analysis. It may be that no one recipient site fits all patients with lower extremity lymphedema, and the decision should be individualized to each patient.

DECLARATIONS

Authors' contributions

Made substantial contributions to study conception, design of study, performed data gathering, analysis, interpretation, and creation and revision of the manuscript: Bruce JG, Ha AY

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Made substantial contributions to study conception, design of study, performed data analysis and interpretation, revision of the manuscript, and provided administrative, technical, and material support: Anolik R

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