

Review

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# Non-vascularised lymph node transfer: future directions for the minimally invasive surgical management of lymphoedema

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## Abstract

Lymphoedema is a common and debilitating condition for which there is no single satisfactory management modality. Physiotherapy is accessible and moderately effective but suffers from the necessity for daily adherence. Surgery is effective in the earlier stages of disease progression but can be morbid and demanding for patients. An evolving surgical technique known as non-vascularised lymph node transfer (NVLNT) aims to tackle the underlying lymphatic drainage deficit in lymphoedema in a minimally invasive manner. Emerging evidence demonstrates promise in animal models and there is very nascent human evidence with mixed results. This is a narrative review that examines the available animal and human literature on NVLNT and draws comparisons between the two to discover methods of translating animal research to human applications. A systematic search was conducted. PubMed and Embase were searched using MeSH terms for NVLNT. Ultimately, 17 papers, including 14 animal and 3 human studies, were found. Within animal studies, NVLNT is efficacious, with results being repeated multiple times. Additionally, methods of optimising lymphangiogenesis, such as the addition of platelet-rich plasma and VEGF-C in addition to fragmentation and pre-inflammation techniques, have been investigated with general success. To date, evidence from human studies is sparse, with few studies, small sample sizes, and variable outcomes. NVLNT is promising as a minimally invasive surgical treatment for lymphoedema; however, further high-quality research in humans with advanced lymphoedema is necessary to prove its validity. Furthermore, adjuvants to grafting explored in animal studies, such as VEGF-C therapy, may increase the efficacy of lymph node



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grafting in humans.

**Keywords:** Lymphoedema, plastic surgery, microsurgery, cancer

## INTRODUCTION

Lymphoedema is a common and debilitating sequela of cancer management. The disruption of lymphatic drainage due to surgical division or radiotherapy-induced destruction of lymphatic pathways leads to a deficit in lymphatic drainage. Seen most commonly in the limbs and increasingly in the head and neck, the swelling in lymphoedema is distinct from vasogenic oedema due to its potential to form into solid fibrofatty infiltrates with time<sup>[1]</sup>. The International Society of Lymphology encapsulates this natural history in a clinical staging system ranging from stage 0 to stage 3, with increasing swelling and fibrosis as patients ascend the stages<sup>[2]</sup>. As such, the effective management of lymphoedema is not focused on fluid balance but rather is centred around bolstering lymphatic clearance.

Currently, the armamentarium of lymphoedema management modalities can be divided into surgical and non-surgical options. The cornerstone of non-surgical management is complete decongestive therapy (CDT). This physiotherapy technique combines compressive garment wear and manual lymphatic drainage and has seen modest yet reproducible success, with the restrictive requirement of daily patient adherence<sup>[3]</sup>. Surgical management of lymphoedema offers patients a significant reduction in swelling associated with lymphoedema and the potential restoration of lymphatic drainage<sup>[4]</sup>. Lymphoedema surgery is broadly divided into reductive and physiological modalities. The frontier of lymphoedema surgery focuses on the physiological restoration of the lymphatic drainage deficit through techniques such as lymphaticovenous anastomosis (LVA) and vascularised lymph node transplant (VLNT)<sup>[4]</sup>.

In particular, VLNT has gained popularity due to its ability to facilitate improvements in advanced and otherwise recalcitrant lymphoedema<sup>[4]</sup>. The technique involves performing free tissue transfer with local lymph nodes resected and transferred en bloc. While effective, the technique is a complex microsurgical procedure imposing surgical morbidity and the cardiorespiratory burden of a general anaesthetic on patients, many of whom already have superimposed co-morbidities<sup>[4]</sup>.

In light of this, non-vascularised lymph node transfer (NVLNT), a surgical technique for inducing lymphangiogenesis without the operative burden of microsurgical anastomosis, is currently being explored in animal and human studies. In essence, NVLNT is a procedure by which lymph nodes are harvested from a distant site, such as the groin or axilla, and are grafted onto the lymphedematous site<sup>[5]</sup>. Emerging animal studies suggest that grafted lymph nodes can undergo lymphangiogenesis at a distant site even without the substantial donor blood supply provided by a flap<sup>[6]</sup>. NVLNT could, therefore, be a surgical modality to reverse the pathophysiology of later-stage lymphoedema without the considerable operative burden of VLNT, making effective lymphoedema management accessible to a wider cohort of patients. This article will explore the biology, surgical methodology, and current animal and human evidence base for the efficacy of NVLNT to date. It will endeavour to offer the current sum of research on this emerging lymphoedema management technique.

## METHODS

A systematic search of PubMed, Embase, and Scopus databases was performed from their inception until December 2023. The search strategy utilised a combination of relevant keywords and MeSH terms. The following search terms were used (Lymph node gra\* OR Lymph node transfer OR avascular lymph node

transfer OR lymphatic tissue transfer). During the review process, any relevant studies discovered through references were also manually added. These papers underwent title and abstract screening, and selected papers underwent full-text screening for final inclusion into the narrative review. These steps were undertaken independently by two authors (RR and JC). The only stringent inclusion criterion for this review is that the paper must explore NVLNT; all papers that mentioned the necessity for vascularisation of tissue transfer were excluded. All human and animal experimental studies that covered a broad range of clinical and experimental endpoints were included. Studies were analysed using a narrative synthesis and discussed in the main text of this narrative review.

## **The current literature on NVLNT**

### *Literature search and study characteristics*

Out of 381 identified results, 144 duplicates were removed and 232 underwent title and abstract screening. Of these, 210 were removed and 26 underwent full-text screening. During the full-text screening, 1 paper was discovered through reference searching and was included manually. Ultimately, 17 papers were included in this review.

Fourteen papers were controlled experimental animal studies examining a variety of animal species, including mice, minipigs, sheep, and rabbits. These generally used experimental endpoints such as biopsy and SPECT-CT to determine the efficacy of their various NVLNT techniques. Of the three human studies, one was a controlled prospective trial, one was a single-arm retrospective cohort study, and one was a case report. Volumetric analysis, functional scores, and patient-reported outcome measures were used to gauge efficacy [Table 1].

### *Mechanisms for NVLNT*

The regeneration of grafted lymphatic tissue has been documented since the 1920s when studies by Jaffe and Richter demonstrated in animal models that portions of the thymus could be avascularly grafted and demonstrate regrowth at a distant site<sup>[7]</sup>. However, controversy has surrounded the idea that a similar grafting process was possible with lymph nodes. While opposition to this notion through the work of Tilak and Howard in 1965 believed that vascular supply needed to be preserved to support lymphangiogenesis<sup>[8]</sup>, the work of Pabst and Rothkötter in 1988 demonstrated that grafted lymph nodes could induce lymphangiogenesis without the presence of a donor blood supply<sup>[9]</sup>.

Mechanisms for lymphangiogenesis in a grafted lymph node have not been thoroughly elucidated. However, existing literature on direct lymphangiogenesis (without grafting)<sup>[10]</sup> proposed pathways to lymphangiogenesis in vascularised models, and the amalgamation of experimental studies can be used to theorise a process of imbibition, cell-mediated lymphangiogenesis and maturation and remodelling. To this end, lymphangiogenesis of a grafted lymph node is similar to that of skin graft take<sup>[10]</sup>.

### *Imbibition*

In the first hours to days after lymph nodes have been transplanted into a new site, they survive based on the diffusion of oxygen and nutrients into cells. However, this is only a temporary measure and does not provide a sufficiently nutritive environment for lymph nodes to continue to survive [Figure 1]<sup>[11]</sup>.

### *Cell-mediated lymphangiogenesis*

In response to an unfavourable cellular environment, pro-lymphangiogenic factors such as VEGF-C, VEGF-A, and fibroblast growth factor are released by B cells, endothelial cells, and platelets to the grafted lymph node<sup>[12]</sup>. These factors bind to receptors on lymphatic endothelial cells, such as VEGF-A/C binding to

**Table 1. Study characteristics of included animal trials**

Author	Year	Study design	Animal model	Specific aim	LO model	Outcome	Shortcomings
Pabst <i>et al.</i> <sup>[9]</sup>	1988	RCAT	Minipig	Proof of concept of NVLNT	None	Transplanted lymph nodes demonstrated regrowth at 6 months	Preliminary, proof of concept. Not validated in a lymphoedema model
Fu <i>et al.</i> <sup>[5]</sup>	1998	RCAT	New Zealand white rabbit	Demonstrating NVLNT in mitigating the onset lymphoedema in response to surgical lymphatic disruption	Surgical ligation of auricular lymph vessels	Ear volumes in transplanted rabbits approached those of the negative control at 5 months Indirect lymphography demonstrated no dermal backflow in transplanted rabbits	Intervention was performed prior to the clinical establishment of lymphoedema
Hadamitzky <i>et al.</i> <sup>[13]</sup>	2009	RCAT	Lewis rats	Determining the effect of PRP to augment lymphangiogenesis	Surgical ligation of inguinal lymph vessels	The introduction of subdermal PRP enhanced rate of lymphangiogenesis even when compared to immune induction with sheep erythrocytes	As above
Tobbia <i>et al.</i> <sup>[6]</sup>	2009	RCAT	Dorset sheep	Comparing VLNT to NVLNT	Surgical ligation of popliteal lymph vessels	VLNT is more consistent and provides superior lymphatic drainage as compared to NVLNT as quantified by limb volume measures and lymphangiography	As Above
Blum <i>et al.</i> <sup>[15]</sup>	2010	RCAT	Minipig	The effect of various lymph node fragmentation techniques on lymphangiogenesis	Surgical ligation of inguinal lymph nodes	The optimal fragmentation pattern was when the lymph node was divided into two pieces with the capsule maintained (Butterfly)	As above
Lähtenvuo <i>et al.</i> <sup>[11]</sup>	2011	RCAT	Pig	Comparing VEGF-C and VEGF-D gene therapy in promoting lymphangiogenesis	Surgical ligation of inguinal lymph nodes	VEGF-C treated subjects demonstrated both increased histological lymphangiogenesis as well as increased functional lymphatic drainage on XR-Lymphangiography	As Above
Sommer <i>et al.</i> <sup>[19]</sup>	2012	RCAT	Lewis rat	Evaluating the effect of VEGF-C gene therapy on lymphangiogenesis	Surgical ligation of axillary lymph nodes	VEGF-C groups demonstrated more robust histological lymphangiogenesis as well as a greater ICG measured lymphosome	As Above
Joseph <i>et al.</i> <sup>[14]</sup>	2014	RCAT	Mouse	Comparing the induction of sterile inflammation pre and post lymph node grafting in lymphangiogenesis	Surgical ligation of inguinal lymph nodes	Histological assessment demonstrated that sterile inflammation induced post transplantation resulted in the most extensive lymphangiogenesis	As above
Tervala <i>et al.</i> <sup>[16]</sup>	2015	RCAT	Mouse	Similar to Lähtenvuo <i>et al.</i> <sup>[11]</sup>			
Shioya <i>et al.</i> <sup>[17]</sup>	2016	RCAT	Mouse	Demonstrating the efficacy of standard NVLNT as measured by ICG lymphangiography	Surgical ligation of popliteal lymph nodes	ICG lymphangiography and measuring rat paw volumes demonstrated lymphangiogenesis	As above
Hadamitzky <i>et al.</i> <sup>[24]</sup>	2018	RCAT	Minipig	Evaluating the effect of cryopreservation of lymph nodes on the lymphangiogenic capacity of transplanted lymph nodes	No true lymphoedema model as only superficial lymph nodes were harvested	Cryopreservation did not hinder the ability of transplanted lymph nodes to reintegrate	No lymphoedema model
Maeda <i>et al.</i> <sup>[18]</sup>	2018	RCAT	Mouse	Evaluating whether microsurgical attachment of a transplanted lymph node to a recipient lymphatic vessel would encourage lymphangiogenesis	Surgical ligation of popliteal lymph nodes	The first documented attempt at restoring anatomical organisation of lymphatics by non-vascularised means demonstrated good histological lymphangiogenesis	Intervention was performed prior to the clinical establishment of lymphoedema
Hadamitzky <i>et al.</i> <sup>[12]</sup>	2022	RCAT	Minipig	Combining existing adjuvants of VEGF-C and	Surgical ligation of inguinal	Combined VEGF-C and “Butterfly” fragmentation	As above

				"Butterfly" fragmentation in order to assess lymphangiogenesis	lymph nodes	increased SPECT-CT and histologically measured lymphangiogenesis more than either technique alone	
Kim <i>et al.</i> <sup>[25]</sup>	2023	RCAT	Mouse and minipig	Examining the dynamics of NVLNT using immunohistochemical testing	Surgical Ligation of inguinal lymph nodes	Immunohistochemistry as well as secondary investigation methods of lipidol lymphangiography and MR lymphangiography all favoured NVLNT compared to a negative control	As above

NVLNT: Non-vascularised lymph node transfer; PRP: platelet-rich plasma; VLNT: vascularised lymph node transfer.

VEGFR-3, and induce endothelial proliferation and tubule formation<sup>[10]</sup>. This formation has been shown to be omnidirectional and will also attach to existing lymphatic channels within the recipient site to bolster the affected lymphatic network [Figure 2]<sup>[12]</sup>.

Maturation and remodelling

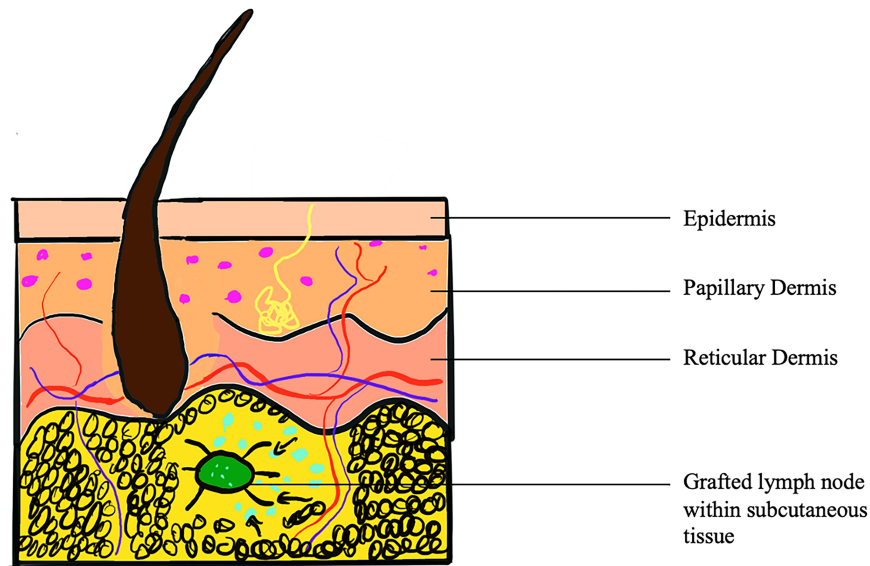
As a new network of lymphatic channels is formed, the presence of TGF-beta, IFN-gamma, IL-6, and other cytokines released from B Cells, T Cells, and found in the extracellular matrix of the recipient site regulate and remodel the nascent lymphatic network such that maturation is achieved [Figure 3]<sup>[6,13,14]</sup>.

*Efficacy in animal models*

The sum of NVLNT research in experimental animal models has explored its efficacy in inducing lymphangiogenesis and reducing lymphoedema-related oedema across multiple species. Additionally, the value of adjuvant techniques to optimise the degree of lymphatic regrowth while reducing donor burden, such as the use of platelet-rich plasma (PRP), exogenous VEGF-C, inducing sterile inflammation of the nodes prior to transplant, and fragmenting lymph nodes, has been explored.

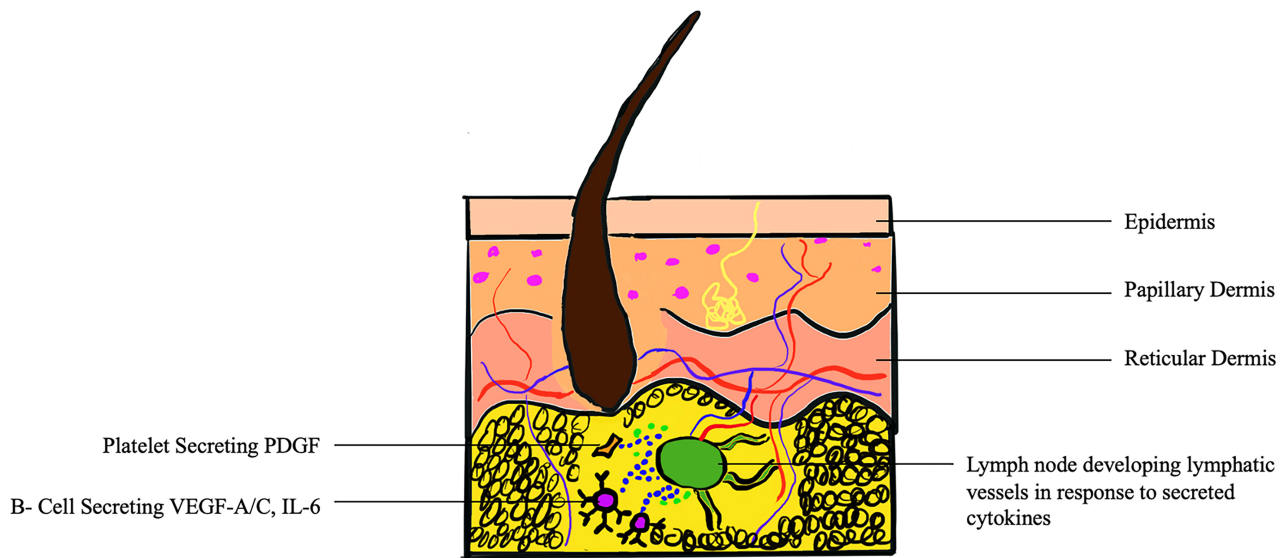
With regard to the variety of animal models, both small and large animals have been utilised to demonstrate lymphangiogenesis after engraftment. With regards to smaller animal models, seven studies utilised models such as the Lewis rat, mouse, and New Zealand white rabbit. Six studies utilised larger animal models such as minipigs, regular pigs, and Dorset sheep. One study utilised both mouse and minipig models. The authors of the papers reported no special considerations or variables between smaller and larger animal models. Additionally, during analysis, no discernible differences in outcome measures between small and large animal models were discovered.

As mentioned earlier, the first experimental proof of NVLNT was in 1988 by Pabst and Rothkötter in a minipig model<sup>[9]</sup>. This study compared the degree of histological lymphangiogenesis after NVLNT of both inguinal and mesenteric lymph nodes grafted to either a distal subcutaneous or subfascial site. The regrowth of the lymphatic architecture in all groups suggested that avascular grafting may be explored in further studies. Furthermore, the study found that inguinal lymph nodes transplanted in the subdermal plane grew best among the four groups.



Stage 1- Imbibition: Freshly grafted lymph node absorbs nutrients and oxygen through diffusion. No vascular supply yet established

**Figure 1.** Schematic showing process of grafted node undergoing imbibition at recipient site.

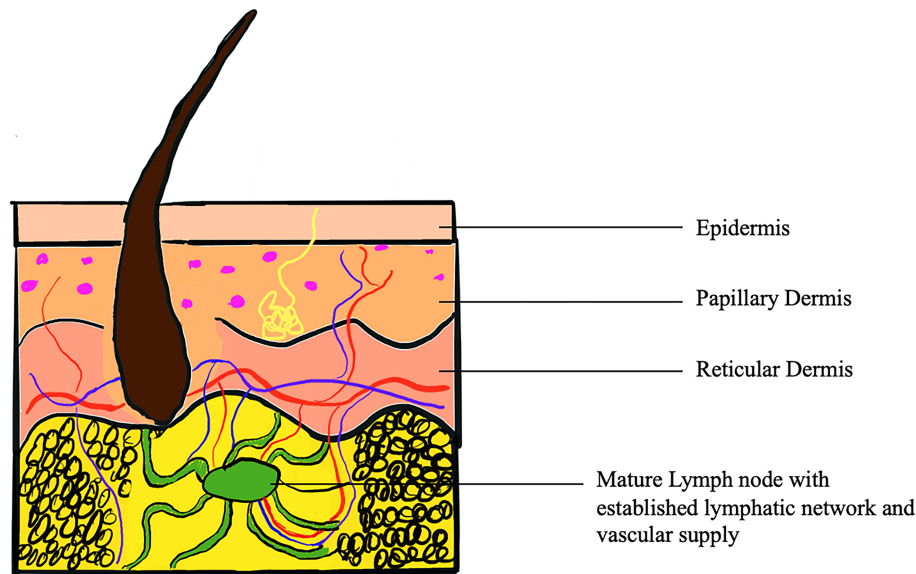


Stage 2- Cell Mediated Lymphangiogenesis: B-Cells, Platelets and other cells secrete cytokines such as VEGF-C and PDGF which bind to the grafted lymph node and stimulate differentiation and growth of lymph vessels and establishment of a vascular supply

**Figure 2.** Schematic displaying process of lymphangiogenesis at recipient site including influence of cytokines and other mediators.

Building on this early success, the first study to examine the ability of NVLNT to prevent oedema in a lymphoedema model was undertaken by Fu *et al.* in 1998<sup>[5]</sup>. New Zealand white rabbits underwent surgical





Stage 3- Maturation and Remodelling: In response to regulatory cytokines such as TGF-beta and interferon- gamma, nascent lymphatic networks mature.

**Figure 3.** Schematic showing the final maturation phase involved in the process of a grafted lymph node.

division of the lymphatics supplying their ears. The control group received a sham NVLNT surgery where the intervention group had lymph nodes from the contralateral ear grafted to the recipient ear. The subjects were assessed by volumetric, lymphoscintigraphic, and histological analysis. They found a statistically significant reduction in volume within the intervention group on postoperative day 30, with the intervention subjects, on average, returning to baseline within 60 days while the control group remained oedematous. Lymphography was concordant with these findings, demonstrating the formation of a new lymphatic drainage system only in the intervention group. Finally, scanning electron microscopy demonstrated patent nascent lymphatic vessels within the ears of the intervention group. These findings not only repeated the success of Pabst *et al.* in inducing lymphangiogenesis, but also demonstrated that this was clinically significant within an albeit isolated and controlled lymphoedema model<sup>[9]</sup>.

These findings have been repeated in multiple contemporary studies with larger numbers of subjects across multiple animal species<sup>[15,16,17,18]</sup>. Furthermore, as the molecular understanding of lymph node engraftment has evolved, novel molecular and biological techniques to increase the rate of lymphangiogenesis have been explored.

#### *Augmenting lymphangiogenesis*

An understanding of the molecular and cellular factors in the regeneration of lymph nodes has prompted the investigation of the exogenous addition of these into experimental models in an attempt to increase the yield of lymphangiogenesis. These adjuvants have included surgical techniques such as different methods of fragmenting lymph nodes prior to grafting, as well as biochemical methods such as the addition of VEGF-C and PRP to grafted lymph nodes and the induction of sterile inflammation within lymph nodes prior to grafting.

Fragmentation of lymph nodes is a technique that involves cutting whole lymph nodes into multiple parts in order to increase the number of regeneration centres without increasing the number of explanted lymph nodes from the donor site<sup>[15]</sup>. This is imperative from a lymphoedema standpoint due to the necessity to preserve the lymphatic drainage of the donor site and prevent an iatrogenic donor site lymphoedema. While it has been shown by Hadamitzky *et al.* that the engraftment of whole lymph nodes produces the greatest level of regeneration per given regeneration centre, fragmenting lymph nodes has become common practice in experimental studies investigating NVLNT<sup>[12]</sup>. As a result, multiple fragmentation methods have been developed in an attempt to increase the number of potential regeneration centres while maintaining the ability of each fragment centre to induce lymphangiogenesis. Currently, there are four established fragmentation techniques<sup>[12,15]</sup>.

- Salami slice: where the lymph node is cut axially multiple times before having fragments sutured together end to end.
- Butterfly: where the lymph node is cut in half coronally but is still left attached by the lymph node capsule.
- Transverse fragmentation: where the lymph node is cut axially and completely in half.
- Transverse fragmentation with capsulectomy.

Hadamitzky *et al.* in their three-stage large-scale minipig experimental model demonstrated that after whole node grafting, it was transverse fragmentation without capsulectomy that provided superior regeneration of lymph nodes in recipient animals<sup>[12]</sup>.

An earlier work on Lewis Rats by Hadamitzky *et al.* in 2009<sup>[13]</sup> demonstrated that the addition of PRP enhanced the rate of regrowth of lymphatic networks in NVLNT. They demonstrated that the postoperative subdermal addition of PRP induced enhanced regeneration of lymphatics compared to a negative control group of rats.

Hamiditzky *et al.* would then examine the impact of the most lymphangiogenic platelet-derived compound, VEGF-C, in a minipig model<sup>[12]</sup>. VEGF-C would prove to be superior in generating new growth of lymphatics compared to two other purportedly lymphangiogenic compounds: Streptococcus suis and tetanol. These findings were buttressed by an experimental study conducted by Sommer *et al.* in Lewis rats, which demonstrated the functional benefit of VEGF-C augmented grafting<sup>[19]</sup>. Not only were rats in the VEGF-C group able to produce more histologically robust lymphatic networks, but these were also shown to be superior at lymphatic drainage and regenerate in irradiated tissue as well. These studies lend credence to the idea that VEGF-C is an important growth factor in the proliferation, differentiation, and organisation of *de novo* lymphatic channels in grafted areas.

Finally, due to concerns about VEGF-mediated cancer recurrence in the intended post-cancer lymphoedema population, the induction of non-carcinogenic sterile inflammation prior to lymph node grafting was explored by Joseph *et al.*<sup>[14]</sup>. The hypothesis for this was factors such as TGF-beta and interferon-gamma, despite playing an important role in lymphatic remodelling, were largely anti-lymphangiogenic compounds, and the induction of inflammation in lymph nodes would downregulate these factors and potentially induce greater rates of lymphatic growth<sup>[14]</sup>. Furthermore, the increased differentiation of B cells, implicated in lymph node growth, by this inflammation would further reinforce a pro-angiogenic state. Joseph *et al.* induced sterile inflammation in murine lymph nodes prior to harvesting and grafting these lymph nodes at a distant site<sup>[14]</sup>. They found that both the rate of lymphangiogenesis and the drainage capability of the new lymphatic networks in the sterile inflammation group were significantly superior to the negative control.



### *Efficacy in human studies*

Lymph node grafting in the animal model appears viable, efficacious, repeatable, and augmentable. However, the translation of this research to the human setting is often complicated and unpredictable. This is evidenced by the fact that despite proof of concept of NVLNT by Pabst and Rothkötter in animals over three decades ago, there have only been three human studies of NVLNT in lymphoedema populations [Table 2].

The most encouraging of these is a 10-year follow-up controlled trial on lower limb lymphoedema patients by Belcaro *et al.*<sup>[20]</sup>. The study recruited 9 intervention patients who received NVLNT and also selected 8 patients who underwent mainstream lymphoedema management with CDT. NVLNT was performed as follows: 1-3 lymph nodes were harvested in the neck, groin, and axilla, fragmented similarly to salami slicing, and placed without suturing along the course of the great saphenous vein within the subdermal plane. Patients were followed up over 10 years and had their limb volumes, limb circumference, and ultrasound-measured tissue thickness tracked. Limb volume was significantly different between the two groups, with the NVLNT group demonstrating an 11% reduction in volume increase. Circumference was similarly encouraging within the intervention groups. Finally, tissue thickness was 59% less in the intervention group. While this demonstrates early optimism for NVLNT in humans, it must be noted that in addition to a small sample size and modest findings, this study was done exclusively in non-cancer patients who did not undergo radiotherapy.

A more recent study undertaken by Travis *et al.* in 2015 examined the effect of NVLNT on upper limb lymphoedema in an uncontrolled cancer population<sup>[21]</sup>. The cohort of 10 underwent a procedure similar to that of Belcaro *et al.*'s study, with the key difference being that whole lymph nodes were grafted into the patients' wrists and the follow-up period was shorter, lasting only 12 weeks<sup>[20]</sup>. While many patients in this study reported a subjective feeling of relief and modest return of function, objective volumetric measurements demonstrated a non-significant volume reduction of 89.6 mL with a 95% confidence interval of -320.4 mL to +141.1 mL.

Supplementary to this, a case report by Brian *et al.* described a 3-year follow-up on a patient with upper limb lymphoedema secondary to breast cancer-related lymph node clearance who received whole node grafting<sup>[22]</sup>. The patient experienced a 36% reduction in limb volume with a significant recovery of function. However, it must be noted that no control measures were undertaken, and this patient also continued their regular CDT postoperatively.

### *Limitations and future directions*

An examination of animal studies on NVLNT reveals that, in experimental settings, its efficacy has been proven and reproducibility is strong. Furthermore, mechanistic explanations for lymphangiogenesis and lymphatic remodelling are beginning to be formed. However, in human populations, the evidence base is much more tenuous, with a small number of low-power studies demonstrating modest outcomes. This is a common theme when translating animal-based research into human models due to the increased biological, ethical, and social complexity that is associated with human research. In the case of NVLNT in lymphoedema, among many others, the incongruence between animal and human studies may be explained by three methods of reasoning.

### *Advanced lymphoedema*

In humans, the burden of lymphoedema is disproportionately concentrated among patients who have advanced-stage lymphoedema (ISL 2 and higher). In these stages, fibro-fatty transformation is predominant,

**Table 2. Study characteristics of included human trials of lymph node grafting**

Author	Year	Study design	Number of patients	Site of disease	Aetiology	Time since resection	Severity of lymphoedema	Experimental methodology	Harvest site	Recipient sites	Outcome/s	Complications
Belcaro <i>et al.</i> <sup>[20]</sup>	2008	Prospective	17	Lower limb	Non-cancer, nil radiation	> 5 years	Oedema scale: T: 4.3 (0.7) C: 4.3 (0.5)	Lymph node sectioning and transplant	Neck = 2 Axillary = 2 Inguinal = 6	Along great saphenous vein	Treatment group showed significant improvement compared to controls in limb volume, oedema scale score, size of limbs and skin thickness	Nil
Travis <i>et al.</i> <sup>[21]</sup>	2015	Prospective	10	Upper limb	Axillary dissection	> 6 months (mentioning stable lymphoedema)	60% ISL Stage 2 40% ISL Stage 3	Two whole lymph nodes transplanted	Inguinal	Wrist + Supratrochlear nodes	Truncal cone volume reduction of 89.6 mL on average (SD: 136.5 ml)	Seroma = 1
Brian and McEwan <sup>[22]</sup>	2017	Case report	1	Upper limb	Axillary dissection	1 year	ISL Stage 2	Two whole lymph nodes transplanted	Inguinal	Wrist + Supratrochlear nodes	Volume reduced by 295ml, good flowing lymphatic channel on imaging	Nil

\*Data presented as mean (standard deviation). T: Treatment group; C: control group; ISL: international society of lymphology; SD: standard deviation.

and the resultant swelling is especially difficult to manage. In fact, whether ISL stage 3 lymphoedema can be effectively managed at all remains in question<sup>[23,24,25]</sup>. Within all animal models that have currently been explored, NVLNT was either not examined in a lymphoedema model or was undertaken at the time of surgical disruption of lymphatic networks in the control populations. In essence, all animal studies did not allow time for lymphoedema to establish within animal models before examining the efficacy of NVLNT, and as a result, a “prophylactic” graft was applied. This means that the efficacy of NVLNT is not readily validated in established lymphoedema even within animal models.

This is especially pertinent when considering the study population of the available human evidence. In Travis *et al.*'s cohort, all patients were ISL stage 2 or higher, with 40% of patients being ISL stage 3<sup>[21]</sup>. Given this, even a modest improvement in limb volume with subjective patient satisfaction may be a valuable outcome in the most stubborn and difficult-to-treat form of lymphoedema.

Therefore, future animal models could attempt to measure the efficacy of NVLNT in subjects who have histologically proven fibro-fatty transformation of lymphoedema.

No adjuvants used

Secondly, most animal studies demonstrate that the addition of any adjuvant therapy, whether it be sterile infection, PRP, or VEGF-C, elicits considerable

improvements in lymphangiogenesis compared to a control group.

Comparatively, no such adjuvant (outside of lymph node fragmentation) was used in any of the human studies. PRP is readily available for human use in wound healing and aesthetic applications and may be used in a clinical trial in lymphoedema patients. However, the consideration of tumorigenesis when using PRP and VEGF-C in patients with a history of cancer must be balanced against potential benefits to lymphangiogenesis. This may help explain the relative lack of adjuvant use in human studies.

Nevertheless, the induction of sterile inflammation in donor lymph nodes is specifically explored in animal models by Joseph *et al.* for future use in human cancer populations<sup>[14]</sup>. Their work purports that the induction of sterile inflammation does not increase the risk of cancer recurrence in the same way that the addition of pro-lymphangiogenic factors may.

Thus, the careful exploration of the carcinogenic capacity of PRP and VEGF-C, as well as the safety and feasibility of inducing sterile inflammation in human studies, could help champion the use of adjuvants to increase rates of lymphatic neogenesis.

#### Study design and characteristics

Finally, it must be noted that all available human evidence is relatively low in power and, therefore, cannot be broadly extrapolated to all lymphoedema populations. The specificity of Belcaro *et al.*'s study, which focuses on patients with lower limb, non-cancer lymphoedema, and the lack of a control group in both Travis *et al.*'s cohort study and Brian *et al.*'s case report suggest that more research in humans is necessary before a conclusive opinion about NVLNT in humans can be formed<sup>[20-22]</sup>. Furthermore, all included human studies did not mention any adjuvant oncological therapy that patients underwent prior to the development of lymphoedema such as radiation therapy. Currently, additional human clinical trials examining NVLNT in a variety of lymphoedema populations are being undertaken and may shed more light on this technique in the near future.

## CONCLUSION

Lymphoedema is a painful and debilitating condition that affects hundreds of millions across the world. Established management modalities for lymphoedema suffer from lack of efficacy, patient dissatisfaction, and operative burden. Currently, a proof of concept for the minimally invasive procedure of NVLNT has been shown in multiple animal models, with many demonstrating techniques to optimise lymphangiogenesis in these models. However, research in humans is significantly less substantial. While NVLNT appears generally safe in humans, it results in variable and possibly only modest improvements in lymphoedema. The future of NVLNT may incorporate adjuvants, proven effective in animals, to bolster the efficacy of NVLNT in humans such that an accessible and relatively burden-free solution to lymphoedema can be found.

## DECLARATIONS

### Authors' contributions

Investigation, resources, writing - original draft and editing: Rajaram R  
Conceptualisation, resources, writing - original draft and editing: Cevik J  
Conceptualisation, writing - editing, supervision: Rozen WM

**Availability of data and materials**

Not applicable.

**Financial support and sponsorship**

None.

**Conflicts of interest**

Rozen WM is an Editorial Board member of the journal *Plastic and Aesthetic Research*. Rozen WM was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, and decision making. The other authors declared that there are no conflicts of interest.

**Ethical approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

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