Re-Evaluating Lymphatic Surgery

*Let It Flow*

Harm Winters
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Re-evaluating lymphatic surgery

*let it flow*

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te Amersfoort
Promotor
prof. dr. D.J.O. Ulrich

Copromotoren
dr. N.J. Slater
dr. S.L.M. Hummelink

Manuscriptcommissie
prof. dr. S.J. Bergé
dr. C.J.M. van der Vleuten
prof. dr. M. Mani (Uppsala Universitet, Zweden)

Paranimfen
Myriam Winters
Daan Viering
Voor Roel
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Chapter one

Introduction and aim of this thesis
Anatomy and physiology of the lymphatic system

The lymphatic system consists of a network of lymphatic organs and lymphatic vessels. The lymphatic organs (lymph nodes, spleen, tonsils and thymus) play an important part in the immune system by generating and differentiating lymphocytes. The lymphatic vessels are responsible for the resorption of lipids from the small intestine, activating the immune cascade by transporting antigen-presenting cells to the lymph nodes and draining the excess amount of interstitial fluid to the venous system.¹

In the healthy lymphatic system, interstitial fluid is collected by the lymphatic capillaries and pre-collectors in the interstitial space. The capillaries have a wall of single-layer cells that overlap. Between these endothelial cells are small slits that allow for lymph fluid to enter the canals during absorption phases.² ³

The pre-collectors consist of multiple layers and contain small valves which are situated every 2-3mm. The main function of the pre-collectors is to absorb the lymphatic fluid and transport it to the lymphatic collectors. These lymphatic collectors consist of 3 layers and are covered with smooth muscle fibres in a circular and longitudinal direction allowing for contraction of the lymphatics. The diameter

![Diagram of the lymphatic system](image-url)

**Figure 1.** Anatomy of the lymphatic capillaries, pre-collectors and collectors within the superficial and deep lymphatic system
of the collectors is 100-600μm. Each segment of the lymphatic collectors between two valves is called a lymphangion.

The lymphatic contractility in combination with the valves, promotes the drainage of lymph fluid towards the systemic circulation. In the extremities, there is the superficial lymphatic network and the deep lymphatic network. Interestingly, in contrast to the venous system, the valves in lymphatic connectors that pierce the fascia and connect the two lymphatic systems are oriented in a way that promotes lymph fluid from the deep to the superficial system. In the upper extremity, the

![Anatomy of the lymph nodes and the watershed territories.](image)

**Figure 2.** Anatomy of the lymph nodes and the watershed territories.
fluid is then collected by the supraclavicular, infraclavicular and axillary lymph nodes after which it is eventually drained to the systemic circulation (Figure 2).³ ⁵

Physiologically about 90% of the arterial blood flow in the capillaries is resorbed by the venous system while only 10% is collected by the lymphatic system.³ When the net amount of lymphatic fluid is increased, for example during exercise, venous insufficiency or infection, the lymphatic system can increase drainage capacity tenfold to avoid overload of the system. This increase is the effect of more rapid contractions of the lymph vessels, usage of collateral lymphatic circulation, and natural anastomoses between lymph vessels and veins. However, when this system is overloaded, lymphoedema may occur.

**Lymphoedema**

**Decompensation of the lymphatic system**

Oedema occurs when the lymphatic system is decompressed, as the capability for increased lymphatic drainage proves to be insufficient. There can be a state of high output or low output oedema. In high output oedema, the decompensation is caused by an increased capillary filtration rate, for example due to infection or thermal burns. Low output failure occurs when the capillary filtration rate is normal but the lymphatic drainage is impaired. Because of the accumulation of protein-rich fluid, the process of swelling is accelerated due to the colloid osmotic pressure. This causes a chronic inflammatory state resulting in lymphangiosclerosis and eventually irreversible non-pitting oedema.

Lymphoedema can be divided into primary and secondary lymphoedema. In primary lymphoedema, the lymphatic drainage is insufficient due to a congenital or inherited condition. Usually, lymphatic vessels are hypoplastic or less functional because of disrupted motor functions of the lymphangions but also cases of primary lymphoedema due to lymphatic hypertrophy have been described.³ The onset of primary lymphoedema is usually before age 35 (75%), it affects women more often than men, and the incidence is higher for the lower extremity than the upper extremity.⁶ ⁷

Secondary lymphoedema occurs as a result of a specific condition or medical procedure due to which the lymphatic system is damaged and drainage is impaired. Causes of secondary lymphoedema include infection, inflammatory disorders, chronic forms of lymphatic overload and cancer and cancer treatment. Worldwide, the most common cause of lymphoedema is filariasis, is caused by infection by the *Wuchereria bancrofti* parasite.⁸ However, in western society lymphoedema is most often secondary due to malignancies and its treatment.⁹
Breast cancer-related lymphoedema
Of all malignancies and cancer treatments, secondary lymphoedema is most often seen after breast cancer treatment. Causes include damage to the lymphatic system due to radiation therapy and chemotherapy but most often because of the dissection of lymph nodes. The incidence of lymphoedema after treatment for breast cancer varies widely according to literature, but in general, about one in five patients treated for breast cancer will experience lymphoedema to some degree. An extensive review about the incidence of unilateral lymphoedema after breast cancer demonstrated that the risk of lymphoedema is approximately four times higher for women who had an axillary node dissection (19.9%) compared to those who had undergone only sentinel node biopsy (5.6%). Known risk factors to develop lymphoedema are axillary lymph node dissection, radiation therapy to the axillary region, postoperative seroma in the axilla, and obesity. The complaints of patients with Breast Cancer Related Lymphoedema (BCRL) vary from a heavy feeling in the arm to swelling and recurrent infections and it is known to have a severe impact on patients Quality of Life (QoL).

Treatment of lymphoedema
Conservative treatment of lymphoedema
From a historical perspective, the main treatment for BCRL has always been conservative and includes manual lymphatic drainage and application of compression garments amongst other techniques. The hallmark of conservative lymphoedema treatment is the complete decongestive therapy (CDT) protocol in which compression bandaging, therapeutic exercise, manual lymphatic decompressive massage and hygiene measures are all combined. This form of treatment is maintained by a specialised physical therapist and consists of an intensive initial phase where bandaging and therapy are applied 5 days a week for 6 weeks and a maintenance phase which is mostly patient-directed. While deemed effective in reducing pain and volume of the affected arm this protocol is very demanding in both time and effort.

Surgical treatment of lymphoedema
Ablative surgical procedures
Besides conservative strategies, a variety of surgical treatments for lymphoedema have been described in the literature. These procedures can be divided into ablative or reconstructive approaches. Examples of ablative approaches are the infamous Charles procedure and the modified Charles procedure where the lymphoedematous tissue is excised, after which the resulting skin defects are covered with skin grafts. Another, more frequently used ablative procedure, is
liposuction by which lymphoedematous tissue and therefore the lymphatic load are reduced. While providing an excellent way to reduce the volume of an affected limb, continuous compression therapy remains mandatory after liposuction to prevent progression of the disease.

Reconstructive surgical procedures

Lympho-venous anastomoses

Reconstructive or physiologic surgical procedures aim to improve drainage of the lymphatic fluid. By creating anastomoses between functional lymphatics and veins excess lymphatic fluid can be shunted and drained by the venous system. While experimental surgical procedures to create lympho-venous anastomoses have been described since 1963, O’Brien was the first to thoroughly evaluate the use of LVA for patients with obstructive lymphoedema.\(^{21}\) Initially, results were variable and in a large proportion of patients the condition of the affected extremity worsened.\(^{22}\) However, with the evolution of surgical microscopes and microsurgical equipment, it became possible to create anastomoses between lymphatics and veins with a diameter of 0.3 mm, which is much smaller than the vessels used previously. Because of lower venous pressure in smaller veins, there might be less venous backflow into the lymph vessels and therefore less occlusion by thrombosis.\(^{23, 24}\) Koshima and his colleagues were the first to describe LVA with this so-called ‘super microsurgery’.\(^{23, 25}\)

![Illustration of lymphatico venular anastomosis between a lymphatic vessel and a vein of the subdermal venous network. Reprinted by permission from Springer Nature, Breast Cancer-Related Lymphedema by Heli Kavola, Sinikka Suominen (2018)](image)
Vascularised lymph node transfers

Another method to reconstruct the function of the lymphatic system is by transplanting functional lymph nodes included in a free flap to the affected area.\textsuperscript{26, 27} Initial reports describing the use of avascular lymph nodes or lymph node fragments in animal experiments showed mixed results.\textsuperscript{28, 29} However, when vascularisation is preserved, promising outcomes are described regarding volume reduction and QoL improvement in patients suffering from lymphoedema.

While the exact mechanism by which vascularized lymph node transfer (VLNT) alleviates lymphoedema symptoms remains to be fully elucidated, there are two leading theories. The first is that the naturally occurring LVAs in lymph nodes allow for the flap to act as a pump to drain the lymph fluid directly to the venous system. This theory is supported by Cheng and his colleagues who demonstrated uptake of indocyanine green (ICG) in the efferent vein of a free flap containing lymph nodes when ICG is injected into the edge of the flap.\textsuperscript{30} Another proposed mechanism of action is that the lymphatic function of the affected area is regenerated through induction by growth factors produced in the lymph nodes which stimulate lymphangiogenesis.\textsuperscript{31-33}

To harvest the lymph nodes, multiple donor sites for free flaps are available. Most popular are the submental flap based on the submental artery, and the groin flap based on the superficial circumflex iliac or the superficial inferior epigastric artery. A major advantage of the groin flap is that these lymph nodes can easily be included in the deep inferior epigastric artery perforator (DIEP) flap a free flap from the abdomen which is commonly used for autologous breast reconstruction. This allows for simultaneous treatment of BCRL for patients who wish to undergo autologous breast reconstruction.

A commonly feared complication of VLNT is donor site lymphoedema. However, the lymph nodes adjacent to the superficial inferior epigastric artery have been demonstrated to drain the abdomen.\textsuperscript{34, 35} Therefore, when these nodes are included in a DIEP flap, the risk of donor site lymphoedema is considered minimal. Over the past years VLNT has become a promising element in the treatment of lymphoedema.
Chapter one

Aim of this thesis

The aim of this thesis is to evaluate the results that can be achieved with lymphaticovenular anastomoses and lymph node transplantation in adjunct to DIEP flap breast reconstruction for patients with BCRL. This is achieved by studying the patients that underwent reconstructive lymphoedema surgery in the Radboud university medical centre and by analysing available literature.

Outline

Part I – Lymphaticovenular anastomoses
In chapter two an unusual case is presented of a patient with Noonan syndrome suffering from vulvar lymphangiectasia. While numerous previous therapies failed, a new two-stage procedure is described exploring the benefits of pre-emptive LVA prior to performing surgery that coincides with high risk for postoperative Lymphoedema.

When starting to offer lymphaticovenular anastomoses to treat patients with breast cancer-related lymphoedema questions were raised about the optimal peri-operative treatment. Multiple ideas which are often counter-intuitive are proposed in the literature. In chapter three the literature is systematically reviewed to evaluate optimal perioperative care for patients undergoing LVA.

In chapter four the results of LVA in treating patients with BCRL are evaluated. The effects on change in volume difference, QoL and use of compression garment is demonstrated.

While positive results regarding LVAs are presented by our group and in literature, the fate of the LVAs remains unsure, especially since animal models demonstrate that a large proportion of LVAs lose patency. In chapter five we explore the use of ICG to evaluate the patency of LVA.

Part II – Vascularised lymph node transplantation for BCRL
Many different outcomes such as volume difference between arms, QoL, infection rate and use of compression garment are used when the results with vascularized lymph node transplantation (VLNT) are published. In addition, some groups tend to include patients who underwent secondary procedures like liposuction in their results. To gain a complete overview of the most relevant outcomes after VLNT a systematic review and meta-analysis of the literature is presented in
Chapter six including a broad spectrum of outcomes while excluding patients with secondary procedures during follow-up.

VLNT is an invasive procedure with a potential risk for donor site lymphoedema. However, when combined with DIEP flap breast reconstruction, lymph nodes that drain the abdomen are transplanted to the axilla minimizing this potential risk. Furthermore, the inclusion of lymph nodes in the DIEP flap is a minor additional effort resulting in a lot of potential benefits. In Chapter seven the results of VLNT combined with DIEP flap breast reconstruction in our institution are evaluated.

In addition to lymph nodes in the groin, the submental area offers a potential donor site for VLNT. In Chapter eight the use of pre-operative CT scans to assess the lymph nodes in the submental area is explored to determine if they may assist in pre-operative planning.

In Chapter nine a general discussion is presented along with future perspectives. Chapter ten provides a summary of this thesis in English and in Dutch.
Chapter one

References


Introduction and aim of this thesis


Introduction and aim of this thesis
Chapter two
Lymphovenous anastomosis and secondary resection for Noonan syndrome with vulvar lymphangiectasia

H. Winters, H.J.P. Tielemans, D.J.O. Ulrich

*Plastic and Reconstructive Surgery – Global Open, 2016*
Abstract

In this case report, we describe the use of a 2-stage approach to treat severe recurrent vulvar lymphangiectasia in a patient with Noonan syndrome. First, 3 functional lymphatic vessels were identified and anastomosed to venules in an end-to-end fashion. Then, in a second surgical procedure, the vulvar lesions were resected as much as possible and the vulva was reconstructed. By the 12-month follow-up, the patient had recovered well. Although there were still some small vesicles on the left labia there was no more ooze, itch, and pain. Lymphatic mapping using indocyanine green showed improvement of the oedema of her vulva region and patent LVA. In addition to the demonstration of this 2-stage approach, this case report also demonstrates the benefits of pre-emptive LVA before performing surgery that may be at high risk for postoperative lymphoedema.
Introduction

Noonan syndrome (NS) is a relatively common autosomal dominant disorder first described in 1963 by Dr. Noonan. Characteristics include Minor facial dysmorphism, congenital heart defects, short posture, webbed neck, (minor) retardation, chest deformity (pectus excavatum, pectus carinatum), lymphatic dysplasia and bleeding diathesis. Lymphatic dysplasia is described to occur in up to 20% of patients with NS, most frequently occurring in the dorsal limb. Cutaneous lymphangiectasia, also called acquired lymphangioma, is a benign cutaneous disorder involving the pathologic dilatation of dermal and subcutaneous lymphatic channels. The lesions formed by these malformed channels can have a ‘frog spawn’ like appearance. As a result of these damaged lymph channels, lymphoedema can develop in the affected body part. Twenty-two cases of primary lymphangiectasia (also referred to as Lymphangioma circumscriptum (LC)) have been described and confirmed by histopathology. Vulvar lymphangiectasia associated with NS is a rare phenomenon that, to our knowledge, has been only described once before. For the treatment of lymphangiectasia, no differentiation has been made between acquired and congenital lymphangiectasia. Observation and surgery seem to be the preferred strategy. We present a patient with recurrent vulvar lymphangiectasia and Noonan syndrome who has been treated successfully with a two-stage approach using lympho-venous anastomosis (LVA) followed by excision of the vulvar lesion and reconstruction.

Methods and results

In this case study, a 25-year-old female patient with Noonan syndrome is presented with major lymphangiectasia of both labia majora and minora. The patient was primarily concerned with the frequent oozing, itching, and severe pain the lesions were causing. In addition, the recurrence and uncertainty about the treatment were bothering her. Patient history revealed growth retardation, atrial septal defect, pulmonary stenosis, excision of a tierfell naevus as an infant, and hearing loss with frequent ear infections. Vulval oedema, as well as significant oedema of her left leg, was present. In the past, the lymphangiectasia was treated more than 15 times with cryotherapy, excision, coagulation, and shave-excision. Unfortunately, these treatments relieved the symptoms only temporarily. Within 2-5 months postoperatively, her lesions recurred rapidly. It is suspected that the aetiology of her vulval problem is related to former shave excisions of a tierfell naevus as an infant with damage of the superficial lymphatic vessels and the genetic susceptibility due to Noonan syndrome.
Lymphatic mapping using Photodynamic Eye (PULSION Medical Systems AG, Munich, Germany) with an injection of 1 cc of indocyanine green in the feet and popliteal region showed pitting lymphoedema of the vulvar region and tortuous lymphatic channels with 3 suitable lymph vessels for lymphovenous anastomosis (LVA) (Figure 1). To relieve the patient of her symptoms and to offer a sustained treatment for the lymphangiectasia, a surgery creating three end-to-end lymphovenous anastomosis (LVA) was performed two weeks after lymphatic mapping. This procedure aimed to facilitate adequate drainage of the lymphangiectasia and thereby preventing recurrence. The surgical procedure was performed in general anaesthesia and the diameter of the lymphatic vessels was 0.5 mm. The patient recovered free of complications (Figure 2). Thirteen weeks after the LVA surgery, the vulvar lesions were resected as much as possible in a second surgical procedure (Figure 3). Reconstruction was performed with advancement flaps of the labia majora and wedge excision of the labia minora. The patient was given cefazoline for 3 days and was dismissed on the fourth-day post-surgery. Histopathology confirmed the diagnosis lymphangiectasia. The patient recovered without complications. At 12 months follow up, the patient is doing well. Although there are still some small vesicles on the left labia (figure 4), there is no more oozing itch and pain. Lymphatic mapping using indocyanine green showed improvement of the oedema of her vulva region and patent anastomoses.

Figure 1. Marking of the lymphatic vessels prior to surgery using injections of indocyanine green and Photo Dynamic Eye.
Lymphovenous anastomosis and secondary resection for Noonan syndrome with vulvar lymphangiectasia

Figure 2. Lymphangiectasia of the vulva; scars at the site of the LVAs prior to excision.

Figure 3. Immediate postoperative result after resection of the lymphangiectasia and reconstruction using advancement flaps and wedge excision of the labia minora.
**Discussion**

Vulval lymphangiectasia is a rare disease and is usually reported following surgery/radiotherapy for carcinoma of the cervix or vulva, tubercular inguinal lymphadenitis, or Crohn's disease of the vulva.\(^2,5,6\) It can be asymptomatic, pruritic, burning, or painful. It is an unpleasant but benign condition, with a severe impact on the patient's quality of life.\(^7\) Histologically, dilated lymphatic channels are present in the superficial and mid-dermis, few dilated lymphatics are seen in the deep dermis.\(^8\) As the lesions progress, functional impairment regarding urination and sexual intercourse can develop, in addition to cosmetic problems. However, the treatment of lymphangiectasia can be very challenging due to the high recurrence rate after surgery which is reported to be 23.1%.\(^5,9\) The prognosis for patients with diffuse lymphangiomatosis is poor if the condition is resistant to standard therapies.\(^9\) More conservative treatments such as skin care compression are difficult to apply considering the location of the lesions.\(^10\) Carbon dioxide lasers causing superficial vaporization of the lesions have been also described in the treatment.\(^7\) However, this treatment may lead to pain, aggravation of the lesions, and keloid formation. Ghaemmaghami et al. conclude that major labiaectomy appears to be more successful than other methods including LVA. However, the evidence cited to support this is 29 years old and the technique to create LVAs has been changed dramatically.\(^9\) Recently, Yamamoto et al. evaluated the use of multiple site LVAs for
Lymphovenous anastomosis and secondary resection for Noonan syndrome with vulvar lymphangiectasia

the treatment of genital lymphoedema complicated with severe lymphorrhea. Their approach was successful and they stated that multi-site LVAs can serve as the most effective therapy for lymphoedema. The initial treatment with LVA was performed to prevent recurrence of lymphangiectasia after resection of the lesions. Since the Lymphangiectasia did indeed not recur, this case study suggests that preoperative LVA might be worthwhile prior to performing any surgery that may be at high risk for postoperative lymphoedema.

Summary

This case report is, to our knowledge, the first to describe this two-stage approach in the treatment of severe vulvar lymphangiectasia. The treatment consists of creating Lympho-Venous Anastomosis (LVAs) followed by reconstruction of the vulva. In our opinion, adequate drainage facilitated by LVAs might eradicate the underlying cause of the lymphangiectasia and lymphoedema and thereby prevent recurrence after the reconstruction of the vulva. The combination of LVA and secondary resection seems to be a therapeutic option in patients with these rare problems. In addition, this case demonstrates the benefits of pre-emptive LVA prior to performing surgery that may be at high risk for post-operative lymphoedema.
Chapter two

References


Lymphovenous anastomosis and secondary resection for Noonan syndrome with vulvar lymphangiectasia
Chapter three
Peri-operative care for patients undergoing lymphatico-venular anastomosis:
A systematic review

H.Winters, H.J.P. Tielemans, P.N. Sprangers, D.J.O. Ulrich

*Journal of Plastic, Reconstructive & Aesthetic Surgery, 2016*
Abstract

Background
Lymphaticovenular anastomosis (LVA) is a super microsurgical procedure that involves the anastomosis of a functional lymphatic channel to a venule. Although peri-operative care might be an important contributor to the success of this technique, evidence about optimal peri-operative care seems limited. This review aims to summarize the peri-operative methods used by authors reporting on LVA.

Methods
A systematic search of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Perioperative care used by the authors was summarized and listed in a pre-defined form. Studies were also graded on the quality of evidence by the GRADE system and a lymphedema surgery-specific system.

Results
In total, 22 studies were identified describing peri-operative measures. Although most authors were sparse in their description of peri-operative management, most recommended initiation of conventional compression therapy at 1-4 weeks after surgery. Prophylactic antibiotics, elevation of the affected limb, bandaging, low-molecular-weight heparin, prostaglandin E1, and manual pressure therapy were also described. The quality of evidence of the included studies was low on average.

Conclusion
Although super microsurgical LVAs are gaining in popularity, there are no high-quality prospective trials evaluating these new techniques and the description of peri-operative management is scarce. Of the available studies, peri-operative management consisting of prophylactic antibiotics, elevation of the affected limb during the night and hospital stay, and compression therapy 4 weeks post-surgery for 6 months seems to be preferred. Future studies should describe a detailed peri-operative protocol to allow for a better comparison between study results and to determine optimal peri-operative recommendations.
Introduction

Peripheral lymphoedema is a common but serious condition that occurs in up to 250 million people worldwide.\textsuperscript{1} In the western society, oncologic therapies are the main cause of lymphoedema.\textsuperscript{2} While experimental surgical therapies for improvement of lymphoedema have been described since 1963, O’Brien was the first to thoroughly evaluate the microsurgical Lympho-Venous Anastomosis (LVA) technique in the treatment of obstructive lymphoedema.\textsuperscript{3, 4} With this technique, the proximal end of a transected lymphatic vessel is anastomosed ‘end-to-end’ to the main trunk of a large cutaneous vein (e.g. the saphenous vein) to facilitate drainage of lymph fluid into the venous system.\textsuperscript{5} While this treatment initially seemed promising, questions were raised about the effectiveness of this technique in reducing lymphoedema. Puckett et al. demonstrated that patency rates of LVAs of 100% related to 32% decrease of lymphoedema in dogs. However, after three weeks, all anastomoses in this study became occluded, and the lymphoedema state returned to normal or worsened. In 1988, Gloviczki et al. concluded that improvement of lymphoedema was noted in 57% of patients with secondary lymphoedema treated with LVAs. No improvements were noted in patients with primary lymphoedema. Moreover, in 1990 O’Brien et al. showed an improvement of lymphoedema in 54% of patients, whereas the oedema worsened in 46% of the cases.\textsuperscript{5}

These dissatisfying results might be explained by the former technical limitations of the microsurgical suture technique, and the pressures in the venous and lymphatic system.\textsuperscript{6, 7} When the techniques to create LVAs were developed, it was not possible to create precise anastomosis in vessels and lymphatics smaller than 0.8mm in diameter. This led to difficulties finding lymphatics suitable for anastomosis due to disappearance of larger lymphatic trunks in limbs affected by lymphoedema.\textsuperscript{7, 8} Beside, Baumeister and Siuda have demonstrated that the pressure in large veins can be higher than the lymphatic pressure.\textsuperscript{9} Moreover, the pump function of the lymphatics is of great importance as the lack thereof, in combination with a higher pressure in the venous component, could result in venous backflow rendering the anastomosis useless.\textsuperscript{10} In the meantime, technical improvements to create LVAs have been described by Koshima et al. These developments were facilitated by the drastic advancement of microsurgical equipment and microscopes, allowing vessels and lymphatics with a size of 0.3-0.8mm in diameter to be anastomosed. These new techniques are also described as ‘super microsurgery’ or lympho-venular-anastomosis.\textsuperscript{11} It is hypothesized that the treatment with LVAs is now more successful because of the lower pressure in the smaller subdermal venules and the possibility to easily create multiple LVAs.\textsuperscript{12} In accordance, multiple authors describe a successful implementation of LVAs to combat lymphoedema. Techniques used to create these shunts include end-to-end, end-to-side and invagination anastomosis procedures.\textsuperscript{13-17}
While the use of LVAs to treat lymphoedema is gaining popularity, it is generally agreed upon that patients need to be carefully selected and microsurgical treatment is most effective when combined in a patient-tailored treatment plan. As part of this plan, the optimal peri-operative conditions for a patient should be considered. This is especially important because peri-operative conditions such as medication, bandaging, and the number of anastomosis might greatly affect the patency of the anastomosis and therefore the success rate. Moreover, we opine that standardized peri-operative conditions improve the quality of future research. Therefore, the aim of this paper is to review the current literature for peri-operative care undertaken by authors who apply microsurgical LVAs, and determine, if possible, guidelines for optimal peri-operative conditions.

**Methods**

**Search method and study identification**

This systematic review was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA). Studies were identified by searching the electronic databases MEDLINE, EMBASE and Cochrane CENTRAL. Keywords used were ‘lympaticovenous’, ‘lympaticovenular’, ‘lymphovenous’, ‘lymphovenular’, ‘lymphatic venous’, lymphatic venular’ combined with ‘anastomosis’ or ‘shunt’. Terms were searched for in the title and abstract and, where applicable, were also mapped to medical subject headings. No limits were set to language or publication status. Duplicate articles were removed. Then, titles and abstracts were screened for eligibility, and full text articles were retrieved. Full text articles were screened for other relevant articles. The last search was performed on May 10, 2016.

**Inclusion and exclusion criteria**

Original studies describing the use of LVA or lympho-venous anastomosis in the treatment of peripheral lymphoedema in humans were selected. Studies were excluded if they included <5 patients, if they were animal studies or if the article was not in English or Dutch. Studies were also excluded if lympho-venous anastomosis were created to prevent lymphoedema. The quality of evidence was determined according to the GRADE system developed by the grades of recommendation, assessment, development and evaluation working group. Because previous research indicates that most studies provide low quality evidence, a second grading system proposed by Hadamitzky et al. was used (Table). This system was developed to determine the quality of studies on lymphoedema surgery and facilitated differentiation between studies in the low spectrum of evidence. Articles were excluded if they scored a zero on item 6. Screening and inclusion of studies was done independently by authors H.W. and P.A.S., and disagreement was resolved by H.J.P.T.
Peri-operative care for patients undergoing lymphatico-venular anastomosis: A systematic review

<table>
<thead>
<tr>
<th>Quality assessment score for trials on lymphoedema surgery</th>
<th>Points</th>
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<tbody>
<tr>
<td>1. Prospective study</td>
<td>1</td>
</tr>
<tr>
<td>2. Clear study protocol</td>
<td>1</td>
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<tr>
<td>3. Consistent study population with explicit lymphoedema grading</td>
<td>1</td>
</tr>
<tr>
<td>4. Statistical analysis mentioning standard deviation and confidence intervals</td>
<td>1</td>
</tr>
<tr>
<td>5. Follow-up longer than 1 year and stated with standard deviation</td>
<td>1</td>
</tr>
<tr>
<td>6. Specification of adjuvant therapy before and after surgery (type, duration, frequency), eg, manual lymphatic drainage</td>
<td>1</td>
</tr>
<tr>
<td>7. Serial lymphoedema measurement with reliable methods, with intra individual or inter individual control</td>
<td>1</td>
</tr>
<tr>
<td>8. Standardization and clear description of the surgical technique</td>
<td>1</td>
</tr>
<tr>
<td>9. Postoperative assessment of results through direct imaging of lymphatics</td>
<td>1</td>
</tr>
<tr>
<td>10. Reports on serious complications, such as infections, fistula, and wounds</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>10</strong></td>
</tr>
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</table>

*Table 1.* Quality assessment score proposed by Hadamitzky et al.

**Outcomes and data extraction**

Study characteristics including study year, number of patients, follow-up and surgical technique and peri-operative care including pre-operative therapies, use of antibiotics, use of anticoagulation, number of anastomoses created and post-operative management were noted in a pre-defined form.

**Results**

The systematic search strategy in MEDLINE, EMBASE and Cochrane CENTRAL yielded 1222 papers. After title and abstract screening, 48 studies were identified who applied microsurgical LVAs. Of those 48 studies, 19 described a brief peri-operative protocol. The search flowchart is presented in *Figure 1* along with the reasons for exclusion of studies. The peri-operative measures used in the studies are demonstrated below (*Table 2*).
Figure 1. Flowchart according to the PRISMA guidelines.

Medication

Antibiotics were given pre-operatively in five studies: the duration, dosage and type are not specified. In two studies by Demirtas et al. oral antibiotics (ciprofloxacin) were given post-operatively for two weeks after which Penicillin injections were prescribed once per month for one year to prevent infection. In addition, these two studies by Demirtas et al. describe the use of low molecular weight heparin during hospital stay, and aspirin is prescribed for three months. O’Brien et al. describe the use of penicillin and ampicillin. They did not recommend anticoagulation because of the risk of hematoma in the wound. Furthermore, they noted that any preoperative infection could not only damage the lymphatics but also
postpone the surgery for months until all features of inflammation disappeared. Koshima et al. describe the use of prostaglandin E1 to prevent occlusion of the anastomosis. The drug is administered intravenously for 5 days post-surgery after which the medication is continued orally.²⁷, ²⁸

**Compression therapy and bandaging**

Postoperative bandaging was described in seven articles.⁸, ¹³, ²⁴, ²⁵, ²⁹⁻³¹ Fillipeti et al. describe that it is aimed for to improve the lymphatic drainage while preventing a raise in venous pressure.³⁰ Koshima et al. and Chang et al. mention that a low pressure is used while bandaging post-operatively.¹³, ²⁴, ²⁵ Demirtas et al. describe that custom pressure garments (20-30mmhg pressure) were ordered pre-operatively and were dressed on the patient in the operating room post-surgery.¹⁶, ²⁶ Masia et al. describe the use of soft elastic bandaging at the 4th day post-surgery to increase the pressure gradient over the anastomosis.³¹ Elevation of the limb after surgery was reported in six papers, and seventeen out of nineteen papers reported the use of compression garment one to four weeks after surgery. Koshima and colleagues recommend compression therapy for at least six months after which the compression therapy is evaluated and if possible discontinued. The time interval at which the garments are replaced because of the lymphoedema reduction is not described.

**Lymphoedema grading**

Overall, there was no general consensus on the optimal lymphoedema stage of patients eligible for treatment with lympho-venous anastomosis. Staging of the lymphoedema was done with different grading methods. The grading system proposed by Campisi et al. was used in 6 of the included studies, the grading system by the international society of lymphology was used in 3 studies.¹⁴, ¹⁹, ²⁶, ³¹⁻³⁵ A grading system by Cheng et al. and the M.D. Anderson classification were both used once.¹³, ³⁶ Interestingly, Yamamoto et al. used dermal backflow patterns for lymphoedema grading.³⁷ For this method, the findings with Indocyanine Green (ICG) lymphography are classified as ‘splash’, ‘stardust’ or ‘diffuse patterns’.

**Study quality and level of evidence**

Because most studies were of observational nature, the overall quality of evidence according to the GRADE system was low. Thirteen papers scored 1 point, corresponding with a very low evidence classification. Six papers scored 2 points, corresponding with a low evidence classification. When the quality assessment score system proposed by Hadamitzky et al. was used, the average score was 5.7 (range 4-9), indicating most studies were not optimal constructed.
<table>
<thead>
<tr>
<th>Author and publication year</th>
<th>Patients (n)</th>
<th>Lymphoedema stage</th>
<th>Microsurgical technique</th>
<th>Peri-operative care</th>
<th>LVA (n)</th>
<th>Quality assessment score</th>
<th>Quality of evidence (GRADE)</th>
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</thead>
<tbody>
<tr>
<td>Akita et al. 2013 34</td>
<td>96 patients, 192 lower limbs.</td>
<td>Nm.</td>
<td>Supermicrosurgical end-to-end LVA in the control group. Supermicrosurgical end-to-end LVA and valvuloplasty in the study group.</td>
<td>Following surgery the limb was bandaged loosely with compression bandages and kept elevated on a pillow. The recommended length of stay was seven days. 3 weeks after surgery the patients continued conservative therapies (including compression garment). If the ICG imaging status of the limb improved the use of compression garments was ceased.</td>
<td>4.44 In control group. 4.31 in study group</td>
<td>6</td>
<td>Very low</td>
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<tr>
<td>Auba et al. 2012 33</td>
<td>12 patients, 7 upper limbs, 5 lower limbs.</td>
<td>Campisi stage 3.</td>
<td>Supermicrosurgical end-to-end LVA</td>
<td>Post-surgery no bandages were applied. Patients were advised to keep the limb elevated for one week. Compression hosiery was recommended three to four weeks after surgery.</td>
<td>2-5</td>
<td>6</td>
<td>Low</td>
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<tr>
<td>Campisi et al. 2015 34</td>
<td>Nm.</td>
<td>Campisi stage 2a (39%), 2b (52%), 1b (5%), 3a (6%), 3b (6%).</td>
<td>Derivative multiple lymphatic-venous anastomoses and multiple lymphatic venous lymphatic anastomoses.</td>
<td>Microsurgical interventions were embedded into an integrated treatment protocol. Pre-operative the size of the affected limb was reduced in one to two weeks as much as possible. After surgery the pressure of the lymphatic drainage was gradually increased until mechanical lymphatic drainage was performed daily. Physical exercise was recommended.</td>
<td>NS</td>
<td>5</td>
<td>Very low</td>
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<tr>
<td>Study</td>
<td>Patient Population</td>
<td>Anatomical Area</td>
<td>Technique</td>
<td>Postoperative Care</td>
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<td>Chang et al. 2010, 2013</td>
<td>20 patients, unilateral upper limbs</td>
<td>Campisi stage 2 (50%), stage 3 (50%).</td>
<td>Supermicrosurgical end-to-end LVA</td>
<td>The limb was wrapped loosely with compression bandages and kept elevated. Prophylactic intravenous antibiotics were used. Patients were discharged 24 hours post-surgery. Compression garments and therapy were recommended four weeks after surgery.</td>
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<tr>
<td>Damstra et al. 2009</td>
<td>10 patients with secondary upper limb oedema</td>
<td>Campisi stage 3.</td>
<td>Microsurgical LVA</td>
<td>Antibiotics were used preoperatively. After surgery, the extremity was bandaged and elevated at night. Elastic stockings were continued permanently during follow-up.</td>
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<td>Study</td>
<td>Patients</td>
<td>Limb Staging</td>
<td>Treatment</td>
<td>Outcome</td>
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<td>Demirtas et al. 2009, 2010</td>
<td>42 unilateral lower limbs</td>
<td>Campisi stages: 2(12), 3(9), 4(7).</td>
<td>Supermicrosurgical LVA for lymphatics &gt;0.3mm, lymphatic-venous implantation for smaller lymphatics</td>
<td>Postoperatively the limbs were elevated at night. Patients were allowed to walk the day after surgery. Oral antibiotics were prescribed for two weeks followed by monthly penicillin injections for one year. Low molecular weight heparin was used during hospital stay and continued for three months post-surgery. The authors prescribe a custom garment providing 20-30mmHg of compression, which is dressed on the limb in the operation room. Patients were told to wear compressive garments for six months after surgery.</td>
<td>2.5 5 Very low</td>
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<td>Filippetti et al. 1994</td>
<td>25 patients with secondary upper limb LE</td>
<td>An original staging system by the author based on clinical and diagnostic findings. Patients with grade 2 were treated with LVA</td>
<td>Microsurgical LVA</td>
<td>An Ace bandage was applied after surgery and maintained for 10 days. The bandages were positioned in a uniform fashion, to improve lymphatic drainage and not to increase the venous limb pressure. At one-month post-surgery, a cycle of low-pressure therapy (40mmHg) was performed and then repeated at 4-months intervals.</td>
<td>2.5 4 Very low</td>
<td></td>
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<td>Study</td>
<td>Patients Details</td>
<td>Nm.</td>
<td>Methodology</td>
<td>Complexity Level</td>
<td>Rating</td>
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<td>Furukawa et al. 2011&lt;sup&gt;36&lt;/sup&gt;</td>
<td>9 patients with unilateral secondary LE. Patients with severe fibrosis, diabetes or vascular disease were excluded.</td>
<td>Nm.</td>
<td>Lymphaticovenous implantation Compression therapy using a bandage was applied 6 months preoperatively and 6 months postoperatively.</td>
<td>3.7</td>
<td>5</td>
<td>Very low</td>
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<td>Giacalone et al. 2011&lt;sup&gt;19&lt;/sup&gt;</td>
<td>26 patients. 7 upper extremities, 19 lower extremities 5 patients with pitting LE, 21 with non-pitting LE. Campisi Stadium: 2 (7), stadium 3 (15), stadium 4 (4). Derivative lympho-venous anastomosis (size nm.)</td>
<td>Nm.</td>
<td>Following surgery the limb was bandaged and elevated. The use of elastic stockings was maintained during follow-up. Antibiotics were administered pre-operatively.</td>
<td>7</td>
<td>Low</td>
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<td>Ito et al. 2015&lt;sup&gt;38&lt;/sup&gt;</td>
<td>5 patients: 2 with primary LE, 3 with secondary LE. Cheng stadium: 1(3) 2(2). Supermicrosurgical side-to-end LVA</td>
<td>Nm.</td>
<td>Compression garment was used by patients when standing or walking &gt;30 minutes.</td>
<td>2.0</td>
<td>5</td>
<td>Very low</td>
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<td>Study</td>
<td>Patients Description</td>
<td>Nm.</td>
<td>Treatment Description</td>
<td>Rating</td>
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<td>Koshima et al. 2000 20, 2003 31</td>
<td>12 patients 11 severe, 1 moderate LE (no staging). 13 patients with lower limb LE. 6 with primary LE, 7 with secondary LE.</td>
<td>Nm.</td>
<td>Post-operatively, the arm was elevated at night and pressure bandage were applied until 4 weeks after surgery. Later, elastic stockings were used for at least half a year.</td>
<td>4.1</td>
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<td>Koshima et al. 2004 57</td>
<td>57 patients with lower limb LE.</td>
<td>Nm.</td>
<td>Post-operatively, a low-pressure bandage and prostaglandin E1 were applied and patients were allowed to walk freely. A week after surgery patients used elastic stockings for at least six months.</td>
<td>2.1</td>
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<td>Maegawa et al. 2012 58</td>
<td>57 Patients with lower limb LE. 51 patients with secondary LE and 16 with primary LE.</td>
<td>International Society of Lymphology stage 1 (2), stage 2 (17), late stage 2 (29), stage 3 (9)</td>
<td>During and after the operation, no anti-coagulants were being used. All patients underwent complex decongestive physiotherapy (CDP) for 3 to 12 months preoperatively. Postoperative CDP was started 10 to 14 days post-surgery and was performed for at least 6 months.</td>
<td>3.9</td>
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<td>Authors</td>
<td>Study Design</td>
<td>Patient Details</td>
<td>Surgical Details</td>
<td>Postoperative Care</td>
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<td>Masia et al. 2016</td>
<td>31</td>
<td>59 patients. International Society of Lymphology stage 1 and 2</td>
<td>Supermicrosurgical end-to-end or end-to-side LVA</td>
<td>Minimal mobilization was allowed the third or fourth day after surgery. The fourth day, an elastic bandage was applied. Every 2 to 3 hours during the first 6 days, the region immediately distally and proximally to the LVA was massaged. After seven days, the protocol was individualized. Standard protocol consisted of recovering physical activity over the first three weeks avoiding exercise and postures that increase the venous pressure gradient of the limb. The authors recommended swimming or aquatic exercise from the third week (2-3 times a week).</td>
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<td>Narushima et al. 2010</td>
<td>14</td>
<td>14 patients, 17 limbs 2 upper limbs, 12 lower limbs. All secondary LE. Campisi stage 2 (1), stage 3 (14), stage 4 (2).</td>
<td>Supermicrosurgical LVA. 15 flow through, 1 end-to-end, 8 end-to-side, 2 double end-to-end, 2 end-to-end/end-to-side and one π-type.</td>
<td>The first three weeks after surgery no pressure garments were used. After three weeks compression garments were used and physiotherapy was begun.</td>
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<td>O’Brien et al. 1990</td>
<td>50</td>
<td>90 patients with secondary LE. Nm.</td>
<td>Microsurgical end-to-end and end-to-side LVA.</td>
<td>Postoperatively, the limb was elevated and frequent centripetal massage was performed. This was continued for four to five days, at which time the patient was discharged. The patients continued the elevation at night, which was the only conservative measure that was continued. Elevation was discontinued, if possible, after three months.</td>
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<tr>
<td>Study</td>
<td>Patient Characteristics</td>
<td>LVA Details</td>
<td>Peri-operative Conditions and Quality Score (Nm= not mentioned, LE=lymphoedema, nfs= not further specified)</td>
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<td>Yamamoto et al. 2014</td>
<td>6 patients with bilateral secondary LE</td>
<td>Sequential Supermicrosurgical LVA in 6 limbs, multiple Supermicrosurgical LVA in 6 limbs</td>
<td>After surgery, patients continued conservative treatment consisting of wearing an elastic stocking and occasional pumping.</td>
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<td></td>
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<td></td>
<td>Nm. 6 Very low</td>
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<td>Yamamoto et al. 2013</td>
<td>48 patients with primary (6) and secondary (42) LE.</td>
<td>Supermicrosurgical side-to-end LVA with temporary lymphatic expansion.</td>
<td>One week after LVA surgery, patients resumed the same conservative therapies as performed previously to make lymphatic pressure higher than venous pressure.</td>
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<td>11 female patients with compression-refractory peripheral lymphoedema (3 upper limbs, and 8 lower limbs).</td>
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<td>Nm. 6 Very low</td>
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<td>Supermicrosurgical end-to-end and side-to-end LVA under local anesthesia</td>
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**Table 2.** Peri-operative conditions and quality score (Nm= not mentioned, LE=lymphoedema, nfs= not further specified)
Discussion

The aim of this review is to summarize the knowledge on LVA and its peri-operative management. LVA is considered a controversial technique in the treatment of lymphoedema as early studies reporting on this procedure have demonstrated mixed results. In addition, the long term patency of LVAs has been demonstrated to be quite low using conventional microsurgical techniques, stressing the necessity of multiple anastomosis. While modern super microsurgical techniques offer multiple advances in comparison to earlier techniques, the LVAs created are still delicate and the success of the treatment might be co-dependent on the peri-operative management that is applied, as this aids in optimizing the patency rate of the anastomoses.

The goal of peri-operative care is to facilitate drainage through the anastomosis and to prevent occlusion. This might be achieved by bandaging, pressure therapy, anti-coagulants, vasodilating drugs, and prophylactic antibiotics. In the literature identified in this review, five studies describe the use of prophylactic antibiotics. This may reduce the risk of erysipelas, lymphangitis, or cellulitis which also may affect the newly formed anastomosis. While only two authors describe antibiotic measures, it is possible that it is more widely used but not described. The use of prostaglandin E1 to prevent post-operative occlusion is described in two papers. In these studies, the drug is administered intravenously after surgery for five days. Then, it is given in oral form for several weeks. While other authors do not describe the use of Prostaglandin E1 in lymphoedema related microsurgery, there is evidence that prostaglandin E1 might protect the microcirculation of free flaps after ischemia, and that prostaglandin E1 attenuates immune responses. In addition, because Prostaglandin E1 inhibits the expression of adhesion molecules to the endothelium, prostaglandin E1 may have a positive effect on the patency of LVAs. However, its role in lympho-venous microsurgery remains unclear.

Elevation of the affected limb after surgery is described in ten publications. This is in line with the general postoperative management after surgery as elevation reduces the swelling of the affected limb, and results in a lower venous pressure. The decision to apply compression in the first weeks after surgery seems to be twofold. On the one hand, the pressure exerted on the lymphatic channels may force lymphatic fluid through the anastomosis, preventing occlusion. This is supported by studies demonstrating that manual lymphatic drainage and compression therapy lowers the lymphatic pressure in lymphoedema. On the other hand, when the pressure exerted on the limb is too high, it might damage the fragile anastomosis. While it seems possible that early compression yields positive effects after LVA procedures, there is no evidence to support this. Most authors recommend compression therapy for one to four weeks after surgery.
Chapter three

An interesting but not previously described feature of pre-operative treatment might be the reduction of risk factors that could affect the results of LVA-surgery. Since self-reported patient general health, smoking, obesity and hypertension may increase the risk of developing secondary lymphoedema, the reduction of these risk factors in patients before attempting microsurgical procedures might attenuate the success rate of LVA-surgery. From a pathophysiologic point of view, treating hypertension might attenuate LVA patency because this lowers the venous pressure. Future studies should determine if general risk factors such as hypertension, diabetes, obesity, smoking and hyperlipidaemia contribute to the results of LVA procedures and, if so, to what extent.

In this review, five different grading systems to stage lymphoedema severity have been identified. In addition, patients with primary, secondary, and upper, lower limb lymphoedema were studied in included research articles. Recent studies indicate that LVAs may be effective in both upper and lower limb lymphoedema, but a true prospective head-on comparison is not available. The perception that LVAs might be less effective in primary lymphoedema is based on the notion that the lymphatics are hypoplastic in primary lymphoedema. However, more recent research demonstrated that patients with primary lymphoedema still had some functional lymphatics available, which can be identified using ICG imaging. Although there is no consensus about the optimal patient population, the optimal peri-operative management between them will most likely not differ because the LVAs exert the same mechanism between lymphoedema modalities.

Concerning grading systems to assess the severity of lymphoedema, the grading system proposed by Campisi et al. seems to be most widely used, followed by the international society of lymphology grading system. The concept of using ICG imaging in lymphoedema staging however is interesting. The advantage of this ‘dermal backflow’ system proposed by Yamamoto et al. is the real time lymphatic mapping which informs not only about the location of lymphatics, but also about their function. Because the availability of lymphatics with preserved pumping function is essential for the treatment with LVAs, this system might be more accurate in selecting patients in which LVA will be successful. In addition, this system can be used to treat subclinical lymphoedema. It is hypothesized that this early treatment is more effective because the lymphatic function is not yet affected in this early stage.

While the treatment with LVAs seems very promising, our findings indicate that most research articles published on this topic have a low quality of evidence according to the GRADE assessment score, and a mediocre score with the Hadamitzky lymphoedema surgery assessment system. This stresses the necessity for more prospective trials to evaluate the efficacy of LVA-surgery in the treatment of lymphoedema.
Conclusion

While super microsurgical LVAs are gaining in popularity, there are no high quality prospective trials evaluating these new techniques and the description of peri-operative management is scarce. After a systematic search in the available literature, we conclude that there is no standardized peri-operative care for LVA procedures and much of the recommendations are based on expert opinions. Out of the available studies, a peri-operative management consisting of prophylactic antibiotics, elevation of the affected limb during night and hospital stay, and compression therapy 4 weeks post-surgery for six months seem to be preferred. Future studies should describe a detailed peri-operative protocol to improve the comparison of different studies evaluating microsurgical lympho-venous anastomosis.

Conflict of interest or funding

Authors declare no conflict of interest in relation to the content of this article. No funding was received in any form for the current work.
Chapter three

References


Peri-operative care for patients undergoing lymphatico-venular anastomosis: A systematic review


Chapter three


Peri-operative care for patients undergoing lymphatico-venular anastomosis: A systematic review
Chapter four
The efficacy of Lymphaticovenular Anastomosis in Breast Cancer Related Lymphoedema


Breast Cancer Research and Treatment, 2017
Abstract

Introduction
Lymphedema can be a debilitating condition, causing a great decrease in a person’s quality of life (QoL). Treatment with lymphaticovenular anastomosis (LVA), in which an anastomosis is created between the lymphatic and venous system, may attenuate lymphedema symptoms and reduce swelling. In this study, we share the results using LVA to treat breast cancer-related lymphedema (BCRL) at our institution.

Materials and methods
Patients were eligible for inclusion if they suffered from unilateral BCRL, if functional lymphatics were available, if compression therapy was used for at least 6 months, and if the follow-up was 12 months at minimum. Lymph vessel functionality was assessed preoperatively using indocyanine green (ICG). During surgery, 1-3 anastomoses were created and shunt patency was confirmed using ICG. Arm volumes were measured before surgery and at 6- and 12 months follow-up. QoL was measured before surgery and at 6 months follow-up. Arm volume differences between the healthy arm and affected arm were compared between the time points.

Results
Twenty-nine consecutive female patients with unilateral BCRL were included. The preoperative mean difference in arm volumes was 701 ± 435 ml (36.9%). This was reduced to 496 ± 302 ml (24.7%) at 6-month follow-up (p = 0.00). At 12-month follow-up, the mean difference in arm volume was 467 ± 303 ml (23.5%) (p = 0.02). The overall perceived QoL was increased from 5.8 ± 1.1 to 7.4 ± 0.7 (p = 0.00). The functionality score decreased from 2.2 to 1.8 (p = 0.00), the appearance score decreased from 2.6 to 1.9 (p = 0.00), the symptoms score decreased from 2.8 to 1.8 (p = 0.00), and the mood score decreased from 2.7 to 1.5 (p = 0.00). Fifteen patients (53.6%) were able to discontinue the use of compression garments.

Conclusion
Treatment with LVAs is effective in reducing arm volume difference in patients suffering from BCRL. Although no complete reduction of the oedema was achieved at 12 months follow-up, the procedure significantly increased the patient’s QoL.
Introduction

Lymphoedema can be a debilitating condition, causing pain, body image disturbances, frequent infections, restrictions in range of motion, and a great decrease in a person’s quality of life (QOL). (1) Axillary lymph node dissection, radiation therapy to the axillary region, postoperative seroma in the axillary region, and obesity are major risk factors for the development of lymphoedema. (2) Reports on the incidence of lymphoedema following breast cancer treatment vary widely with 24-49% following mastectomies and 4-28% following breast conserving therapy. (3) When the swelling of a lymphoedematous extremity is due to excess fluid, like in the earlier stages of lymphoedema progression, pitting oedema can be observed. When the excess volume is due to adipose or fibrous tissue, pitting oedema will be minimal or absent. (4)

Treatment of lymphoedema consists of both non-operative and operative methods. (5) Conservative treatment is currently considered to be the standard of care. This includes lymphatic-specific massage techniques, exercise, and external compression. The goal of the treatment is to manually compress tissue and to remove the retained interstitial fluid. (6) After this, fitted garments are required to prevent the re-accumulation of fluid. However, this therapy is primarily aimed at delaying progression and is not curative. (7)

Surgical treatments for lymphoedema mainly focus on excisional and reconstructive techniques. Excisional surgery includes debulking and liposuction. (8) Reconstructive options include lymphaticovenular anastomosis (LVA), lymphovenous-lymphatic (LVL) transplant, lymphatic vessel transplantation, and vascularized lymph node transfer (VLNT). (3, 9-11) Currently, reconstructive options are considered to be more effective in early stage ‘pitting’ lymphoedema due to the progressive nature of this condition. In later stages, when there is non-pitting lymphoedema, reconstructive options may not be viable due to the absence of functional lymphatics. (12)

Using LVA, the lymph fluid in the extremity affected by lymphoedema can bypass the natural route of traveling through lymph vessels to the subclavian veins and entering the bloodstream. This technique was first described in 1963 by Laine and Howard in a rat model. (13) In 1969, Yamada performed studies on LVA in dogs. Several other authors have, since then, improved this procedure so it could be utilized in the treatment of lymphoedema in humans. (9) To allow for lymphatic fluid to enter the venous blood stream through a LVA, it is important that pressure in the lymphatic system is higher than the pressure in the recipient vein. Since there may be a lower pressure in smaller venules compared to larger veins, utilizing small venules as recipient vessels might lower the risk of occlusion of the LVA due to venous backflow. (14-16)
With the availability of superfine monofilament sutures and, more recently, indocyanine green (ICG) lymphography, performing LVAs on small subdermal venules and functional lymphatic collectors as small as 0.3 mm has become a practical reality, and promising results utilizing these super microsurgical techniques are emerging. In this study we share the preliminary results using LVA to treat breast cancer related lymphoedema (BCRL) at our institution.

**Patients and methods**

**Patients**
Patients were eligible for inclusion if they suffered from unilateral pitting BCRL and if functional lymphatics were available. Lymphoedema was defined as a volume increase of ≥10% compared to the non-affected arm or self-reported heaviness or swelling, which are commonly used definitions of lymphoedema. No limits were set on the duration of the lymphoedema. The lymphoedema was staged with campisi’s lymphoedema classification. Patient characteristics and base line volume measurements were noted in a pre-defined form. Lymphatic functionality was evaluated pre-operatively using ICG lymphography. For this technique, ICG (0.5%, 0.5 ml, Diagnogreen, Daiichi Pharmaceutical, Tokyo, Japan) was injected subcutaneously in the 2nd webspace of the hand. A photodynamic eye (PDE) was used to identify lymph vessels. Lymphatics were considered functional if ICG lymphography demonstrated a linear pattern according to the Yamamoto ICG staging system (Figure 1).

![Linear pattern demonstrated by ICG lymphography in a patient with BCRL. This pattern indicates that the lymphatics possess contractility.](image)

*Figure 1.* Linear pattern demonstrated by ICG lymphography in a patient with BCRL. This pattern indicates that the lymphatics possess contractility.
Surgical technique

Surgery was performed by two experienced plastic surgeons under general anaesthesia. Lymphatico-venular anastomoses were performed through 3-4 cm incisions at the distal wrist or forearm in the lymphoedematous extremity using a surgical microscope (ZEISS OPMI 800; 25 x to 50x magnification). The subdermal region was dissected to identify lymphatic vessels of 0.3-0.8mm in diameter. This was achieved by using ICG lymphography intraoperatively. Similarly sized adjacent venules were explored to anastomose the vessels and create the LVA. LVAs were generally performed end-to-end using 11-0 nylon sutures. If recipients’ veins were substantially larger, end-to-side anastomoses were performed. Patency of the newly formed anastomosis was confirmed intraoperatively by ICG lymphography. Patients were given a prophylactic antibiotic intraoperatively and for 5 days postoperatively. All patients were discharged within 24 hours. After surgery, the affected arm was wrapped with a special compression bandage (Rosidal TCS, Lohmann & Rauscher, Germany) for 1 week and elevated on a pillow. 1 week after surgery, patients started to continue previous compression therapy which included the usage of compression arm sleeves. After six months the possibility to discontinue compression stockings was evaluated on patient request.

Outcomes

All data was collected according to a standardized protocol at our institution. Therefore volume measurements and QOL scores were available for each patient at pre-determined time points. The outcomes were collected during chart review in a retrospective fashion.

The primary outcome was the percentage reduction in volume difference between the affected and the healthy arm. Volume measurements of both the lymphoedema and healthy extremity were performed using the water displacement technique preoperatively and at three, six, and 12 months follow-up. All measurements were performed by an experienced physiotherapist (CB) using a standardized volumeter and lukewarm water. Previous research indicates water temperatures varying between 20 and 32 degrees does not affect arm volume.23

Secondary outcomes were: the change in QOL after six months follow up, the possibility to discontinue compression garment usage after six months follow-up, and the relation between decrease in volume difference between extremities and the volume decrease of the affected extremity. QOL was measured preoperatively and 6 months after LVA surgery using the LymphQOL ARM questionnaire, a validated questionnaire for patients with lymphoedema of the arm to determine
QOL. In this questionnaire patients rated their overall QOL (range 1-10) in addition to subdomains regarding functionality, appearance, symptoms and patients mood (range 1-4). Regarding these subdomains: a score of one, two, three or four indicates that the swollen extremity affects that subdomain not at all, a little, quite a lot or a lot respectively. An Increase in the overall QOL reflects a positive change in the QOL, while a decrease in the subdomains indicates that the subdomain is less affected by the lymphoedema. Furthermore, the relations between the preoperative variables: difference in arm volumes, BMI, and volume difference reduction and increase of QOL were explored.

Statistical analysis

Paired student t-tests were used to compare the volume changes between the affected and the healthy extremity pre-surgery, 6 months follow-up and 12 months follow-up. Then the percentage decrease in arm volume difference was calculated. In addition, paired student t-tests were used to compare the LYMQOL ARM questionnaire results pre surgery and after 6 months follow-up. A Pearson's correlation analysis was performed to determine the correlation between the decrease in volume difference between arms and the decrease in volume of the affected arm only. Correlations between the percentage arm volume difference decrease after 12 months and: Arm volume difference at baseline, BMI, duration of oedema and number of anastomoses created were calculated.

The increase in QOL was defined as minor or major improvement. Minor improvement was defined as one point increase in the QOL. Major improvement was defined as >2 point increase in the QOL. Then student-t tests were performed to detect differences between minor and major QOL for the variables: Arm volume difference at baseline, BMI, duration of oedema and number of anastomoses created. When a significant difference of means was detected a binary logistic regression was performed to determine the odds for major QOL improvement. All analyses were performed with IBM SPSS Version 22 (IBM Corp., Armonk, N.Y.).

Results

29 Consecutive female patients with unilateral BCRL were eligible for inclusion. Patient characteristics are listed below (table 1). The mean age of these patients was 59 ± 9 years (range 41 – 84 years). Their BMI was 27 ± 4kg/m2 (range 21 – 34). 12 patients had lymphoedema of their left arm, 17 of their right arm. Lymphoedema was diagnosed as 10% volume surplus in comparison of the healthy extremity. Three of the treated patients had less than 10% volume surplus but experienced
complaints because of the oedema nonetheless. All patients demonstrated pitting lymphoedema (stage 1h - 2a according to Campisi). Lymphoedema was present for a mean period of $9 \pm 7,3$ years (range 2 – 39 years). All patients gave informed consent regarding the surgical procedure and ICG injection.

The mean number of anastomoses was $1.8 \pm 0.8$ (range 1-3). Ten patients received 1 LVA, 14 patients 2 LVAs, and 5 patients 3 LVAs. The anastomoses were most commonly performed end-to-end (n=45), followed by end-to-side (n=6), and the invagination technique (n=2). The diameter of the lymphatic vessels used for bypass ranged from 0.3 to 0.7 mm. The mean operative time was $2.8 \pm 0.4$ hours. No postoperative complications, defined as complication occurring within 30 days after surgery, occurred. During follow-up, two patients endured two episodes of cellulitis.

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (range)</td>
<td>57 (25 – 84)</td>
</tr>
<tr>
<td>BMI, kg/m², median (range)</td>
<td>26 (23-34)</td>
</tr>
<tr>
<td>Lymphoedema duration, mean (range)</td>
<td>9 (2-39)</td>
</tr>
<tr>
<td>Right extremity</td>
<td>16 (59)</td>
</tr>
<tr>
<td>Anastomoses</td>
<td>53 (100)</td>
</tr>
<tr>
<td>End-to-end</td>
<td>45 (84)</td>
</tr>
<tr>
<td>End-to-side</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Invagination</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Number of anastomosis, mean (range)</td>
<td>1.8 (1-3)</td>
</tr>
<tr>
<td>Operative time, min, mean</td>
<td>168</td>
</tr>
</tbody>
</table>

Table 3. Patient characteristics.

Volume measurements

The preoperative mean difference in arm volume was $701\pm435$ml. This was reduced to $496\pm302$ml at six months follow-up ($p<0.001$) (Figure 2). At 12 months follow up the mean difference in arm volume was $467\pm303$ml (23.5%) ($p<0.001$) (table 2). Therefore, the percentage volume reduction at six- and twelve months follow-up was 29 and 33%, respectively. Out of 29 patients, 28 patients treated with LVA showed an improvement of the volume difference between arms. The volumetric arm difference increased in one patient (table 3). When the decrease of arm volume difference between the affected and the healthy extremity was compared
to the decrease of volume of the affected extremity only the correlation was \( r=0.60 \) (\( p=0.00 \)).

There was no significant correlation between the volume difference reduction between arms and the variables: Arm volume difference at baseline (\( r=-0.15, p=0.44 \)), BMI (\( r=-0.06, p=0.52 \)), Duration of oedema (\( r=-0.15, p=0.45 \)), number of anastomoses created (\( r=-0.03, p=0.89 \)).

![Volumetric outcomes](image)

**Figure 2.** Average volume differences between the healthy and affected extremity at different time points during follow-up. Significance was reached between baseline and 6 months follow-up (\( p<0.001 \)), between baseline and 12 months follow-up (\( p<0.001 \)) and between 6 months follow-up and 12 months follow up (\( p=0.02 \)).

**Quality of life**

The overall perceived QOL was increased from 5.8±1.1 to 7.4±0.7 (\( p=0.00 \)). The functionality score decreased from 2.2 to 1.8 (\( P=0.00 \)), the appearance score decreased from 2.6 to 1.9 (\( p=0.00 \)), the symptoms score decreased from 2.8 to 1.8 (\( p=0.00 \)) and the mood score decreased from 2.7 to 1.5 (\( p=0.00 \)) (**Figure 3**). 15 Patients (53.6%) were able to discontinue the use of compression garment.

Considering minor versus major improvement in QOL, only the arm volume difference at baseline was significantly higher in the major QOL improvement group. Arm volume difference at baseline was 473ml in the minor improvement
group and 907ml in the major improvement group (p=0.007). The mean BMI was 25.8 in the minor improvement group and 28.6 in the major improvement group (p=0.06). Mean duration of oedema was 10.3 years in the minor improvement group and 8.07 years in the major improvement group (p=0.45). The mean amount of anastomoses created was 2.08 in the minor improvement group and 1.60 in the major improvement group (p=0.08).

The variable arm volume difference at baseline was categorized in groups in which the arm volume difference was increased by 250ml each step. Then a binary logistic regression analysis was performed. The Odds ratio to a major increase in QOL was OR=2.06 (p=0.02, CI=1.10-3.86) per 250ml.

![LYMQOL-arm subdomain score](image)

**Figure 3.** Mean reduction on the LYMQOL-arm index score regarding the subdomains. A lower score in the subdomains indicates that patients were less affected by the lymphoedema in that subdomain.

**Discussion**

Although LVA was considered a controversial technique in the treatment of lymphoedema, it is gaining popularity with the advancement of microsurgical techniques. Previous studies demonstrate mixed results following LVA procedures, but the quality of these studies varies. In addition, most studies evaluating LVA, present the results in primary and secondary lymphoedema of both the upper and lower extremity as one, while the effect of LVA most likely differs per lymphoedema modality.25, 26

This study demonstrates the results of LVA surgery in secondary lymphoedema resulting from breast cancer treatment. And is, to our knowledge, the first to assess the effects of LVA on the QOL of BCRL patients who experienced significant volume
reduction between arms. In addition, although in a relatively small population, it is the first time the relation between pre-operative variables and outcomes are explored.

For this study only patients with unilateral BRCL were included. This allowed for the unaffected arm to be used as inpatient control. Patients included in this study experienced a reduction of 33% of the arm volume difference at 12 months follow up. In one patient the volume difference between arms increased but the QOL increased too. The QOL of patients increased in all but one patient. In this patient there was a volume decrease between arms. The preoperative arm volume difference proved to be a significant predictor to a greater increase of QOL. Interestingly, the decrease in arm volume difference between arms was not larger in patients who experienced a greater increase in QOL. In this study, the possible volume effect of arm dominancy was not taken into account.

In our study population, the patients BMI, the amount of shunts created and the duration of the oedema did not affect the effect of the procedure on volume reduction between arms or QOL. While the QOL was increased in the majority of patients after six months, it is likely that the QOL was further increased after six months due to the great amount of patients that were able to discontinue the use of compression garment.

Because lymphoedema surgery is considered controversial in the Netherlands and its place in the treatment of lymphoedema is still unconfirmed, we were very cautious concerning the discontinuation of compression garments. In the population studied in this paper, patients came with the request to discontinue compression therapy when they noticed attenuation of their complaints. Only then, we advised to slowly phase the discontinuation of compression garments by increasing the time spend without compression garments. Then, if arm volume remained stable or decreased, and the patient noticed no subjective increase of the lymphoedema, the compression therapy could be fully discontinued. For all patients we strongly encouraged the use of compression therapy until minimally 6 months after surgery.

The results demonstrated in this study are in line with recent trials evaluating LVAs in secondary upper limb lymphoedema patients. Chang et al. reported that arm volumes decreased in 74% of patients with upper limb lymphoedema, these patients experienced a volume reduction of 42% of the affected limb.27 Poumellec et al. found a volume reduction of 22.5%, 21.32% and 30.24 in the affected wrist, forearm and arm respectively.28 In our study the effect of LVAs was determined by comparing the volume differences between the affected and the healthy arm between time points, instead of comparing the difference in volume of the affected arm only. This ensures
that the measured results are not affected by variables such as air humidity and temperature and therefore reflects a more precise effect of the procedure. This is underlined by the low correlation between decrease of volume of the affected arm and the decrease of volume difference between arms found in this study (r=0.60).

Volume measurements of both the lymphoedematous and healthy extremity were performed using a water displacement technique. This technique is highly accurate in measuring arm volume with an intraclass correlation coefficient (ICC) of 0.99. More recently however, we started measuring lymphoedema volumes with 3D stereo photogrammetry in our institution. This may measure lymphoedema volumes more accurate and may become the first choice diagnostic tool for lymphoedema volume assessment. The effect of limb dominance on arm volume is known to be statistically significant but small and was not taken into account in this study.

Concerning the peri-operative care for lymphaticovenular anastomosis a protocol was followed based on several recommendations in the current literature. It is however imperative to note that these recommendations are solely based on expert opinions and no evidence is available to support these suggestions. Animal studies indicate that the long term patency of LVAs can be as low as 52%. Therefore it is of great importance to optimize the peri-operative conditions to improve the shunt patency. Because it is currently unknown if peri-operative interventions such as compression therapy directly post-surgery may either harm or benefit the patency, future studies should clearly state peri-operative care that was used. Then it may become possible to optimize the effect of LVA.

Although the results of this study were analysed in retrospect, data was collected according to a standardized protocol at our institution. Therefore, data concerning arm volumes were available for each patient at pre-determined times during follow-up. In addition, pre-operative variables such as ICG lymphography and duration of the lymphoedema were also noted for each patient. To ensure that all anastomoses were patent directly post-surgery, ICG lymphography was used during surgery.

**Conclusion**

Treatment of BRCL with LVA seems an effective strategy in reducing the volume difference between arms and increasing the patients QOL. Interestingly the reduction in volume differences was not correlated to a greater increase in QOL. In addition the amount of shunts created, patients BMI and the lymphoedema duration did not affect volume reduction or the patients QOL. Future research, most preferably in a randomized controlled fashion, should confirm these findings.
Chapter four

References


The efficacy of Lymphaticovenular Anastomosis in BCRL


The efficacy of Lymphaticovenular Anastomosis in BCRL
Chapter five

The long-term patency of lymphaticovenular anastomosis in breast cancer related lymphoedema


*Annals of Plastic Surgery, 2019*
Abstract

Background and objectives
Lymphedema is a condition that can greatly affect patient’s quality of life. Promising results have been described with lymphaticovenular anastomosis (LVA) in the treatment of lymphedema. It is currently unknown at what rate anastomoses remain functional after a longer follow-up. The aim of this study was to determine LVA patency at 1-year follow-up.

Methods
A retrospective chart review was performed on patients who underwent LVA surgery. Patients who had indocyanine green lymphography performed at 12 months follow-up after LVA were included in this study. Volume measurements were performed prior to surgery and at 6 and 12 months follow-up. Patient quality of life was measured prior to surgery and at 6 months follow-up.

Results
Twelve patients met the inclusion criteria. In total, 15 (56.5%) of 23 LVAs were considered patent. In 8 patients (66.7%), at least 1 patent LVA was visible. The volume difference between the healthy and affected arms decreased 32.3% on average. Quality of life increased with 1.4 points on average.

Conclusions
This study is, to our knowledge, the first to evaluate the long-term patency of LVA in upper limb lymphedema. Our study demonstrates that at least 56.5% of the anastomoses created are patent after 1-year follow-up.
Introduction

Lymphoedema is a common condition after breast cancer treatment. This condition can have a detrimental effect on patient's quality of life (QoL) because of pain, body image distortion, frequent infections, and restrictions in range of motion. The incidence of lymphoedema in the literature varies widely per treatment modality but a large meta-analysis indicated that more than one in five women treated for breast cancer will develop lymphoedema.\textsuperscript{1,2} The mainstay treatment of lymphoedema is multimodality and consists of an initial and maintenance phase in which compression therapy has a great role. However, in recent years surgical strategies to improve lymphoedema have gained interest.\textsuperscript{3,5}

Regarding lymphoedema surgery there are two main strategies: excisional and reconstructive surgery. Excisional surgery includes debulking and liposuction. These techniques are often utilised in a more advanced stage of the disease, when there is fat deposition in the extremity. This result in a direct decrease of volume of the extremity, without restoring lymphatic flow.\textsuperscript{3,6} In reconstructive microsurgery, the aim is to restore a functional lymphatic flow, thereby reducing the oedematous volume in a more natural and sustainable manner. Within this area, vascularised lymph node transplantation and (multiple)lymphaticovenular anastomosis (LVA) have been most widely evaluated.\textsuperscript{6,7} Reconstructive options are preferably performed in early stage lymphoedema when ‘pitting’ oedema is still present. In later stages, reconstructive options might be less viable because of the absence of functional lymphatics.\textsuperscript{8}

LVA have been described in patients as early as 1977 by O’Brien et al.\textsuperscript{9} Results, however, were quite variable and in some patients the lymphoedema worsened after surgery.\textsuperscript{10} With the introduction of ‘super microsurgical’ techniques by Koshima et al. it became possible to create anastomoses between 0.3-0.8mm in diameter.\textsuperscript{11} Because there may be a lower pressure in smaller lymphatics and veins there is a lower chance of venous backflow rendering the anastomosis useless.\textsuperscript{12}

While promising results regarding volume and QoL have been described for breast cancer related lymphoedema (BRCL) with LVA, little is known about the long term patency of the anastomoses.\textsuperscript{13,14} Recently, Tourani demonstrated that the long term patency of LVA in dogs is only 52% after at least five months follow-up.\textsuperscript{15} While it might be possible to increase patency rate in human patients by careful patient selection and good peri-operative care, the fate of newly formed LVA remains uncertain.

With indocyanine green (ICG) lymphography it is possible to directly visualise the lymphatic system of the arm. This technique is currently used to determine
the stage of lymphoedema as an adjunct to the more classic lymphoedema staging systems and to evaluate the functionality of lymphatic vessels before surgery. In our institution, we additionally use ICG lymphography to evaluate the patency of the LVA and the dermal backflow pattern one year after surgery. The aim of this study was to determine the patency rate after one year follow-up in patients with BRCL who underwent LVA surgery, and to share our preliminary results.

**Patients and methods**

**Inclusion criteria**
Patients who underwent LVA surgery at our department between 2014 and 2016 were included in this study. Patients were eligible for LVA surgery if there was pitting oedema, they presented with unilateral BCRL (Campisi stage 1-2a) and had previously undergone treatment with compression garment for at least 6 months. Patients were excluded if there were no lymphatics available, determined by contractility observed using ICG lymphography, or if ICG was not performed after one year. Lymphoedema was defined as a volume increase of at least 10% compared to the non-affected arm, or self-reported heaviness or swelling. No limits were set on the duration of the lymphoedema.

**Surgical technique**
The surgical procedure was performed as previously described. Briefly, lymphaticovenular anastomoses were created under general anaesthesia in 3-4 cm incisions by two experienced microsurgeons using a surgical microscope (ZEISS OPMI 800; 25 x to 50x magnification). The anastomoses were created at the distal wrist or forearm depending on the availability of functional lymphatics. Lymphatics of 0.3-0.8mm in diameter were identified with the aid of ICG lymphography. In general, the anastomoses were created in an end-to-end fashion, if the recipient vein was substantially larger than the lymphatic end-to-side anastomoses were created. Intraoperatively the patency of the anastomoses was confirmed by ICG (Figure 1). All patients were given prophylactic antibiotics intraoperatively and for five days post-operative. After surgery, the affected arm was bandaged with a two component compression system (Rosidal TCS, Lohmann & Rauscher, Germany) for 1 week and extremity was elevated on a pillow during night-time. Patients were discharged after 24 hours. One week after surgery compression therapy with compression garments was continued for 3 months.

**Outcomes and follow-up**
For all patients treated with lymphoedema surgery at our institution, results are evaluated according to our standard follow-up protocol at 6 and 12 months post-operative. For this study, a retrospective chart review was performed and outcomes...
were gathered in a pre-defined form.

The primary outcome was patency of the LVAs after one year follow-up. Patency was determined by injecting ICG (0.5%, 0.5 ml, Diagnogreen, Daiichi Pharmaceutical, Tokyo, Japan) subcutaneously in the 2nd webspace of the hand. A photodynamic eye (PDE) (PULSION Medical Systems AG, Munich, Germany) was used to identify lymph vessels. LVAs were considered patent if a linear lymph pattern could be observed over the incision site of the anastomosis (Figure 2, 3).

Secondary outcomes were volume reduction and increase in QoL. Volume reduction was defined as the relative decrease in volume difference between the healthy and affected extremity. Volume measurements were performed at 6 and 12 months follow-up by an experienced physiotherapist using a water displacement technique. QOL was measured with the LYMQOL questionnaire, a validated questionnaire for patients with lymphoelema of the arm. QoL was determined pre-surgery and after six months follow-up.

Figure 1. The overview picture on the left demonstrates the area in which the anastomosis is created. On the right the anastomosis is visible in more detail. While the total pattern would be classified as a ‘splash pattern’ over the incision site a linear pattern is visible.
Chapter five

Figure 2. Indocyanine green lymphography of the wrist. The arrow indicates a linear pattern at the site where the anastomosis is created.

Figure 3. ICG lymphography about 5 cm below the elbow. In the area of the incision site (indicated by the black window) no linear patterns can be observed.

Figure 4. QoL outcomes after six months follow up. A decrease in subdomain scores indicates that patients QoL in this specific domain is less affected by the lymphoedema. All differences were statistically significant (p<0.01).
Statistical analysis

Paired Student’s t-tests were used to determine significance regarding the change in arm volume differences between different time points (pre-surgery – 12 months follow-up, pre surgery – six months follow-up, six months follow-up – 12 months follow-up). In addition, paired Student’s t-tests were used to determine significance between changes in subdomain scores of the LYMQL questionnaire and the overall QoL score of the LYMQL questionnaire.

Results

Twelve patients were eligible for inclusion and had ICG lymphography performed at one year follow-up. Patient characteristics and results are demonstrated below (table 1). The mean age of included patients was 58.6 years (range 53-69 years). Their mean BMI was 26.8 (range 21-34). Eight patients had lymphoedema of their right arm, 4 of their left arm. The lymphoedema was present for a mean period of 7.8 years (range 2-19 years). During surgery 1.8 anastomoses were created on average (range 1-3). No complications occurred post-operatively. One patient endured an episode of cellulitis during follow up. ICG lymphography demonstrated a clear linear pattern over at least one LVA in 8 out of 12 patients (66.7%). In total, 15 out of 23 anastomoses were considered patent (56.5%) (table 1).

The volume difference between the healthy and affected arm decreased with 32.3% (range +36.1% - -65.6%) (p=0.002) on average after one year follow-up. In the first six months follow-up, the average decrease in arm volume difference was 25.5% (range 39,2% - -20,6%) (p=0.004). During the second six months follow-up the average decrease in arm volume difference was 8.9% (range 39,6% - -12,8%) (p=0.055) (table 2).

Regarding QoL, the overall QoL score increased with 1.4 points (range 0-3) (p=0.000) on average (figure 2). The subdomain scores for function, appearance, symptoms and mood decreased with 0.5 (p=0.000), 0.7 (p=0.000), 0.9 (p=0.000) and 0.7 (p=0.000) points respectively (figure 4).
Table 1. Patient characteristics, results and ICG lymphography findings.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>BMI</th>
<th>LE onset (years)</th>
<th>Number of anastomoses</th>
<th>Volume difference (%)</th>
<th>Increase in QoL (points)</th>
<th>ICG findings after one year</th>
<th>Anastomoses with confirmed patency (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69</td>
<td>26</td>
<td>13</td>
<td>2</td>
<td>-27.9</td>
<td>1</td>
<td>Small linear patterns at the site of the anastomosis, anastomoses are patent.</td>
<td>2 (100)</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>26</td>
<td>5</td>
<td>1</td>
<td>-57.6</td>
<td>2</td>
<td>The anastomosis is not visible at the incision site.</td>
<td>0 (0)</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>23</td>
<td>6</td>
<td>2</td>
<td>-36.1</td>
<td>2</td>
<td>The anastomoses are not visible at the incision site. Minimal dermal backflow is observed, lymphatic drainage is clearly improved</td>
<td>0 (0)</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>25</td>
<td>19</td>
<td>1</td>
<td>+36.1</td>
<td>3</td>
<td>A minimal linear pattern is observed at the incision site but with a very low flow, anastomosis is probably patent.</td>
<td>1 (100)</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>24</td>
<td>5</td>
<td>1</td>
<td>-22.1</td>
<td>1</td>
<td>A clear linear pattern can be observed at the incision site, anastomoses are patent.</td>
<td>1 (100)</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>31</td>
<td>13</td>
<td>2</td>
<td>-38.52</td>
<td>1</td>
<td>At the incision sites good lymphatic drainage can be observed, anastomoses are patent.</td>
<td>2 (100)</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>25</td>
<td>6</td>
<td>3</td>
<td>-9.1</td>
<td>1</td>
<td>One anastomosis at the wrist can be seen and is patent, the anastomoses at the elbow cannot be observed and are probably not patent.</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>8</td>
<td>54</td>
<td>29</td>
<td>3</td>
<td>2</td>
<td>-37.4</td>
<td>1</td>
<td>No clear linear patterns can be observed at the incision sites. Lymphatic drainage is improved.</td>
<td>0 (0)</td>
</tr>
<tr>
<td>9</td>
<td>58</td>
<td>21</td>
<td>2</td>
<td>2</td>
<td>-46.8</td>
<td>0</td>
<td>Both anastomoses can be observed at the incision sites, anastomoses are patent.</td>
<td>2 (100)</td>
</tr>
<tr>
<td>10</td>
<td>53</td>
<td>33</td>
<td>6</td>
<td>2</td>
<td>-19.4</td>
<td>2</td>
<td>No linear patterns can be observed at the incision sites, anastomoses are not patent.</td>
<td>0 (0)</td>
</tr>
<tr>
<td>11</td>
<td>53</td>
<td>34</td>
<td>5</td>
<td>3</td>
<td>-62.9</td>
<td>1</td>
<td>The anastomoses can be observed and demonstrate a clear linear pattern, anastomoses are patent.</td>
<td>3 (100)</td>
</tr>
<tr>
<td>12</td>
<td>62</td>
<td>25</td>
<td>11</td>
<td>2</td>
<td>-65.6</td>
<td>2</td>
<td>One anastomosis at the wrist can be observed and is patent. The other anastomosis cannot be observed and is probably not patent.</td>
<td>1 (50)</td>
</tr>
</tbody>
</table>
The long-term patency of lymphaticovenular anastomosis in BCRL

Table 2. Volume measurements before surgery and at 6 and 12 months follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Pre-surgery</th>
<th>6 Months Follow-up</th>
<th>12 Months Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

Figure 5. The overview picture on the left demonstrates the area in which the anastomosis is created. On the right the anastomosis is visible in more detail. While the total pattern would be classified as a ‘splash pattern’ over the incision site a linear pattern is visible.
Discussion

Surgical treatment of lymphoedema has gained interest in the recent years. Especially reconstructive options including treatment with LVA seem promising. With these techniques it is aimed for to restore the original functionality of lymph vessels. In addition to volume decrease after treatment with LVA, an increase in the QoL of lymphoedema patients is reported in literature.\textsuperscript{13,14,19}

While encouraging results have been described with LVA, little is known about the fate of the anastomoses that are created in patients with BCRL. Tourani et al. demonstrated with their meta-analysis that long term patency of LVAs is only 52\% after \(>/=5\) months in canine. If these results are translatable to human patients this would imply that multiple anastomoses are needed per patient to ensure a functional anastomosis at longer follow-up.\textsuperscript{15} In a study by Shih et al. in patients with upper extremity lymphoedema 7 out of 8 LVAs were considered patent at 9 months follow-up. While this seems promising, only three patients were evaluated.\textsuperscript{20}

This study is, to our knowledge, the first to evaluate long term patency of LVA in a cohort of upper limb lymphoedema patients. In our study population 56.5\% of the anastomoses that are created can be found at one year follow-up and demonstrate a linear pattern at the incision site and could, therefore, be considered patent. Interestingly, in two patients (four anastomoses) an improved lymphatic drainage can be observed while the anastomoses themselves cannot be identified with ICG lymphography. In addition, all but one patient experienced volume difference reduction. It is imperative to note that these results are obtained in patients with early stage lymphoedema (Campisi stage 1-2a) therefore the results could be worse in patients with a more progressed disease when the affected lymphatic vessels lose their ability to contract.

Regarding QoL, only one patient did not experience an increase in QoL. She did however experience a volume reduction and the anastomoses proved to be patent. In one patient the volume difference between arms increased. However, her QoL increased and the anastomoses proved to be patent. Because the ICG was injected distally to the anastomosis it was not possible venous backflow was observed through the anastomosis. It is most likely that one LVA was not enough to facilitate a decrease in arm volume difference against the ongoing disease progression.

Previously, the patency of LVAs in lower extremity lymphoedema was investigated by Maegawa et al. They reported patency rates of 75\% at 12 months follow-up and 36\% at 24 months follow-up. They were however, only able to evaluate 79 out of 223 anastomoses because the majority of the anastomoses were located too deep in the subcutaneous tissue.\textsuperscript{21} In our population we evaluated all anastomoses even when no ICG uptake was seen in that region. Because all LVAs were created superficially in
the arm, and previous reports described that ICG fluorescence could be observed one cm deep in the subcutis, we think that including all incision sites to evaluate patency is most accurate in our cohort. In addition, because the anastomoses were created using lymphatics that were visible during ICG lymphography pre-operatively, these lymphatics, if patent, should be visible using ICG lymphography during follow-up.

In this study, only anastomoses that could be observed with ICG lymphography in a linear pattern were considered patent. The anastomoses that were observed demonstrated a short line of ICG uptake over the incision site, indicating that there was a flow through a functional vessel. In most patients, after approximately a centimetre over the incision site the linear pattern disappeared, most likely because the venules entered a deeper layer of the subcutis. Furthermore over a few incision sites the ICG images were hard to interpret (Figure 5)

Our results indicate that the ICG lymphography findings may not correlate with volumetric and QoL outcomes. Because some patients experienced volume reduction while no patent LVAs could be found, it is possible that the sensitivity to find a patent anastomosis is low. On the other hand, it can be hard to interpret outcomes of the LVA surgery because the natural progression of the lymphoedema without intervention cannot be predicted. When volume decrease is absent during follow-up, one may conclude that the procedure was not effective. On the other hand, it may be just as possible that the progression of oedema is ceased because of the treatment with LVA. This could explain the discrepancy between volume decrease and QoL as demonstrated previously.

While the patency alone does not explain QoL increase in our study population, the improvement of dermal backflow patterns may assist in evaluating the procedures success. Furthermore, the results of this study imply that it is beneficial to create multiple anastomoses as it is most likely that not all anastomoses which are created remain functional. Furthermore, while only one patient in our cohort experienced volume increase, it is theoretically possible to damage the lymphoedema system if a functional lymphatic becomes occluded. Therefore it might be interesting to compare LVAs with techniques that don’t disrupt the lymphatic system such as VLNT in the same stage of disease.

Conclusion

While ICG has proven to be an excellent diagnostic tool to evaluate the functionality of lymph vessels its role in determining patency of LVAs remained unsure. Our study demonstrates that at least 56.5% of the anastomoses created are still patent after one year follow-up. In addition, the volume difference between the affected and healthy extremity significantly decreased, and patients QoL significantly increased following LVA surgery in our cohort.
Chapter five

References


Chapter six

A Systematic Review and Meta-Analysis of Vascularised Lymph Node Transfer for Breast Cancer Related Lymphoedema


Journal of Vascular Surgery: Venous and Lymphatic Disorders, 2021
Abstract

Background
Vascularized lymph node transfer (VLNT) has become an increasingly popular technique for treating lymphedema. However, although many studies have been performed, its efficacy in increasing patients’ quality of life (QoL) and reducing lymphedema in the affected body part has remained controversial. In the present systematic review, we summarized the evidence for VLNT for treating breast cancer-related lymphedema.

Methods
The MEDLINE, Embase, and Cochrane Central databases were searched for studies of patients with breast cancer-related lymphedema who had received VLNT. The study methods were assessed using the MINORS (methodologic index for nonrandomized studies) tool. The primary outcomes were the change in volume difference between the arms and QoL. The secondary outcomes were skin infection, complications, and discontinuation of compression garment use.

Results
A total of 17 studies were included for qualitative synthesis and 8 for meta-analysis. The average reduction rate between the healthy and affected arms in the studies included in the meta-analysis was 40.31%. Five studies evaluated QoL, and all five studies reported that QoL was significantly increased. Eight studies had evaluated skin infections, of which three had reported the annual infection rates before and after surgery. In these studies, the infection rate had decreased significantly. Three studies had described the usage of compression garments. When the patients were pooled, 27 of 60 were able to discontinue the use of the compression garment. The donor and recipient complication rates were 12.1% and 7.3%, respectively.

Conclusions
The current evidence indicates that VLNT can improve the volume differences between the arms in patients with unilateral lymphedema by ~40%. In addition, although determined from a few studies, it is likely that VLNT has a positive effect on patient’s QoL, the number of skin infections, and compression garment usage and coincided with a low complication rate.
Introduction

Lymphoedema is a common but serious condition that can occur after treatment for malignancies. According to the literature, the incidence of breast cancer-related lymphoedema (BCRL) varies between 24% - 49% after mastectomies and 4% - 28% after breast-conserving therapies.\(^1\)\(^3\) Major risk factors for the development of lymphoedema are axillary lymph node dissection, radiation therapy to the axillary region, postoperative seroma in the axilla and obesity.\(^4\) The mainstay treatment of lymphoedema is conservative and consists of an initial and maintenance phase in which compression therapy has a great role. However, surgical strategies to improve lymphoedema have gained interest.\(^5\)\(^9\)

Both excisional and reconstructive approaches have been described in the treatment for BCRL. Excisional approaches include the infamous Charles procedure, in which a bulk of the affected extremity is excised, and liposuction, where the subcutaneous fat deposits in the affected extremity are removed.\(^10\) These strategies are most often performed in a later stage of disease when there are no remaining functional lymphatic vessels.\(^7\)\(^11\) Reconstructive options on the other hand aim to restore a lymphatic flow to aid in lymphatic drainage from the affected extremity. Besides lymphaticovenular anastomoses (LVA), promising results have been described using vascularised lymph node transfers (VLNT) to treat lymphoedema.\(^12\)-\(^17\)

The use of lymph node transfers was first described by Shesol et al. in a rodent animal model in 1979.\(^18\) Then, in 1982 the first application of lymph node transplantation was described by Clodius et al.\(^19\) More recently, the work of Becker, Cheng and Chang et al. have popularised the use of VLNT amongst plastic and reconstructive surgeons.\(^13\),\(^20\),\(^21\) While promising results have been described with VLNT, the mechanisms of action are not fully eluded. In addition, multiple variations in donor site (groin, supra-clavicular, submandibular) and acceptor site (wrist, axilla) have been described.

Unfortunately, the majority of published studies are quite heterogenous in patient selection, surgical characteristics and outcome reports. Therefore, this review aims to summarise the current evidence regarding VLNT and to evaluate the efficacy of VLNT in the treatment of BCRL regarding the volume of the affected extremity and patients QoL.
Chapter six

Methods

Search method and study identification
The study is performed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA).22 A systematic search was performed in the electronic databases MEDLINE, EMBASE and Cochrane CENTRAL to identify relevant studies. Keywords used were ‘autologous’ and ‘vascularised’ combined with ‘lymph node transfer’ and ‘lymph node transplantation’. Terms were searched for in the title and abstract and, where applicable, were mapped to medical subject headings. All references were gathered in Endnote version X8 (Clarivate Analytics, Philadelphia, Pennsylvania) after which duplicate articles were removed. Then, titles and abstracts were screened for eligibility, and full text articles were retrieved. To prevent double counts of data, different studies by the same authors were scanned for uniqueness with regard to the included patients. The most recent study with the longest follow-up was chosen in case of overlap. Full text articles were screened for other relevant articles. The last search was performed on June 27, 2019. The review and its protocol are not registered.

Inclusion and exclusion criteria
Studies were eligible for inclusion if they described the use of vascularised lymph node transfer in the treatment of breast cancer related lymphoedema in female patients over the age of 18. Studies were excluded if they included <5 patients, if they were animal studies or if the full text was not available in English, German or Dutch.

The methodological quality and risk of bias of each individual remaining study was assessed using the Methodological Index for Non-Randomised Studies (MINORS) tool (Supplemental Table 1). This instrument was constructed and validated for appraisal of non-randomized trials in surgery.23 The ideal score according to the MINORS assessment was 16 points for non-comparative studies and 24 for comparative studies. All articles selected for inclusion during the search process were scored independently by authors H.W. and N.S. disagreement was resolved by discussion and consensus.

Outcomes and data extraction
Study characteristics were noted in a pre-defined form. The primary outcome was a change in volume difference between the healthy and affected arm and a change in patients QoL. Secondary outcomes were skin infections during follow-up, complication rates and discontinuation of compression garment. Regarding compression garment, only studies which also described compression garment usage before surgery were included. Data extraction was performed by the corresponding author.
**Statistical analysis**

For the meta-analysis data regarding volumetric and circumference outcomes were extracted and entered into Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). In studies describing different treatments, only patients who underwent VLNT were included. Patients who underwent additional liposuction or LVA during follow-up were excluded. New means and standard errors were calculated in the lymph node transfer patients groups to reflect the reduction of volume or circumference difference between arms if possible. This could be a reduction in volume difference, or a reduction in circumference difference. Heterogeneity was determined with the Cochrans Q test and quantified using I2. In case of a positive Cochrans Q test (p<0.05) and a high I2 (>50%) a random-effects model instead of a fixed-effects model was chosen. To visualize the results a forest plot was created with Review Manager.

**Results**

The systematic search strategy in MEDLINE, EMBASE and Cochrane CENTRAL yielded 534 articles. After duplicate removal 280 studies remained and were subjected to title and abstract screening. Out of 280 studies, 240 were excluded because they did not cover the domain or intervention, or were of the wrong article type (e.g. reviews, case reports). The full texts of the remaining 40 articles were then assessed for eligibility. In total 17 studies were included for qualitative synthesis and eight studies were included for the meta-analysis (Figure 1-2). Study characteristics and data extracted from included studies are presented in Table 1.

**Volumetric outcomes**

In total, 13 out of 17 studies described volume outcomes after VLNT. However, only eight studies reported outcomes of both the healthy and affected extremity, or the decrease in extremity differences compared to the difference prior to surgery. These eight studies were analysed and the results are demonstrated in a forest plot (figure 2). The mean reduction of the volume difference between the healthy and affected extremities was 40.31% (CI 31.44-49.17). The follow-up between studies was quite variable. However, the mean follow-up of studies who did demonstrate a greater reduction (49.2, 50.6 and 57.1% reduction rate) was similar to the mean follow-up of studies who demonstrated a more moderate effect (20.1, 30.3, 30.5, 31.8 and 33.2% reduction rate). The average follow-up of both groups was 26.8 and 31.13 months respectively.
Chapter six

**Figure 1.** Flowchart demonstrating inclusion process.

[Flowchart image]

**Figure 2.** Forest plot demonstrating volume differences changes after VLNT.
Out of the studies not included in the meta-analysis, Akita et al. demonstrated improvements on the upper extremity lymphoedema (UEL) index in a group with and without deep inferior epigastric artery (DIEP) breast reconstruction. This was no statistical difference between groups. The scores were 13 and 14 points for the DIEP+VLNT and the VLNT groups respectively. Because baseline UEL index was not noted this study could not be included in the meta-analysis.

Becker et al. demonstrated the long term results of VLNT surgery in 24 patients after a mean follow-up of 8.3 years. All patients underwent physiotherapy prior to surgery and were considered resistant to it; the complete physiotherapy regimen and use of compression garment is not described. Patients with early oedema, no skin infections and good skin elasticity were included as well as patients with long lasting oedema, multiple skin infectious episodes and no skin elasticity. In 10 patients the perimeter difference between the affected and healthy returned to normal, in 6 patients the difference was reduced with more than 50%, in another 6 patients the volume difference was reduced by less than 50%, and in 2 patients the difference between the healthy and affected extremity remained unchanged.

In 2016, Gratzon reported the clinical and psychosocial outcomes after VLNT in 50 patients. They performed circumferential measurements of both arms and calculated arm volumes and lymphoedema reduction rates. In total, only 24 out of 50 patients could be included for statistical analysis regarding volume reduction because of missing data or patients not having reached the 12 months follow-up yet. While the average reduction was comparable to the studies included in the forest plot (42.73%) this reduction was not significant (p=0.052). Because standard deviation or individual patient data was not available these results could not be included in the meta-analysis.

In 2013 Nguyen et al. evaluated on the effects of VLNT on 29 consecutive patients. After 12 months follow-up the average volume difference between the healthy and the affected arm was decreased from 20% to 10% which equals a reduction rate of 50%.

Yang et al. retrospectively compared the results regarding arm circumference reduction between 10 BCRL patients who underwent VLNT in combination with transverse rectus abdominis muscle (TRAM) flap or deep inferior epigastric artery (DIEP) flap breast reconstruction and 10 BCRL patients who underwent physiotherapy alone. Circumference measurements were performed at six locations on the affected extremity. There was a significant reduction from 32.1 cm to 29.1 cm in the VLNT group after one year follow-up. In the physiotherapy group, there was a significant increase of arm circumference in four out of six measured locations of the arm after one year follow-up. The breast reconstruction + VLNT group is not head-on compared to the physical therapy group.
More recently, in 2018 Liu et al. evaluated on the effects on volume and radiologic lymph drainage after VLNT.\textsuperscript{34} Out of 30 patients, 21 experienced a volume reduction of the affected arm after surgery. The average reduction of this group was 47.1\%, the nine patients without volume reduction were not originally included in this number. When recalculating the reduction in volume difference, the overall mean reduction rate is 32.9\% assuming that there was no increase in volume differences. Out of all patients, 37\% demonstrated radiologic improvement of the limb. In seven patients there was an increased transport rate and in four cases the transplanted nodes were visible on lymphoscintigraphy.

Maruccia explored the added effect of scar release in combination with VLNT to the wrist. They performed VLNT in a group of 21 patients and VLNT with scar release of the axilla in a group of 18 patients. The mean reduction rate between arms was 42.2\% in the group receiving VLNT after 24 months. At 24 months follow-up they found no additional volume difference reduction in the group who received an axillary scar release in addition to the VLNT.

**Quality of life**

Of all included studies, five evaluated patients QoL after VLNT.\textsuperscript{28, 30, 32, 35, 36} Four studies used the LYMQOL questionnaire. This validated questionnaire rates four specific domains (function, appearance, symptoms and mood) with a score from one to four in addition to a general QoL rating from one to ten. A score of one indicates that the specific domain is not affected by the lymphoedema at all while a score of four implies the domain is greatly affected due to the lymphoedema.

Gratzon et al. demonstrated an improvement of patients QoL after VNLT in a prospective study.\textsuperscript{32} They measured QoL with the LYMQOL before surgery and at one, three, six, nine- and 12-months follow-up. In addition to the LYMQOL, patients also scored the amount of pain and heaviness they experienced on a scale from one to 10 where 10 is maximum pain or heaviness and 0 is no pain or heaviness. In total the results of 50 patients were evaluated. The overall QoL significantly increased from 5.7 to 7.8 after 12 months follow-up and all subdomain scores significantly decreased. In addition, the amount of pain (3.97 to 0.39) and heaviness (5.52 to 1.67) decreased significantly (p<0.01).

In 2018, Aljaaly et al. also reported on the QoL after VLNT.\textsuperscript{30} They found that the general QoL increased significantly with 5.5 points and that all the subdomains scored decreased significantly. Upon subgroup analysis they found that, after 12 months, patients who received a VLNT to the volar side of the wrist instead of the dorsal side had a better score regarding the general QoL and the appearance
subdomains (p<0.05).

In addition, Patel et al. also used the LYMQOL to evaluate the effect of VLNT QoL. They included 25 patients of which 15 patients suffered from upper extremity lymphoedema. The average follow-up in the upper extremity lymphoedema patients was $25.4 \pm 8.4$ months. In all subdomains the QoL increased significantly after 3 and 6 months. The functionality domain reached significance after 12 months. The overall quality of life increased from 2.1 to 5.8 points. Interestingly, the patient reported scores were almost maximal prior to surgery indicating that only patient with severe complaints on all subdomains were analysed in this study.

The final study using the LYMQOL as outcome measure for QoL was published by Maruccia et al. In 39 patients they compared results of VLNT with scar release, and VLNT alone. They found better scores regarding all subdomains in the LYMQOL questionnaire (p<0.05). Furthermore, the authors note in the results section that there were significant better scores in the group also receiving scar release. However, when looking at the provided data, the difference between groups in all subdomains is less than one point. Therefore, one might question the clinical relevance of this difference.

Another study, performed by De Brucker et al. assessed patients QoL before surgery and at an average of 29 months follow-up using the ULL-27 questionnaire. This questionnaire had an overall QoL score and three different subdomains; physical functioning, psychological dimension and social dimension. 25 Female patients were included and 22 patients underwent simultaneous free-flap breast reconstruction. The QoL was significantly increased for the overall scores and the subdomain scores (p=0.001). It is imperative to note that the majority of patients underwent breast reconstruction in addition to the lymphoedema treatment which makes it difficult to isolate the effect of the VLNT. However, the 3 patients who underwent only VNLT all experienced an increase in overall QoL.

**Secondary outcomes**

**Skin infections**

Eight studies evaluated the result of VLNT on the incidence of skin infections (erysipelas or cellulitis). In 2006, Becker demonstrated that after VLNT 17 out of 24 patients did not endure any skin infection and seven patients experienced one skin infection during 8.4 years follow-up. Prior to surgery, patients were categorised in two stages following the authors own staging system. Patients in
stage one (n=6) had endured at most two episodes of skin infections, had preserved skin elasticity and the perimeter of the affected arm did not exceed 30% more than the contralateral arm. Stage 2 patients (n=18) had endured more than two skin infection episodes, had impaired skin elasticity and had an increased perimeter of the affected arm between 30 and 50% compared to the healthy arm. While this is one of the few studies reporting on the incidence of cellulitis after VLNT, it is not possible to compare the incidence of cellulitis before and after the procedure with the data provided.

Patel et al. described the results of their prospective study including the effect of VLNT on skin infections.28 Patients were eligible for VLNT from grade 2 or higher on Cheng's lymphoedema grading scale which implies a circumference difference of >20% and total lymphatic occlusion on lymphoscintigraphy. They included 25 patients of which 15 had oedema of the upper limb. Out of these patients the incidence was reduced from 3.5 ± 3.3 infections per year to 0.7 ± 0.9 skin infections per year (p=0.05).

Dionyssiou et al. did also report on the results of VLNT regarding skin infections. They randomized patients in two groups. In group A (n=18) they performed VLNT after which patients were treated with physiotherapy and compression therapy for six months, in group B (n=18) patients were treated with physiotherapy and compression therapy alone for six months.26 All patients included suffered from ISL stage two lymphoedema and endured at least one episode of skin infection during the last year. In the VLNT group the incidence of skin infections was reduced from 1.94 to 0.277 episodes per year (p=0.000). In the physiotherapy group the incidence was reduced from 1.61 to 1.16 episodes per year (p=0.016). While there was a significant reduction in both groups, the reduction in patients treated with VLNT was far greater.

More recently, Engel et al. described the effect of VLNT. In their series the hand and arm were used as recipient sites. The incidence of cellulitis was reduced from 7.4 ± 2.3 to 2.6 ± 2.3 episodes per year for patients who received VLNT only and from 8.0 ± 1.8 to 2.8 ± 1.8 for patients receiving VLNT in addition to microvascular breast reconstruction. The decrease of episodes did not statistically differ between patients that did or did not undergo simultaneous breast reconstruction.

In addition, de Brucker et al. also described the change in skin infection rate in their study. All patients included suffered from lymphoedema stage one or two, the staging system is not described. Prior to surgery 6 out of 25 patients suffered from recurrent skin infections.35 After VLNT the incidence of skin infections in three patients was reduced from two episodes to one episode per year. In the remaining three patients, infections did not occur during follow-up (mean 29 ±14 months).
Furthermore, Gratzon et al. reported on the decrease of cellulitis incidence in 10 patients that had suffered from skin infections between the onset of the oedema and the VLNT. Following surgery seven patients had experienced no skin infections, two patients endured one episode and one patient suffered from two episode. Because the amount of infections per year is not mentioned. Reduction rates could not be calculated.

Maruccia and Aljaaly et al. both published their results with VLNT in 2019 and 2018 respectively. Mariccua explored the addition of scar release with lipofilling to VLNT. While they found no difference between groups regarding the incidence of skin infections, in total infection rate was reduced from 3.5 episodes to 0.5 episodes per year on average. Aljaaly compared dorsal versus volar placement of VLNT to the wrist, when both groups are combined, the infection rate was reduced from 3 episodes annually to 0.5 episodes annually.

**Compression discontinuation**

Out of the included studies three described the use of compression therapy during follow-up.\textsuperscript{31, 35, 38} Granzow demonstrated a significant decrease in the use of compression garment in patients who underwent VLNT (n=8) (p=0.009). Before surgery, 87% of patients used their compression garment for more than 8 hours a day and 13% of patients used their garments for 4 to 8 hours a day. During follow up, the majority of patients (75%) could discontinue compression therapy or only use compression garment when there was an increased risk to limb swelling (e.g. during exercise). Out of the other patients’ 12.5% used compression garment for 4 to 8 hours a day and another 12.5% used their garment for more than 8 hours a day.

In addition to the evaluation of QoL after VLNT, de Brucker et al. also evaluated the reduction in compression garment use. Prior to surgery patients had at least six months of compression therapy without volume reduction of the limb. Out of 25 patients, fifteen (60%) were able to discontinue compression therapy. The criteria for compression garment discontinuation are not provided. The average follow-up was 29 months (range, 8 to 64 months).

Recently, Akita evaluated the addition of DIEP flap breast reconstruction to the effect of VLNT amongst other outcomes they reported quite thoroughly on the use of compression garment.\textsuperscript{31} In their study patients were divided in two groups. One group underwent VLNT, the other underwent VLNT in addition to a DIEP flap breast reconstruction. Compression therapy and manual lymph drainage were stopped during hospital admission and resumed at time of discharge. At six and 12 months follow up ICG lymphography was performed to visualise dermal backflow patterns. If there was a dermal backflow reduction of 75% at six months follow-up patients were encouraged to decrease compression garment usage. In nine out of 27 patients
an improved dermal backflow pattern was seen and they could completely stop the use of compression garment. In four patients no improved dermal backflow pattern was seen but the UEL index and subjective symptoms improved. They could discontinue compression garment usage during daytime. At 12-months follow-up the dermal backflow in all patients that reduced or discontinued compression garment usage did not worsen. In total more patients could reduce compression garment in the VLNT + DIEP flap group (10 out of 14) than in the VLNT group (3 out of 14) (p=0.04).

When these results are pooled, compression garment could be discontinued in 27 out of 60 patients (45%). The percentage of patients that could stop wearing compression garment was comparable in the studies from Granzow et al. and de Brucker et al. Which were 75 and 60% respectively. The paper from Akita et al. reports a lower discontinuation rate which was 35%. Only the study from Akita et al. described under which conditions it was decided that patients would discontinue using compression garment.

Complication rate
Sixteen out of 17 studies reported on complications which are summarized in Table 2. Out of the 16 studies describing complications, two do not mention complications at the donor site. When the complications described in these 16 studies are pooled, the total complication rates at the donor and recipient site are 12.1% and 7.3% respectively. Donor site lymphoedema occurred in two patients. In one patient the oedema of the leg coincided with wound dehiscence. The swelling was controlled with compression garment and it improved after the wound dehiscence healed.29 The other patient was successfully treated with LVA at the ankle.27
**Table 1. Study characteristics.**

<table>
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<tr>
<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>Diagnosis confirmation/Inclusion criteria</th>
<th>Duration (average)</th>
<th>Donor site</th>
<th>Recipient site</th>
<th>Arm difference reduction</th>
<th>N, reduction</th>
<th>Complications</th>
<th>Donor site</th>
<th>Complications</th>
<th>Follow-up</th>
<th>MI-NORs score</th>
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<td>Akita</td>
<td>2017</td>
<td>27</td>
<td>Splash/ Stardust DBP</td>
<td>Nm.</td>
<td>Groin</td>
<td>Axilla</td>
<td>13.5 ± 5.4 point UEL reduction</td>
<td>Nm.</td>
<td>2 seroma</td>
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<td>None</td>
<td>19.1 ± 1.7 months</td>
<td>19/24</td>
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<td>Aljaaly</td>
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<td>Lymphoscintigraphy, ICG</td>
<td>25.9±2.7 months</td>
<td>Submental</td>
<td>Wrist</td>
<td>42.2 ±32.1</td>
<td>Nm.</td>
<td>2 venous congestion</td>
<td>Nm.</td>
<td>12 months</td>
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<td>Becker</td>
<td>2006</td>
<td>24</td>
<td>-</td>
<td>56.5 months</td>
<td>Groin</td>
<td>Axilla</td>
<td>10 total reduction, 6 &gt;50% reduction, 6&lt;50% reduction, 2 no reduction</td>
<td>20/24</td>
<td>None</td>
<td>8 lymphorrea</td>
<td>8.3 years on average</td>
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<td>Brucker</td>
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<td>25</td>
<td>Stage 1 or 2 (system not specified)</td>
<td>42 ± 42 months</td>
<td>Groin</td>
<td>Axilla</td>
<td>Nm.</td>
<td>Nm.</td>
<td>1 infection resulting in complete flap loss</td>
<td>3 repeated seroma, 4 wound healing problems of which one required surgical management</td>
<td>29 ± 14 months</td>
<td>11/16</td>
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<td>18</td>
<td>Lymphoscintigraphy, ≥ infection episode, Stage 2 ISL</td>
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<td>Groin</td>
<td>Axilla</td>
<td>57.06% on average (p=0.000)</td>
<td>18/18</td>
<td>None</td>
<td>2 prolonged lymphorrea</td>
<td>18 months</td>
<td>19/24</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Stage</td>
<td>Lymphoscintigraphy</td>
<td>Duration</td>
<td>Site</td>
<td>Lesion</td>
<td>Dehiscence</td>
<td>Type</td>
<td>Healing</td>
<td>Comments</td>
<td></td>
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<td></td>
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<tr>
<td>Engel</td>
<td>2017</td>
<td>45</td>
<td>total obstruction on lymphoscintigraphy and late grade II, III, and IV (cheng grading system)</td>
<td>31.3 ± 11.4 months</td>
<td>Groin/Submental</td>
<td>41 Wrist, 3 elbow</td>
<td>31.78% on average</td>
<td>Nm.</td>
<td>None</td>
<td>1 lymphoedema managed by LVA*</td>
<td>47.8 months on average</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gharb**</td>
<td>2011</td>
<td>11</td>
<td>Stage 2 ISL/Lymphoscintigraphy</td>
<td>Nm.</td>
<td>Groin</td>
<td>9 wrist 2 forearm</td>
<td>30.46% on average</td>
<td>8/11</td>
<td>1 forearm cellulitis 1 partial flap necrosis</td>
<td>1 inguinal seroma</td>
<td>39.5 months on average</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granzow</td>
<td>2014</td>
<td>8</td>
<td>Lymphoscintigraphy</td>
<td>3.8 years</td>
<td>Groin</td>
<td>Axilla</td>
<td>Nm.</td>
<td>Nm.</td>
<td>1 axillary seroma, 2 delayed healing</td>
<td>None</td>
<td>25 months on average</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gratzon</td>
<td>2017</td>
<td>50 (24 for statistical analysis)</td>
<td>ISL stage 1/2 or recurrent cellulitis requiring IV antibiotic therapy.</td>
<td>4.87 years</td>
<td>Lower abdomen (42), Chest wall (5), neck (3)</td>
<td>Axilla</td>
<td>58.7% on average (p=0.052)</td>
<td>Nm.</td>
<td>3 SSI, 1 wound dehiscence, 1 hematoma, 1 bleeding, 1 non healing wound</td>
<td>6 SSI, 3 wound dehiscence,</td>
<td>12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin</td>
<td>2009</td>
<td>13</td>
<td>Lymphoscintigraphy</td>
<td>33 months</td>
<td>Groin</td>
<td>Wrist</td>
<td>50.55% on average (p&lt;0.01)</td>
<td>12/13</td>
<td>1 venous congestion managed by re-operation, 1 SSI.</td>
<td>None</td>
<td>56.1 months on average</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu</td>
<td>2018</td>
<td>30</td>
<td>ISL stage 1, 2 and late 2</td>
<td>6 years</td>
<td>Groin</td>
<td>Axilla</td>
<td>47.06 ±27.92</td>
<td>21(70%)</td>
<td>0</td>
<td>0</td>
<td>22.11±7.83 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maruccia</td>
<td>2019</td>
<td>39</td>
<td>Lymphoscintigraphy/ stage 2, 3 ISL</td>
<td>25±3 months</td>
<td>Groin/Gastroepiploic</td>
<td>Wrist</td>
<td>42.57±9.9</td>
<td>Nm.</td>
<td>0</td>
<td>0</td>
<td>24.15±5.71 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montag</td>
<td>2019</td>
<td>24</td>
<td>ISL stage 2, 3</td>
<td>43.6±47.61 months</td>
<td>Groin</td>
<td>Wrist/Axilla</td>
<td>20.1±44.9</td>
<td>Nm.</td>
<td>Nm</td>
<td>Nm</td>
<td>18 months</td>
<td>20/24</td>
<td></td>
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<td>---------</td>
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<td></td>
</tr>
<tr>
<td>Nguyen</td>
<td>2015</td>
<td>29</td>
<td>Nm.</td>
<td>3.3 years</td>
<td>Groin</td>
<td>Axilla</td>
<td>50% on average</td>
<td>23/29</td>
<td>3 delayed wound healing, 1 partial flap necrosis, 1 thrombosis which required surgery</td>
<td>1 delayed closure, 1 abdominal bulge, 1 groin seroma, 1 swelling managed by compression garment</td>
<td>11 months on average</td>
<td>9/16</td>
<td></td>
</tr>
<tr>
<td>Patel</td>
<td>2014</td>
<td>15</td>
<td>Lymphocintigraphy, ICG/ grade 2-4 Chang grading scale</td>
<td>37.1± 30.5 months</td>
<td>Groin and submental</td>
<td>Wrist</td>
<td>24.4% (p=0.03)</td>
<td>Nm.</td>
<td>No complete or partial flap losses.</td>
<td>Nm.</td>
<td>12 months</td>
<td>20/24</td>
<td></td>
</tr>
<tr>
<td>Saaristo</td>
<td>2012</td>
<td>9</td>
<td>Patients with symptoms duration &lt;10 years</td>
<td>Groin</td>
<td>Axilla</td>
<td>30.6% on average</td>
<td>Decrease in 7/9 patients,</td>
<td>2 axillary seroma</td>
<td>1 abdominal seroma, 2 delayed wound closure</td>
<td>6 months</td>
<td>8/16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang</td>
<td>2017</td>
<td>10</td>
<td>&gt;3.1cm circumference difference, symptoms &gt;6months</td>
<td>Nm.</td>
<td>Groin</td>
<td>Axilla</td>
<td>3cm on average (affected arm only)</td>
<td>Nm.</td>
<td>1 fat necrosis</td>
<td>None.</td>
<td>12 months</td>
<td>9/16</td>
<td></td>
</tr>
</tbody>
</table>

*Total complication* rate of flaps was 8.3% but this included breast reconstructions without VLNT. Concerning VLNT, one case of donor site lymphoedema was reported which was treated with one LVA at the ankle.

** For our review only patients who did not undergo additional liposuction during follow-up were included.

*** Infection rates for the VLNT group are not explicitly described.

LE = lymphoedema

DBP = dermal backflow pattern

Nm. = not measured
Chapter six

Table 2. Complication rate after VLNT

<table>
<thead>
<tr>
<th></th>
<th>Recipient site n (%)</th>
<th>Donor site n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seroma/lymphorrea</td>
<td>5 (1.4)</td>
<td>22 (1.7)</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>5 (1.4)</td>
<td>6 (2.1)</td>
</tr>
<tr>
<td>Delayed wound healing</td>
<td>6 (1.6)</td>
<td>7 (0.2)</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>1 (0.3)</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Partial flap necrosis/ fat necrosis</td>
<td>3 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphoedema</td>
<td>0</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Venous congestion</td>
<td>3 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Hematoma</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal bulging</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Total</td>
<td>27 (7.3)</td>
<td>41 (12.1)</td>
</tr>
<tr>
<td>Total patients included</td>
<td>369</td>
<td>338</td>
</tr>
</tbody>
</table>

Discussion

While there have been numerous studies evaluating VLNT published recently in medical literature, there is still controversy about the efficacy of such procedures. In addition, a broad range of outcomes across a broad range of patient groups is reported which makes it difficult for a clinician to obtain a complete picture about the current evidence regarding VLNT surgery. The aim of this review is to summarise all relevant outcomes of a selective patient group, patients with secondary upper extremity lymphoedema. We found that although there are many technical differences to take into account, the reduction of arm difference in volume or circumference is similar for most studies and effects on secondary outcomes were positive.

Volumetric and circumference outcomes were evaluated based on eight studies which were included in a meta-analysis. The average reduction of the volume or circumference difference between the healthy and affected arm was 40.31% (CI 31.44-49.17). Interestingly, just three studies were set up in a prospective fashion. The biggest limitation on evaluation of arm difference reduction was the lack of thorough description of compression garment usage before and after VLNT in most studies. It is possible that patients were more compliant to compression therapy after surgery. Therefore without a standardised protocol the possible bias caused by compression garment could not be excluded.
The effect of VLNT on QoL was assessed by two prospective studies and three retrospective studies using validated questionnaires. Four studies used the LYMQOL and one study used the ULL27 questionnaire. While all five studies demonstrated a significant increase in patients QoL following VLNT, the evaluation of QoL may be hampered by suboptimal conditions in one study. In this study by Brucker et al., patients received two questionnaires 12 months after surgery. They reported on their QoL before and after surgery at the same moment during follow-up. Therefore, the pre-op QoL which was analysed may not reflect the actual QoL prior to surgery. In addition, the VLNT was combined with breast reconstruction in 22 out of 25 patients which may also affect patients QoL.

One of the most feared complications of VLNT is donor site lymphoedema which could theoretically result from the removal of healthy lymph nodes. Interestingly only two patients who underwent VLNT developed lymphoedema at the donor site. In one patient the oedema was controlled with compression garment and the swelling improved after the wound dehiscence healed. The other patient which was successfully treated with LVA at the ankle. One of the measures to avoid this complication could be utilizing reversed lymphatic mapping as described by Dayan et al.. For this technique technetium is injected in the first and second webspace of the foot and ICG is injected in the abdomen. Then, during surgery, the lymph nodes draining the leg can be identified by a gamma probe, and the lymph nodes draining the abdomen can be identified with a near infrared camera. This allows for a safe selection of transplantable lymph nodes. The by far most common complication was seroma formation at the donor site which in some cases required repeated puncture.

When reviewing the current literature, we identified no trials which were able to compare conservative treatment head on to VLNT. Only the study by Lin et al. used an adequate control group (VLNT + microsurgical breast reconstruction versus only microsurgical breast reconstruction). To further evaluate the effect of VLNT, prospective trials are needed with a fixed compression therapy protocol to isolate the effect of the transplanted lymph nodes.
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Conclusion

BCRL can be a debilitating condition and may severely affect patients QoL. While reconstructive surgical techniques including VLNT are being used for over 40 years, solid prospective evidence about its efficacy is scarce. The current evidence indicates that VLNT can reduce the difference between a patients healthy and affected arm by about 40%. In addition, although based on few studies, it is likely that VLNT has a positive effect on patients QoL, the number of skin infections and compression garment usage while coinciding with a low complication rate. Further trials should confirm these findings to compare VLNT to conservative management.

Conflict of interest or funding

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References


Chapter seven

DIEP flap breast reconstruction combined with vascularized lymph node transfer for patients with breast cancer-related lymphoedema

H. Winters, MD, H.J.P. Tielemans, MD, S. Hummelink, Msc, PhD, N.J. Slater, MD, PhD, D.J.O Ulrich, MD, PhD

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Abstract

Introduction
Lymphedema is a condition which heavily impacts patients QoL. For patients who desire autologous breast reconstruction, lymph nodes can be included in the Deep Inferior Epigastric Artery (DIEP) flap combining vascularized lymph node transfer and autologous breast reconstruction.

Material and methods
Patients who received autologous breast reconstruction with a DIEP flap in combination with vascularized lymph nodes were included in this study. Volume measurements pre and post-surgery were analysed and surveys including two versions of the ULL-27 questionnaire to measure QoL before and after surgery were sent.

Results
In total, 45 out of 64 patients returned the questionnaires. The average follow-up was 51 months. The total ULL-27 score increased by 12.6 points on average (p = 0.00). The subdomain scores (physical, psychological and social) also significantly increased (p = 0.00). In addition, 69% of patients were able to decrease physiotherapy, 63% of patients were able to decrease compression garment usage and the incidence of skin infections decreased in 6 patients out of 7 patients who had recurrent skin infections prior to surgery. The volume difference between the affected and the healthy arm did not significantly change (407 ml-406 ml, p = 0.988).

Conclusions
Vascularized lymph node transfer in combination with DIEP flap breast reconstruction can cause a significant improvement in lymphedema-related QoL, even when a volume difference decrease is absent. It can also decrease compression garment usage and reduce the need for physiotherapy. Future prospective studies should evaluate these findings and identify patients that benefit most from such procedures.
Introduction

Lymphoedema occurs when the lymphatic system is unable to divert the lymphatic fluid that is being filtrated into the interstitial space. Eventually, because of stasis of the protein-rich lymph fluid, adipocytes proliferate and deposition of collagen fibers in the extracellular matrix and around collecting lymphatics occurs after which oedema becomes ‘non-pitting’ and irreversible.¹ In western society, the main cause of lymphoedema is due to malignancies or secondary to their treatment.²,⁴ Lymphoedema develops in about one in five women after treatment for breast cancer.⁵ For women undergoing axillary lymph node dissection the incidence to develop lymphoedema is roughly four times higher compared to woman who receive sentinel-lymph-node biopsy.⁶

Lymphoedema can greatly affect a patient’s quality of life by causing pain, recurrent infections, restrictions in range of motion and body image disturbances. The mainstay treatment of Breast Cancer Related Lymphoedema (BRCL) remains conservative and includes the usage of compression sleeves and physiotherapy which are optimally combined into complete decongestive therapy. However, in recent years the surgical treatment of lymphoedema is gaining popularity and promising results are demonstrated in current literature.⁷,¹⁰

Reconstructive surgical treatment of lymphoedema focuses on restoring the original functionality of the lymphatic system. Lymphatico-venular anastomoses (LVA) can be created to shunt the excess lymphatic fluid to the venous system bypassing the more proximal obstruction.¹¹,¹² This treatment seems most effective when functional lymphatics are still available. In more advanced lymphoedema stages, vascularized lymph node transfer (VLNT) can be used to treat lymphoedema.⁷, ¹³,¹⁴ The use of VLNT was first described by Shesol et al. in a rodent animal model in 1979.¹⁵ Three years later Clodius described the first patients receiving VLNT.¹⁶ Becker, Cheng and Chang et al. further popularized its use in the treatment of lymphoedema.¹⁷-²¹

While multiple studies have described VLNT to treat lymphoedema, there is no consensus about the optimal donor and acceptor site. In general, VLNT is more invasive compared to LVA. However, the VLNT procedure can easily be combined with autologous breast reconstruction with the deep inferior epigastric artery perforator ( DIEP) flap, with minimal additional operation time and morbidity.¹⁰,²² Donor site lymphoedema is also rare following this procedure.¹⁸,²³

This study describes our experience and results of VLNT combined with DIEP flap breast reconstruction in patients suffering from BCRL, with a focus on quality of life, physio- and compression therapy usage and arm volume difference.
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Patients and methods

Study design
For this study a retrospective chart review was combined with a cross-sectional patient survey study design. Approval from our hospital ethics committee was received (File number 2021-7382).

Inclusion criteria
Patients were eligible for inclusion if they suffered from BCRL and underwent microvascular breast reconstruction with a deep inferior epigastric artery (DIEP) flap including VLNT. Modified ULL-27 questionnaires were sent to all patients postoperatively. Lymphoedema was defined as a volume increase of ≥10% compared to the non-affected arm or self-reported heaviness or swelling. Patients who underwent liposuction or an LVA procedure in addition to the lymph node transfer were excluded.

Data collection

Patient demographics
The electronic medical records were searched for patients eligible for inclusion. Patient characteristics and demographics were entered into a pre-defined case report form. The patients that were identified were sent ULL-27 questionnaires by mail.

Quality of Life (QoL)
A modified ULL-27 questionnaire was used to measure QoL which contained two identical ULL-27 questionnaires and some unique questions to gain insight in the incidence of skin infections, lymphoedema therapy, and compression garment usage before and after surgery. (Table 1) Patients were asked to complete one ULL-27 survey based on their pre-operative status and one on their current post-operative status. In addition, patients were asked if they would recommend patients with similar complaints to undergo the same procedure.

The ULL-27 questionnaire is designed and validated to assess upper extremity lymphoedema specific quality of life. The questionnaire contains 27 questions which are divided into 3 domains (physical, psychological and social). A score from 1 to 5 is given for each question where 5 indicates a high quality of life and 1 indicates a low quality of life. For all domains separately, a combined score was calculated between 0 and 100 where 100 indicates maximal QoL.

Volume measurements
The electronic medical records were evaluated for volume measurements of the healthy and affected arm prior to and post-surgery. Data were extracted and
collected in a pre-defined form. Volume measurements were performed with a water displacement technique. The amount of water that was displaced by the extremity was considered the arm volume. Then, the volume difference between the healthy and affected extremities was calculated.

**Statistical analysis**
Baseline patient characteristics were noted for the included patients and the non-responder group. Then chi-square and Student’s t-tests were performed to identify statistically significant differences between responders and non-responders. For assessment of change in QoL, paired Student’s t-tests were used to compare the mean ULL-27 scores for each domain and in total before and after surgery. Healthy and affected extremity volumes were calculated after which paired student t-tests were performed to identify a difference in volumes prior to and post-surgery. For all tests, a p-value <0.05 was considered significant.

**Surgical technique**
The patients’ pre-surgical workup includes a CT angiography of the abdomen for perforator localization. A pinch test was used to determine flap size. Perforators were marked with ultrasound Doppler (Dopplex SD2, Huntleigh Healthcare Ltd, Cardiff, Wales, United Kingdom) or with a handheld projection device (using CT images) that also projected the lymph nodes.\(^{25, 26}\) During DIEP flap harvest, when preparing the superficial epigastric vein as rescue vein for the flap, lymph nodes close to the origin of the superficial epigastric artery were identified by palpation and included in the flap. When positioning the flap, extra care was taken to ensure that the lymph nodes were positioned in the axilla. Postoperatively a two-component compression garment (Rosidal TCS, Lohmann & Rauscher, Germany) was applied to the affected arm for two weeks after which patients would continue their regular pre-operative compression garment and therapy schedule.

**Results**
In total, 64 patients who underwent a DIEP flap breast reconstruction combined with a lymph node transfer between 2012 and 2020 were identified and sent modified ULL-27 questionnaires. Completed copies were received from 45 patients. Patient demographics of included patients and the non-responder group are demonstrated in Table 2. There were no significant differences between both groups. For all operated patients there were no cases of donor site lymphoedema reported following surgery.
Quality of life
Modified ULL-27 surveys were completed by 45 patients. The average follow-up was 51 months (range 4 – 88). The QoL ULL-27 score increased in 75.6% of patients (n=34). The score remained the same in 15.6% of patients (n=7) and the score decreased in 8.9% of patients (n=4). On average for the whole group, the total ULL-27 score increased by 12.66 points (p=0.000), the physical domain score increased by 13.65 points (p=0.000), the psychological domain increased by 11.11 points (p=0.000) and the social domain increased by 9.50 points (p=0.002). All improvements were statistically significant.

Physiotherapy
Prior to surgery, 36 patients (80%) used some form of physiotherapy. In this group, 25 patients (69%) were able to decrease the frequency of physiotherapy and 13 patients (36%) were able to stop physiotherapy completely.

Compression garment usage
Compression garments were used by 35 patients (78%) pre-operatively. Of these patients, 22 (63%) were able to decrease the use of compression garments after surgery. In addition, 14 patients (40%) were able to stop using compression garments completely.

Skin infections
Skin infections for which antibiotic treatment was necessary occurred in 7 patients prior to surgery. After surgery, of these patients, 6 experienced a decrease in skin infection incidence of which 3 patients experienced no more infectious episodes (Table 3).

Correlations and predictors to an increased ULL27 score
There was a significant moderate correlation between an increase in quality of life according the total ULL27 score and; pre-operative physiotherapy usage (r= 0.37, p=0.02), decrease in physiotherapy usage post-surgery (r=0.32, p=0.04), decrease in compression garment usage (r=0.40, p=0.01). No significant correlations were found between increased QoL and; ISL stage, pre operative compression garment usage, recurrent infections pre-operatively and decrease of infections after surgery. In a multiple regression analysis including ISL stage, pre-operative physiotherapy, pre-operative compression garment usage and pre-operative recurrent infections, no significant predictors to an increased QoL were identified.

Complications
Out of the 45 included patients three re-operations were required in two patients. One patient was re-operated to treat an infected hematoma at the donor site. The other patient was re-operated twice, once to revise the arterial
anastomosis, and later for treatment of an infected seroma at the donor site. Three patients experienced superficial wound dehiscence at the abdomen which was conservatively managed and 2 patients experienced donor site seroma for which one patient received multiple aspirations.

**Volumetric outcomes**
A volumetric assessment was performed in 35 patients pre- and post-operatively. The average follow-up time was 13.48 months (range 1 – 66). For the total group, there was no significant change in arm volume difference before and after surgery (407 ml versus 406 ml respectively, p=0.988). In total, 22 out of 35 patients (65.71%) experienced a decrease in the volume difference of the arm. The mean decrease for this group was 30.88% (range 22.15 – 39.61%). The change in volume difference between arms per patient is demonstrated in Figure 1.

*Figure 1* Change in volume differences between healthy and affected extremities over time per patient. Green line: Decrease of volume difference; grey line: Increase of volume difference.
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Discussion

This study demonstrates that patients lymphoedema-specific QoL is significantly improved after VLNT performed concurrently with DIEP flap breast reconstruction. In addition, most patients were able to decrease compression garment usage and physiotherapy. However, on average these improvements did not coincide with a decrease in arm volume difference.

Over the past years, multiple studies have been published on the results of lymph node transplantation for lymphoedema. While the most of these studies found a decrease in arm volume difference most of them involved small sample sizes, a retrospective study design and included patients who received additional procedures such as liposuction. 8-10, 27-29 Nonetheless, when results are pooled an average reduction of 40% is found.30

In our cohort, there was no significant change in arm volume difference. This might be because of the decrease in compression garment usage or physiotherapy during follow-up. Alternatively, it could be because of the wide inclusion criteria that were used to determine if a patient was suitable for surgery. The risk for the development of donor site lymphoedema is kept to a minimum because the lymph nodes that are used in addition to the DIEP flap drain the abdomen.31, 32 Therefore, we also included patients with minimal arm volume differences or patients with progressive oedema. Because there is such a broad range of lymphoedema stages in our population it is difficult to gauge the result of the procedure by volume measurements alone since it is impossible to differentiate the outcome of the surgery from the natural progression of the disease.

Although arguably even more important than volumetric outcomes, lymphoedema-specific QoL is less commonly used as an outcome measurement to assess the result of VLNT.30 For this study, the ULL-27 questionnaire was used because it has proven to be a reliable and valid method to assess lymphoedema-specific QoL.33 A significant increase in the overall QoL score as well as on the individual physical, psychological and social subdomains were found. The increase of those scores is consistent with other results found in the literature.9 We believe that the discontinuation of compression sleeves and reduction of physiotherapy necessary to control the oedema are important factors that attribute to the improved QoL. Even though the overall QoL in the studied cohort improved, 24.5% percent of patients did not experience an increased QoL. Future studies should identify which patients would benefit most from VLNT and if this can be determined pre-operatively.

A limitation of our study is its retrospective design. Because of this design, the two ULL-27 surveys were sent at the same time during follow-up allowing for the
introduction of recall bias. However, our results are consistent with previous studies using different questionnaires.\textsuperscript{9, 28, 34–36}. Furthermore, only since recent years have volumetric extremity measurements been part of our standard clinical work-up. Therefore, a large proportion of the retrospectively analyzed patients did not have a pre-operative volume measurement available.

A major advantage of this study is that we present a full spectrum of outcomes regarding QoL, arm volume differences, skin infections and lymphoedema therapy. This set of outcomes in a cohort with an average follow-up of more than four years offers insights in what patients might expect after undergoing VLNT. In addition, this allows the clinician to offer more detailed information prior to surgery which aids in better shared decision-making.

**Conclusions**

Vascularized lymph node transfer in combination with DIEP flap breast reconstruction can cause a significant improvement on lymphoedema related QoL, even when a volume difference decrease is absent. It can also decrease compression garment usage and reduce the need for physiotherapy. Furthermore, when adding VLNT to DIEP flap reconstruction only minor additional effort is required with little additional risk to complications. Future prospective studies should evaluate these findings and identify patients that benefit most from such procedures.
Table 1. Topics from the Upper Limb Lymphoedema-27 Questionnaire

<table>
<thead>
<tr>
<th>Physical functioning domain</th>
<th>Do you, because of your arm, experience:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Difficulties finding a comfortable position while sleeping?</td>
</tr>
<tr>
<td>2.</td>
<td>Difficulties with self-care eg. washing your face or hair?</td>
</tr>
<tr>
<td>3.</td>
<td>Difficulties when grasping objects like opening a door/ turning off the tap?</td>
</tr>
<tr>
<td>4.</td>
<td>Difficulties while sleeping, do you wake up frequently, do you experience pain?</td>
</tr>
<tr>
<td>5.</td>
<td>Difficulties while walking because of a heavy, pressing of swollen sensation?</td>
</tr>
<tr>
<td>6.</td>
<td>Difficulties grasping objects from height? Hanging clothes to dry?</td>
</tr>
<tr>
<td>7.</td>
<td>Difficulties when taking public transport?</td>
</tr>
<tr>
<td>8.</td>
<td>Difficulties when choosing clothes?</td>
</tr>
<tr>
<td>9.</td>
<td>Difficulties to remain in a position for a long time?</td>
</tr>
<tr>
<td>10.</td>
<td>Difficulties to hold objects like cutlery, a book, a vase?</td>
</tr>
<tr>
<td>11.</td>
<td>Difficulties in your working relationships and tasks?</td>
</tr>
<tr>
<td>12.</td>
<td>A numb feeling in your arm?</td>
</tr>
<tr>
<td>13.</td>
<td>Feelings of swollen, tense, hard skin?</td>
</tr>
<tr>
<td>14.</td>
<td>A tingling, burning or itching sensation in your arm?</td>
</tr>
<tr>
<td>15.</td>
<td>A heavy or swollen feeling of the arm?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychological domain</th>
<th>Do you, because of your arm, experience:</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.</td>
<td>Feeling the wish to become angry?</td>
</tr>
<tr>
<td>17.</td>
<td>Feeling sad?</td>
</tr>
<tr>
<td>18.</td>
<td>Feeling a lack of self-confidence?</td>
</tr>
<tr>
<td>19.</td>
<td>Feeling fearful?</td>
</tr>
<tr>
<td>20.</td>
<td>Having confidence in the future?</td>
</tr>
<tr>
<td>21.</td>
<td>Feeling well in one’s self?</td>
</tr>
<tr>
<td>22.</td>
<td>Feeling discouraged?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Social domain</th>
<th>Do you, because of your arm, experience:</th>
</tr>
</thead>
<tbody>
<tr>
<td>23.</td>
<td>Feeling fearful of looking in the mirror?</td>
</tr>
<tr>
<td>24.</td>
<td>Difficulties in your social life, while having diner, going to the cinema, shopping?</td>
</tr>
<tr>
<td>25.</td>
<td>Difficulties enjoying good weather, in life outside the house?</td>
</tr>
<tr>
<td>26.</td>
<td>Difficulties in emotional life with spouse or partner?</td>
</tr>
<tr>
<td>27.</td>
<td>Difficulties with personal projects, holidays, or hobbies?</td>
</tr>
</tbody>
</table>
Table 2. Patient characteristics and non-responder analysis

<table>
<thead>
<tr>
<th></th>
<th>Included patients n=45</th>
<th>Non-responders n=19</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50</td>
<td>51</td>
<td>0.62</td>
</tr>
<tr>
<td>BMI</td>
<td>27.2</td>
<td>27.3</td>
<td>0.93</td>
</tr>
<tr>
<td>Duration of symptoms (months)</td>
<td>43.9</td>
<td>45.7</td>
<td>0.89</td>
</tr>
<tr>
<td>≥1 skin infection</td>
<td>7</td>
<td>5</td>
<td>0.27</td>
</tr>
<tr>
<td>ISL stage 1</td>
<td>15</td>
<td>6</td>
<td>0.77</td>
</tr>
<tr>
<td>ISL stage 2</td>
<td>22</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>51.1</td>
<td>43.8</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Table 3. Infection rates pre- and post-surgery

<table>
<thead>
<tr>
<th>Patient</th>
<th>Infections per year Pre-surgery</th>
<th>Post-surgery</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>4</td>
<td>0</td>
<td>88</td>
</tr>
<tr>
<td>2.</td>
<td>4</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>3.</td>
<td>3.5</td>
<td>1.5</td>
<td>50</td>
</tr>
<tr>
<td>4.</td>
<td>3</td>
<td>1</td>
<td>49</td>
</tr>
<tr>
<td>5.</td>
<td>1.5</td>
<td>2.5</td>
<td>87</td>
</tr>
<tr>
<td>6.</td>
<td>1</td>
<td>0</td>
<td>47</td>
</tr>
<tr>
<td>7.</td>
<td>1</td>
<td>0</td>
<td>48</td>
</tr>
</tbody>
</table>
Chapter seven

References


DIEP flap breast reconstruction with vascularized lymph node transfer for patients with BCRL
Chapter eight
Submental flap for vascularised lymph node transfer; a CTA-based study on lymph node distribution


Journal of Surgical Oncology, 2020
Abstract

Background
Amongst various options of vascularized lymph node transfers, the submental flap has the lowest risk for iatrogenic lymphedema. The aim of this study was to gain insight into the distribution, number, and size of lymph nodes along the mandible using computed tomography angiography (CTA).

Methods
A total of 52 CTA scans of the head/neck region were evaluated retrospectively. Lymph nodes in the submental and submandibular region, related to the origin of the submental artery, were recorded using a three-dimensional coordinate system and standardized using an iterative closest point algorithm. Results were analysed for gender, location, size, and number.

Results
The mean number and size of lymph nodes were $5.30 \pm 2.00$ and $5.28 \pm 1.29$ mm, respectively. The mean distance of the lymph nodes to the origin of the submental artery was $25.53 \pm 15.27$ mm. There was no significant difference between both sides when comparing size (left: $5.39 \pm 1.28$; right: $5.17 \pm 1.34$; $P = .19$), number (left: $5.46 \pm 2.10$; right: $5.17 \pm 1.96$; $P = .49$), and distance (left: $24.78 \pm 12.23$; right: $26.32 \pm 14.73$; $P = .19$). No significance was found between males and females concerning number ($P = .60$), size ($P = .50$), and distance ($P = .06$).

Conclusion
The variance of lymph node distribution along the mandible may warrant conducting a CTA scan to maximize the number of transferred lymph nodes and aid in flap design.
Introduction

Lymphoedema is a chronic and progressive swelling due to lymphatic dysfunction and occurs mostly in extremities. The initial treatment of lymphoedema consists of compressive decongestive therapy that utilizes special compression garment, manual lymph drainage and skin care. Where conservative therapy focuses on preventing further swelling of the extremity, surgical options can be considered as an attempt to slow down and halt the pathophysiological deterioration process associated with chronic lymphoedema.

In lymphaticvenous anastomosis (LVA), lymph fluid is diverted into the venous system. An important limitation of an LVA is that it can only be performed in the early stages of lymphoedema, as a superficial functional lymphatic vessel is necessary for a successful procedure and outcome.

Patients who are lacking suitable functional lymphatic vessels, necessary for an LVA, can be candidates for a vascularized lymph node transfer (VLNT). In this procedure, lymph nodes are transferred from a healthy donor site to the affected limb. VLNT aims to tackle the physiologic impairment by replacing the lost lymph nodes and potentially induce the regeneration of lymphatic vessels. To date, various VLNT donor sites have been described such as the groin flap, the supraclavicular flap, the submental flap, the gastro epiploic flap, the mesenteric and the thoracic lymph node flap. With this arsenal of free lymph node flaps available, the preferred flap for treating lymphoedema of the extremity is the submental flap, due to a large quantity of lymph nodes and low risk for iatrogenic lymphoedema.

The improvement of lymphoedema after the surgery is correlated to the number of lymph nodes transferred and their vascularization, hence imparting a meticulous flap design and harvest. The imperative of including the maximal number of the lymph nodes with perinodal tissue is traded off against the increasing size of the flap, which in turn results in a larger visible submental scar. The submental lymph nodes, however, may all be located proximal to the origin of the submental artery, making the distal part of the flap skin redundant, hence departing from the rationale calling for a larger flap. It would, therefore, be beneficial to gain insight into the distribution of the lymph nodes in this area to determine optimal balance between inclusion of the most lymph nodes to be transferred and size of the flap.

The aim of this study was to investigate the distribution, number and size of lymph nodes along the mandible using computed tomography angiography (CTA) to gain insight into the variability of the lymph nodes in this area.
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Materials and methods

In this retrospective study, patients who had undergone a head/neck CTA for a follow-up of a head and neck malignancy, or for staging of tumors located in other regions than head and neck, were included in the study. Head/neck scans were acquired in a helical mode in cranio-caudal direction at 120kV tube voltage where iomeron 300 mg/ml (Bracco Imaging SpA, Milan, Italy) had been used as an intravenous contrast agent. Exclusion criteria for this radiologic study comprised of lymph adenopathy or lymph node dissection in the CTA report, insufficient image quality, presence of tumor or metastatic disease or unclear origin of the submental artery.

In total 52 CTA scans (n=23 male, n=29 female) of satisfactory imaging quality were included to assess 100 sides (n=48 bilateral, n=4 unilateral) for lymph node anatomical features. The mean age of the group was 61.77 ± 13.78 years. The mean body mass index (BMI) was 26.68 ± 4.86 kg/m².

Analysis of CTA scans

The submental artery branches of the facial artery and provides the essential blood supply to the submental flap. During the procedure of harvesting the submental flap, its origin from the facial artery acts as an anatomical landmark. Therefore, lymph nodes were recorded at each side using the origin of the submental artery as a central coordinate in the CTA scans (Figure 1). Lymph nodes in the submental and submandibular region (IA and IB) were recorded between the hyoid bone, the angles of the mandible, the mental protuberance and the bellies of the digastric muscle. In each evaluated side the coordinates of the landmarks were determined; the ipsilateral and contralateral angle of the mandible and the chin. This process was performed on all included CTA scans using post-processing software Aquarius iNtuition Viewer 4.4.12 (TeraRecon, Foster City, California, United States).

The locations of lymph nodes were recorded by a first observer (VP); validation was performed by randomly selecting 10% of the recorded scans and re-evaluated by a second observer (SH). We compared the number of nodes at the levels IA and IB strictly confined within predefined anatomical landmarks (hyoid bone, angles of the mandible, mental protuberance and belly of the anterior digastric muscle). An observed agreement of 0.90 was calculated during this validation process.

The gathered data were analysed using MATLAB 2016b (The MathWorks Inc., Natick, Massachusetts, United States). The heterogeneous lymph node coordinates were standardized through an Iterative Closest Point (ICP) algorithm, unifying all lymph node coordinates into a single coordinate system. The mean coordinates of the ipsi- and contralateral angle of the mandible and the chin were calculated from the
entire dataset and used as fixed registration points for the ICP algorithm. In order to obtain a rotation and translation matrix, the moving registration points included landmarks pertaining to each individual patient. All lymph node coordinates from the same patient could be transposed into a single coordinate system using the individually obtained rotation and translation matrix.

Three-dimensional graphic presentation of all standardized lymph nodes was achieved by creating spheres at each individual location with the corresponding radius of the lymph node within MATLAB. The spheres representing lymph nodes, mandible and blood vessels were rendered within AutoDesk MeshLab (San Rafael, California, United States), retaining global anatomical orientation.

A Students T-test (Excel 2013, Office, Microsoft, United States) was used for subgroup analysis, and parameters were considered significant at the value $p \leq 0.05$.

**Figure 1.** Axial slice of a head/neck CTA scan. The origin of the right submental artery is centered in the coordinate system. Two lymph nodes encircled in red.
Chapter eight

Results

A total of 530 lymph nodes were located in 100 evaluated one-sided level IA/IB cervical regions. The mean number and size of lymph nodes were $5.30 \pm 2.00$ and $5.28 \pm 1.29$ mm, respectively. The mean distance from the lymph nodes to the origin of the submental artery was $25.53 \pm 15.27$ mm (Table 1). In the analysis of the number of lymph nodes between either side (left: $5.46 \pm 2.10$; right: $5.17 \pm 1.96$) no significant difference was found ($p=0.49$). Furthermore, the size of the lymph nodes (left: $5.39 \pm 1.28$ mm; right: $5.17 \pm 1.34$ mm) and distance to the origin of submental artery (left: $24.78 \pm 12.23$ mm right: $26.32 \pm 14.73$ mm) showed no significant difference ($p=0.43$ and $p=0.19$ respectively).

When comparing the number of lymph nodes between males and females (male: $5.20 \pm 2.05$; female: $5.41 \pm 1.96$), no significant difference was found ($p=0.60$). The size of lymph nodes did not significantly differ either (male: $5.20 \pm 1.13$ mm, female: $5.38 \pm 1.46$ mm, $p=0.50$), nor did the distance to the origin of submental artery (male: $26.56 \pm 13.32$ mm, female: $24.37 \pm 13.68$ mm, $p=0.06$). These results are summarized in Table 2. Figure 2 depicts the distribution of lymph nodes along the mandible. The majority of the lymph nodes were approximately found between 1 to 4 cm from the origin of the submental artery as illustrated in Figure 3.

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics of study population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Included scans</strong></td>
</tr>
<tr>
<td><strong>Excluded scans</strong></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td>Male: 29 (55.77%)</td>
</tr>
<tr>
<td>Female: 23 (44.23%)</td>
</tr>
<tr>
<td><strong>Included sides on scans</strong></td>
</tr>
<tr>
<td><strong>Mean age</strong></td>
</tr>
<tr>
<td><strong>Mean body mass index</strong></td>
</tr>
<tr>
<td><strong>Mean amount of lymph nodes</strong></td>
</tr>
<tr>
<td><strong>Mean size of lymph nodes</strong></td>
</tr>
<tr>
<td><strong>Mean distance of lymph nodes to origin submental artery</strong></td>
</tr>
</tbody>
</table>
Submental flap for VLNT; a CTA-based study on lymph node distribution

Table 2. Number, size and location of lymph nodes, comparison between side and gender

<table>
<thead>
<tr>
<th></th>
<th>left</th>
<th>right</th>
<th>p-value</th>
<th>Male</th>
<th>Female</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of lymph nodes</td>
<td>5,46 ± 2,10</td>
<td>5,17 ± 1,96</td>
<td>0,49</td>
<td>5,20 ± 2,05</td>
<td>5,41 ± 1,96</td>
<td>0,60</td>
</tr>
<tr>
<td>Size (mm)</td>
<td>5,39 ± 1,28</td>
<td>5,17 ± 1,34</td>
<td>0,43</td>
<td>5,20 ± 1,13</td>
<td>5,38 ± 1,46</td>
<td>0,50</td>
</tr>
<tr>
<td>Distance to origin (mm)</td>
<td>24,78 ± 12,23</td>
<td>26,32 ± 14,73</td>
<td>0,19</td>
<td>26,56 ± 13,32</td>
<td>24,37 ± 13,68</td>
<td>0,06</td>
</tr>
</tbody>
</table>

Figure 2. Distribution and size of lymph nodes. Gray spheres correspond with size and location along a standardized mandible relative to the submental artery (red). A, anterior-posterior view. B, posterior-anterior view. C, caudal-cranial view

Figure 3. Percentage of lymph nodes in relation to the distance to origin of the submental artery
When comparing the number of lymph nodes between left and right side for each patient, 18.8\% (n=9) no significant difference was found in our study population. Most patients (50\%, n=24), showed a difference of one lymph node between either side. Albeit much less frequent, a difference of two nodes (20.8\%, n=10), three nodes (8.3\%, n=4) and four nodes (2.1\%, n=1) between the cervical sides was also found (Table 3).

**Table 3.** Difference in amount of nodes between both sides of the neck per individual patient

<table>
<thead>
<tr>
<th>Difference in number of lymph nodes between both sides</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9 (18.8)</td>
</tr>
<tr>
<td>1</td>
<td>24 (50)</td>
</tr>
<tr>
<td>2</td>
<td>10 (20.8)</td>
</tr>
<tr>
<td>3</td>
<td>4 (8.3)</td>
</tr>
<tr>
<td>4</td>
<td>1 (2.1)</td>
</tr>
</tbody>
</table>

**Discussion**

Vascularized lymph node transfers (VLNT) have gained a momentum in treatment of early and end-stage lymphoedema. Following the VLNT, the lymphoedema accumulates in the flap and its lymph nodes, followed by redistribution of the collected fluid into the bloodstream. Although the exact working mechanism remains unknown, couple of studies, both in animals and humans, showed promising results.

Various VLNT donor sites have been described such as the groin flap, the supraclavicular flap, the submental flap, the gastro epiploic flap, the mesenteric and the thoracic lymph node flap. Compared to the other flaps the submental flap has a relatively high number of lymph nodes and a low risk for iatrogenic lymphoedema. While some studies looked into the anatomy and lymph node characteristics of the submental region based on cadaveric dissections, others have focused on the clinical setting describing the value and limitations of ultrasound and MR for visualization of submental lymph nodes. To our knowledge no previous study described the added value of a preoperative CTA modality pertaining to the exact number and anatomical localization of level IA/B lymph nodes in order to maximize the number of vascularized lymph nodes to be transferred within the smallest size of the submental flap desirable.
The findings of this study show that anatomical location of the submental lymph nodes varies, both among patients as well as between the left and right side of the mandible. CTA scan can be of value for the surgeon to identify the cervical side with the most lymph nodes available in level IA/IB and based on these findings create the most suitable design for the flap. Furthermore, knowledge of the location of the nodes helps to preserve not only the hilar blood supply of the nodes, but also the surrounding fatty tissue by keeping a safe distance to the nodes while dissecting the submental flap. This perinodal fat contains high levels of growth factor (VEGF-C), which plays an important role in subsequent lymphatic regeneration, and should be preserved.1,18,20

To preserve a maximal number of the submental nodes the soft tissue around the submental and facial artery bifurcation is included in the flap.3

An average number of 5.3 nodes was found in the submandibular triangle, disagreeing with previously published results (3.2 and 3.3 lymph nodes, respectively, found in a cadaver study of Tan and Cheng).3,20 This indicates that possibly more lymph nodes can be transferred when an accurate assessment of a CTA scan is done preoperatively. Most nodes were found between approximately 1 and 4 cm distance from the origin of the submental artery. This indicates that a surgeon can safely navigate to the origin of the submental artery by first locating the facial artery, resting assured that lymph nodes will not be missed or denuded during the dissection. The immediate vicinity of the submandibular gland itself is the most demanding area of the surgical dissection because of the imperative to preserve level IB lymph nodes, their vascularity, and vascularity of the flap given the anatomical variability of the submental artery. There is a great variability of the anatomy pertaining to submental artery course at the superior border of the submandibular gland, but also traversing inside the gland and between its lobes. Level IB lymph nodes are intimately juxta positioned to the submandibular gland and both the lymph nodes and perinodal tissue can receive part of its vascularization through the branches arising in the submandibular gland and penetrating its capsule.

Given the above, the rationale during the flap harvest and especially when in the vicinity of the submandibular gland is to follow the facial artery, open the capsule of the submandibular gland and if encountered make sure that submental artery is protected. To protect level IB lymph nodes and perinodal tissue we will always include submandibular gland capsule in our flap. Sometimes it can lead to partial submandibular gland removal. To date we have not encountered any adverse effects correlated to partial removal of the submandibular gland, such as salivary fistula or sialocele.
Chapter eight

For a future study, we would like to examine the benefits of the preoperative mapping of lymphatic vessels that are entering the flap carrying vascularized lymph nodes using indocyanine green (ICG) fluorescence. In theory, a lymphaticovenous anastomosis between lymphatic vessels of the flap and lymphatic vessels at the recipient site may further expedite and improve the outcome of VLNT.

Conclusion

A retrospective analysis of the CTA scans of the head and neck region was performed to study anatomical location, number and size of submental lymph nodes in relation to the origin of the submental artery. It was found that the lymph nodes were randomly distributed along the mandible, both in the study population as well as within a single individual. The anatomical variation found in level IA/IB lymph nodes warrants conducting a CTA scan to maximize the number of transferred lymph nodes and aid in optimal submental flap design.

Conflict of interest statement

The authors have no financial disclosure.
References


Chapter eight


Submental flap for VLNT; a CTA-based study on lymph node distribution
Chapter nine

General discussion
Conservative versus surgical treatment

Currently, the mainstay of lymphoedema treatment is conservative therapy. General measures advised by the International Society of Lymphology (ISL) include self-monitoring, limb elevation, maintenance of ideal body weight, avoidance of infection/injury, and avoidance of constricting garments/extremity cuffs. 1, 2

Besides these general measures, conservative treatment consists of compression bandaging, compression sleeves, pneumatic compression, physiotherapy, manual lymph drainage, and exercise. For patients with ISL 2 and 3, these components can be combined in complete decongestive therapy. 3 Ko et al. found that, with this program, the excess volume of the affected arm could be decreased by 59% on average. However, this program is very intense and time-consuming. Non-compliant patients lost about 33% of their initial benefit. 4 This data implicates that the volume reduction of 59% can only be maintained by sustaining daily intense therapy for prolonged periods. 5 For patients, the balance between the burden of the lymphoedema symptoms and how the treatment to reduce these symptoms affect their daily life is what influences their willingness to adhere to treatment.

Lately, microsurgical advances allow for smaller anastomoses to be made which gave a new impulse to lymphatic surgery. The benefit of LVA and VLNT compared to conservative treatment is that these treatments offer alleviation of lymphoedema symptoms without adding an extra burden on patients’ daily life after they have recovered from the procedure. 6-9 Alternatively, it might be possible to stabilize lymphoedema symptoms while allowing for less intensive conservative treatment. This thesis confirms that LVA and VLNT might indeed be able to attenuate lymphoedema symptoms to such a degree that it increases patients’ QoL.

Outcome measurements

It is important to standardize outcome measures in lymphoedema surgery to generalize outcomes throughout different studies. One of the most widely used outcomes is the change in volume or circumference of the affected arm compared to the healthy arm. This is a very clear way to quantify the improvement of swelling and outcomes are relatively easy to obtain by circumferential measurements or by using a water displacement technique. 10 Even the use of 3D-stereophotogrammetry has been described to successfully obtain volume measurements of arms. 11-12 While the use of arm volumes as an outcome measure seems valid, it comes with certain downsides. Patients who suffered from years of lymphoedema often tried the most available conservative treatment options and found a specific mixture that works well for them. Therefore, the treatment at baseline prior to surgery is
very heterogeneous while the treatment post-surgery is, in the setting of a clinical trial, similar for all patients who underwent surgery. In a research setting, this allows for bias since the measured effect in volume change could be attributed to the conservative part of the treatment. In addition, if patients choose to decrease conservative treatment during follow-up because they feel the surgery attenuated their symptoms, the decrease in volume might stagnate or even reverse.

To objectively use volume difference changes to assess the success of lymphoedema surgery for reconstructive procedures, patients must have stable lymphoedema complaints for a prolonged period of time with a homogenous conservative treatment plan prior to surgery. Then, postoperatively, patients should follow a similar plan only decreasing conservative therapy after certain follow-up points and in close consultation with their physician. However, this approach requires patients to adapt treatment to what might be less optimal for them and this might come with increased lymphoedema symptoms on the one hand or overtreatment on the other hand.

In the case where it is not feasible to perform a prospective study with such a standardized treatment protocol, it is important to take into consideration the other factors that might affect (or hinder) volume reduction of the affected limb. In chapter seven, for example, it is demonstrated that while no significant change in volume difference between arms was found, the use of compression sleeves and physiotherapy significantly decreased.

A more general outcome to measure the success of lymphoedema treatment is the change in QoL before and after surgery. This summarizes all the subjective benefits of the procedure and balances them with the downsides. The only drawback of this approach is the possibility of bias due to the placebo effect, which is known to occur with surgical procedures. To overcome this problem, future prospective studies evaluating lymphoedema surgery might add lymphoscintigraphy and ICG dermal backflow staging to their outcomes. By identifying new or improved drainage routes with such techniques, a strong objective component is added to put the change in QoL and limb volume in perspective.
Timing and technique

The benefit of creating LVAs is that, for a surgical procedure, it is minimally invasive and the complication rate is low.\textsuperscript{15-17} In addition, the rationale of the procedure, creating alternative drainage routes to bypass a more proximal obstruction, seems viable. However, only lymphatic vessels relatively unaffected by the progression of lymphoedema can be used for LVAs as lymphatic vessels lose their contractility when lymphoedema worsens. Usually, the lymphatics remain functional for a limited amount of time when the disease progresses which leaves a narrow time frame for treatment.

Nevertheless, in chapter 4 it is demonstrated that some patients with a longer duration of symptoms do have functional lymphatics and that good results regarding QoL and volume reduction can be achieved with LVA in this group. However, the use of ICG lymphography is necessary to identify these patients.

When there are no functional lymphatics available in the affected extremity, VLNT and liposuction can be used to alleviate lymphoedema symptoms. The benefit of VLNT is that it aims to restore lymphatic drainage by natural LVA’s occurring in the lymph nodes and by promoting lymphangiogenesis as is elaborated in chapter one. However, the technique to transplant vascularized lymph nodes requires more technical proficiency and the procedure takes longer to perform than liposuction. In addition, in contrast to VLNT, the results with liposuction are more predictable since it provides a direct volume reduction after which compression therapy is always necessary.

Regarding VLNT there are different acceptor sites for treating BCRL described throughout the literature. If the main mechanism of action consists of promoting lymphangiogenesis, the axilla would be the optimal donor site as this is the region where the damage to the lymphatic system has occurred. However, a distally located acceptor site, or the location where a patient has most complaints, is a more sensible place to use if the transferred lymph nodes are considered to act as a pump by the naturally occurring LVA’s. In addition, a lower acceptor site may benefit from gravity allowing for more lymphatic fluid to be shunted. In chapter six, only seven out of 17 included studies evaluating the effect of VLNT used the wrist, elbow, or forearm as the acceptor site. The average volume difference reduction rate in studies included in the meta-analysis is 35.9% on average for the studies using a distal acceptor site (n=6) and 35.8% for studies using the axilla as acceptor site (n=3). While head-on comparisons are needed to determine if there is a significant difference in outcomes between acceptor site locations, it seems that acceptor site location may not contribute greatly to the results of VLNT.
Future of lymphatic surgery

In the current Dutch lymphoedema guidelines dating from 2014, it is stated that while lymphovenous reconstructions have been performed for more than 30 years there is no robust evidence of its efficacy and therefore these procedures should be considered experimental. However, in recent years lots of new data regarding the efficacy of such procedures have been published. In this thesis, a significant increase in QoL and a significant reduction of arm volume difference are observed after LVA. In the coming years, these findings should be confirmed in prospective randomized trials.¹⁸

Once the role of LVA in the treatment of lymphoedema has been confirmed, the next step in optimizing lymphoedema care is to identify which patients are most at risk to develop lymphoedema. As demonstrated in chapter two, pre-emptive LVAs could be efficient in preventing lymphoedema. Therefore, if patients who will develop lymphoedema are identified in a very early stage or even before its development, LVAs can be created pre-emptively which could prevent decompensation of the lymphatic system.

One group, already follows this approach to such an extent that they performed LVA during axillary node dissection for patients with a BMI ≥30 or with a transport index ≥10.¹⁹ They found an incidence of secondary arm lymphoedema of 4.05% after four-year follow-up. In addition, a systematic review exploring the role of prophylactic LVA in preventing cancer-related lymphoedema found a significant reduction in the incidence of lymphoedema when patients were treated with LVA (OR 0.33). Currently, it is not feasible to perform lymphatic reconstructions for every patient undergoing ‘high-risk surgery’ such as axillary node dissection because of overtreatment. However, when it is possible to predict which patients will develop lymphoedema before the initial treatment, pre-emptive LVAs could be implemented in general practice.

When no functional lymphatics remain, or if a patient wishes to receive autologous breast reconstruction with the DIEP flap, VLNT can be used to alleviate lymphoedema symptoms. However, while the results with VLNT from our department (chapter seven) as well as the results summarised in our systematic review are promising (chapter eight), they are also quite variable.

This corresponds to our clinical observations in which we noticed that many patients were convinced that the procedure helped them reduce affected arm volume while decreasing compression garment usage after a period in which the lymphoedema was stable. On the other hand, other patients did not notice any improvements regarding QoL, additional therapy and volume difference between
arms. While VLNT might not be effective for every patient, when combined with breast reconstruction the VLNT is only a minor extra procedure with little additional risk on top of the reconstruction. Therefore, we would recommend offering additional VLNT to DIEP flap breast reconstruction for women suffering from lymphoedema. When VLNT is performed as a standalone procedure the probability that a patient will benefit from the procedure needs to be maximized. Therefore future studies should aim to create a prediction model to identify the patients who would benefit from VLNT.

All in all, over the last years, surgical techniques to treat lymphoedema have been refined aiming to offer a more definite solution for a chronic condition. Future studies should focus on identifying which patients can benefit most from different surgical interventions based on individual characteristics and the lymphoedema stage. With this information, it becomes possible for healthcare professionals to include LVAs, VLNT and liposuction in a patient-tailored treatment plan proportionate to each patient’s wishes and expectations.
References


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Summary

Part I

Chapter one provides an introduction and outline for the current thesis. The basic anatomy of the lymphatic system is outlined and different mechanisms of action for reconstructive surgical treatments are proposed. Chapter two demonstrates the successful treatment of a patient with Noonan syndrome suffering from vulvar lymphangiectasias. Initially, she was treated more than 15 times with cryotherapy, excision, coagulation, and shave excision. Unfortunately, these treatments only temporarily relieved the symptoms. A two-stage procedure was performed in which lymphovenous anastomoses LVA’s were created, after which the lesions were excised and reconstruction was performed with advancement flaps. This case demonstrated the potential for performing LVA’s pre-emptive to procedures with high risk for postoperative lymphoedema.

In chapter three a systematic review is presented in which the optimal perioperative care for patients undergoing LVA is examined. Multiple ideas are proposed in different studies which are sometimes counter-intuitive. Out of the available studies, peri-operative management consisting of prophylactic antibiotics, the elevation of the affected limb and compression therapy four weeks post-surgery for six months seem to be preferred, based on expert opinions.

The first results achieved with LVA in a cohort of patients with unilateral breast cancer related lymphoedema (BCRL) are demonstrated in chapter four. Overall, there was a 33% significant reduction in arm volume difference between the healthy and affected arm after 12 months follow-up. In addition, the quality of life (QoL) which was measured with the LYMQOL was significantly increased. Fifteen patients (53.6%) were able to discontinue compression garments during follow-up. Interestingly, no correlations were found between decrease in arm volume and increase in QoL. This might be because of the relatively low sample size or because of the discontinuation of compression garments in some patients.

While LVA’s seem to be an effective treatment for BCRL, the fate of the anastomoses remained uncertain. Animal experiments have demonstrated that the patency rate of LVA’s is only 52% after five months of follow-up in dogs. If these results are translatable to humans this would imply that multiple anastomoses are necessary to ensure a prolonged benefit to lymphatic drainage. In chapter five a retrospective cohort study including 12 patients is presented in which the patency rate of LVA’s after more than one year of follow-up is explored. Indocyanine green (ICG) lymphography is used to determine lymphatic flow or backflow over the site where the anastomoses were created. In total, for 15 out of 23 LVA’s that were evaluated (56%) a linear pattern was observed indicating that the anastomosis was patent.
However, an absence of this pattern might not exclude patency. Furthermore, all patients in whom no linear pattern was visible still experienced a decrease in volume difference between arms. While ICG is a great diagnostic tool for diagnosing lymphoedema and determining if functional lymphatics are available for LVA surgery, its role in determining the result of such procedures remains uncertain. Comparing dermal backflow patterns may be beneficial in future studies.

Part II
Another reconstructive procedure to aid lymphatic drainage is the transplantation of lymph nodes to the affected extremity. It is hypothesized that the newly transplanted nodes aid in the regeneration of lymph vessels by excreting growth factors. In addition, the anastomoses between lymph vessels and veins that occur naturally in lymph nodes allow for the transplanted tissue to act as a ‘sponge’, shunting lymph fluid to the venous system.

In chapter six the current literature is reviewed and outcomes with vascularized lymph node transfer (VLNT) in patients with BCRL are summarized. This review is unique in exclusively selecting patients with the same aetiology of lymphoedema and presenting all relevant outcomes after the procedure. In addition, patients who received additional procedures such as liposuction and LVAs were excluded from the analysis allowing for a more clear comparison between studies. Overall a reduction of volume difference of 40.31% was found in a total of 150 patients. In all five studies that measured QoL, the QoL was significantly increased during follow-up. Infection rates were reported scarcely. In the three studies reporting yearly infection rates, this rate was significantly decreased. When all patients from studies reporting on compression garment usage were pooled, 27 out of 60 patients were able to discontinue compression garments. Donor and recipient complication rates were 12.1 and 7.3%, respectively. While results included in the review are very positive, the quality of the studies is not optimal. Very few studies are prospective in nature and there seems to be a risk of publication bias for which it was not possible to correct.

While the lymph nodes used for VLNT can be transplanted alone as a free flap, it is also possible to include them in a larger free flap such as the deep inferior epigastric artery perforator DIEP flap in which the inguinal lymph nodes can be included. Because the addition of lymph nodes to the DIEP flap requires minor additional effort to an already invasive surgical procedure this addition might be highly beneficial for patients suffering from BCRL who wish to receive autologous breast reconstruction. In chapter seven results of VLNT in addition to DIEP flap breast reconstruction for patients with BCRL are demonstrated. No significant change of arm volume difference was observed overall but QoL significantly increased. In addition, 63% of patients were able to decrease compression garment usage and
40% were able to stop using compression garments completely. The majority of patients (80%) used some form of physiotherapy prior to surgery. Sixty-nine percent of patients were able to decrease physiotherapy frequency and 36% were able to stop physical therapy completely.

Besides the inguinal lymph nodes, lymph nodes of the submental area may be used for VLNT. In chapter eight the use of CTA scans is explored to assist in pre-operative planning for VLNT from the submental area. On average, no difference was found between the size of the lymph nodes, the distance to the origin of the submental artery, and the number of lymph nodes, between the right and left side. However, there was significant variance in the number of lymph nodes between the left side and the right side between patients. In 68.8% of patients, this difference was less than two lymph nodes, whereas in 31.2% of patients the difference was two or more lymph nodes. This variance in the number of lymph nodes per patient might warrant a pre-operative computed tomography angiography (CTA) scan to aid in optimal pre-operative planning.
Nederlandse samenvatting

Deel I
In hoofdstuk een worden de thema’s van dit proefschrift geïntroduceerd aan de hand van de functie, werking en anatomie van het lymf festelsel. Verder wordt ingegaan op de oorsprong van de lymfoedeemchirurgie en de veronderstelde werking van lymfov eneze anastomosen en gevasculariseerde lymfekliertransplantaties ter behandeling van lymfoedeem.

Een voorbeeld van een goed resultaat behaald met lymfoon eneze anastomosen wordt gedemonstreerd in hoofdstuk twee waar de casus wordt beschreven van een patiënt bekend met het Noonan syndroom met hierbij recidiverende vulvaire lymphangiectasie. Ondanks veelvuldige behandelingen waaronder excisie en coagulatie bleven de lymatische afwijkingen recidiveren. Om de onderliggende oorzaak te behandelen werden er in een eerste tempo meerdere lymfoon eneze anastomosen aangelegd die het vulvaire gebied konden draineren. Vervolgens werden de afwijkingen in een tweede tempo geëxcideerd waarna de vulva werd gereconstrueerd. Tijdens de poliklinische controle na 12 maanden waren er nog enkele blaasjes a vue maar was de patiënt verder klachtenvrij. Deze casus illustreert het potentiële voordeel van preventieve behandeling met lymfoon eneze anastomosen voor patiënten die een ingreep ondergaan met een hoog risico op postoperatief lymfoedeem.

Hoewel de behandeling met lymfoon eneze anastomosen niet nieuw is, is er nog weinig bekend over het optimaliseren van de behandelresultaten. Zo zijn er in verschillende onderzoekscentra verschillende, en soms tegenstrijdige, protocollen betreffende de perioperatieve zorg. In hoofdstuk drie wordt de perioperatieve zorg voor patiënten die behandeld worden met lymfoon eneze anastomosen zoals beschreven in de medische literatuur samengevat. Het gebruik van profylactische antibiotica, het hooghouden van de extremiteit en compressietherapie worden het meest beschreven. Dit is niet gebaseerd op wetenschappelijk bewijs.

De eerste resultaten met lymfoon eneze anastomosen in een cohort van 29 patiënten met unilateraal borstkankergerelateerd lymfoedeem wordt beschreven in hoofdstuk vier. Er was in deze groep een gemiddelde statistisch significante afname van 33% van het volume verschil tussen de aangedane en niet aangedane arm na 12 maanden. Tevens verbeterde de kwaliteit van leven in deze groep patiënten significant. In totaal konden 15 patiënten (53,6%) stoppen met het gebruik van compressie kousen. Er werd geen relatie gevonden tussen de afname van het volumeverschil en de toename in kwaliteit van leven.
Ondanks de eerste veelbelovende resultaten met lymfoveneuze anastomosen is het nog onduidelijk of de anastomosen gedurende langere tijd postoperatief doorgankelijk blijven. Dierexperimenteel onderzoek heeft aangetoond dat de doorgankelijkheid van lymfoveneuze anastomosen slechts 52% is na 5 maanden. Als deze resultaten transleerbaar zijn naar mensen zouden er meerdere anastomosen nodig zijn om een langdurig resultaat te kunnen bewerkstelligen. In hoofdstuk vijf wordt een retrospectieve cohort studie beschreven waar met indocyanine groen (ICG) lymfografie wordt gekeken naar de doorgankelijkheid van de anastomosen in 12 patiënten minimaal een jaar na de procedure. Als er over het litteken een lineair patroon zichtbaar is kan worden gesteld dat er sprake is van lymfatische afvloed over de anastomose. Over 65% van de anastomosen was een lineair patroon zichtbaar. Echter, in de overige gevallen was het soms lastig vast te stellen hoe de lymfatische drainage precies verliep. Daarbij hadden ook patiënten waarbij geen lineair patroon gezien werd over het litteken toch een afname van volume verschil tussen de armen. Het lijkt erop dat ICG lymfografie de doorgankelijkheid van lymfoveneuze anastomosen niet goed kan vaststellen. Echter, het gebruik van ICG lymfografie om pre- en postoperatief de dermale terugvloed van lymfe te bepalen en dit te gebruiken als uitkomstmaat lijkt veelbelovend.

Deel II
Een andere reconstructieve procedure om de lymfeafvloed te bevorderen is door gevasculariseerde lymfeklieren te transplanteren naar het aangedane gebied. Er wordt gedacht dat het werkingsmechanisme van gevasculariseerde lymfekliertransplantaties uit twee componenten bestaat. Aan de ene kant wordt de vorming van nieuwe lymfebanen gestimuleerd door groeifactoren welke door de getransplanteerde lymfeklieren worden uitgescheiden en aan de andere kant werken de getransplanteerde klieren als een soort pomp door de natuurlijke verbindingen tussen het lymfatische en het veneuze systeem binnen de lymfeklieren.

In hoofdstuk zes is de huidige medische literatuur onderzocht en zijn de uitkomsten van gevasculariseerde lymfekliertransplantaties voor patiënten met borstkankergerelateerd lymfoedeem samengevat en geanalyseerd. Deze analyse is uniek omdat het alle relevante uitkomsten weergeeft voor een specifieke groep patiënten. Tevens zijn alle resultaten behaald voor patiënten welke ook alternatieve chirurgische behandelingen hebben ondergaan (zoals liposuctie) geëxcludeerd. Er werd een gemiddelde afname van volumeverschil tussen de aangedane en niet aangedane arm gevonden van 40,3% over in totaal 150 patiënten. In alle vijf de studies die de kwaliteit van leven maten werd een significante toename van kwaliteit van leven gezien. De incidentie van cellulitis/erysipelas voor en na de ingreep zijn slecht gerapporteerd. In de 3 studies die dit wel goed omschreven werd een afname van het aantal infecties per jaar gezien. Als de patiënten van alle studies werden samengenomen konden 27 van de 60 patiënten stoppen met
het gebruik van een compressiekous. Complicaties ter plaatse van de donorsite kwamen bij 12,1% van de patiënten voor. Complicaties ter plaatse van de acceptor site bij 7,3% van de patiënten. Over het algemeen zijn de resultaten beschreven in de geïncludeerde studies erg goed. Echter, de kwaliteit van de studies is niet optimaal waarbij er slechts enkele prospectief waren opgezet. Tevens kan er sprake zijn van publicatiebias.

De lymfeklieren kunnen als vrije lap getransplanteerd worden naar het aangedane gebied. Het is ook mogelijk de lymfeklieren te inclueren in een vrije lap van het abdomen (de deep inferior epigastric artery (DIEP) lap) welke veel gebruikt wordt om een borst te reconstrueren. Het toevoegen van de lymfeklieren is in dit geval slechts een kleine extra stap met een hoop potentiële voordelen voor vrouwen met lymfoedeem. In hoofdstuk zeven worden de resultaten beschreven met gevasculariseerde lymfekliertransplantaties in combinatie met een DIEP-lap-borstreconstructie bij 45 patiënten. Er werd geen significante afname van volume verschil tussen de armen gezien. Wel was er sprake van een significante toename van kwaliteit van leven. Tevens konden 63% van de patiënten het gebruik van compressie kousen verminderen. Veertig procent kon het gebruik helemaal staken. De meerderheid van de patiënten (80%) maakte gebruik van een vorm van fysiotherapie voor de ingreep. Hiervan kon 69% de frequentie verminderen en 36% kon de fysiotherapie staken.

Naast lymfeklieren in de lies kunnen ook lymfeklieren in het submentale gebied gebruikt worden voor gevasculariseerde lymfekliertransplantaties. In hoofdstuk acht wordt onderzocht of het maken van een computer tomografie (CT) scan meerwaarde biedt in de preoperatieve planning van deze ingreep. Er zijn in totaal 100 zijden (50 links en 50 rechts) onderzocht. Er werd geen verschil gevonden in de grootte van de lymfeklieren, de afstand tot de oorsprong van de submentale arterie en het aantal lymfeklieren tussen de linker en rechter zijden. Er was per patiënt echter wel een significant verschil tussen het aantal lymfeklieren links en rechts. In 68% was dit verschil minder dan 2 lymfeklieren. In 31.2% was dit verschil per kant 2 klieren of meer. Hieruit blijkt dat een CT-scan toegevoegde waarde kan hebben in de preoperatieve planning om een optimaal aantal lymfeklieren te inclueren.
Appendices

I  Research data management
II  List of publications
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V  Curriculum vitae
Research data management

The data obtained during this PhD at the Radboud university medical center (Radboudumc) have been captured and stored on the department server. Data remains accessible by the PhD candidate, (co-)promotors and co-authors. The surveys that were collected for chapter seven will be stored in the local file archive of the department of plastic surgery.

The datasets used for chapter three to eight can be obtained by correspondence to the corresponding authors of the published studies upon reasonable request.
List of publications

DIEP flap breast reconstruction combined with vascularized lymph node transfer for patients with breast cancer-related lymphedema
Winters H, Tielemans HJP, Paulus V, Hummelink S, Slater NJ, Ulrich DJO
*European Journal of Surgical Oncology, 2022*

A Systematic Review and Meta-Analysis of Vascularised Lymph Node Transfer for Breast Cancer Related Lymphedema
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Winters H, Tielemans HJP, Hameeteman M, Paulus VAA, Beurskens CH, Slater NJ, Ulrich DJO
*Breast Cancer Research and Treatment, 2017*

Peri-operative care for patients undergoing lymphaticovenular anastomosis: A systematic review
Winters H, Tielemans HJP, Sprangers PN, Ulrich DJO
*Journal of Plastic, Reconstructive & Aesthetic Surgery, 2016*

Lymphovenous Anastomosis and Secondary Resection for Noonan Syndrome with Vulvar Lymphangiectasia
Winters H, Tielemans HJP, Ulrich DJO
*Plastic and Reconstructive Surgery – Global Open, 2016*
List of presentations

The efficacy and patency of lymphaticovenular anastomosis in breast cancer-related lymphedema
Oral presentation, EURAPS scientific meeting, Madrid, 2018

The use of pre-operative CT scan measurements for predicting complications in patients undergoing large ventral hernia repair with the component separation technique
Oral presentation, International Hernia Congress, Miami, 2018

De doorgankelijkheid van lymfoveneuze anastomoses na een jaar follow-up
Oral presentation, NVPC dagen, Eindhoven, 2017

De reproduceerbaarheid en verschillen tussen drie 3D-fotosystemen
Oral presentation, NVPC dagen, Eindhoven, 2017

Peri-operative care for patients undergoing lymphaticovenular anastomosis
Oral presentation, BAPRAS/FAPRAS winter scientific meeting, Helsinki, 2017

Current insights in extracorporeal perfusion of free tissue flaps and extremities - A systematic review and data-synthesis
Poster presentation, BAPRAS/FAPRAS winter scientific meeting, Helsinki, 2017

Lymphovenous anastomosis and secondary resection for noonan syndrome with vulvar lymphangiectasia
Oral presentation, World Symposium on Lymphedema Surgery, Barcelona, 2017

Het effect van lymfoveneuze anastomoses ter behandeling van borstkanker gerelateerde lymfoedeem
Oral presentation, NVPC dagen, Amsterdam, 2017

The use of pre-operative CT scan measurements for predicting reherniation in patients undergoing large ventral hernia repair
Oral presentation, EURAPS research council, Pisa, 2017
Appendices

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Curriculum vitae


Na de studie geneeskunde heeft Harm eerst brede klinische ervaring opgedaan als ANIOS bij de afdeling heelkunde in Ziekenhuis de Gelderse Vallei in Ede om vervolgens van start te gaan als ANIOS bij de plastische chirurgie in het Haaglanden Medisch Centrum in Den Haag. Hierna heeft hij zijn klinische ervaring verder uitgebreid door te werken als ANIOS plastische chirurgie in het Radboudumc, het Medisch Centrum Leeuwarden en het Universitair Medisch Centrum Utrecht. Tijdens zijn ANIOS periode werd de laatste hand gelegd aan dit proefschrift.
Re-Evaluating Lymphatic Surgery

Let It Flow

Harm Winters

2022