Effectiveness and cost-effectiveness of lymphaticovenous anastomosis for cancer patients who suffer from chronic peripheral lymphedema

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Primary Objective:The primary objective is to assess the efficacy of LVA surgery in comparison to sham procedure in patients with cancer related lymphedema in the context of improvement of Lymph-ICF score at 12 and 24 months follow up. Secondary…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Spleen, lymphatic and reticuloendothelial system disorders
Study type	Interventional

Summary

ID

NL-OMON56227

Source
ToetsingOnline

Brief title
The N-LVA study

Condition

- Spleen, lymphatic and reticuloendothelial system disorders
- Skin and subcutaneous tissue therapeutic procedures

Synonym
edema, Lymphedema

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: ZonMw;subsidieregeling veelbelovende zorg

Intervention

Keyword: Cancer-related lymphedema, Lymphaticovenous anastomosis, Lymph-ICF, Sham procedure

Outcome measures

Primary outcome

The primary endpoint will be the change in Lymph-ICF score at 12 and 24 months follow-up. To assess the effectiveness of the treatment we will use the Dutch version of the *Lymphedema Functioning, Disability, and Health* (Lymph-ICF) questionnaire. This questionnaire assesses the impairments in function, activity limitations, and participation restrictions of patients with lymphedema. It is a validated, disease-specific questionnaire, consisting of items (questions) across 5 domains. Each item is scored on a VAS, ranging from 0 to 100. The total score on the Lymph-ICF is equal to the sum of the item scores, divided by the total number of answered items. A higher score on the Lymph-ICF indicates more problems with functioning related to lymphedema. For the upper limb a decrease of 11 points represents a statistically significant difference and a decrease of 15 points indicates a clinically relevant difference. The 15-point cut-off was used for this sample size calculation.

For lower limb lymphedema a decrease of 20 points or more in total score and each domain separately (except life and social life domain score) are considered clinically relevant. For the life and social life domain score, a

difference of 40 points is considered clinically relevant. The 20 points

cut-off point was used for the sample size calculation for the lower limb.

HRQoL will be assessed at inclusion and 3, 6, 12, and 24 months after

randomization.

Secondary outcome

- The excess limb volume;

- The extremity circumference;

- Discontinuation of conservative treatment;

- Postoperative complications;

- Patency of the LVA;

- Patient costs, QALYs, and incremental cost-effectiveness.

Study description

Background summary

Lymphedema is a chronic and progressive disorder caused by disruption or dysfunction of the lymphatic system. It is marked by the progressive accumulation of protein-rich fluid within the interstitium and fibro-adipose tissue, which ultimately exceeds the capacity of the lymphatic system to transport fluid. This fluid overload leads to fibrosis, due to stromal and parenchymal proliferation and excessive deposition of the extracellular matrix. Swelling associated with lymphedema can occur anywhere, including arms, legs, genitals, face, neck, chest wall, and oral cavity. However, it is predominantly observed in the upper and lower extremities.

Lymphedema can be congenital or acquired. Congenital or primary lymphedema is a rare disorder caused by genetic mutations that leads to underdevelopment or dysfunction of the lymphatic system. Whereas acquired or secondary lymphedema is a consequence of trauma, systemic disease, infection, or surgery. In developed countries, the most frequent cause of secondary lymphedema is a result of oncological treatment for several solid tumors, including breast,

melanoma, head and neck, gynecological, and genitourinary malignancies.

The time course for the development of lymphedema after cancer treatment is dependent on the extensiveness of the treatment received. In BRCL the risk of lymphedema was the highest after 12-30 months post-operatively. After gynecological cancers, the highest onset frequency was reported after the first year of the cancer diagnosis. In the case of lymphedema after melanoma the highest frequency of lymphedema was reported after one year.

Cancer-related lymphedema has an overall incidence of 15.5% and is highest in patients receiving radiation therapy (31%). According to Cormier et al. (2010), the pooled incidence of lymphedema in cancer was 15.5% with an individual incidence of 16% in melanomas (5% upper extremity and 28% lower extremity), 20% in gynecological cancer i.e endometrial cancer, vulva cancer and ovarian cancer, 10% in urogenital cancers and 30% in sarcomas in the upper and lower extremity.

In the Netherlands, around 15.000 women develop breast cancer each year of which around 25% (3.750 patients) develop lymphedema. For cervix and ovarian cancer, 30-50% of 2.100 cases each year develop lymphedema which is between 600 and 1.050 patients. Lymphedema after bladder, prostate, or male genitalia cancer develops lymphedema in 15-30% of around 21.300 cases which are between 3.195 and 6.390 patients.

Given the lack of standardized diagnostic criteria, diagnosis of lymphedema is based primarily on presentation and examination findings. Limb volume measurements using a tape measure, water displacement, perometry, bioimpedance, and lymphoscintigraphy can corroborate the diagnosis. An increase in limb volume of <10% in comparison to the healthy extremity can indicate (sub)clinical lymphedema. The severity of lymphedema is categorized as mild (<20% increase in extremity volume), moderate (20-40%), or severe (>40%). Up until now, the most common classification is the clinical classification of lymphedematous swelling defined by the International Society of Lymphology (ISL). Furthermore, the near-infrared fluorescence imaging (NIRF) with indocyanine green (ICG) is used to determine the dermal backflow stage as standard care in the out-patient clinic. NIRF also makes it possible to assess if a patient has viable lymphatics for LVA surgery.

Patients with CRL not only suffer from the physical but also the psychosocial consequences of lymphedema. The physical symptoms include swelling, heaviness of the extremity, pain, paresthesia, reduced range of motion, and weakness. Particularly, lower extremity lymphedema (LEL) may also evoke immobility, ulcers/skin breakages, and weeping of the lymphedematous region. Patients with lymphedema have a higher propensity for cellulitis and erysipelas infections. CRL is also associated with psychosocial symptoms such as depression, anxiety, and difficulty in social, domestic, vocational, and sexual domains. To manage symptoms and prevent disease progression lifelong maintenance is required which

results in a radical adjustment of daily living (ADL) to comply with treatment. Patients with CRL also experience financial repercussions due to treatment costs but also due to the inability to work following lymphedema onset are not without financial repercussions.

To this date, there is no definite cure for lymphedema. Currently, conservative therapy, namely complex decongestive therapy is the golden standard for the treatment. Complex decongestive therapy consists of manual lymphatic drainage, compression therapy, and skin/wound care. CDT is often indicated in patients with more than 5-10% excess volume starting with compression stockings.

At the beginning of this millennium microvascular surgery was developed and anastomoses in vessels as small as 0.3mm in diameter were made possible. This meant the beginning of *super microsurgery*. Because of these technical refinements, it is now possible to create multiple bypasses between lymphatic vessels (ranging from 0.3 mm - 0.8 mm) and smaller venular vessels (< 0.8 mm) with lower pressure than previously possible. These venules and lymphatic vessels can be found in the subdermal plane. The minimal invasiveness of this procedure is another advantage, as it can be performed under local anesthesia. Usually, 1 to 4 anastomoses are made at several points within a lymphedema arm. LVA surgery aims to reduce arm volume, reduce episodes of cellulitis, discontinuation of compressive garments, and most importantly regain the ability to participate in social activities and ultimately improve the quality of life. With the advancement of super microsurgery, LVA is gaining traction as an effective surgical treatment for extremity lymphedema.

Multiple studies have evaluated the safety and efficacy of LVA surgery in the extremities. These studies report a volume-reductive effect between 6% and 85%. However, the success rate is dependent on multiple factors such as technique and lymphedema stage. Chang et al. published results on a prospective study concerning 30 patients with BCRL. After 1-year follow-up, a mean reduction of 61% in the early-stage group (MD Anderson stage I or II) was reported, whereas a mean reduction of 17% in the late-stage group (MD Anderson stage III or IV) was presented. Overall, 96% of the patients presented subjective improvement in their symptoms. Cornelissen et al. prospectively performed a study on the improvement in quality of life after LVA in women with BCRL. They found a decrease in circumference, although not statistically significant. Furthermore, a statistically significant improvement in Lymph-ICF scores after 1-year of follow-up using a validated questionnaire (Lymphoedema Functioning, Disability and Health). Moreover, 85% of the patients discontinued compressive stockings. Winters et al. performed a retrospective study on the efficacy of LVA in BCRL on 29 patients. After 1-year follow-up, the percentage volume reduction was 33%. Only one patient showed an increase in volume. The overall perceived quality of life also increased. Fifteen patients were able to discontinue the use of compression garments.

For the lower extremity, a systematic review conducted by Rosian et al. has

shown positive outcomes, however, there is variation in limb size reduction. This is often dependent on the severity of lymphedema, the amount of anastomosis along with the risk factors associated with lymphedema. The highest reduction rates reported after LVA ranged between 51.1% and 63.8%, with better results achieved in the early stages of lymphedema.
Another systematic review conducted by Verhey et al. included 74 studies analyzing the efficacy of LVA in patients with lower extremity lymphedema and reported an overall average reduction in limb volume of 22.67%, and a reduction of excess limb volume of 45.52%. Overall complications were rare with a postoperative pelvic reoccurrence of lymphedema in one out of 10 patients, postoperative infections in two out of 12 patients, and subcutaneous ecchymosis in 6 patients overall. Conversely, 15 out of 74 studies noted a complete or partial reduction of cellulitis. Concurrently, a meta-analysis by Basta et al. reported low incidences of minor complications. Complications reported are not different from the standard complications which can be expected after this small surgery (infection and bleeding). Furthermore, an improvement of subjective symptoms such as a reduction in pain, heaviness, sense of anxiety, and increased self-confidence and self-esteem was seen in 90% of the population.

Overall, a systematic review and meta-analysis by Nacchiero et al. corroborated the abovementioned data that LVA can result in statistically significant improvement of outcomes such as limb volume, arm circumference, and QOL. However, until now the studies available are small non-randomized studies and the quality of the studies is lacking. Furthermore, there is a large variability in outcome measures and mixed results. No large-scale prospective or randomized studies have been published on the efficacy of LVA.

Based on the findings that:
a) Chronic CRL is associated with ADL impairment, a strong negative psychosocial impact, and reduced quality of life
b) CRL is a progressive and chronic disease
c) Treatment in the early phase of CRL increases treatment effectivity
d) Current (conservative) treatment is not aimed at repairing the impaired lymphatic function
e) Lymphatic microsurgery is one of the treatments that may help regain normal lymphatic function,
We have formulated the following hypotheses that will be studied in this project:

Patients undergoing lymphatic microsurgery for persistent CRL will have:
1) Higher Lymph-ICF and EQ5D scores,
2) Less ELV (measured by bioimpedance and circumference measurement).

Pilot data MUMC+
Since 2015 the Department of Plastic and Reconstructive surgery at the Maastricht University Medical Center (MUMC) has been conducting studies on the

effect of LVA surgery, headed by dr. Qiu Shao.
Qiu et al. conducted a prospective trial on the efficacy of LVA surgery in patients with secondary lymphedema. In this study, 100 patients were included with upper and lower extremity lymphedema. A statistically significant increase in the total Lymph-ICF score was reported after 2 years, measured with the validated Lymph ICF questionnaire. Overall mean circumference was not significantly different. The percentage of patients that could reduce compression garments in the upper and lower extremity group was 65% and 40%, respectively. Number of cellulitis episodes per year and MLD sessions per week showed a mean decrease of respectively 0.6 and 0.8 in the upper extremity and 0.4 and 1.0 in the lower extremity group.

Furthermore, Wolfs et al. (2019) assessed long-term patency in 25 women with BRCL who received LVA surgery, with a total of 47 anastomoses. In the current study, in three-quarters of patients, at least one anastomosis was considered patent. Compared with the non-patent group, the patent anastomosis group showed more improvement in QoL, a decrease in arm circumference, and a higher discontinuation rate of compression stockings, indicating a conceivable positive correlation between a patent anastomosis and clinical improvement after LVA .

A RadboudUMC pilot study (2017) with 29 patients also showed a statistically significant increase in HRQoL (from 5.8±1.1 to 7.4±0.7; p=0.00) measured by the LYMQOL questionnaire (scored between 0 as the worst and 10 as best), 54% discontinued compression stockings.

Since 2018 the *Veelbelovende Zorg* subsidized (ZonMw 852001904) *The Lymph Trial* is being conducted, a randomized controlled trial on the (cost) effectiveness of LVA surgery in comparison to CDT in patients with BRCL (NL67059.068.18/ METC 18-024). In this trial, the primary outcome is HrQOL measured by the Lymph-ICF. The secondary outcome measures are excess limb volume, cost-effectiveness, and discontinuation of MLD and compressive garments. The one-year result will be available in 2024.

The N-LVA study will be an extension of the current study, where patients with CRL of the upper and lower extremity with viable lymph vessels will be included. To compensate for the placebo/sham effect, a double-blind sham-controlled trial is proposed in concordance with *Veelbelovende zorg* (ZonMw) main subsidy provider of this trial.

Study objective

Primary Objective:
The primary objective is to assess the efficacy of LVA surgery in comparison to sham procedure in patients with cancer related lymphedema in the context of improvement of Lymph-ICF score at 12 and 24 months follow up.

Secondary Objectives:
- To assess the effect of LVA on excess limb volume compared to sham procedure;
- To determine the discontinuation rate of conservative treatment after LVA and Sham procedure (the percentage of patients who will be independent of compression stockings and the percentage of patients who will discontinue MLD);
- To assess the cost-effectiveness of LVA.

All endpoints set at 12 and 24 months. All the included patients will be continue followed until the start of the first analysis.
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Study design

A multicenter, double-blinded, randomized sham-controlled trial (RCT). Patients will be included in the Maastricht University Medical Centre, Radboud University Medical Centre, and Erasmus Medical Center. There are two study groups. The first group will receive LVA surgery and the second group will receive a sham surgery. The total duration of the study is 72 months. Inclusion period will take maximally 36 months. The follow-up will last 24 months. The last 6 months will be used for data analysis and writing the end report.
Due to the nature of the study the surgeon performing the both procedures will not be blinded. Both the researcher and/or research nurse and patients will be blinded for the study. The blinded researchers will perform the measurements during follow up.

Intervention

Adult patients with refractory, cancer-related lymphedema in the upper or lower extremity, who are eligible for surgery, will be randomly allocated to one of the two treatment groups:
1. LVA group;
2. Sham group.

Group 1. Lymphaticovenous anastomosis (LVA):
LVA involves anastomosing lymphatic vessels (0.3 to 0.5 millimetres in diameter) to small veins in the subdermal plane to bypass obstructions of the lymphatic transport. The surgical technique follows the technique of other international surgeons.
Before the start of the surgery, the patient will be blinded with noise-cancelling headphones and blindfolds. Then the patient lies comfortably on the operation table, after which the affected limb is prepared for surgery. A limb table is used. Before marking the incision, a mix of bupivacaine (Marcaïne®) and epinephrine (1:100.000) is injected at the site of the incision to achieve local anaesthesia and optimal hemostasis. Based on the ICG lymphangiography mapping, incisions of 1, 5 to 2 cm are made at the

predetermined sites. The incisions are made at the level where the lymphatic vessels are obstructed to prevent any damage to the viable part of the lymphatic system. Using a surgical microscope (25-40x magnification), the lymphatic vessels are visually identified. When a viable lymphatic vessel is identified, it is anastomosed to a similarly sized adjacent recipient venule in the subdermal plane. The anastomoses are usually made in an end-to-end fashion when both the lymphatic vessel and venule have about the same caliber, otherwise, an end-to-side anastomosis is made. The end-to-end anastomoses are created with an 11-0 or 12-0 suture, indicating the need for advanced, supermicrosurgical instruments. The patency of the LVA is confirmed by direct visual examination under the microscope. Generally, 1 to 4 anastomoses are made in a lymphedematous extremity. The superficial wound is closed using uninterrupted, intracutaneous sutures, using 4-0 Monocryl, and is covered with adhesive plasters and a bandage. The total operation time is approximately one to three hours.

Group 2. Sham procedure:
As with the LVA operation, the patient is also blinded during the surgery, using noise-cancelling headphones and a blindfold. The set-up for the surgical floor will be identical to the regular surgery, with a surgical microscope, supermicrosurgical instruments, and designated surgical personnel. Local anesthesia is used to numb the predetermined sites, whereafter a shallow incision of the dermis of 1,5 to 2 cm is made. After the incision, no LVA is made. To mimic the approximate duration of a regular LVA procedure, the sham operation will then take approximately one to one and a half hours. At the end of the procedure, the superficial wound is closed in the same manner as in the LVA procedure; with uninterrupted, intracutaneous sutures, using 4-0 Monocryl and covered with adhesive plasters and a bandage.

Study burden and risks

In the context of the study, the following measurement moments are included:

- Introductory interview: ICG Lymphography to determine whether the candidate is suitable. In patients with lymphedema of the lower extremities, lymphscintigraphy is also performed and possibly an echo Doppler to confirm/exclude the diagnosis.
- First interview with researcher: Lymph-ICF questionnaire and EQ-5D-5L questionnaire (digital), this takes approximately 10 minutes.
Weight, height and other relevant patient characteristics are recorded in the EHR. Circumference measurements with tape measure, this takes 3-5 minutes. Bio-impedant spectroscopy, takes about 15 minutes. Completing the patient diary (digital), takes 5 minutes.
- Intervention: LVA or sham procedure, duration approximately 1.5 hours.
- 3 months follow-up: Lymph-ICF questionnaire and EQ-5D-5L questionnaire (digital). Weight, height and other relevant patient characteristics are recorded in the EHR. Circumference measurements with tape measure. Bioimpedant

spectroscopy. Complete patient diary (digital).
- 6 months follow-up: Lymph-ICF questionnaire and EQ-5D-5L questionnaire (digital). Weight, height and other relevant patient characteristics are recorded in the EHR. Circumference measurements with tape measure. Bioimpedant spectroscopy. Complete patient diary (digital).
- 12 months follow-up: Lymph-ICF questionnaire and EQ-5D-5L questionnaire (digital). Weight, height and other relevant patient characteristics are recorded in the EHR. Circumference measurements with tape measure. Bioimpedant spectroscopy. Complete patient diary (digital). Also ICG Lymphography to assess whether anastomoses are patent.
- 18 months follow-up: Lymph-ICF questionnaire and EQ-5D-5L questionnaire (digital). Weight, height and other relevant patient characteristics are recorded in the EHR. Circumference measurements with tape measure. Bioimpedant spectroscopy. Complete patient diary (digital).
- 24 months follow-up: Lymph-ICF questionnaire and EQ-5D-5L questionnaire (digital). Weight, height and other relevant patient characteristics are recorded in the EHR. Circumference measurements with tape measure. Bioimpedant spectroscopy. Complete patient diary (digital). Also ICG Lymphography to assess whether anastomoses are patent.

Risks:
The lymphscintigraphy examination entails minimal radiation exposure. However, this examination is also part of regular patient care.
With ICG Lymphography, ICG fluid is injected, which can be painful for a short time.
The risk and chance of complications of LVA (and the sham procedure) are low, as the lymph vessels used are already damaged. The healthy lymphatic tissue is spared. Further, the procedure takes place in the subcutaneous layer of the skin to a depth of 1.5 cm. No major vessels or other structures are present at this level, minimizing the risk of bleeding or infection. At the latest, the procedure can be performed under local anesthesia. All things considered, the risks and burden for the patient are low and acceptable.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- 18 years old or older;
- Treated for cancer and underwent treatment of either axillary or inguinal nodes/ or radiotherapy.
- Early stage lymphedema (ISL I-II) in the upper or lower extremity, and diagnosed by lymphoscintigraphy for the lower extremity;
- Unilateral lymphedema;
- Viable lymphatic vessels as determined by indocyanine green (ICG)Lymphography (stage II-III) (23);
- Refractory lymphedema that underwent at least three months of conservative treatment;
- Informed consent.

Exclusion criteria

- History of lymphatic reconstruction in the past 10 years;
- Late-stage lymphedema of the extremity (ISL classification >= II lymphedema) with evident fat deposition and/or fibrosis;
- Patients with active distant metastases, treated with palliative intent;
- Patients with the active treatment of primary cancer, i.e. surgery, radiotherapy, and/or chemotherapy. Note: patients receiving adjuvant targeted and/or endocrine treatment are eligible;
- Edema due to venous insufficiency, evaluated by venous duplex ultrasound of the deep and superficial venous system;

- Active infection in the lymphedematous extremity;
- Bilateral lymphedema;
- Lymphedema present in genital or breast area only;
- Primary lymphedema;
- Non-viable lymphatic system as determined by ICG Lymphography (stages IV and V).

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-12-2023
Enrollment:	110
Type:	Actual

Ethics review

Approved WMO Date:	28-08-2023
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-09-2023
Application type:	First submission

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL84169.068.23