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The N-LVA Study: effectiveness and cost-effectiveness of lymphaticovenous anastomosis (LVA) for patients with cancer who suffer from chronic peripheral lymphoedema – study protocol of a multicentre, randomised sham-controlled trial

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ABSTRACT

Introduction Cancer-related lymphoedema is one of the most debilitating side-effects of cancer treatment with an overall incidence of 15.5%. Patients may suffer from a variety of symptoms, possibly resulting in a diminished health-related quality of life (HRQoL). A microsurgical technique known as lymphaticovenous anastomosis (LVA) might be a promising treatment option. The objective of this study is to evaluate whether LVA is effective and cost-effective compared with sham surgery in improving the HRQoL.

Methods and analysis A multicentre, double-blind, randomised sham-controlled trial conducted in three university hospitals in the Netherlands. The study population comprises 110 patients over the age of 18 years with unilateral, peripheral cancer-related lymphoedema, including 70 patients with upper limb lymphoedema and 40 patients with lower limb lymphoedema. A total of 55 patients will undergo the LVA operation, while the remaining 55 will undergo sham surgery. The follow-up will be at least 24 months. Patients are encouraged to complete the follow-up by explaining the importance of the study. Furthermore, patients may benefit from regular monitoring moments for their lymphoedema. The primary outcome is the HRQoL. The secondary outcomes are the limb circumference, excess limb volume, changes in conservative therapy, postoperative complications, patency of the LVA and incremental cost-effectiveness.

Ethics and dissemination The study was approved by the Medical Ethical Committee of Maastricht University Medical Center on 20 September 2023 (NL84169.068.23). The results will be presented at scientific conferences and published in peer-reviewed medical journals.

Trial registration number NCT06082349.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This multicentre, sham-controlled randomised trial has broad inclusion criteria, allowing patients with lymphoedema following various types of cancer to participate.
⇒ This is a double-blind trial, where both patients and investigators will be blinded.
⇒ Blinding of the plastic surgeons is not possible due to the nature of the interventions.
⇒ The cost-effectiveness analysis adheres to Dutch guidelines for health economic evaluation and may therefore not be directly transferable to other countries.

INTRODUCTION

One of the most debilitating side-effects of cancer treatment is cancer-related lymphoedema (CRL). It is characterised by the progressive accumulation of protein-rich fluid within the interstitial compartment, causing dysfunction of the lymphatic system.[1 2] The fluid overload eventually leads to adipose tissue deposition and fibrosis.[3]

Patients with CRL may experience a high burden of disease. The progressive swelling can lead to sensations of heaviness, pain, paraesthesia, reduced range of motion, weakness and immobility. Furthermore, individuals with CRL have a higher propensity for cellulitis and erysipelas. In addition, patients may also experience a variety of psychosocial symptoms, such as depression, anxiety, and difficulties in social, domestic, vocational, and sexual domains. Altogether, patients with CRL may experience a diminished health-related quality of life (HRQoL)

in comparison with cancer survivors who have not developed lymphoedema.[4–8]

CRL can arise after oncological treatment for several solid tumour types, including breast, melanoma, head and neck, gynaecological and genitourinary malignancies.[9] While it may manifest in various regions of the body, it predominantly affects the upper and lower extremities.[2] The most prevalent form is breast cancer-related lymphoedema (BCRL), occurring in 24–49% of cases after mastectomy and 4–28% after lumpectomy.[10] The overall incidence of CRL is 15.5%, ranging from 10% in genitourinary cancers to 30% in sarcomas, with the highest rates observed in patients receiving additional radiotherapy (31%).[9] Other factors that contribute to the risk of developing CRL include lymph node dissection, obesity, pre-existing medical conditions and genetic predisposition.[11–18] Moreover, the risk of developing lower limb CRL also varies depending on the type of lymph node dissection performed. For melanoma treatment, inguinal lymph node dissection is recommended, whereas gynaecological and prostatic cancer treatments often involve pelvic and para-aortic lymphadenectomy. The latter approach preserves superficial lymph nodes in the limb, resulting in a lower risk of developing lower limb CRL compared with melanoma treatment.[19] In BCRL, the highest risk for the development of lymphoedema is between 12 and 30 months postoperatively. Gynaecological cancers and melanoma exhibit the highest onset frequency after the first year of diagnosis.[18 20–22]

To date, there is no definitive cure for lymphoedema. The gold standard for its treatment remains conservative therapy, consisting of complex decongestive therapy (CDT). CDT aims to ameliorate the symptoms of lymphoedema through bandages, compression garments, manual lymphatic drainage (MLD) and skin therapy. However, CDT requires lifelong maintenance and does not alleviate psychological symptoms. Multiple surgical techniques have been proposed to cure lymphoedema, however, with significant limitations.[23] Among these techniques is lymphaticovenous anastomosis (LVA), a microsurgical technique that has been refined throughout decades, particularly after the introduction of super-microsurgery by Koshima *et al*.[24] The LVA is a bypass between lymphatic vessels (ranging from 0.3 mm to 0.8 mm in diameter) and adjacent subcutaneous veins of similar size. The objective of LVA surgery is to partially restore the blockage in the lymphatic system, reduce volume, minimise skin infections, reduce the need for conservative therapy, and most importantly, improve the patients' HRQoL.[25–27]

Several studies have evaluated the effectiveness of LVA surgery in treating lymphoedema. In a meta-analysis by Nacchiero *et al*,[27] a significant positive effect of LVAs in treatment of lymphoedema was reported, with a combined OR of 0.07 (95% CI: 0.04 to 0.13, p<0.001). Only six of the included studies were clinical trials, none of which had a control group, and their pooled analyses resulted in an OR of 0.34 (95% CI: 0.14 to 0.81, p<0.01).[27] In a systematic review by Verhey *et al*,[28] an objective improvement after LVA (eg, volume reduction), ranging from 23.3% to 100%, was reported in patients with lower limb lymphoedema. The greatest degree of improvement was seen in patients with early-stage lymphoedema.[28] Similarly, a review by Cornelissen *et al*[29] on the effectiveness of LVA in BCRL reported improvement rates on circumference and volume measurements, ranging from 50% to 100%.[29] Nonetheless, it is important to note that available studies are small and non-randomised. According to a systematic review by Rosian and Stanak,[30] the evidence supporting the effectiveness of LVA is 'very low'. The review emphasises methodological shortcomings in the available evidence and concludes that no definite conclusions can yet be drawn regarding the effectiveness of LVA surgery.[30]

The first multicentre randomised controlled trial (RCT) evaluating the (cost-)effectiveness of LVA compared with CDT in patients with BCRL, 'the Dutch LYMPH trial', is presently ongoing.[31 32] The current study, 'the N-LVA Study', is a continuation of 'the Dutch LYMPH trial' and compares LVA surgery with sham surgery. The main goal of 'the N-LVA Study' is to assess whether LVA surgery is effective in comparison with sham surgery. A sham-controlled trial is chosen as the best possible comparator to investigate the true effect of LVA surgery and to examine whether there is a placebo effect.

METHODS AND ANALYSIS

Study design

'The N-LVA Study' is a multicentre, double-blind, RCT conducted at Maastricht University Medical Center, Radboud University Medical Center and Erasmus University Medical Center in the Netherlands. A total of 110 patients with CRL will be recruited at the outpatient clinic of the participating hospitals: 70 patients with upper limb lymphoedema and 40 patients with lower limb lymphoedema. The inclusion and exclusion criteria are shown in table 1. The coordinating researcher or research nurse obtains written informed consent (see online supplemental data I for the informed consent form). After inclusion, the patients will be randomised into one of the two treatment groups with a 1:1 allocation through the electronic case report form (eCRF) in Castor EDC. The randomisation will be stratified per limb (upper/lower). The investigator, research nurse and patients will be blinded throughout the duration of the trial. Due to the nature of the study, the surgeons cannot be blinded. The start date of the study is December 2023 and the anticipated completion date is March 2029. The final version of the protocol is V.5, dated 28 August 2023. The protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials 2013 statement[33] (see online supplemental data II for the checklist). A flow chart of the study design is shown in figure 1.

Sample size calculation

The sample size calculation was performed to be able to detect a clinically relevant difference in the score on

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
► Adult patients (18 years or older) ► Cancer treatment with treatment of either the axillary or inguinal lymph nodes with/without radiotherapy ► Early stage lymphoedema of the upper or lower limb (stage 1–2 on the ISL classification) as diagnosed by lymphoscintigraphy for the lower limb ► Unilateral lymphoedema ► Viable lymphatic vessels as determined by ICG lymphography (stage II–III on the ICG classification)[53] ► At least 3 months of conservative therapy (refractory lymphoedema) ► Informed consent	► History of lymphatic reconstruction in the past 10 years ► Late-stage lymphoedema of the upper or lower limb (stage >2 on the ISL classification) with evident fat deposition and/or fibrosis ► Bilateral lymphoedema ► Non-viable lymphatic vessels as determined by ICG lymphography (stage IV and V on the ICG classification)[53] ► Active treatment of primary cancer, that is, surgery, radiotherapy and/or chemotherapy. *Note: patients receiving adjuvant targeted and/or endocrine treatment are eligible* ► Active distant metastases and receiving treatment with palliative intent ► Lower limb oedema due to venous insufficiency as determined by echo-Doppler examination of the deep and superficial venous system ► Active infection of the lymphoedematous limb ► Lymphoedema in the genital or breast area only ► Primary lymphoedema

ICG, indocyanine green; ISL, International Society of Lymphology.

the Lymphedema Functioning, Disability and Health (Lymph-ICF) Questionnaire between groups at 24-month follow-up. A difference in Lymph-ICF score of 15 points for the upper limb and 20 points for the lower limb is deemed clinically relevant, with an estimated SD of 20 points.[34 35] Because of the difference in cut-off point per limb, the randomisation is stratified and analysed separately based on the location of lymphoedema. Using an alpha of 0.05, the following sample size was calculated to achieve a power of 80%: for the upper limb, a minimum of 28 patients per group is required, resulting in a total of 56 patients. To account for a potential drop-out rate of 20%, a total of 70 patients is included. For the lower limb, a total of 16 patients is needed per group, totalling 32 patients. Taking a potential drop-out rate of 20% into account, 40 patients will be included. Drop-outs will not be replaced. Altogether, 110 patients will be included in this study, that is, 55 patients per treatment group with a 1:1 allocation.

CDT protocol

All eligible patients must undergo at least 3 months of CDT prior to inclusion. Throughout the duration of the study, patients are encouraged to continue CDT, as it is considered as standard care. If the patient does not already have a dedicated lymphoedema therapist for CDT, the patient will be referred by the investigator. The patients already undergoing CDT can continue their therapy as accustomed. Generally, patients in the Netherlands are treated according to the Dutch and German guidelines for CDT, referred to as the 'Verdonkmethod' and 'Asdonkmethod', respectively.[36 37] CDT involves two phases. In phase 1, the goal is to reduce swelling through compression bandaging and MLD. In phase 2, after the swelling of the limb is sufficiently reduced, patients are fitted with a compression garment.[36 38] To provide a structured framework for lymphoedema therapists, standardised treatment protocols have been developed for both upper and lower extremities, adhering to the aforementioned guidelines. See online supplemental data III and IV for the CDT protocols of the upper and lower limbs, respectively. However, therapists can determine the appropriate frequency accordingly. Patients can document details regarding conservative treatment through a digital patient survey.

Preoperative protocol

At the outpatient clinic, patient eligibility is determined by assessing the indocyanine green (ICG) stage and identifying viable lymphatic vessels through near-infrared fluorescence (NIRF). Injections are prepared by dissolving 25 mg of ICG into 5 mL 'water for injection', to obtain a concentration of 5 mg/mL. For diagnostics of the upper extremity, 0.1 mL is injected intradermally into both the second and fourth web spaces, and 0.2 mL in both the first and fourth web spaces of the affected lower limb. Using NIRF, viable lymphatic vessels are outlined with a surgical marker, and the incision site for the LVA or sham procedure is determined. Afterwards, a colour photo is taken of the marked limb, positioned alongside a measuring tape. During surgery, the photo is used as a reference for the incision site for the LVA or sham surgery.

Surgical protocol

Group A: LVA

Preoperatively, the patient is placed in supine position. The affected limb is positioned and sterilised for surgery. During surgery, the patient is then blinded by concealing the surgical area with a surgical drape to prevent the patient from observing. The patient is also fitted with

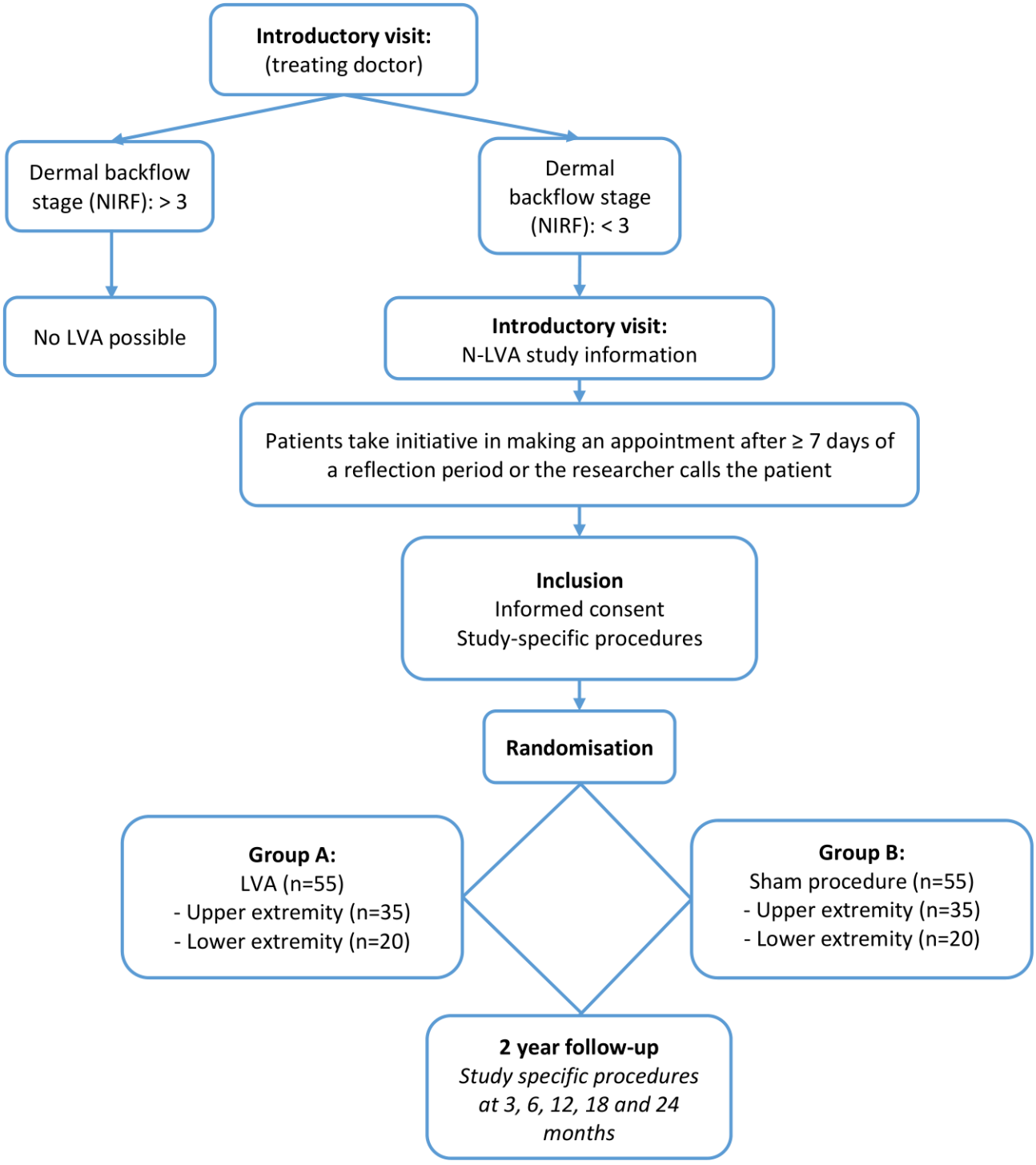

Figure 1 Overview of the study design. LVA, lymphaticovenous anastomosis; NIRF, near-infrared fluorescence.

noise-cancelling headphones to block out the medical personnel's communication. The incision site or sites are marked at the predetermined locations. Local anaesthesia and hemostasis are achieved by injecting epinephrine and bupivacaine (1:100.000) at the site of the incision. Incisions of 1.5–2 cm are made in the subdermal plane at the marked location. Using a surgical microscope (25–40× magnification), the subdermal lymphatic vessels and veins are identified and anastomosed. When the calibre of the lymphatic vessel and the vein is congruent, the LVA is performed in an end-to-end fashion; otherwise, an end-to-side anastomosis is made. The anastomosis is created using 11-0 or 12-0 Ethilon sutures. Generally, one to four LVAs are made during one procedure. The superficial wound is closed using uninterrupted, intracutaneous sutures with 4-0 Monocryl or transcutaneous sutures with 5-0 Ethilon, according to the surgeon's preference. Once the wounds are closed, the headphone and blindfolds are taken off and the patient is provided with postoperative care instructions. The total operation time

is approximately 90–120 min. The plastic surgeon will document the procedure in the electronic patient file.[39]

Group B: sham surgery

Upon the patient's arrival in the operating room, the setup will be identical to that of the LVA operation, with the microscope prepared, designated surgical personnel present and all the necessary super-microsurgical instruments readily displayed. The patient lies comfortably on the operation table, after which the affected limb is prepared for surgery. The patient is prepared for surgery and blinded in nearly the exact same manner as in the LVA operation, with two exceptions. First, based on preoperative photos, the incision site is marked 2 cm adjacent to (one of) the predetermined site(s) to avoid damage to the lymphatic vessels as to allow for future LVA surgery. Second, rather than performing the actual operation, the plastic surgeon simulates the procedure by applying pressure with anatomical forceps in the surgical area. To mimic the approximate duration of a regular LVA procedure, the total operation time is approximately 90–120 min. The superficial wound is closed using the same technique as in the LVA procedure. Following surgery, the patient is provided with postoperative care instructions specifically for LVA surgery.

Postoperative protocol

The postoperative protocol is identical for both groups. After surgery, the limb is bandaged for at least 3 days. Afterwards, compression therapy can be resumed, according to the patient's regimen. Patients are instructed not to receive any kind of MLD directly at the level of the surgical wound in the first 4 weeks after surgery. If needed, the sutures can be removed by the general practitioner or nurse. Strenuous physical activity is not recommended until after the first 6 weeks.

Outcomes

The primary outcome is change in HRQoL. The secondary outcomes are change in limb circumference and excess limb volume, changes in conservative therapy, postoperative complications, patency of the LVA, costs, generic HRQoL and incremental cost-effectiveness. The follow-up period is at least 24 months; thereafter, a subset of patients will partake in the extended follow-up, which will take place annually. The extended follow-up will involve a maximum of three additional annual visits. All outcomes, except for LVA patency, are measured at baseline, 3, 6, 12, 18 and 24 months postoperatively, followed by an annual assessment during the extended follow-up. The assessment of LVA patency is performed by the plastic surgeon or technical physician and occurs solely after 12 and 24 months and annually during the extended follow-up. The patient survey is additionally sent out at 9 and 15 months. All follow-up measurements are recorded in the eCRF within Castor EDC, and digital questionnaires are automatically sent through the eCRF.

Primary outcome

Health-related quality of life

The primary endpoint is HRQoL, measured by the Dutch version of the Lymph-ICF Questionnaire (2019) after 24 months. The Lymph-ICF is a validated, disease-specific questionnaire to asses impairments in daily function, activity limitations and participation restrictions. There are two versions of the Lymph-ICF: one for the upper limb and one for the lower limb, consisting of 29 and 28 questions, respectively. Questions are categorised across five domains, namely physical function, mental function, household activities, mobility activities, and life and social activities. Each question is scored on a Visual Analogue Scale from 0 to 100. The total score is equal to the sum of the individual question scores, divided by the total number of questions answered. A decrease in score represents an improvement in HRQoL.[34 35]

Secondary outcomes

Limb circumference

The limb circumference is measured at fixed points using measuring tape. The upper limb is measured at the olecranon, 5 and 10 cm above and below the olecranon, at the wrist and at the dorsum of the hand. For the lower limb, measurements are taken at the superior edge of the patella, 10 and 20 cm above and below the patella, at the lateral malleolus and on the dorsum of the foot. The Upper and Lower Limb Lymphedema Indexes are derived from these measurements and are adjusted for body mass index.[40 41]

Excess limb volume

Excess limb volume is measured through BioImpedance Spectroscopy, a method that measures the electrical impedance of tissues to an electric current. This makes it possible to measure the excess limb volume and quantify the amount of fluid in different body compartments.[42] Both the absolute excess limb volume in the affected limb and the relative difference in excess limb volume compared with the unaffected limb are calculated to evaluate the effect of the LVA operation. A clinically relevant difference between the LVA and sham groups is indicated by the minimal clinically important difference of a 20% reduction in excess limb volume. For accurate measurements, patients are expected not to eat or drink 1 hour before the measurement and should have an empty bladder.

Monitoring of conservative therapy

The changes in conservative therapy are assessed through an electronic patient survey to record the frequency of treatments received (ie, skin therapy visits, number of compression garments, etc).

Postoperative complications

All postoperative complications are recorded to monitor safety.

Patency of the LVA

NIRF is used to assess the patency of the LVAs, as well as to determine the ICG stage based on the extent of dermal backflow.

Costs, generic HRQoL and cost-effectiveness

Costs related to lymphoedema are measured by assessing individual-level healthcare resource use, out-of-pocket expenses, use of informal care and productivity loss. Examples of cost categories included are intervention costs, costs for outpatient clinic visits, diagnostic procedures, hospital admissions, visits to the general practitioner, lymphoedema therapist, other allied healthcare professionals, and home care services.

Hospital-related care data are extracted from the hospital information system. For all other costs, patients complete the adapted version of the iMTA Medical Consumption Questionnaire and the iMTA Productivity Cost Questionnaire.[43–45] To calculate the patient's total costs, the volume of resource use, per cost category, is multiplied by the Dutch cost price using reference prices provided by the Dutch guidelines for cost analysis in healthcare.[46]

Generic HRQoL is assessed by the EQ-5D-5L.[47] The Dutch tariff is used to calculate utility scores that are used as input for the quality-adjusted life year (QALY).[48] Cost-effectiveness is expressed in an incremental cost-effectiveness ratio (ICER), that is calculated by dividing the difference in the costs between LVA and sham surgery by the difference in QALYs.

Data analysis plan

All analyses will be performed according to the intention-to-treat principle. In case of over 5% of incomplete records, data will be imputed using multiple imputation with fully conditional specification to prevent loss of precision and to reduce the likelihood of bias.

Baseline characteristics will be stratified by location and by treatment arm, and reported as mean and SD for continuous variables, and count and percentage for categorical variables. In case continuous variables are skewed, we will use the median and first and third quartiles to summarise the distribution.

The paired samples t-test will be used to assess changes in Lymph-ICF scores within each group (upper and lower limb, and treatment allocation) from baseline to 12 and 24 months. Between-group differences will be compared using the independent-samples t-test. In case of baseline imbalance, differences per follow-up moment will be computed using multivariable linear regression analysis, adjusted for the offending baseline characteristics. Linear mixed-effects regression will be used to analyse longitudinal changes over the follow-up period and compare both groups, with a random intercept on group and slope for time. The variance–covariance matrix for random effects will be left unstructured. The correlation of measurements over time will be simplified using an autoregressive model of order 1. Should model convergence issues occur, an alternative will be sought that results in the lowest Akaike Information Criterion. Regarding the secondary outcome measures, besides cost-effectiveness analyses, the same between-group statistical analysis will be performed. The occurrence of post-operative complications and the patency of the LVAs will be described as count and percentage, and compared between groups using Pearson's X^2 test. In case of low expected cell counts, Fisher's exact test will be used. In the presence of baseline imbalance, we will use multivariable logistic regression analysis and present results as OR with 95% CI.

Economic evaluation

A trial-based economic evaluation will be performed from a societal perspective and with a time horizon of 2 years to assess the cost-effectiveness of LVA compared with sham surgery, adhering to the Dutch guidelines for health economic evaluation.[49]

The cost-effectiveness analysis will be conducted according to the intention-to-treat principle. Missing cost and effect data will be imputed using multiple imputation methods.[48] Each of the imputed datasets will be analysed separately and results are pooled using Rubin's rules.

Cost-effectiveness will be expressed in an ICER: the incremental costs per QALY. Cost and QALY differences are estimated using regression analysis, and are adjusted for baseline differences. To address the uncertainty surrounding the differences in costs and effects, non-parametric bootstrapping with 5000 replications is used and the bootstrapped cost and effect pairs are plotted on a cost-effectiveness plane. If relevant, the ICER is calculated by dividing the difference in costs by difference in QALYs. A cost-effectiveness acceptability curve will visualise the probability that LVA is cost-effective for a range of willingness-to-pay thresholds. The impact of uncertainty surrounding deterministic parameters (eg, cost prices) will be explored using one-way sensitivity analyses. Additionally, scenario analyses will explore the impact on the ICER when a healthcare perspective is taken and when a per-protocol analysis is used.

Subgroup analyses will be performed for patients with upper limb lymphoedema and patients with lower limb lymphoedema, to address possible heterogeneity. Finally, a Budget Impact Analysis is performed to analyse the financial consequences related to implementing LVA in the Netherlands.[49]

Ethics and dissemination

Data monitoring

Data will be handled confidentially and will remain at the research site at all times. The investigator will store the source data in a locked place. Follow-up data will be stored in the online database of Castor EDC. Only the principal investigator, site investigators and coordinating investigator will have access to this database with a password-secured account. The investigators will only be granted access to data from their own centre. An

independent investigator will perform the randomisation within Castor EDC and will only have access to the randomisation section within the database. Identifying data will be stored in coded form and the key will only be known to the principal investigator, coordinating investigator, site investigators, study monitors, members of the review committee and the Dutch Health Care Inspectorate. Processing data will take place in accordance with the European Union General Data Protection Regulation and the Dutch Act on implementation of the General Data Protection Regulation.[50 51]

No data monitoring committee will be appointed, as the study is classified as low risk. Additionally, no interim analyses will be performed.

Harms

LVA is a minimally invasive operation with a low risk and complication rate. The risks are low because the lymphatic vessels that are used are already damaged at the level where the LVAs are made. Furthermore, the incision that is made is small and superficial, approximately 1.5 cm in depth. At this level, no big vessels or other structures are present. The risks of both the LVA and sham procedures are surgery related and include wound infection, minor bleeding, wound (healing) problems, and skin reaction to plasters or bandages. Risks are further minimised by operating under local anaesthesia. Adverse events (AEs) will be documented in the eCRF and serious AEs will be directly reported to the sponsor.

Auditing

The Clinical Trial Center Maastricht will frequently monitor the study's progress in accordance with their protocol, as is requested by the board.

Research ethics approval

Ethical approval was obtained in September 2023 from the Medical Ethical Committee Academic Hospital Maastricht/Maastricht University (NL84169.068.23/METC 23-023). This approval is valid for all participating centres. This study will be conducted according to the principles of the Declaration of Helsinki, recently changed in Fortaleza (2013), and in accordance with the Medical Research Involving Human Subjects Act.[52]

Protocol amendments

All amendments will be made in consultation with all participating centres and the Medical Ethical Committee that gave a favourable opinion will be notified.

Patient and public involvement

A consultation group with professional and patient associations involved will meet annually throughout the duration of the study to provide feedback.

Dissemination policy

The study is registered in the trial register at www.clinicaltrials.gov with trial registration number NCT06082349. The results will be presented at scientific conferences and published in peer-reviewed medical journals. Requests for data sharing will be assessed individually, considering them for appropriate research purposes after the completion of the trial and publication of primary manuscripts.

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Contributors The study was conceptualised and designed by YMJJ, HT, RvdH, DV, SH and SSQ. SvK provided statistical expertise and MK provided cost-effectiveness expertise. AK, YMJJ, DV, SH and SSQ finalised the study design and protocol. All authors collaborated on refining the study protocol and approved the final version.

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Disclaimer Results will be published regardless of the outcomes at the end of the study, independent of the funding provider.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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Radboudumc Maastricht UMC+ Erasmus MC Universitair Medisch Centrum Rotterdam

Bijlage D: toestemmingsformulier proefpersoon

Behorende bij de Nederlandse lymfechirurgie (LVA) studie.

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn goed genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen met het onderzoek. Of om ermee te stoppen. Ik hoef dan niet te zeggen waarom ik wil stoppen.
- Ik geef de onderzoeker toestemming om mijn huisarts en/of specialist die mij behandelt te laten weten dat ik meedoe aan dit onderzoek.
- Ik geef de onderzoeker toestemming om mijn informatie op te vragen bij mijn huisarts en/of specialist die mij behandelt over mijn medisch verleden, allergieën en medicatie.
- Ik geef de onderzoeker toestemming om mijn huisarts of specialist informatie te geven over onverwachte bevindingen uit het onderzoek die van belang zijn voor mijn gezondheid.
- Ik geef de onderzoeker toestemming on mijn gegevens te verzamelen en gebruiken. De onderzoekers doen dit alleen om de onderzoeksvraag van dit onderzoek te beantwoorden.
- Ik weet dat voor de controle van het onderzoek sommige mensen al mijn gegevens kunnen inzien. Die mensen staan in deze informatiebrief. Ik geef deze mensen toestemming om mijn gegevens in te zien voor deze controle.
- Ik weet dat ik niet zwanger mag worden tijdens het onderzoek.
- Wilt u in de tabel hieronder ja of nee aankruisen?

Ik geef toestemming om mijn gegevens te bewaren om dit te gebruiken voor ander onderzoek, zoals in de informatiebrief staat.	Ja ☐	Nee☐
Ik geef toestemming om mij eventueel na dit onderzoek te vragen of ik wil meedoen met een vervolgonderzoek.	Ja ☐	Nee☐
Ik geef de onderzoekers toestemming om na het onderzoek te laten weten welke behandeling ik heb gehad/ in welke groep ik zat.	Ja ☐	Nee☐

- Ik wil meedoen aan dit onderzoek.

Mijn naam is (proefpersoon): ……

Handtekening: …… Datum : __ / __ / __

Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.

Wordt er tijdens het onderzoek informatie bekend die die de toestemming van de proefpersoon kan beïnvloeden? Dan laat ik dit op tijd weten aan deze proefpersoon.

Naam onderzoeker (of diens vertegenwoordiger):……

Handtekening:…… Datum: __ / __ / __

De proefpersoon krijgt een volledige informatiebrief mee, samen met een getekende versie van het toestemmingsformulier.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	8
Funding	#4	Sources and types of financial, material, and other support	21
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	21
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18-20
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants,			

interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-13
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a, patients are allocated to one group and will receive either lymphaticovenous anastomosis or sham surgery
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-13
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each	13-16

		outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8, 13
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8, 19
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8, 18-19

Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	18-19
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8, 18-19
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a, the risk of the study was classified as 'negligible' , emergency unblinding is therefore not necessary
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-16
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).	18-19

		Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-18
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-18
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16-18
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a, the risk of the study was classified as 'negligible', a DMC was therefore not assigned
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	20
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18-19
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20-21

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20-21
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	20-21
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20-21
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental data I
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

Notes:

- 11b: n/a, patients are allocated to one group and will receive either lymphaticovenous anastomosis or sham surgery
- 17b: n/a, the risk of the study was classified as 'negligible' , emergency unblinding is therefore not necessary
- 21a: n/a, the risk of the study was classified as 'negligible', a DMC was therefore not assigned This checklist was completed on 07. March 2024 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

Supplemental data – Protocol CDT for the upper limb

Protocol for Complex Decongestive Therapy (CDT) for the upper limb

The first phase of CDT, or *initial treatment phase*, entails general skin care, manual lymphatic drainage, exercises aimed at improvement of mobility/range of motion and compression therapy using bandages. The second phase of CDT, or *maintenance phase*, aims to sustain the reduced limb volume attained during the initial phase. This is achieved through compression therapy using a therapeutic elastic stocking for the arm. Skincare, mobility exercises, and manual lymphatic drainage (MLD) may be continued in this phase as necessary.

Patients must have had at least three months CDT before randomization

Manual lymphatic drainage (MLD)
This is the manual stretching and pressure application to the skin in slow, rhythmic and circular motions to stimulate the activity in the lymphatic vessels to increase lymphatic fluid drainage. The pressure applied is adjusted to the type of edema. The MLD techniques are designed to stimulate lymph flow from distal to proximal lymphatics. The goal of MLD is to re-route the flow of stagnated lymphatic fluid around obstructed or blocked areas into the more centrally located healthy lymphatic vessels. The lymphatic fluid eventually drains into the venous system.

Skin care
Cleansing of the skin with a pH-neutral product and application of a perfume-free, pH-neutral cream to the skin of the patient.

Pre-treatment of the neck-shoulder region
The patient is in supine position.

- Start at the supraclavicular lymph nodes in direction of the terminus;
- Continue towards the sternocleidomastoid muscle, bilaterally;
- Proceed towards the axillary lymph nodes, following the direction of the central, lateral and subscapular lymphatics.

Treatment of the flank

- Start from the infra-clavicular region, moving from the sternum distally towards the axilla using the “anastomosis hold”;
- Proceed towards the pectoralis muscle, proceeding medially and distally towards the axilla;
- Move from the breast area distally towards the flank;
- Follow the intercostal space and proceed to the parasternal space;
- On the contralateral side, start from the parasternal region and then move to the intercostal region;
- Apply the “anastomosis grip” across the sternum towards the contralateral axilla;

The patient transitions from a supine position to a flank position with the skin therapist seated behind, positioning the scapula in protraction.

- Continue the drainage towards the contralateral side;
- Continue from the trans-dorsal anastomosis towards the axilla of the contralateral side.

Supplemental data – Protocol CDT for the upper limb

Treatment of the arm

The patient returns to a supine positon.

- Conduct drainage on the upper arm, both ventrally and dorsally, towards the supra- and sub-clavicular lymph nodes, respectively;
- Continue with drainage ventrally at the deep cubital (*cubitales profundi*) and dorsally towards the superficial cubital (*cubitales superficiales)*.

Treatment of the hand

- Apply the “carpal tunnel hold” for drainage of the hand;
- Drain the dorsal side of the hand towards the dorsal side of the underarm;
- Drain the palmar side of the hand towards the ventral side of the underarm;
- Direct the fingers and thumb towards the dorsal side of the underarm.

Finish the treatment at the neck

Note: In case of fibrosis, apply the “fibrosis hold”.

Compression therapy: multi-layered bandaging

- Apply padding on the hand, fingers and arm with cotton tricot, synthetic wool (10 cm width), and gauze bandaging (4 cm width). Use a pressure pad in case of edema, and secure the padding with tape;
- Apply a 6 cm short stretch bandage, starting at the wrist, covering the hand and underarm;
- Apply a 10 cm short stretch bandage, starting at the wrist progressing proximally, bandaging clockwise;
- Apply another 10 cm short stretch bandage, starting at the wrist and moving towards the proximal region, bandaging counterclockwise;
- The bandage should only be removed during the next treatment session by the skin therapist.

Frequency and duration of conservative treatment

- CDT Phase 1 will continue for 6 weeks, occurring three times a week, with each session lasting 45 minutes (30 minutes MLD and 15 minutes for skincare, compression therapy, and exercises);
- In CDT Phase 2, measure the arm for a therapeutic elastic stocking (pressure class 2). Additionally, continue CDT as in Phase 1: twice a week in weeks 7 and 8, and once a week from weeks 9 to 12.

Supplemental data – Protocol CDT for the lower limb

Protocol for Complex Decongestive Therapy (CDT) for the lower limb

The first phase of CDT, or *initial treatment phase*, entails general skin care, manual lymphatic drainage, exercises aimed at improvement of mobility/range of motion and compression therapy using bandages. The second phase of CDT, or *maintenance phase*, aims to sustain the reduced limb volume attained during the initial phase. This is achieved through compression therapy using a therapeutic elastic stocking for the arm. Skincare, mobility exercises, and manual lymphatic drainage (MLD) may be continued in this phase as necessary.

Patients must have had at least three months CDT before randomization

Manual lymphatic drainage (MLD)
This is the manual stretching and pressure application to the skin in slow, rhythmic and circular motions to stimulate the activity in the lymphatic vessels to increase lymphatic fluid drainage. The pressure applied is adjusted to the type of edema. The MLD techniques are designed to stimulate lymph flow from distal to proximal lymphatics. The goal of MLD is to re-route the flow of stagnated lymphatic fluid around obstructed or blocked areas into the more centrally located healthy lymphatic vessels. The lymphatic fluid eventually drains into the venous system.

Skin care
Cleansing of the skin with a pH-neutral product and application of a perfume-free, pH-neutral cream to the skin of the patient.

Treatment of the leg with intact inguinal lymph nodes and after sentinel node procedure

1. *Pre-treatment:*

- Begin with the treatment of the neck-shoulder region. The patient lies in a supine position: start at the supraclavicular lymph nodes in the direction of the terminus.
- Continue towards the sternocleidomastoid muscle bilaterally, concluding at the terminus.

2. *Abdominal breathing exercise*:

The patient is in supine positon with the knees bent, feet flat on the ground.

- Instruct the patient to inhale calmly through the nose 16 times, allowing the abdomen to rise, and exhale slowly through the mouth, letting the abdomen descend.
- The patient should repeat this abdominal breathing exercise 1 to 2 times daily.

3. *Treatment of the front side of the leg*

- Begin with the inguinal lymph nodes. These are located in the femoral triangle. Perform standing circles, 4 next to 4, with two starting laterally and 3 starting medially;
- Continue with the thigh, making coordinated thumb-hand circles in multiple lanes. Start medially, then make transverse strokes in multiple lanes;
- Continue with the knee, performing transverse strokes on the medial side;
- Make alternating thumb-circles around the patella in multiple lanes, 4 next to 4 circles of the patella;
- Continue with the popliteal lymph nodes, perform standing circles in the popliteal fossa;
- Continue with the lower leg, making alternating thumb-hand circles on the calf and transverse strokes on the lower leg;
- Continue with the ankle area by making 4-finger circles on the Achilles tendon simultaneously with both hand, lateral and medial, in the recesses along the Achilles

tendon. Make alternating thumb circles between the medial and lateral malleoli in multiple lanes;
- Continue with the dorsum of the foot with alternating thumb-circles in multiple lanes. Treat the sole of the foot if there is edema;
- Perform the "hallux (big toe) grip", perform transverse strokes, 3 starting points;
- Finish with the toes, perform transverse strokes, no direct pressure with the other hand.

4. *Treatment of the back side of the leg*

- Begin with the inguinal lymph nodes, perform finger circles, 4 next to 4;
- Continue with the thigh, making coordinated thumb-hand circles lengthwise in multiple lanes. Then make transverse strokes in multiple lanes;
- Continue with the knee, performing modified transverse strokes on the medial side;
- Continue with the popliteal fossa, making alternating coordinated thumb-hand circles in multiple lanes through the popliteal fossa, standing circles hand over hand in the popliteal fossa;
- Continue with the lower leg, making alternating coordinated thumb-hand circles lengthwise in multiple lanes, as well as transvers strokes in multiple lanes;
- Continue with the Achilles tendon by making thumb circles medially and laterally along the tendon;
- Finish by making simultaneous alternating thumb circles under the sole of the foot and thumb thumb circles on the heel with the thumbs pointing cranially.

Treatment of secondary lymphedema in the leg

1. *Drainage area*

- Neck;
- Axillary lymph nodes (on the same side);
- Flank: transverse strokes in the flank from the leg towards the axillary lymph nodes;
- Abdominal treatment (excluding maneuvers in the irradiated area);
- Inguinal lymph nodes (non-affected side);
- Pubic bone: 4 next to 4 circles over the pubic bone towards the non-affected side;
- Axillary lymph nodes (on the same side);
- Transverse strokes in the flank towards the axillary lymph nodes;
- Gluteal area (on the same side): coordinated thumb-hand circles towards the axillary lymph nodes, 4 next to 4 finger circles towards the axillary lymph nodes.

2. *Edema border area*

- All familiar maneuvers can be applied here. We consider collateral drainage possibilities and treat from the cleared groin area.

3. *Edema area*

- Perform edema and fibrosis maneuvers on the affected leg.

Frequency and duration of conservative treatment

- CDT Phase 1 will continue for 6 weeks, occurring three times a week, with each session lasting 45 minutes (30 minutes MLD and 15 minutes for skincare, compression therapy, and exercises);
- In CDT Phase 2, measure the arm for a therapeutic elastic stocking (pressure class 2). Additionally, continue CDT as in Phase 1: twice a week in weeks 7 and 8, and once a week from weeks 9 to 12.