Lymphovenous anastomosis for breast cancer-related lymphedema: A cohort study

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Introduction

Lymphedema remains a significant concern for breast cancer patients, undergoing cancer treatment.(1) It is a chronic and gradually developing condition with swelling of the arms and hands due to excessive fluid in the interstitium.(2) In addition to this increased volume, many patients experience pain, sensory disturbances, arm heaviness, frequent infections, restriction in their range of motion and a negative impact on their quality of life and bodily image. (1,3,4) Despite efforts to address this condition using conservative approaches like decongestive therapy and physical therapy, the need for effective treatment options persists. (5–7) Surgical treatments are currently being carried out worldwide, in an attempt to improve the treatment of lymphedema. Lymphovenous anastomosis (LVA) is one of these surgeries, a super-microsurgical reconstructive intervention.(2) By bypassing the lymphatic system, using patients own venules through super-microsurgical anastomosis, the aim is to restore the lymphatic drainage.(8) It has shown promising results and is gaining popularity worldwide. Despite this increasing popularity, there is still a lack of proper studies of its actual effect. Therefore, further studies with a systematic approach are in demand. (2,9–12)

The aim of this single-armed cohort study is to assess the effect of LVA in breast cancer related lymphedema. In order to evaluate the effect of LVA, we need to test if LVA leads to reduced arm volume by comparing preoperative volume to postoperative volumes, and improvement in quality of life. The study is conducted at Odense University Hospital, Lillebælt Hospital Vejle, Roskilde Hospital and Herlev Hospital, and builds upon the experiences and outcomes gained from our pilot study at Odense University Hospital.

We hope to improve and add knowledge to this field of research through local and national collaboration in Denmark. Another goal is to implement the patient group in the Department of Plastic Surgery at Odense University Hospital, as lymphedema patients is a partly neglected patient group.

Method

This is a multi-center cohort study investigating the effect of LVA for treatment of pitting lymphedema. The study population consists of adult, female patients with upper extremity pitting lymphedema secondary to breast cancer treatment, see table 1 for inclusion criteria. Patients referred to the Departments of Plastic Surgery at Odense University Hospital, Lillebælt Hospital Vejle, *, Zealand University Hospital Roskilde* and Herlev Hospital for clinical assessment of their lymphedema will be invited to participate in the study, if they are deemed suitable for LVA surgery by the consulting surgeons. Patients will receive both oral and written information regarding the study by their surgeons and are given the possibility of withdrawal at any time. Only patients who provide written, informed consents will be enrolled in the study. Patients provide their consent to engage in the study and for the investigators to access their medical records to obtain demographic personal data. The consent gives the trial manager, sponsor and sponsor's representatives as well as any supervisory authority direct access to obtain information in the patient's medical record, including electronic medical records, in order to see information about the subject's health, which is necessary as part of the implementation of the research project and for control purposes, including self-control, quality control and monitoring, which they are obliged to carry out.

Inclusion criteria
• *Age >18* • *Female* • *Unilateral arm lymphedema secondary to breast-cancer treatment*

• *Active pitting lymphedema* • *Presence of dermal backflow in indocyanine green lymphography* • *Identifiable lymphatic vessel(s) in the affected arm using an infrared camera and indocyanin green* • *Able to provide informed consent* • *Able to read, understand and complete Danish questionnaires*

Table 1: Inclusion criteria

Patients will be included in the outpatient by the operating surgeon. Following inclusion the patient will be examined in the outpatient clinic prior to LVA surgery for baseline measures, and at six- and twelve months follow-up, were data will be collected, see figure 1. The primary outcome measure is changes in arm volume measured by water displacement volumetry and arm circumferential measurements. Both the volume of the affected and healthy arms will be measured, thereby employing the patients as their own reference for comparison. (13)
Secondary outcome measures include:

1) Changes in body compositions measured with bioimpedance
2) Changes in health-related quality-of-life measured with LYMPH-Q
3) Changes of arm function measured with DASH
4) Changes in general quality-of-life measured with SF-36
5) Patency of anastomosis validated by ICG lymphography
6) Changes in ICG lymphography image
7) Changes in arm fibrosis measured with SkinFibroMeter

The primary investigator, or other project staff trained in the measurement methods, will see participants at baseline and follow-up consultations at six- and twelve months. Questionnaires will be sent to the patient online at baseline, and three-, six-, nine- and twelve months. Collected data will be entered into a secure database.

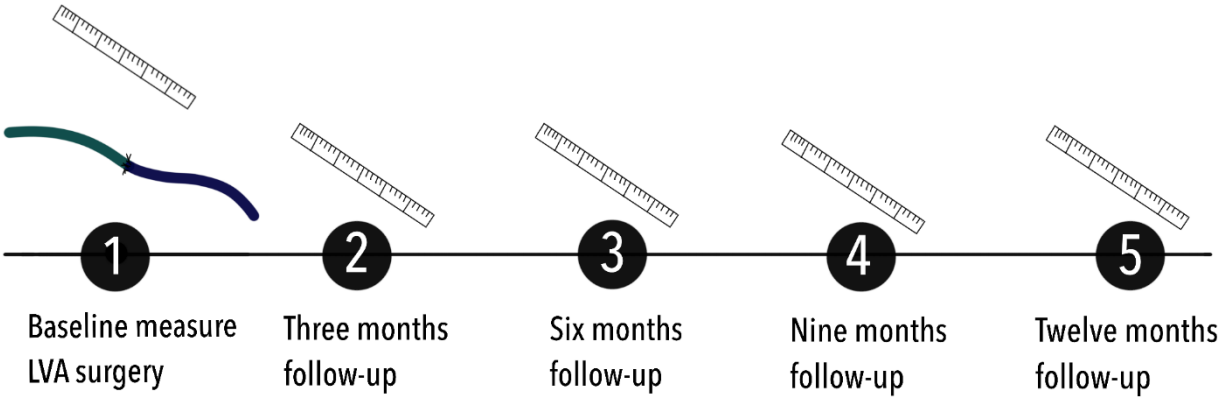

Figure 1: Illustration of timeline and patients' follow-up.

Patient demography will be registered at the baseline consultation and through medical journals. This include: name, CPR-number, age, height, weight, dominant side, side of lymphedema, relationship status, level of education, lymphedema duration, current lymphedema treatment, type of cancer surgery, laterality of surgery and whether or not lymphadenectomy or radiation therapy was given. The information will provide a concise and organized way to present key characteristics of the study population.Clinical

photos and video recordings will be captured of the patient before, during and after surgery. The objective is to document the research and facilitate its dissemination. The patient provides written informed consent to access their medical records and for photo- and video recordings through their consent for trial participation.

Consulting surgeons at the Department of Plastic Surgery at Odense University Hospital and Herlev Hospital will perform the LVA surgeries. The LVAs will be conducted using either local or general anesthesia, determined by the number of planned anastomoses and the patient's preference. Patients are not allowed to undergo other medical or surgical treatments for lymphedema during their trial period. Conservative treatments, such as compression garments and lymph press machines, are accepted.

Primary and secondary outcome measures

Arm volume

Arm volume of both the lymphedema arm and healthy arm is measured with arm circumferential measures and water displacement volumetry. Based on the formula of a blunt cone, the extremity volume is calculated for both arms using the arm circumferential measures. Water displacement volumetry is performed using a validated basin of water. After lowering the patient's arm into the water and removing it, an equal volume of water displace into another basin. The amount of displaced water is measured in grams and converted to milliliters for both arms. (13) Measurements will be taken initially at baseline and subsequently at six, and twelve months during follow-up.

Bioimpedance Spectroscopy (BIS)

Using the SOZO® (Impedimed, Brisbane, Australia) with its manufactures software, we measure patients' body composition. It is a stand-up bioimpedance with electrodes at the patients' hands and feet. By sending small electric impulses between the electrodes, the body composition is calculated based of the resistance of the different tissue.(14) The same device also measure the impedance of each arm's extracellular fluid, resulting in a lymphedema-index (L-Dex). An L-Dex score above 10 is considered diagnostic for lymphedema.(15) Measurements will be taken initially at baseline and subsequently at six and twelve months during follow-up. Data will be used to evaluate potential fluctuation of body compositions, and changes in both L-Dex score and extracellular fluid.

Patient Reported Outcome Measures (PROMs)

Using validated questionnaires, we are able to measure the patient's experiences of their health status and quality-of-life, recording potential changes over time. To cover patients quality-of-life, upper arm disability and symptoms, we will use both the DASH and the SF-36 questionnaires, in addition to LYMPH-Q Upper Extremity Module; a questionnaire designed specifically for patients with upper extremity lymphedema secondary to breast cancer.(16–18) All three questionnaires are in Danish and answered either in the clinic or online at home, before surgery and at three-, six-, nine- and twelve months follow-up. The patient reported outcome measures' (LYMPH-Q, DASH and SF-36) raw scores will be transformed to a score of 0 to 100, with 100 being the best quality-of-life.

Indocyanine Green Lymphography (ICG lymphography)

Indocyanine Green (ICG) lymphography is an imaging technique, used to visualize lymphatic vessels. After injection of a fluorescent dye, ICG, in the interdigital web space of the hand, the dye is absorbed by the lymphatic system. By using near-infrared light, the fluorescent lymphatic vessels are visualized. It provides

valuable information about lymphatic flow, drainage pathways and potential obstructions. In this project, ICG lymphography has three roles. Firstly, it aids in pre-operative planning. Secondly, the lymphedema is evaluated using visual patterns. Lastly, it assesses anastomosis patency at follow-up consultations. (19,20) Indocyanine Green (ICG) lymphography will be conducted during the baseline assessment and at the six-month follow-up.

Skin Fibrosis Measurement

The measurement of skin fibrosis is conducted using the SkinFibroMeter (SFM), a device from Delfin Technologies Ltd. in Finland. It assesses fibrosis by measuring resistance in the skin using an indenter on the prove, applied briefly five times against the skin. Measurements are compared with the opposite arm. Previous studies have demonstrated correlation between SFM readings and the stages of lymphedema.(21) Assessments will be made at baseline, and both six- and twelve months follow-up.

Surgery duration

Similar surgical techniques are used at the two hospitals in Denmark performing LVA. We will compare the duration of surgery at the two centers, and explore any differences.

Recruitment process and informed consent

The inclusion of patients will take place at the Departments of Plastic Surgery at Odense University Hospital, *Lillebaelt Hospital Vejle, Zealand University Hospital Roskilde* and Herlev Hospital. Potential project participants will be identified by the physicians at the departments through patient visits in the outpatient clinic. There is no requirement to transmit information from the medical records to the project for participant identification or recruitment. Information as well as receiving consent will take place as follows:

1) Patients will receive both oral and written information regarding the study by their physician, the main investigator or other health care personnel who have received delegated authority for information dissemination. This will happen while they are in the outpatient clinic for their lymphedema examination.
2) The right to have a co-sitter present during the information process will be respected, providing an opportunity for participants to have a supportive individual present during the conversation. If the co-sitter is not present during the information session, and the patient wishes to have them present for the conversation, patients can also give verbal consent to be contacted by phone at a mutually convenient time for both the patient and co-sitter.
3) Should an obstacle arise in informing the patient about the project during their outpatient visit, they will be able to give verbal consent to be contacted by the principal investigator for information about the project by phone or email. This requires the physician to note in their medical record that consent has been given, as well as ensuring contact information is available.
4) Patients are entitled to a 14-day reflection period, following the legislation, between the delivery of information, and the formal process of obtaining informed consent. If the patient chooses to grant immediate consent without the need for additional contemplation, this can be finalized during the initial contact. The patient retains the choice to sign the informed consent form until the day of the surgery, at the latest.
5) Patients will be informed that participation is voluntary.
6) All participants in the project hold the right to withdraw from the study at any time, without this decision affecting their treatment options within the department.
7) Only patients who provide written, informed consents will be enrolled in the trial.

Sample size and data analysis

All data will be stored at a secure database at Research Electronic Data Capture (REDCap) via OPEN.(22)

Power calculations for paired means were performed using STATA 17 (STATA 17, StataCorp LCC, 4905 Lakeway Drive, College Station, TX 77845 USA). The preliminary results from our pilot study were utilized to determine the sample size, considering a mean volume of 907 mL at baseline and 818 mL three months after LVA, along with a standard deviation of ±205. (19) Assuming an 80% power for a two-sided test at a significance level of 0.05, the calculated sample size amounts to 44 patients. Accounting for a potential dropout rate of 5%, the final total sample size is determined to be 47 patients. (20)

To evaluate changes in arm volume measurements at baseline, six-, and twelve months follow-up, the mixed-effects model will be used. The results will be reported as estimated coefficients, p-values, and confidence intervals. Additionally, graphical representations will be created to visualize changes in volume measurements over time. Similarly, the questionnaire answers and body composition will also be analyzed using the mixed-effects model to assess their variations over the study period.
The patency of the anastomoses will be examined using a paired t-test. To evaluate differences in surgery duration between centers, the independent samples t-test will be used under the assumption of normally distributed data. Any dissimilarities observed between the two centers will be qualitatively described. Patient demography will be presented as means and standard deviation if normally distributed, and as median and range if the distribution is skewed. Any drop-outs during the study will be recorded.

The statistical analysis will be performed in SPSS software (IBM SPSS Statistics, version 26.0, OBM Corp., Armonk, N.Y.) or STATA 17 (STATA 17, StataCorp LCC, 4905 Lakeway Drive, College Station, TX 77845 USA).

Data management

The data protection regulation and the data protection law are complied with in this project.
OPEN REDCap – Research Electronic Data Caputure, will be applied for a secure storage of all data. Only members of the research group will have access to this database. No contractual agreement that limits this access is relevant.

Safety

LVA is considered a safe and valid treatment for lymphedema. There is a theoretical risk of worsening the patients' lymphedema when doing surgery on the lymphatic system, however, to our knowledge, this has not been described in the literature. (2) Other potential risks include wound problems, infection, and altered sensibility at the incision site. The procedure is considered minimally invasive with limited pain and discomfort.(10) The ICG lymphography is also considered safe and easy to perform.(19,23) The patient might experience minor discomfort after die injection, such as local itching or a burning sensation.(2) To limit this discomfort, patients are numbed with lidocaine prior to ICG injection. After injection, patients will be monitored for 60 minutes in case of an allergic reaction caused by the dye. There is no exposure to radiation during ICG lymphography. (23)

Patients are under the clinical supervision of their respective departments and can reach out for any concerns or side effects. They are covered by patient reimbursement, as they are receiving treatment within the public health service. Additionally, all patients will be provided with the main investigator's contact information.

Ethics

The project will be conducted following *Good Clinical Practice* (GCP), *The Danish Code of Conduct for Research Integrity* and *General Data Protection Regulation* (GDPR).(23,24) *The Research Ethics Committee of the Region of Southern Denmark* will be applied for approval of this study, and the project will be registered in the Region of Southern Denmark.
The project will be registered at ClinicalTrials.gov. All types of outcomes—positive, negative, and inconclusive—will be disclosed on ClinicalTrials.gov and efforts will be made to publish them in an international journal.

The risk associated with LVA in the context of a clinical trial, is deemed justifiable for several reasons. Firstly, LVA is a well-established surgical procedure and considered safe for lymphedema treatment. (2) Secondly, the study incorporates careful participant selection, thorough preoperative assessment, and postoperative monitoring to ensure any adverse events are detected and addressed promptly. Moreover, the potential advantage of LVA, including enhanced lymphatic drainage, decreased arm swelling, and improved quality of life, surpasses the controllable risks.

Funding

This study is economically sponsored by:

- *The University of Southern Denmark Research Foundation* - 33.000 DKK allocated for the purchase of project equipment.
- *ACROBATIC* (*Research Collaboration Across Surgical Oncology for Better Patient Care*) - 548.852 DKK allocated to cover the one-year salary of the main investigator.
- *The Vissing Foundation* - 235.000 DKK allocated for the purchase of project equipment.

Funding will cover the study expenses and salary of the main investigator. It will be administered via an account that is subject to public audit. The main investigator does not possess any financial ties to the sponsor or other parties involved in the trial.

All the Departments of Plastic Surgery at Odense University Hospital, Lillebælt Hospital Vejle, Roskilde Hospital and Herlev Hospital as well as the primary investigator have taken the initiative for this study. Neither of the Departments nor the main investigator has any financial interests in this project. None of the patients will receive financial benefit from participating in this trial.

Feasibility

This study will be conducted by Caroline Lilja, MD. and Ph.D.-student, as the main investigator under the supervision of Jørn Bo Thomsen, Dr., MD., Ass. Prof.. Regardless of positive or negative data, results are planned to be published in an international journal.

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