Lymphaticovenous anastomosis as a surgical treatment for breast-cancer related lymphedema

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Introduction

Late and long term sequelae following breast cancer treatment, such as lymphedema, affects patients quality of life due to many factors, amongst these are reduced functional ability due to affected shoulder and arm function, emotional problems and negative view on body image following treatment. (1,2)

A growing body of literature shows promising results for reconstructive surgery as a physiological treatment of secondary lymphedema, resulting in a decreased rate of sequelae following breast cancer treatment, such as reduced volume of the affected extremity and episodes of erysipelas, improved quality of life and functionality of the limb. (3–7) However, there is a lack of systematics when it comes to patient characteristics and surgical procedure, which necessitates further studies to address this challenge. Recent research emphasizes the importance of correctly identifying which vessels to anastomose, in order to select the most suitable vessels and patients for treatment; to carefully plan and personalise the treatment plan, based on the patient's physiology. (2,6,8–11)

The primary aim of this study is to investigate and test if we can correctly identify lymphatic vessels and venoles in close proximity to each other using combined ICG lymphography and ultra high frequency ultrasonography for identification prior to LVA surgery.

Background

Breast-cancer related lymphedema is a life-disabling side-effect of breast cancer treatment, affecting more than 1 in every 5 patients. (12,13) With breast-cancer being the most common cancer diagnosis in women, affecting up to 2.3 million new cases globally, and with a generally high survival rate of 80% or higher in developed countries, the number of breast-cancer survivors with long-term sequela is significant. (14,15) In 2020, 5083 patients were diagnosed with breast cancer in Denmark, which based on the incidence, gives an estimated number of 800 or more of these patients will develop lymphedema per year. (16)

Due to a disruption to the lymphatic system with inadequate drainage, protein-rich lymph fluid is accumulated in the interstitial tissue, causing excessive swelling of the upper extremity, breast, and truncus of the treated side. (17) This accumulation of fluid promotes chronic inflammation in

the extracellular matrix and fibrosis and hypertrophy of the adipose tissue, followed by annihilation of the lymphatic vessel lumen due to sclerosis. (8)

Compression garments and physiotherapy have been considered the standard treatment and rehabilitation for lymphedema. (18) Some of the disadvantages with these treatments include variability in patient compliance, clinical effect and lack of statistical significant results. (19)

As breast cancer is the most common cancer among women, with an increasing survival rate due to improved treatment, the rehabilitation and treatment options for long-term sequela are in high demand, affecting patients physical and mental health. (2–6,20–22)

These long-term sequelae include swelling, arm heaviness, tightness, pain, weakness and affected functionality of the arm. Moreover, breast-cancer survivors with breast cancer related lymphedema report emotional sequelae, including deterioration of generic mental health, social role functioning, life and social activities and bodily pain. (1,20,22) In addition to this, the condition generally worsens over time, emphasising the need for long-term treatment of lymphedema.(18,23)

Physical interruption of flow, radiation, and obesity has been proposed as major causes of breast cancer related lymphedema because of lymphatic vessel ectasia and dysfunctional valves. The volume of interstitial fluid exceeds the rate of lymphatic flow, resulting in a state of increased interstitial fluid; what we know as lymphedema. This stasis of fluid cause a chronic inflammation with deposition of fibro-adipose tissue, which in turn further decreases the lymphatic function. (8,23) Lymphovenous anastomosis surgery is an attempt to re-establish the lymphatic flow, utilizing the patient's own lymphatic- and venous vessels.(17) Other treatment modalities that have been proposed as treatment options for lymphedema includes lymph node transplantation, liposuction and de-bulking procedures, stem-cell therapy and medical therapy. (8,24)

Prior to this study, we reviewed the literature of the field; a literature search was conducted focusing on lymphovenous anastomoses. Several studies and reviews emphasize the importance of preoperative planning based on disease pathophysiology. Surgical treatment seems effective in selective patient groups, but systematic studies for this are lacking. (2,10,11,25–27) It is based on this lack of knowledge of patient characteristics and preoperative planning that the project's hypothesis and idea was formed.

ICG lymphography is commonly used for identification of lymphatic vessels, and is considered superior to other modalities such as computed tomography (CT) and lymphoscintigraphy. (27,28) The ICG dye in the lymphatic vessels can be detected by an infrared camera. However, until recently, the identification of adjacent venoles remained a challenge. Ultra high frequency ultrasound may have solved the challenge of identifying the small venoles prior to surgery. The combined use of ICG lymphography and ultra high frequency ultrasound may be the key to optimise patient selection and preoperative planning of lymphovenous anastomosis surgery. (27,29–31)

We therefore wish, based on the knowledge, to add to the knowledge regarding targeted surgical treatment of lymphedema. Hopefully this pilot study that uses a combination of an ICG camera and ultra high frequency ultrasound will enable us to propose an algorithm, that can be used for lymphedema patient, when selecting between surgery and other treatment modalities. Thus, we hope our method helps to specify which patients may benefit from surgery. The primary aim of this pilot study is to investigate and test if we can correctly identify lymphatic vessels and venoles in close proximity to each other using a combination of indocyanine green (ICG) lymphography and ultra high frequency ultrasound prior to lymphovenous anastomosis.

Material and methods

ICG lymphography is a technique for visualization of the superficial lymphatic systems. By injecting ICG subcutaneously, it enables a real-time visualization of the lymphatic networks through a minimally invasive procedure. ICG is a non-toxic tracer with low risk of complications; 0.17% risk in general, and 0,02% for nonsevere shock, by intravenous injection. Severe allergic reaction, including anaphylactic shock, affects fewer than 1/10.000 patients. (32,33)

The ICG lymphography is performed and used for visualisation of the superficial lymphatics for preoperative planning, using 0.1 mL ICG (2.5 mg/mL Verdye, Diagnostic Green, Ascheim, Germany). The dye is injected subcutaneously at the wrist, near the ulnar border of the palmaris longus tendon, and in the 1st and 3rd web space of the hand. Scans are performed using an infrared camera, the HyperEye medical system (MNIRC-501, HEMS; Mizuho Co., Tokyo, Japan). During real-time visualization, lymphatic vessels are drawn up on the patients arm using a permanent marker. (32,34)

Ultra high frequency ultrasound (>30MHz) has the ability to visualize small, superficial anatomical layers. (10,30,35) Using this ultra high frequency ultrasound, following the mapped lymphatic vessels, venous vessels are found nearby and likewise mapped for anastomosis. The ultrasound scans are performed using a 70MHz probe (Vevo® MD Imaging System, Fujifilm, VisualSonics Inc.). The number of LVA anastomosis sites is set to a minimum of two sites per extremity. The number of mapped lymphatics vessels and venoles are compared to the number identified during surgery and recorded.

The secondary outcomes includes: 1) changes of arm volume over time, 2) changes of lymphatic flow pattern before and after surgery by ICG lymphangiography, 3) changes in health-related quality of life by the use of the LYMPH-Q questionnaire and 4) changes in L-Dex score and body composition measured with bioimpedance before and 3 months after LVA surgery. (32,36,37,37–39)

Volume calculation

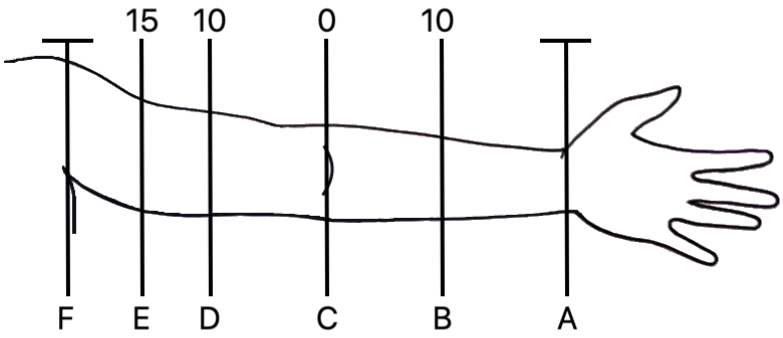

Figure 1: Illustration of circumference tape measurements

Manual circumferential measurements are taken from both arms for volume calculation, see figure 1, based on the formula for multiple blunt cones:

$$Volume = \frac{1}{3} * \pi * ({r_1}^2 + r_1 r_2 + {r_2}^2) * h$$

The formula is based on the measurements illustrated in figure 2.

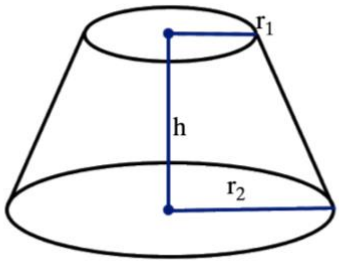

Figure 2: Measurements for volume calculations of a blunt cone

Water displacement volume assessment

The water displacement test estimates the volume of the arm, based on lowering the extremity in a basin of water, and calculating the water volume difference in mL.

Classification of lymphedema

Video recordings of ICG lymphographies are stored for later classification of the lymphedema. Staging will be done using the MD Anderson scale; a classification system based upon pattern recognition of the dermal backflow from the ICG lymphography, see table 1. (32)

MD Anderson stage	**ICG lymphograpgy findings**
Stage 0	No dermal backflow
Stage 1	Many patent lymphatics and minimal dermal backflow
Stage 2	Moderate number of patent lymphatics and segmental dermal backflow
Stage 3	Few patent lymphatics with extensive dermal backflow
Stage 4	Dermal backflow involving the hand
Stage 5	ICG does not move proximally to injection site

Table 1: MD Anderson classification based upon ICG lymphography findings.

Quality of life

The LYMPH-Q Upper extremity module questionnaire is a validated patient-reported outcome tool for women with breast cancer related lymphedema. The module contains seven individual scales, measuring: symptoms, function, appearance, psychological function, and satisfaction with

information on lymphedema and satisfaction with arm sleeve. Each scale gives an independent score, which can be used for comparison of change over time. (37)

Impedance measurements

L-Dex score is a measurement of extracellular fluid of the arm. A stand-on device with electrodes at the hands and feet, estimates the extracellular fluid trough electric impulses between these electrodes. It is a non-invasive procedure without any discomfort for the patient. A number between -10 and 10 is considered normal, and diagnostic for lymphedema if above 10. The score correlates with the limb volume and lymphatic function. (38,39)

The same stand-on device also measures body composition through electric impulses, including total body water (TBW) (L), extracellular fluid (ECF) (L), intracellular fluid (ICF) (L), protein and minerals (%), fat mass (FM) (kg), active tissue mass (ATM) (kg) and skeletal muscle mass (SMM) (kg). Following calculations will be compared prior to surgery and 3 months after:

- ECF/TBW (%)
- ICF/TBW (%)
- TBW/weight (%)
- (Proteins and minerals)/weight (%)
- FM/weight (%)
- ATM/weight (%)
- SMM/weight (%)

Design and population

This study is designed as a hypothesis generating pilot study with a planned inclusion of 10 patients with a 3 months follow-up period. The research unit has previously conducted studies on the same patient group with the inclusion of 20 patients over a similar project duration. It is therefore considered realistic with the inclusion of 10 patients for the current pilot study for the given period of time.

The inclusion of patients, the surgical procedure and follow-up evaluation will take place at the Department of Plastic Surgery Odense University Hospital (OUH), Denmark, over a period reaching from the 1st of February 2022 till the 31st of January 2024.

The study population is based upon patients who is referred to the outpatient clinic at the Department of Plastic Surgery OUH for assessment of their upper-extremity lymphedema. Only patients who is clinically evaluated to be a candidate for the lymphovenous anastomosis, will be informed and invited to participate in this trial. Information about the surgical procedure is given by a specialist in plastic surgery at the outpatient clinic. Information about the study will be given to the patient in the outpatient clinic no later than 14 days before scheduled surgery, under normal private conditions by the primary investigator.

Patients will receive both oral and written information regarding the project, and are given a reflection time following the legislation over a period of 14 days, with the possibility of withdrawal at any time. The patient is also informed orally and in written form about the possibility of an attendant, which is recommended to the patient.

Only patients who provide written, informed consent will be enrolled in the project.

Included patients will be seen for baseline measurements prior to surgery, and for follow-up evaluation 3 months after the intervention. In addition, the patient will be seen in the department, 14 days and 3 months after surgery, for suture removal and examination, as part of the department's treatment follow-up.

If patient decline to participate in the study, they will still receive the surgery, follow their own course of treatment in the department, separate of this study.

Patients with breast cancer related pitting-lymphedema in one of their upper extremities, who is above the age of 18 and capable of providing informed consent, is included. If pitting edema does not occur, the patient may not be included. However, if the patient's lymphedema has lasted for over 24 months, if she currently is smoking or if there are any untreated or uncontrolled primary breast-cancer, which can cause further damage to the lymphatics and influence the measurements of this study, the patient is excluded from the study, see table 2.

Inclusion criteria:	**Exclusion criteria:**
• Female	• Duration of disease over 24 months
• Iatrogenic lymphedema following treatment for breast cancer in upper extremity	• Smoker
• Possible to obtain informed consent	• Untreated or uncontrolled primary cancer

• Age>18	• No applicable lymphatic vessels identified, using ICG lymphangiography
	• No applicable venous vessels identified using ultra high frequency ultrasound

Table 2: Patient inclusion and exclusion criteria.

Included participants will undergo surgical intervention with LVA, in the affected upper extremity. Prior to surgery, pre-operative mapping of relevant lymph- and venous vessels using respectively ICG lymphography and ultra high frequency ultrasound for visualization, evaluation and selection, will be performed.

During real-time ICG lymphangiography, lymphatic vessels are mapped on the patient's arm, in relation to its dermal backflow pattern. Then, following the mapped lymphatic vessels using ultra high frequency ultrasound, venoles will be identified nearby and equally mapped. Videos and pictures of the patient arms and ICG lymphangiography will subsequently be performed.

After detection of applicable vessels per-operatively, the lymphatic vessels and venoles will be dissected and anastomosed in a ratio of 1:1.

Risks, adverse events and disadvantages

LVA is considered a safe and valid treatment for lymphedema. (3,40,41)

There are already well-established centres in Europe, USA and Australia, offering surgical treatment for breast cancer related lymphedema. However, studies present different results regarding the decrease in arm volume, reaching from insignificant to significant. (6,7,24) Even so, as previously described, surgical treatment seems effective in selective patient groups, but systematic studies for this are lacking. (2,10,11,25,26)

As in any surgery, there will be a small scar from the surgical incision, which tend to fade over time. (42) Other potential, general adverse events include wound problems, bleeding, infection and cardio vascular events such as thrombosis. The overall risk of a severe and fatal events occurring during surgery is generally small. (43) Adverse effects specific for the LVA procedure includes worsening of the patient's lymphedema. (2,40,44) A review with a safety assessment for the LVA procedure found no reported serious adverse events based on 217 included studies. Otherwise skin irritation was found as an adverse event of the site of contrast injection in two

patients (10%). (41) In case of a known or unknown adverse event, or adjacent pain, relevant treatment will be initiated.

The ICG lymphangiography is considered both safe and easy to perform. The patient might experience minor discomfort when injecting dye intradermal into the hand. In order to ease this discomfort, patients are numbed using infiltration of lidocaine at the site on injection. Patients undergoing the clinical assessment, will be monitored 60 minutes after the injection for an allergic reaction caused by the dye applied, including anaphylactic shock. In case of an allergic or anaphylactic incidence, relevant treatment will be initiated. (32)

The LVA procedure is considered minimally invasive, but based on the duration of the operation, the surgery will be performed under general anesthesia.

Patients generally experience minimal pain after surgery. If this is not the case, appropriate pain treatment will be given. (45)

Collection of Data

Pre-operative: The patients will be examined in the outpatient clinic by the primary investigator. Circumference tape measurement and water displacement will be executed for volume quantification of both arms, in addition to bioimpedance for measurements of L-Dex score and body composition. A questionnaire regarding quality of life in relation to living with lymphedema, LYMPH-Q, will also be completed prior to the intervention.

ICG lymphography will subsequently be performed by the operating surgeons and the primary investigator for mapping of lymphatic vessels. (33,34)

Ultra high frequency ultrasound will be used for mapping veins adjacent to the lymphatic vessels for anastomosis. The number of vessels and their location for anastomosis will be registered and mapped prior to surgery.

Video recordings of the ICG lymphography is performed for staging of lymphedema. Photos of the patient's arms will be recorded as well.

During surgery: The number of actual applicable lymphatic vessels and venous veins found during surgery will be registered, and also whether these were usable for anastomosis.

3 months post-operative follow-up: Patients will be examined in the outpatient clinic for circumference tape measurement and water displacement for volume calculation of both arms, in addition to bioimpedance for measurements of body composition and L-Dex score, in addition to ICG lymphangiography. The patients will be asked to complete the LYMPH-Q questionnaire once again.
Cases of adverse side effects will be collected continuously.

Collected data provides the following for comparison, as previously described:
1) The primary outcome is comparison of the number of lymph vessels and venoles found during surgery and the number originally planned.
2) Arm-volume measurements for each patient will form the basis for calculating the volume difference between the patient's arms. The volume difference before and after surgery will be compared. This applies to data collected from both manual measurements and water-displacement test.
3) Comparison of ICG lymphography video recordings before and 3 months after intervention, with changes in MD Anderson classification system of lymphedema.
4) Changes in LYMPH-Q scores for each individual scale from before and 3 months after intervention.
5) Changes in L-Dex score measured by stand-up bioimpedance before and 3 months after surgery. (38,39)
6) Changes in measurements of body compositions before and 3 months after LVA surgery.

Database

OPEN REDCap – Research Electronic Data Capture, will be applied for a secure storage of all data. REDCap is a worldwide online system developed for non-commercial clinical research. Data will be stored on OPEN's servers in the Region of Southern Denmark. Here, data is entered via an encrypted connection and meets current data protection requirements. The database will primarily be used to enter and store clinical data, as well as a few simple calculations based on these clinical data, for example BMI calculation. Only members of the research group will have access to this database. No contractual agreement that limits this access, is relevant.

As a starting point, the database will exist until the 31st of January 2024. As the study is a pilot study, there is, however, the possibility of extension with the inclusion of several test subjects for further exploratory study.
Objective measured data, as well as any general personal data that does not already appear in the patient journal, will originally be collected by the primary investigator during the examination. Collected data and data from the patient's record is then transferred to the REDCap database by the primary investigator. Written informed consent for participating in the project, including collecting information from the patient's examination and journal, is obtained at the patients' first consultation in the outpatient clinic. Only patients who provide written, informed consent is enrolled in the project. No data is collected nor known to the researcher prior to this.
The consent gives the trial supervisor, sponsor and sponsor's representatives as well as any control authority direct access to obtain information in the patient's medical record, as part of the implementation of the research project as well as for control purpose.
The LYMPH-Q questionnaire is completed prior-to and 3 months after the intervention on paper form, which is subsequently entered into the REDCap database by the medical student.
Collected data includes the patients name, social security number, age, height and weight, BMI, gender, breast cancer diagnosis, treatment prior to the study in relation with their breast cancer diagnosis, duration and stage of lymphedema in upper extremity, number of mapped and applicable vessels pre- and per-operatively, number of anastomosis made during surgery, number of days of hospitalization, operation description, description of admission, name of the operators, pictures, videos and measurements from before, during and after the surgery, known allergies, medicine list, smoking status and any side effects or complication related to the surgery or 3 months after.

Sample size and Statistics

No statistical methods are applied in evaluating the sample size and power for this pilot study, as it is a hypothesis generating study. (46) In the case of positive results, this pilot study will form the basis for further clinical study with calculation of a relevant population size.
With the previous experience in the research unit with inclusion of 20 lymphedema patients, it is considered realistic to include 10 patients for this pilot study. In addition, there are already three patients referred to the Department of Plastic Surgery, OUH, who has been evaluated as relevant candidates for LVA surgery.

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)*. (47,48)
The Research Ethics Committee of the Region of Southern Denmark has been applied for approval for this project, and the study is registered at the region of Southern Denmark.
In this study, personal data will be processed. In this regard, the Data Protection Act and the Data Protection Regulation will be followed.

Impact

We expect this pilot study to provide more knowledge upon the effect of LVA in specific patient characteristics, and form the basis for further clinical investigation of a larger sample size in case of positive results. This will potentially contribute to reduce the incidence of long-term sequela following breast cancer treatments and improve quality of life. Regardless the result, this study will have a clinical value.

Economy

This study will be economically sponsored by The Danish Cancer Society Foundation.
The funding of 120.000 DKK, will cover the one-year salary of the pre-graduate medical student starting 1st of February 2022 till 31st of January 2023.
Funding are paid to a bank account at the institution, where salary is subsequently paid monthly to the student.
Banking information:

Jyske Bank

Reg.no.: 7562 acc.no.: 0001090051

OUH's SE no.: 30049179

Southern Denmark Region's CVR no.: 29190909

P-no.: 1003309680

Both the Department of Plastic Surgery Odense University Hospital and the medical student have taken the initiative for this study. Neither author of the Department of Plastic Surgery Odense University Hospital has any financial interest in this article. No patients will receive financial benefits from participating in this clinical study.

Feasibility

The pre-graduate student is responsible of writing the protocol for this study, provide necessary funding, participate in patient inclusion and examinations and assist during surgery, carry out the data analysis, and writing the article. The Department of Plastic Surgery OUH offers office facilities. Both supervisors provide necessary knowledge and experience to conduct this project within one year.

Publication Plan

This study will be conducted as a pre-graduate research study with Caroline Lilja, Stud. Med. as the primary investigator. Positive, negative, and inconclusive results will all be attempted published in an international journal.

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