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Optimization of diagnostic and treatment modalities to influence the natural history of breast cancer-related lymphedema

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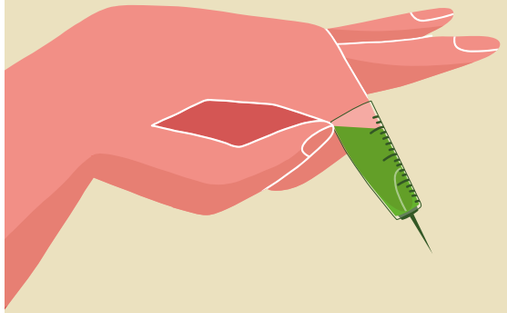
ABBREVIATIONS

ADBS	arm dermal backflow stages
AE	adverse events
AI	aromatase inhibitor
ALND	axillary lymph node dissection
BCRL	breast cancer-related lymphedema
BCS	breast-conserving surgery
BIS	bioelectrical impedance spectroscopy
BMI	body mass index
BMP	bone morphogenetic protein
C/c	circumference at each end of the segment
CI	confidence intervals
cm	centimetre
DB	dermal backflow
DLT	decongestive lymphatic therapy
GEE	generalized estimating equations
ICC	intraclass correlation coefficient
ICG	indocyanine green
IDA	invasive ductal adenocarcinoma
ILA	invasive lobular adenocarcinoma
ISL	International Society of Lymphology

K	Kappa coefficient
LN	lymph node
LRV	lymphedema relative volume
ME	mastectomy
MET	metabolic equivalent of task
MLD	manual lymph drainage
NIRFLI	near-infrared fluorescence lymphatic imaging
NPV	negative predictive value
OR	odds ratio
PDE	photodynamic eye
PPV	positive predictive value
PWC	percentage of water content
RCT	randomized controlled trial
RF	risk factor
RT	radiotherapy
SD	standard deviation
SLNB	sentinel lymph node biopsy
TDC	tissue dielectric constant
V	volume
WK	Weighted Kappa coefficient



General introduction

THE LYMPHATIC SYSTEM

It took centuries to find out the anatomy and function of the lymphatic system. It started with Hippocrates (ca. 460-377 B.C.) over Eustachius (1510-1574)[1] and Thomas Bartholin (1616-1680).[2-5] Finally, it was microscopist Antoni van Leeuwenhoek (1632-1723) [6] who was able to visualize the details of the lymphatic system.

The lymphatic system is described as the third circulatory system although there are some differences with the venous and arterial system. It is not a real circulatory system and the propulsion of the lymph is not mediated by a central heart pump, but by tissue pressure and the muscle pump (intrinsic and extrinsic). The lymphatic system has a unidirectional flow, bringing lymph from peripheral tissues to the venous circulation in the neck. It is present in all of the organs and tissues besides hair, nails, mature cartilage and retina.[7]

In the past it was taught that venous reabsorption played the most important role in reducing interstitial fluid (the Starling principle).[8] However recent research has shown that there is no reabsorption by the venous end of the capillaries. Instead there is filtration along the entire capillary bed and the fluid regulation depends on lymphatic transport. This means that the function of the lymphatic system is more important than previously taught.

Besides playing a role in fluid homeostasis, the lymphatic system is important for the absorption of lipids from the intestines and in the immunologic response as well.[9]

The lymphatic system consists of lymphatic organs and lymph vessels **(Figure 1)**. The lymphatic organs can be divided into primary and secondary organs. The primary lymphatic organs, such as the bone marrow and thymus, are producing lymphocytes and play a role in maturation of these lymphocytes. Lymph nodes, spleen and tonsils are secondary lymphatic organs. They trap foreign material and filter the lymph. The human body has approximately 700 lymph nodes spread widely over the body.[7] The amount of lymph nodes in the axilla can vary between eight and fifty, mostly ten to twenty-four nodes can be found.[7]

The lymph vessels can be divided in a superficial and a deep system. The superficial lymphatic system drains the skin and tissues above the fascia, the deep system drains the muscles, bones and organs. These two systems are connected by perforator vessels.[7]

For instance, in the upper limb, the superficial and the deep system drain mainly into the axillary lymph nodes. An additional pathway that can be present, is the pathway of Mascagni which is situated in the deltoideopectoral sulcus and drains into the supraclavicular lymph nodes.

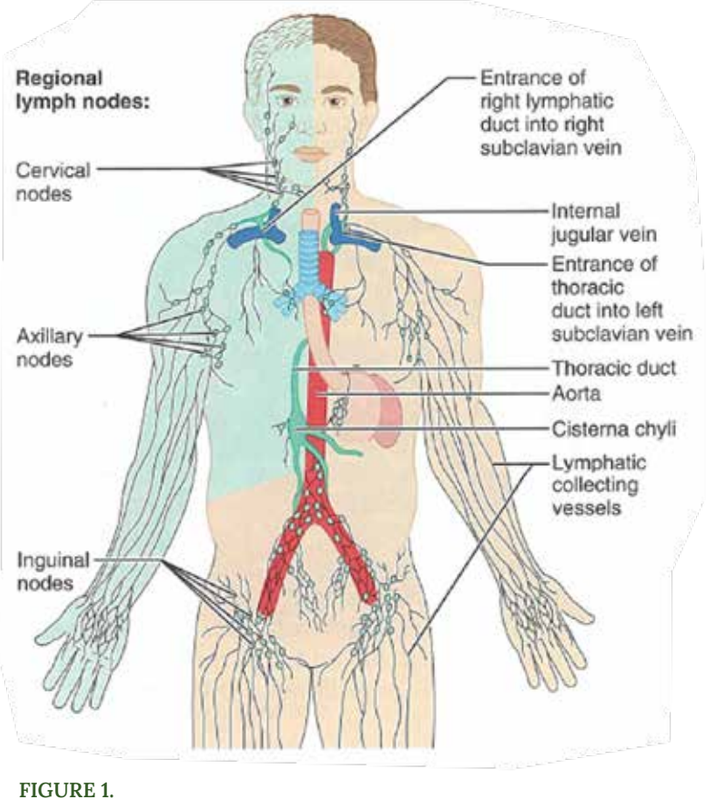


FIGURE 1.
Overview of the lymphatic system. Reprinted with permission of Pearson Education, Inc., New York. [10]

Fluid drains from the capillaries **(Figure 2)** into the pre-collectors and then in the collectors. The collectors are lined with smooth muscle cells and have lymphangions or vessel segments, which are separated by valves and are responsible for the unidirectional flow as they gradually contract and push the lymph forward. This is called the intrinsic muscle pump. Lymph collectors form a lymphatic trunk and these lymphatic trunks discharge into the venous system at the jugulosubclavian area.[7]

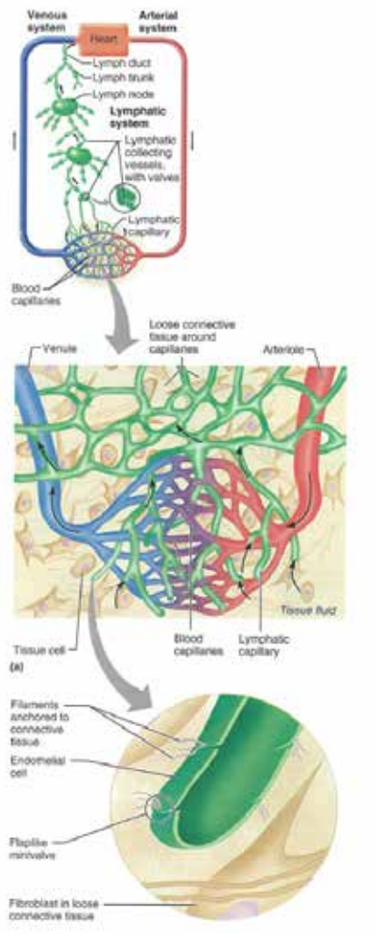


FIGURE 2.
Distribution and special structural features of lymphatic capillaries. 2004. Reprinted with permission of Pearson Education, Inc., New York[10]

LYMPHEDEMA

Lymphedema is caused by an imbalance between lymph production and lymph transport. This happens when the microvascular filtration rate is higher than the drainage. This imbalance can be due to an overproduction of lymph with an intact lymphatic system, called high-output failure. A high capillary permeability (burn wounds,...) or high hydrostatic pressure (cardiac failure,...) can be the cause. If the production of lymph is normal but an abnormal lymphatic system is present, low-output failure can occur. Examples of this are mechanical damage by trauma, surgery, radiotherapy or a congenitally abnormally developed lymphatic system.[11] We can distinguish primary and secondary lymphedema. In primary lymphedema there is an anomaly in the development of the lymphatic system, often the result of a genetic disorder. This is less common, especially in upper limbs. The majority of patients presents with secondary lymphedema due to damage or to acquired malfunction of the lymphatic transport and/or to an overload of interstitial fluid.[8] Surgery, infection, malignancies and advanced venous insufficiency are the possible causes.

Breast cancer-related lymphedema (BCRL) is the swelling of the upper limb after treatment for breast cancer. **Figure 3** shows lymphedema of the hand and arm after breast cancer treatment. Estimates of incidence rates of BCRL have varied over time, especially since the introduction of less invasive techniques such as sentinel node procedures and radiotherapy. According to a review of DiSipio et al. the incidence of arm lymphedema was about four times higher in women who had an axillary lymph node dissection (19.9%) than in those who had sentinel lymph node biopsy (5.6%).[12] The overall incidence of lymphedema in sentinel node negative breast cancer patients ranged from 0% to 63.4%.[13] A study by Rockson et al. suggested that in almost 75 % of the cases, lymphedema is established in the first year after breast cancer treatment.[14] BCRL decreases the patient's quality of life not only because of the enlargement of the diseased limb but it is also associated with other physical problems, such as decreased mobility and recurrent infection, and is often accompanied by psychosocial problems, such as stress and decreased ability to perform occupational activities.[11, 15, 16]

FIGURE 3.
Arm and hand lymphedema after breast cancer treatment

Numerous studies and reviews have identified possible risk factors for the development of BCRL.[12, 17-19] Axillary lymph node dissection, modified radical mastectomy, high Body Mass Index and a greater number of lymph nodes dissected are being suggested as risk factors for the development of BCRL.[12, 19] As treatment modalities for breast cancer have changed over the past years, an extensive up-to-date systematic review of the literature is needed.
Not only a damage to the lymphatic transport and therefore lymphatic failure, but also a high filtration rate is hypothesized to play a role in the development of edema. In patients who progress to BCRL the filtration rate is greater than women who did not develop BCRL.[20] This is due to elevated peripheral lymph flows in muscle as well as in the subcutis of both arms.[20]

Clinical evaluation of lymphedema

Lymphedema can progress from a soft pitting edema to a hard fibrotic or soft fatty and non-pitting edema. Lymph stasis will not only cause extravasation of fluid in the interstitium but will also promote lipogenesis, fibrosis, inflammation, lymphangiogenesis and immunosuppression.[21] A clinical staging system for lymphedema is being used (stage 0 to 3) according to the severity.[11] In stage 0 fluid accumulation is present but not clinically apparent (subclinical edema), meaning it is not visible but by clinical examination such as palpation it can be detected. Stage I refers to a swelling that subsides with elevation of the limb. Stage IIa represents swelling that does not subside with limb elevation; pitting is manifest. In stage IIb no pitting is visible and fibrosis together with lipogenesis emerges. Stage III is the most advanced form, the so called 'lymphostatic elephantiasis' with skin abnormalities and further fibrosis of the tissue.

There are several clinical assessment tools to evaluate BCRL.[11,22] Most available methods assess the volume of the limb by either circumference measurements **(figure 4)**, from which the volume is calculated [23], or water displacement [24], whereby the extremity is immerged in a container of water and the amount of the displaced water is weighted [25], or by opto-electronic perometry, an infrared optical scanner that assesses the external surface of the limb and calculates its volume.[26] In addition, the amount of water in the edematous limb can be assessed by means of the pitting test [27,28], by measuring the extracellular fluid with bioelectrical impedance spectroscopy (BIS) [29] or by measuring the local water content of the skin with tissue dielectric constant (TDC).[28,30] Lastly, measurement of the skin fold thickness (Stemmer test) can be performed with an increased thickness being a typical sign for lymphedema.[31] Although there is a range of different tools, there still is no consensus on which tool to use. Water displacement is still considered the gold standard for measuring the volume of the arm.[11, 24] In a study by De Vrieze et al, five different methods

FIGURE 4.
Circumference measurements of the arm

were used to evaluate the excessive arm volume and the authors concluded that the calculated volume based on arm circumferences was the best method to assess the excessive volume of the arm.[22]

Imaging the lymphatic system

Historically, lymphangiography has been the technique to image the lymphatic system. An infusion of an iodinated contrast medium is injected intradermally or a cannula is inserted through a microsurgical incision into the lymphatic vessel. These techniques are not easy to perform and have become obsolete.[32]

Lymphoscintigraphy

Currently, the most commonly used diagnostic tool for examination of extremity lymphedema is lymphoscintigraphy. This technique, first described by Sherman and Ter-Pogossian in 1953, directly images the lymphatic system.[33,34] A radiopharmaceutical (99mTc-nanocolloid) is injected intradermally in the foot or hand of the patient and the uptake of the tracer in lymphatic tissue is followed with sequential gamma imaging.[35] The technique is recommended by the International Society of Lymphedema and the American Venous Forum guidelines.[11] This technique not only provides dynamic imaging of the lymphatics and the lymph nodes, but also provides a semi-quantitative data of radionuclide transport. Movement of the colloid from the injection site, the transition time to the knee, groins or axilla, the absence or presence of major lymphatic collectors, the number and size of vessels and nodes, the presence of dermal backflow (reflux to the capillary network), presence of collaterals and symmetric activity with the opposite side are all recorded.[11]

Signs of lymphedema include poorly visualized lymphatic collectors, delayed nodal enhancement and dermal backflow (DB). Lymphoscintigraphy is not only able to provide the diagnosis of lymphedema but can give a quantitative evaluation. In addition it can be used to assess the efficacy of therapies for treatment of lymphedema e.g. after lymphovenous anastomosis or lymph node transfer.[36]

Although lymphoscintigraphy is still the gold standard, there is no standardization regarding radiotracer, radioactivity doses, different injection volumes, intracutaneous versus subcutaneous injection, number of injections, different protocols of passive and active physical activity, varying imaging times, static and/or dynamic techniques.[37,38]

Near-infrared fluorescence lymphatic imaging or lymphofluoroscopy

Near-infrared fluorescence lymphatic imaging (NIRFLI) or lymphofluoroscopy is another minimally invasive technique to image the lymphatic system. Fluorescence is a phenomenon of light emission with a certain wavelength from a material when it is irradiated by light from another wavelength **(Figure 5)**. The irradiated and emitted lights are called 'excitation light' and 'fluorescence light', respectively[39]. Fluorescein sodium is excited by visible light, indocyanine green (ICG) by near-infrared light **(Figure 4)**. The injection of ICG intradermally allows to visualize lymphatics in the upper 2 cm of the skin using an infrared camera system that captures the fluorescence.[40, 41]

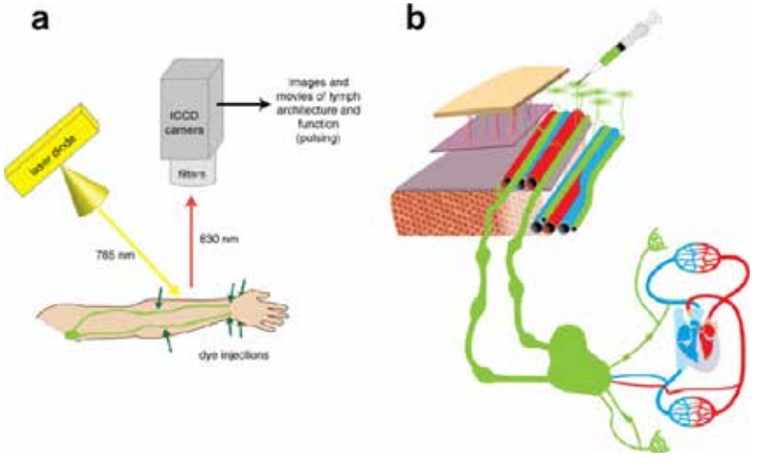


FIGURE 5.
Fluorescence imaging. a.The emitted excitation light, b. Indocyanine Green (ICG) is injected intradermally, captured by the capillary network and transported in precollector and collectors. (Illustration adapted from: Lymphatic abnormalities in the normal contralateral arms of subjects with breast cancer-related lymphedema as assessed by near-infrared fluorescent imaging[39])

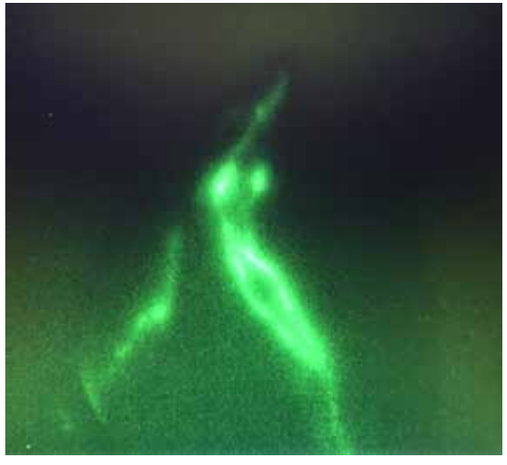


FIGURE 6.
Lymphofluoroscopy of the arm

The images themselves can be classified according to the severity of the disturbance of the lymphatic transport. In healthy subjects, lymphofluoroscopy shows a linear lymph transport pattern. In **figure 6** a linear transport is visible. In patients with lymphedema, three dysfunctional DB patterns of lymphatic transport can be distinguished **(Figure 7)**. The first one is the splash pattern, representing a dispersed tracer in tortuous lymphatic channels. The second one is the stardust pattern, which demonstrates spotted fluorescent signals, representing the effusion of lymph fluid out of the lymphatic capillaries into the interstitium. The last type of pattern is the diffuse pattern where the tracer is widely distributed without identifiable spots. In this pattern, besides the accumulation in the lymphatic capillaries and lymph precollectors, lymph is stagnated in the interstitium.[42, 43] This DB will develop when a lymphatic obstruction occurs and lymph flow will pass back to the dermal capillaries trying to search for an alternative way. When the lymphedema becomes more severe, less normal lymph vessels can be visualized and more DB will be present. Nguyen et al suggested a ICG lymphangiography staging scale describing this nicely[36]: stage 0 represents a normal lymphatic system, stage 1-4 represents the visualization of more and more DB and less lymph vessels, stage 5 shows a total obstruction without uptake of ICG from the injection place. This scale gives more details than the previous suggestion by Yamamoto et al describing 5 stages of arm DB.[43]

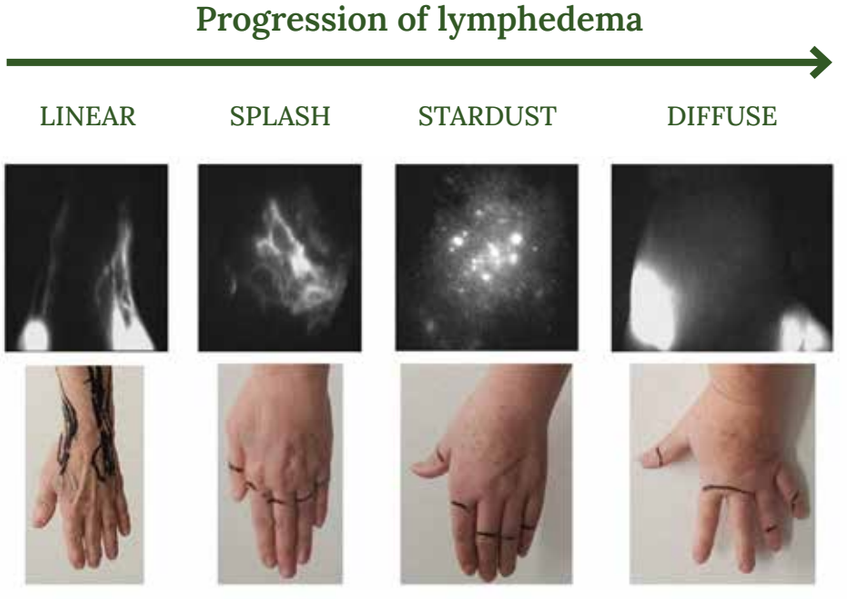


FIGURE 7.
Classification of lymph transport pattern; black markings: a) normal linear lymph vessels, b) splash pattern on the hand, fingers are normal, c) stardust pattern on hand, distal dorsal arm and proximal part of fingers I, III, IV and V, d) diffuse pattern on hand, distal dorsal arm and fingers I, IV and V.

Different studies have demonstrated that lymphofluoroscopy is a valid imaging technique to evaluate superficial lymphatic transport in subjects with BCRL.[44, 45] Mihara et al[44] compared ICG lymphography with lymphoscintigraphy in secondary lower limb lymphedema. In this prospective trial, 29 patients with lymphedema after gynecological cancer were included, sensitivity and specificity of both investigations were calculated. In another study,[45] the same diagnostic tools in patients with secondary lymphedema of upper and lower limb and idiopathic edema (suspected primary lymphedema) were compared. Both concluded that ICG lymphography is a more accurate method and it is useful for assessing the indications for surgery (the abnormal pattern progresses or expands to the next stage). Compared to the lymphoscintigraphy, this technique does not use a radionuclide, has a lower cost and showed a benefit for early detection of lymphedema.[45]
Quantification of the ICG is at this moment not possible yet, as ICG is only seen in the superficial system and detection of ICG in the deep system is not possible. Reliability studies of the scoring of this NIRFLI are still lacking.

Detection and intervention of subclinical BCRL

Detection of lymphedema in a subclinical state defined as fluid accumulation is present but not clinically apparent, has become more and more important. Preoperative and postoperative measurements at regular times are needed to be able to detect subclinical lymphedema.
Different methods have been used to detect and intervene on subclinical lymphedema, but there still is no agreed gold standard for the diagnosis of subclinical lymphedema. In some studies a threshold of ≥ 3% volume increase is defined as a subclinical lymphedema.[46] Bundred et al enrolled 964 patients in a prospective study with BIS and perometry measurements and found that BIS detected more patients with BCRL, the threshold for early intervention being a 5-10% volume increase.[47] Another publication by this group stated that BIS alone without circumference measurement will overestimate the diagnosis of BCRL.[48] A study by Lahtinen et al, found that the combination of volume measurement and TDC is the most efficient for early detection, measuring different aspects of arm lymphedema.[49]
Different types of interventions have been used, but also without an international consensus. Except for manual lymph drainage and exercise alone, which are proven not to be efficient as a preventive measure for BCRL.[50]
It is important to start treatment in an early phase to prevent further evolution of the BCRL to fibrous and fatty tissue[12,17,51] but another purpose of early detection and intervention could be to prevent the evolution towards BCRL.
A study by Stout et al, investigated if wearing a compression garment could alleviate subclinical lymphedema and could be discontinued. A volume increase

of ≥ 3% (measured with perometry) was set as a threshold to start treatment with exercises and a compression garment (ready-made, 20-30 mmHg). Intervention continued during 4,4 weeks. After the intervention a statistically significant decrease of volume was realized.[52] This result was maintained up to a follow-up of 4.8 months with wearing the garment only during activity. Soran et al performed monitoring with BIS in their study and they were able to detect subclinical lymphedema in 33% of the patients and reduced the range of BCRL from 36.4% in the control group to 4.4% in the early intervention group (physical therapy, garments, education,..).[53] The study by Kilgore et al followed-up high-risk patients with BIS and started self-massage and compression garments when the threshold was met.[54] In 34% of the patients subclinical lymphedema was seen and after 4 weeks of intervention 82% of the patients returned to normal baseline range.[54] Unfortunately, these last two studies didn't use a control group.
Lymphofluoroscopy is a valid imaging technique for early detection of BCRL according to the study by Akita et al.[55] One hundred ninety-six patients planned to receive surgical treatment for breast cancer were included. Twenty-five percent (50 patients) developed a dermal backflow pattern within the first year after the surgery: 24 splash pattern and 26 stardust, diffuse or no transport. When a stardust pattern was seen treatment with skin care, exercise, elevation and the use of a compression sleeve was started. In 24 patients the abnormal pattern (stardust or diffuse) remained visible up to the last follow-up visit (20.1 +/- 3.4 months), in 9 patients a splash pattern remained visible and in 17 patients the pattern returned to normal. In this study it is presumed that only a stardust pattern is a predictor for the development of BCRL and not the splash pattern. The question whether a disturbance of the lymphatic transport (any dermal backflow pattern) visualized by lymphofluoroscopy is a risk factor for the development of BCRL has never been investigated before.

Treatment of lymphedema

Decongestive lymphatic therapy (DLT) remains the gold standard for treatment of BCRL[11,56] This conservative treatment consists of two phases. The first phase is an intensive phase and according to the severity of the lymphedema it lasts 1 to 4 weeks. This phase consists of skin care, manual lymph drainage, multi-layer bandaging, exercises, nutritional advice and education. In the second phase, the maintenance phase, the aim is to stabilize the result that was achieved in the intensive phase. Exercises, skin care, self-management, compression therapy, such as wearing a flat-knitted garment, manual lymph drainage and nutritional advice are part of this maintenance phase.[11,57] Different studies have shown that DLT is an effective treatment for reducing lymphedema volume.[56,58,59] In daily practice, especially manual lymph drainage is used as a treatment for BCRL, although the con-

tribution of the manual lymphatic drainage in the treatment of BCRL is limited.[60, 61] Lymphatic surgery consist of two types of surgery depending on the severity of the lymphedema. Reconstructive surgery such as lymphovenous anastomosis and vascularized lymph node transplantations aim to restore the impaired lymphatic transport. A review by Cornellisen et al concluded that there is a need for more prospective, randomized trials with uniform evaluations and long-term follow-up to show the added effect of these techniques on top of a good conservative treatment.[62] Circumferential suction-assisted lipectomy is another type of surgery where the damaged tissue is being removed to improve functioning of the patient and reduce the rate of infections.[31] This technique has proven to be efficient in patients with more advanced lymphedema in which the swelling is dominated by fat deposition and fibrosis.[63] The use of garments stays mandatory after this surgical intervention.[64]

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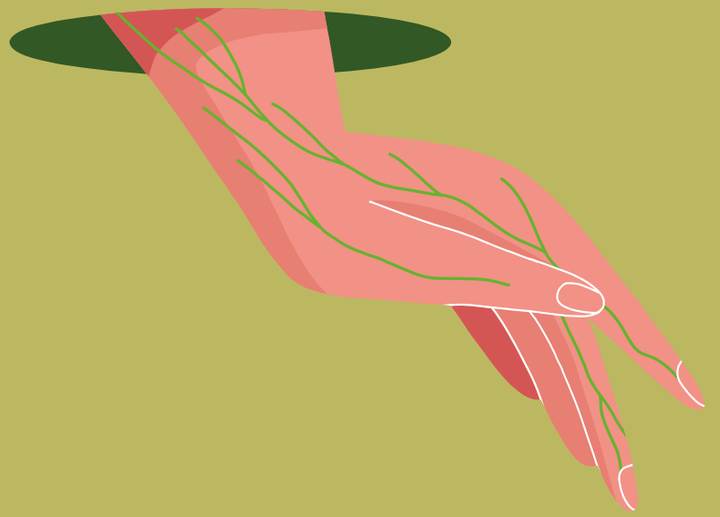

General hypothesis and specific aims

General hypothesis

In this thesis we **hypothesize** that

1.
ICG lymphofluorscopy is a useful evaluation tool that can be used in the management of breast cancer-related lymphedema.

2.
ICG lymphofluoroscopy is an important evaluation tool that can be used for early detection of breast cancer-related lymphedema.

Specific aims

The **specific aims** of this thesis are:

AIM 1:
To investigate the correlation between dermal backflow visualized by lymphofluoroscopy and the clinical assessment of BCRL **(chapter 1)**.

AIM 2:
To investigate in patients with BCRL the interrater reliability of the scoring of the lymphatic transport, investigated through lymphofluoroscopy **(chapter 2)**.

AIM 3:
To investigate in patients with early disturbance of the lymphatic system (visualized by lymphofluoroscopy) which clinical assessment method relates the most with the presence of this early disturbance **(chapter 3)**.

AIM 4:
To perform a systematic review regarding the risk factors for the development of BCRL **(chapter 4)**.

AIM 5:
To investigate early disturbance of the lymphatic transport visualized by lymphofluoroscopy as a risk factor for the development of BCRL **(chapter 5)**.

AIM 6:
To investigate the impact of a compression garment, on top of the usual care, in breast cancer patients with early disturbance of lymphatic transport **(chapter 6 and 7)**.

1

Correlation between clinical assessment and lymphofluoroscopy in patients with breast cancer-related lymphedema: a study of concurrent validity

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ABSTRACT

Background:
A disturbance of the superficial lymphatic system (dermal backflow) in patients with breast cancer-related lymphedema (BCRL) can be visualised by near-infrared fluorescence imaging or lymphofluoroscopy. In clinical practice, exact measurement of the dermal backflow is difficult. The purpose of the study is to investigate the concurrent validity between the clinical assessments and the lymphofluoroscopy in patients with BCRL.

Methods:
Forty-five patients with BCRL stage I to IIb received lymphofluoroscopy and clinical assessments of their edematous limb (pitting status, skinfold thickness, skin elasticity, water content, lymphedema volume, extracellular fluid). The correlation between the clinical assessments and the result of the lymphofluoroscopy was determined.

Results:
The best overall agreement with dermal backflow was found for the clinical assessment pitting status, skinfold thickness and water content. Overall sensitivity was excellent for lymphedema volume (92.5%), high for skinfold thickness (86.6%) and water content (75.0%) and moderate for pitting status (67.7%). Overall specificity was excellent for skin elasticity (94.7%), high for pitting status (83.4%) and moderate for skinfold thickness (61.6%) and water content (74.8%). In the evaluation of the whole arm, measurements of the excess volume were significantly greater for patients in an advanced stage of dermal backflow in comparison with patients in an earlier stage of dermal backflow ($p = 0.002$).

Conclusions:
The clinical assessments skinfold thickness, local water content and lymphedema volume are the most appropriate tools to detect dermal backflow according to the lymphofluoroscopic images. To confirm the absence of dermal backflow, pitting status can be recommended.

INTRODUCTION

Breast cancer-related lymphedema (BCRL) is the swelling of the upper limb after treatment for breast cancer (secondary, acquired lymphedema). The regional swelling is usually a result of a disturbed transport capacity (related to radiotherapy and/or surgery) and an increase in lymph load.[1–3]
There are different methods to evaluate BCRL in a clinical setting, yet there is no consensus concerning the best standard measurement tool.[4] The volume of the limb can be assessed with circumference measurements; based upon these data excess volume can be calculated.[5] Water displacement is another technique to assess the volume.[6] Hereby, the extremity is immerged in a container of water, the amount of the displaced water represents the volume of the limb.[7] The amount of water in the edematous limb can also be assessed by means of a pitting test,[8] bioelectrical impedance spectroscopy (BIS)[9] or the tissue dielectric constant (TDC).[10,11] Measurement of the skin fold thickness (Stemmer sign) can be performed, an increased thickness is a typical sign for lymphedema.[12]

Near-infrared fluorescence imaging of the lymphatic system, also called lymphofluoroscopy, is an imaging technique that can be used to assess the lymphatic architecture. A tracer, indocyanine green (ICG), is injected in the patient's limb. Once excited by a near-infrared light, ICG emits a fluorescent photon. By visualising this fluorescence of near-infrared light the lymph flow can be observed.[13,14] The technique provides real-time video images of the lymphatic transport. This real-time imaging is an advantage as you clearly see the lymph vessels and areas of disturbances immediately on the screen and are able to mark these areas on the affected limb. The patient can visualise the images himself and will be able to understand the pathology better.

In healthy subjects, lymphofluoroscopy shows a linear lymph transport pattern. Three dysfunctional backflow patterns of lymphatic transport can be distinguished in patients with lymphedema. The first one is the splash pattern, representing a dispersed tracer in tortuous lymphatic channels. The second one, more severe disturbed pattern, is the stardust pattern, which demonstrates spotted fluorescent signals, representing the effusion of lymph fluid out of the lymphatic capillaries into the interstitium. The last type of pattern is the diffuse pattern by which the tracer is widely distributed without identifiable spots. In this pattern, besides the accumulation in the lymphatic capillaries and lymph precollectors, lymph is stagnated in the interstitium.[15]

The information obtained by lymphofluoroscopy can be used to optimise the treatment of BCRL. By clearly identifying the dermal backflow areas and the remaining lymph vessels, manual lymph drainage can be adjusted according to that image. This fluoroscopy-guided manual lymph drainage is an individual-tailored approach.[16] The pressure of the therapist's hands will be different in an area where dermal backflow can be seen. A more severe dermal backflow pattern requires a higher pressure. The lymph flow stimulating effect of this technique was demonstrated in healthy volunteers and in patients with breast cancer-related lymphedema.[17,18] Also according to the images, adjustment to the compression hosiery can be made. Unfortunately, lymphofluoroscopy is a rather intensive examination, that needs to be performed in a medical setting and requires specific and expensive equipment. The question is whether the result of the lymphofluoroscopy can be partially estimated by a clinical assessment of lymphedema so that lymphofluoroscopy will not be necessary in all cases but an individualized treatment can still be offered.

Therefore, the purpose of this study was to examine the concurrent validity between the clinical assessment of a patient with lymphedema and the results obtained from lymphofluoroscopy.

MATERIAL AND METHODS

Participants

Patients with BCRL of the arm and/or hand were recruited at the University Hospitals of Leuven and the University Hospital of Antwerp for the EFforT-BCRL trial (Effectiveness of Fluoroscopy-guided manual lymph drainage for treatment of BCRL).[16] Data of the first 45 patients were collected between February 2016 and March 2017. The same inclusion and exclusion criteria were used as in the EFforT-BCRL trial: 1) patients with BCRL and >18y, 2) chronic lymphedema (>3months present, stage I to IIb) and 3) at least 5% difference (measured with circumference measurements) between both arms/hands adjusted for dominance. Exclusion criteria were allergy for iodine, sodiumiodine or Indocyanine Green, increased activity/benign tumours of the thyroid gland, edema of the upper limb from other causes, active metastasis of the cancer, reconstructive or debulking surgery of the lymphatic system in the past, inability to participate during the entire study period and mentally or physically unable to participate. This study was approved by the Ethical Committee of the University Hospitals Leuven (S-number 58689) and Antwerp. All participants signed informed consent. For this study the STROBE statement was used.

Study design

In this cross-sectional study, all included patients underwent near-infrared fluorescence imaging and a series of clinical measurements of their edematous limb, with a maximum of 3 weeks between both assessments. Only measurements at baseline were used.

Lymphofluoroscopy – All lymphofluoroscopies were performed by the same vascular surgeon, who is experienced in performing these investigations and was assisted by an experienced physical therapist. A standard protocol for lymphofluoroscopy was applied [16]. With one syringe of 1 ml, a solution of 0.2 ml ICG, saline water and pure water was strictly injected intradermally at the first and fourth web space, dorsally in the hand of the edematous limb. To visualise the lymphatic system, an infrared camera system (PDE camera®, Hamamatsu, Japan) was used.
All the information about the lymphatic transport was documented in a standard evaluation document. The active lymph nodes and vessels as well as the dysfunctional backflow patterns (splash, stardust, diffuse) were drawn on a body diagram **(Figure 1)**.

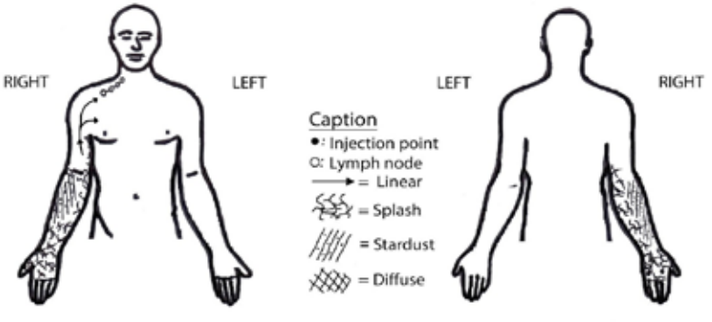

FIGURE 1.
Example of a body diagram based on the lymphofluoroscopic images

Clinical assessment – **Table 1** gives an overview of the different clinical assessments. Three experienced investigators performed all measurements. To ensure blinding, the investigator of the clinical measurements was different from the one performing the lymphofluoroscopy.

TABLE 1.
Description of the different clinical assessment

Clinical assessment	*Measurement procedure*	*Indication of*	*Outcome measurements*	*Processing*
Pitting status	The therapist gives a vertical pressure with the thumb for 5 seconds at the following 7 locations: hand, ventral and dorsal forearm, elbow, ventral and dorsal upper arm and shoulder (see **Figure 3**). The degree of pitting/depression after the release of thumb pressure is determined.[8]	Amount of free-fluid in the superficial interstitial tissue space	pitting is clearly present = 2 the presence of pitting is doubtful = 1 the skin immediately returns to starting position = 0	0 = no pitting 1 = pitting (doubtful and clearly present)
Skinfold thickness	The examiner picks up the skinfolds between thumb and index finger at the same 7 locations. The skinfold thickness of the edematous side is compared to the non-edematous side.	Skinfold thickness	no increase in skinfold thickness in comparison to the non-edematous side = - an increase in skinfold thickness in comparison to the non-edematous side (stemmer's sign) = +	0 = no increase in skinfold thickness 1 = increase in skinfold thickness
Elasticity	Lymphedema is considered hard or soft through manual palpation at the same 7 locations. Edematous side is compared to non-edematous side.	Fibrosis	no or soft edema = - hard edema = +	0 = no or soft edema 1 = hard edema
Water content	A vertical contact is performed with the MoistureMeterD Compact® (Delfin) to measure the TDC at the same 7 locations. As result, a high electromagnetic wave is sent through the skin, penetrating 2.5 mm in depth. This wave will only be absorbed by water. Therefore less reflection of the wave indicates more water. This degree of reflection/ water content can be read on the display of the MoistureMeterD.[11,12]	Water content	% water content (PWC)	0 = PWC edematous side/ PWC non-edematous side < 1.2 1 = PWC edematous side/ PWC non-edematous side ≥1.2 [11]
Lymphedema volume	The arm is inserted into a tank filled with water up to the wrist (to determine hand volume; point A in figure 3), half of the forearm (to determine volume of lower part of the forearm; point B), the elbow fold (to determine volume of the upper part of the forearm; point C) and 10 cm above the elbow fold (to determine volume of the upper arm; point D). The overflow of water is measured with help of the volume meter Belgrado. This amount of water displacement of the edematous and contralateral side are compared with each other in order to be able to determine a possible increase in volume.	Lymphedema volume	Volume of hand, lower part of the forearm, upper part of the forearm and upper arm in ml.	0 = <5% difference in volume between the edematous and non-edematous side 1 = ≥5% difference in volume between the edematous and non-edematous side[24] Lymphedema volume of whole arm (%) (compared to ADBS)
Extracellular fluid	A bioimpedance spectroscopy device (L-dex U400, ImpediMed®) sends a varying frequency of current flow through a body part and the resistance to this (low) flow is determined. Electrodes were placed on the dorsum of the hands and foot.	Extracellular fluid at level of the arm	L-dex value ("lymphedema index"). Indication of difference in amount of water in the extracellular space between the edematous side and the contralateral side.	L-dex value (compared to ADBS)

Data processing

First, two researchers analysed the lymphofluoroscopic image independently. Thereafter they discussed their findings to reach a consensus about the evaluation of the lymphofluoroscopy. Finally, they analysed the clinical assessments.

Lymphofluoroscopy – A transparent body diagram with the reference points was placed on the body diagram of the lymphofluoroscopy, the presence of dermal backflow at 7 different reference points **(Figure 2)** was determined (yes/no). Secondly, arm dermal backflow stage was determined. Five different stages are differentiated (ADBS stage I-V): ADBS I shows a splash pattern, in ADBS II a stardust pattern is seen proximally to the olecranon, in ADBS III the stardust pattern exceeds the olecranon, in ADBS IV the stardust pattern is seen in the whole arm and in stage V a diffuse pattern is detected. This is a severity staging system that illustrates a significant correlation with clinical stage.[19]

Clinical assessment – Results of the clinical measurements of pitting status, skinfold thickness, elasticity and water content (scored as positive or not positive, detailed description of the scoring is presented in Table 1) were evaluated at the same reference points **(Figure 2)** as used in the evaluation of the lymphofluoroscopy.

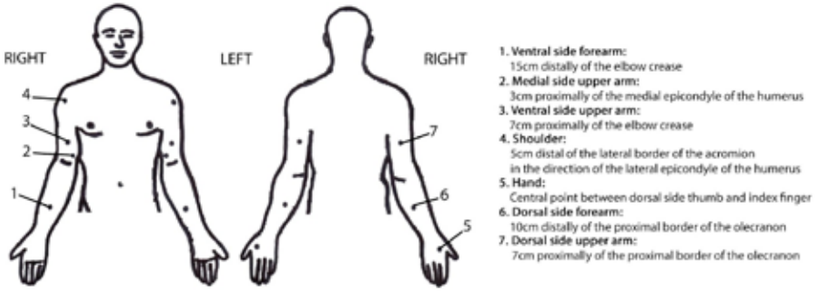

FIGURE 2.
Description of the different reference points needed for the local clinical assessments and to determine the presence of dermal backflow

The lymphedema volume was assessed by the water displacement method and by bioelectrical examination. The water displacement method reference points are shown in **Figure 3**. The volumes of the different regions defined by the water displacement reference points were matched to the reference points of the above-mentioned clinical measurements to enable comparison: the volume of the hand (up to point A) corresponded to the reference point at the dorsum of the hand (point 5), the volume of the lower part of the forearm (up to point B) to the point at the ventral side of the forearm (point 1); the volume of the upper part of the forearm to the point at the dorsal side of the forearm (point 6); the volume of the upper arm to the points at the medial side of the upper arm, ventral side of the upper arm and dorsal side of the upper arm (point 2, 3, 7).

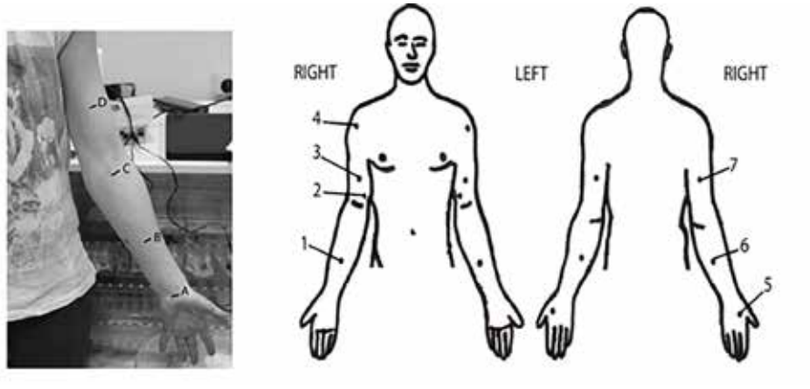

FIGURE 3.
Matching the reference points for volume measurement (A-D) to the reference points for the other clinical measurements (1-7).

Concurrent validity – To determine the correlation between the lymphofluoroscopy and the clinical assessments, the results of the clinical measurements (pitting status, skinfold thickness, skin elasticity, water content and lymphedema volume) were compared to the presence of the dermal backflow (yes/no, independent of the type of dermal backflow pattern) seen by the lymphofluoroscopy at the 7 reference points. The results of the lymphedema excess volume and extracellular fluid of the whole arm were compared to the different stages of the arm dermal backflow. The sensitivity and specificity of the clinical assessments were analysed with lymphofluoroscopy being the gold standard.

Data analysis

Statistical analyses were performed with SPSS 24.0. A 5% level of significance was applied. Patient and clinical characteristics were described using descriptive statistics.

To determine the agreement between the lymphofluoroscopy (0 = no backflow, 1 = dermal backflow (splash, stardust, diffuse)) and the clinical assessments (pitting status, skinfold thickness, elasticity, water content, lymphedema volume) (0 or 1, see **Table I)**, Cohen's Kappa statistics was used. The Kappa coefficients were interpreted as follows: <0.400 was a weak agreement, between 0.400 and 0.744 was a moderate agreement, between 0.745 and 0.900 was a strong agreement and >0.900 was a very strong agreement.[20]
Sensitivity and specificity were interpreted as follows: <60% was a weak sensitivity or specificity, between 60% and 74% was a moderate sensitivity or specificity, between 75% and 90% was a high sensitivity or specificity and >90% was an excellent sensitivity or specificity.

A Kruskal-Wallis test was used to compare the lymphedema volume of the whole arm and extracellular fluid of the arm to the arm dermal backflow stages (ADBS). To make comparison possible, three different groups were created based on the ADBS. The first one included ADBS I which represented an early stage of dermal backflow. The second one represented a partial stardust pattern (ADBS II and III). The third one described an advanced lymphatic dysfunction (ADBS IV and V). To compare the differences between the stages, post-hoc analyses were performed with the Mann-Whitney U-test. Due to multiple comparisons and the associated risk of type I error, a Bonferonni correction was applied to the significance level.

RESULTS

Forty-five patients with a mean age of 61.3 years (range 37-82; SD 9.9) were included in the study. Body mass index (BMI) ranged between 20.9 and 39.3 (mean: 27.8; SD: 4.8). Detailed patient characteristics are summarized in **Table 2**.

TABLE 2.
Overview of the characteristics of the included patients

	N	*Mean (SD) / Frequency (%)*[a]
Age (y)	45	61.3 (9.9)
BMI (kg/m²)	45	27.8 (4.8)
Duration of lymphedema (months)	45	42.0 (67.5)[b]
Lymphedema volume (ml)	45	533.0 (336.1)
Lymphedema excess (%)	45	29.6 (18.1)
Time since surgery (months)	45	82.0 (75.8)
Side of surgery	45	
- Left		21 (47%)
- Right		24 (53%)
Surgery on the dominant side	45	23 (51%)
Breast surgery	45	
- Mastectomy		28 (62%)
- Breast-conserving surgery		17 (38%)
Type of cancer	45	
- Ductal		37 (82%)
- Lobular		8 (18%)
Tumor stage	44	
- T1		11 (25%)
- T2		25 (57%)
- T3		6 (14%)
- T4		2 (4%)
Node stage	43	
- N0		12 (28%)
- N1		25 (58%)
- N2		5 (12%)
- N3		1 (2%)
Lymphedema stage	45	
- I		9 (20%)
- IIa		18 (40%)
- IIb		18 (40%)
Radiotherapy	45	44 (98%)
Chemotherapy	45	40 (89%)
Endocrine therapy	45	39 (87%)
Target therapy (Herceptin)	44	10 (22%)
Arm dermal backflow stages (ADBS)	45	
- ADBS 1		12 (27%)
- ADBS 2		1 (2%)
- ADBS 3		25 (56%)
- ADBS 4		6 (13%)
- ADBS 5		1 (2%)
Lymphatic transport	45	
- Linear		45 (100%)
- Splash		36 (80%)
- Stardust		33 (73%)
- Diffuse		1 (2%)
Interval between clinical assessment and lymphofluoroscopy (days)	45	7 (11.5)[b]
Duration of lymphofluoroscopy (minutes)	41	107.0 (19.1)

[a]Mean and standard deviation for continuous data; frequency and percentage for discontinuous data.
[b]Not normal distributed: median (interquartile range)

Table 3 shows the agreement between the presence of dermal backflow and the clinical measurements at the 7 reference points. For lymphedema volume, a moderate agreement was found for the hand (Kappa = 0.636) and ventral forearm (Kappa = 0.545). A strong agreement was noticed for the dorsal forearm (Kappa = 0.760). For pitting status, evaluation of the skin fold and water content, an overall moderate agreement was found. The clinical outcome parameter elasticity showed a moderate agreement for the shoulder region (Kappa = 0.483).

TABLE 3.
Correlation between lymphofluoroscopy (dermal backflow yes/no) and clinical measurements (positive or negative test 0/1).

Clinical measurements	*Reference point*	N	*Agreement N (%)*	*Correlation Kappa*	P
Pitting status	Hand	45	32 (71%)	0.451	0.001*
	Ventral forearm	45	36 (80%)	0.444	0.002*
	Dorsal forearm	45	39 (87%)	0.585	<0.001*
	Elbow	45	26 (58%)	0.153	0.302
	Ventral upper arm	45	29 (64%)	0.200	0.143
	Dorsal upper arm	45	36 (80%)	0.571	<0.001*
	Shoulder	45	39 (87%)	0.182	0.205
	OVERALL	315	237 (75%)	0.508	<0.001*
Skinfold thickness	Hand	45	35 (78%)	0.524	<0.001*
	Ventral forearm	45	36 (80%)	0.286	0.048*
	Dorsal forearm	45	40 (89%)	0.638	<0.001*
	Elbow	45	31 (69%)	0.303	0.011*
	Ventral upper arm	45	32 (71%)	0.381	0.010*
	Dorsal upper arm	45	28 (62%)	0.298	0.018*
	Shoulder	45	35 (78%)	0.074	0.550
	OVERALL	315	237 (75%)	0.486	<0.001*
Elasticity	Hand	45	25 (56%)	0.202	0.024*
	Ventral forearm	45	20 (44%)	0.113	0.188
	Dorsal forearm	45	19 (42%)	0.092	0.259
	Elbow	45	20 (44%)	0.021	0.747
	Ventral upper arm	45	27 (60%)	0.022	0.768
	Dorsal upper arm	45	25 (56%)	-0.042	0.720
	Shoulder	45	43 (96%)	0.483	<0.001*
	OVERALL	315	179 (57%)	0.161	<0.001*
Water content	Hand	45	34 (76%)	0.523	<0.001*
	Ventral forearm	45	35 (78%)	0.405	0.005*
	Dorsal forearm	45	35 (78%)	0.413	0.003*
	Elbow	45	24 (53%)	-0.054	0.636
	Ventral upper arm	45	35 (78%)	0.528	<0.001*
	Dorsal upper arm	45	31 (69%)	0.375	0.011*
	Shoulder	45	42 (93%)	0.366	0.012*
	OVERALL	315	236 (75%)	0.498	<0.001*
Lymphedema volume	Hand	45	37 (82%)	0.636	<0.001*
	Ventral forearm	45	39 (87%)	0.545	<0.001*
	Dorsal forearm	45	42 (93%)	0.760	<0.001*
	Elbow	45	25 (56%)	0.004	0.970
	Ventral upper arm	45	23 (51%)	0.141	0.131
	Dorsal upper arm	45	25 (56%)	0.219	0.019*
	Shoulder	/	/	/	/
	OVERALL	270	191 (71%)	0.338	<0.001*

* = statistical significance was determined at the level of $p < 0.05$.

Table 4 shows the sensitivity and specificity of the different clinical measurements in comparison to the dermal backflow patterns obtained by lymphofluoroscopy. Overall sensitivity was excellent for lymphedema volume (92.5%), high for skinfold thickness (86.6%) and water content (75.0%) and moderate for the clinical outcome parameter pitting status (67.7%). Overall specificity was excellent for elasticity (94.7%), high for pitting status (83.4%) and moderate for the clinical outcome parameters skinfold thickness (61.6%) and water content (74.8%).
The agreement of dermal backflow with lymphedema volume and extracellular fluid of the whole arm was determined by the different stages of the ADBS.

TABLE 4.
Sensitivity and specificity of clinical measurements

Clinical measurements	*Reference point*	*N*	*Positive tests*	*True positives*	*Sensitivity*	*Specificity*
Pitting status	Hand	45	15 (33%)	14 (93%)	53.8%	94.7%
	Ventral forearm	45	33 (73%)	30 (91%)	83.3%	66.7%
	Dorsal forearm	45	35 (78%)	33 (94%)	89.2%	75.0%
	Elbow	45	23 (51%)	15 (65%)	57.7%	57.9%
	Ventral upper arm	45	10 (22%)	6 (60%)	33.3%	85.2%
	Dorsal upper arm	45	15 (33%)	12 (80%)	66.7%	88.9%
	Shoulder	45	5 (11%)	1 (20%)	33.3%	90.5%
	OVERALL	315	136 (43%)	111 (82%)	67.7%	83.4%
Skinfold thickness	Hand	45	32 (71%)	24 (75%)	92.3%	57.9%
	Ventral forearm	45	39 (87%)	33 (85%)	91.7%	33.3%
	Dorsal forearm	45	36 (80%)	34 (94%)	91.9%	75.0%
	Elbow	45	38 (84%)	25 (66%)	96.2%	31.6%
	Ventral upper arm	45	15 (33%)	10 (67%)	55.6%	81.5%
	Dorsal upper arm	45	31 (69%)	16 (52%)	88.9%	44.4%
	Shoulder	45	9 (20%)	1 (11%)	33.3%	81.0%
	OVERALL	315	200 (63%)	143 (72%)	86.6%	61.6%
Elasticity	Hand	45	6 (13%)	6 (100%)	23.1%	100%
	Ventral forearm	45	13 (29%)	12 (92%)	33.3%	88.9%
	Dorsal forearm	45	13 (29%)	12 (92%)	32.4%	87.5%
	Elbow	45	3 (7%)	2 (67%)	7.7%	94.7%
	Ventral upper arm	45	2 (4%)	1 (50%)	5.6%	96.3%
	Dorsal upper arm	45	6 (13%)	2 (33%)	11.1%	85.2%
	Shoulder	45	1 (2%)	1 (100%)	33.3%	100%
	OVERALL	315	44 (14%)	36 (82%)	22.0%	94.7%
Water content	Hand	45	19 (42%)	17 (89%)	65.4%	89.5%
	Ventral forearm	45	32 (71%)	29 (91%)	80.6%	66.7%
	Dorsal forearm	45	31 (69%)	29 (94%)	78.4%	75.0%
	Elbow	45	39 (87%)	22 (56%)	84.6%	10.5%
	Ventral upper arm	45	16 (36%)	12 (75%)	66.7%	85.2%
	Dorsal upper arm	45	22 (49%)	13 (59%)	72.2%	66.7%
	Shoulder	45	2 (4%)	1 (50%)	33.3%	97.6%
	OVERALL	315	161 (51%)	123 (76%)	75.0%	74.8%
Lymphedema volume	Hand	45	26 (58%)	22 (85%)	84.6%	78.9%
	Ventral forearm	45	38 (84%)	34 (89%)	94.4%	55.6%
	Dorsal forearm	45	38 (84%)	36 (95%)	97.3%	75.0%
	Elbow	45	38 (84%)	22 (58%)	84.6%	15.8%
	Ventral upper arm	45	38 (84%)	17 (45%)	94.4%	22.2%
	Dorsal upper arm	45	38 (84%)	18 (47%)	100%	25.9%
	Shoulder	/	/	/	/	
	OVERALL	270	216 (80%)	149 (69%)	92.5%	38.5%

Table 5 describes the number of patients, median and interquartile range for lymphedema excess volume and extracellular fluid of the whole arm for the different stages of ADBS. There was a significant difference between the lymphedema excess volume for the different ADBS (p = 0.004). The excess volume was significant greater for patients in ADBS II/III in comparison with patients in ADBS I (p = 0.002). There was borderline significant difference in excess volume for patients in ADBS IV/V in comparison with patients in ADBS I (p = 0.090). There was no significant difference in excess volume between ADBS II/III and ADBS IV/V (p = 1.000).
The amount of extracellular fluid did not show a significant difference for the different ADBS (p = 0.100). More specifically, no significant difference was found in amount of extracellular fluid between ADBS I and II-III (p = 0.144), ADBS I and IV-V (p = 0.136) and ADBS II-III and IV-V (p = 1.828).

		N	*Median*	IQR	P
Lymphedema excess volume (%)					0.004*
	ADBS I	12	8.0	20.0	
	ADBS II and III	26	29.5	31.0	
	ADBS IV and V	7	26.0	28.4	
Extracellular fluid (L-dex)					0.100
	ADBS I	12	12.5	25.7	
	ADBS II and III	26	33.1	46.9	
	ADBS IV and V	7	32.3	39.5	

* = statistical significance was determined at the level of p < 0.05.
N= number of patients

TABLE 5.
Description of number of patients (N), median, interquartile range (IQR) and p-value (P) for lymphedema excess volume and extracellular fluid of the whole arm for the different arm dermal backflow stages (ADBS).

DISCUSSION

To our knowledge, this is the first study investigating the concurrent validity between clinical assessments and dermal backflow obtained from lymphofluoroscopy in patients with BCRL.

The pitting test showed an overall moderate agreement with the presence of dermal backflow. Especially the hand, dorsal forearm, ventral forearm and dorsal upper arm had a moderate agreement with dermal backflow. For these regions, the result of the pitting test agreed with the lymphofluoroscopic image. A high overall specificity was found for the pitting test. Be aware that in this study only stage I to IIb lymphedema patients were included. One of the inclusion criteria for the EFforT-BCRL trial was the presence of pitting somewhere in the limb. Patients with lymphedema stage III, where the pitting is no longer present because of advanced fibrotic changes, did not take part of the study. In conclusion, patients in stage I to IIb lymphedema without pitting are likely not to have dermal backflow.

The skinfold thickness showed an overall moderate agreement with the presence of dermal backflow. Especially the hand and dorsal forearm had a moderate agreement with dermal backflow. A high overall sensitivity for skinfold thickness was seen. Therefore, if an increased skinfold thickness is found in patients with lymphedema stage I to IIb, a disrupted lymphatic transport can be expected.
A weak agreement was seen between elasticity and the presence of dermal backflow. If manual palpation indicates that there is no or soft edema, the presence of dermal backflow cannot be excluded. Alternatively, in case of hard edema, the presence of dermal backflow may not be expected. The weak agreement corresponds to what is described in the literature, e.g. advanced fibrotic and fatty changes are rare in stage I to IIb lymphedema.[21] Consequently, the lymphatic transport can be disturbed without a positive clinical test for elasticity. Therefore elasticity is not a suitable parameter to evaluate lymphatic transport in stage I to IIb lymphedema patients.

For the water content, an overall moderate agreement was seen. For the regions hand, ventral forearm, dorsal forearm and ventral upper arm, the result of the water content correlated with the lymphofluoroscopic image. A high overall sensitivity and a moderate overall specificity could be shown. These results correspond to the hypothesis of Czerniec et al[22] that patients in the first stages of lymphedema usually show a positive test of water content. In conclusion, patients in stage I to IIb lymphedema who do not have a positive test of water content are likely to have no disturbed lymphatic transport and if an increased water content is noticed, dermal backflow can be expected.

Lymphedema volume demonstrated a strong agreement with the dorsal forearm and a moderate agreement for the hand and ventral forearm. In these regions, the volume measurement was appropriate to evaluate lymphatic transport. An excellent overall sensitivity for the clinical outcome parameter lymphedema volume was seen. If an increased lymphedema volume is found, presence of dermal backflow can be expected.
In the evaluation of the whole arm, lymphedema excess volume was significant greater for patients in an advanced stage of dermal backflow (stardust pattern at the upper arm) in comparison with patients in a mild stage of dermal backflow (splash pattern somewhere in the arm).

This study has several strengths. First, all investigators were blinded to the fluoroscopic images. Patients had a wide range of age and BMI which makes our population representative for all patients with breast cancer-related stage I to IIb lymphedema. A number of six clinical measurements, performed by experienced clinical therapists, were compared to lymphofluoroscopy. Second, each patient completed both the clinical assessment and lymphofluoroscopy, leading to no missing data. Third, the interval between clinical assessment and fluoroscopy had to be a maximum of 3 weeks; however, examinations were completed in a mean time of only 9.1 days. Fourth, beside the statistical analysis with Cohen's Kappa, also sensitivity and specificity were calculated.

The study has a few limitations. To determine the correlation between lymphofluoroscopy and clinical measurements, dichotomous variables were necessary to make statistics possible. Therefore, cut-off values were installed to be able to formulate the clinical measurements water content and lymphedema volume, which can entail a certain amount of error. Nevertheless, Mayrovitz et al.[23] demonstrated for the water content that a ratio of 1.2 and above could be useful to indicate lymphedema if measured with the MoisterMeterD in women who have previously been surgically treated for breast cancer. For the lymphedema volume, a threshold of 5% was used. Ancukiewicz et al.[24] showed that for the diagnosis of lymphedema, the use of relative arm volume changes (5% or 10%) is preferred. The current study selected a relative arm volume difference between oedematous and non-oedematous side of 5% as cut-off for the lymphedema volume because an overestimation of lymphedema was more wanted than an underestimation.

The results of the present study indicate that several clinical assessments can be used to assess whether dermal backflow can be expected or not, in patients with stage I to IIb lymphedema. The most appropriate clinical measurements to estimate lymphatic transport disturbances are pitting status, skinfold thickness, water content and lymphedema volume. More specifically, if an increased skinfold thickness, water content or lymphedema volume is noticed, dermal backflow will most likely

be present. If no pitting or increased water content is present, dermal backflow will probably be absent. Assessing the skinfold thickness, pitting status and volume measurements can be performed in clinical practice by the health care provider as an estimation for the disturbance seen on lymphofluoroscopy. Even patients can assess skinfold thickness and pitting status themselves.
For all these clinical assessments, elbow and shoulder region showed a rather bad correlation with the presence or absence of dermal backflow. Therefore, these regions are not appropriate to estimate dermal backflow.

Information about the presence or absence of dermal backflow can be useful in optimisation of treatment of breast cancer-related lymphedema. The lymphatic system is usually damaged by surgery and/or radiotherapy and the lymphatic transport needs to find an alternative pathway. In the treatment of BCRL, it can be necessary to adapt the compression therapy to the patients' specific lymphatic transport. For example, in a patient with dermal backflow of the lower arm and not on the upper arm, an adapted compression garment can be chosen, e.g. only compression to the hand and lower arm will be necessary and manual lymph drainage can be adjusted according to the image (fluoroscopy-guided lymph drainage). The remaining lymph vessels will be emptied and a higher pressure will be applied to the area with dermal backflow. When a stardust or diffuse pattern is seen, a higher pressure has to be applied than on a splash pattern.

In the current study only patients with arm lymphedema stage I to IIb were included. Future research should also include patients with lymphedema stage III and patients with lower limb lymphedema. Further, this study only made a difference between dermal backflow or not. Future research should be focused on the gradation of dermal backflow and the clinical assessments of lymphedema.

CONCLUSION

The study results indicate a correlation between certain clinical assessments and the presence of a dermal backflow pattern visualised during lymphofluoroscopy in patients with BCRL stage I to IIb. Therefore, these clinical measurements can actually be used to obtain more information about dermal backflow in clinical practice. The clinical assessment parameters skinfold thickness, water content and lymphedema volume seem to be the most appropriate examinations to detect dermal backflow clinically. To confirm the absence of dermal backflow, pitting status is a suitable test.

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2

The interrater reliability of scoring of the lymphatic architecture and transport through Near-InfraRed Fluorescence Lymphatic Imaging in patients with breast cancer-related lymphedema.

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ABSTRACT

Introduction:
Of the 1.38 million women who are diagnosed every year with breast cancer worldwide, 21% will develop arm lymphedema. The Near-InfraRed Fluorescence Lymphatic Imaging (NIRFLI) is an effective method for real time evaluation of the lymphatic system. Reliability studies of the scoring of this NIRFLI are lacking. The aim of this study is to investigate if the evaluation of the superficial lymphatic architecture and transport in patients with breast cancer-related lymphedema through NIRFLI can be performed in a reliable way.

Methods:
The outcome parameters used to assess the agreement were presence of lymphatic transport out of the injection sites, of dermal backflow patterns, of efferent lymphatic vessels and of lymph nodes. The NIRFLI evaluations were scored before and after break separately by two assessors.

Results:
The trial was approved by the Ethical Committee of University Hospitals Leuven. Twenty patients with lymphedema of the arm and/or hand were included. After the injection, there was a weak to very strong agreement for the presence of transport out of the injection sites (K = .459 - 1.000). The interpretation of the type of dermal backflow pattern varied from a weak (WK = .452) to very strong agreement (WK = 1.000) between the two assessors. The agreement of the visualization of the efferent lymphatic vessels was weak before and after the break (K = .490 and K = .571) and the agreement regarding the presence of lymph nodes was very strong (K = 1.000).

Conclusion:
Overall there was a moderate to strong agreement between the assessors when evaluating the lymphatic architecture and transport through NIRFLI.

INTRODUCTION

Worldwide, 1.38 million women are diagnosed with breast cancer. Numerous symptoms and disabilities are reported after treatment for breast cancer.[1-3] One of these reported disabilities is breast cancer-related lymphedema (BCRL). Lymphedema is defined as “an external (or internal) manifestation of lymphatic system insufficiency and deranged lymph transport”.[4] There is a need for good accessible imaging techniques with high resolution to visualize the lymphatic system. These techniques can be used to diagnose and monitor lymphedema.[5-6]

Lymphoscintigraphy is commonly used as an imaging tool. This technique gives qualitative and quantitative information that has a good sensitivity and specificity for diagnosing lymphedema.[7,8,9] It provides, additionally to diagnosis, dynamic imaging of the lymphatic architecture.[7,8]

A more recent visualization tool is the Near-InfraRed Fluorescence Lymphatic Imaging (NIRFLI). The NIRFLI is a valid imaging tool for the lymphatic system of the upper and lower limb.[8,10] Indocyanine Green (ICG) is injected intradermally and transported through the lymph vessels. A near infrared camera visualizes the superficial lymphatic architecture and shows a real time image. This tool offers detailed information on the superficial lymphatic network, without making use of ionizing radio-colloids.[5,11,12] Besides normal lymph vessels, three types of dermal backflow can be distinguished: splash, stardust and diffuse pattern.[13] The validity of NIRFLI is good compared to the lymphoscintigraphy for diagnosing lymphedema.[10,14,15] The main limitation of the NIRFLI is that only the superficial lymphatic capillary network up to two centimeters depth can be visualized.[9,10,12,15-16]
The NIRFLI is a subjective evaluation method because the evaluation of the images is based on the interpretation of the images by the assessor.[17] It is important to know if different assessors interpret the imaging in the same manner. The level of agreement between the assessors is called the ‘interrater reliability’.[17] To be able to implement the NIRFLI in the clinical practice for evaluation of the lymphatic system and to use it in clinical studies, evidence of interrater reliability is necessary. Therefore, the aim of this study was to investigate whether in patients with BCRL two different assessors can evaluate the lymphatic architecture and transport through NIRFLI in a reliable way.

METHODS

Study design

This observational study was a sub-study of a large randomized controlled trial to determine the effectiveness of the fluoroscopy-guided manual lymph drainage (MLD) for the treatment of BCRL (EFforT-BCRL trial).[18] During this study the patients received a NIRFLI at baseline, after three weeks of intensive decongestive treatment and after six months of maintenance treatment. One patient received an extra measurement after one year of treatment. For this study, patients were randomly selected at any of these measurement points. The evaluation of patients occurred at the departments of oncology and vascular surgery of the University Hospitals Leuven and at the General Hospital Groeninge in Kortrijk. Patients were evaluated between October 2018 and February 2020.
The Effort-BCRL trial was approved by the main Ethical Committee of the University Hospitals Leuven (CME reference S58689, EudraCT Number 2015-004822-33). The study has been registered in clinicaltrials.gov (NCT02609724).

Eligibility criteria

The same inclusion and exclusion criteria were used as in the EFforT-BCRL trial: 1) patients with BCRL and >18y, 2) chronic lymphedema (>3months present, stage I to IIb) and 3) at least 5% difference (measured with circumference measurements) between both arms/hands adjusted for dominance. Exclusion criteria were: 1) allergy to iodine, sodiumiodine or ICG, 2) increased activity/benign tumours of the thyroid gland, 3) edema of the upper limb from other causes, 4) active metastasis of the cancer, 5) reconstructive or debulking surgery of the lymphatic system in the past, 6) inability to participate during the entire study period and 7) mentally or physically unable to participate. All patients signed informed consent. For this study the STROBE statement was used.

Assessment

To visualise the lymphatic system, an infrared camera system (PDE camera®, Hamamatsu, Japan) was used. A detailed explanation of the procedure of NIRFLI and the distinction between the phases of the procedure that the assessors performed together and separately are shown in **table 1**. At the end of phase one, each assessor drew the visible lymphatic vessels, the lymphatic nodes and the dermal backflow patterns on the body diagram while the other assessor left the room.
Phase two consisted of an hour break with a standardized activity program. This program consisted of five minutes of squeezing of the hand, ten minutes of rest, five minutes of circle motions with the wrist and ten minutes of rest. This standardized activity program was repeated within the hour. After performing the scan in phase three, again the visible lymphatic vessels, the lymphatic nodes and the dermal backflow patterns were written down. The first assessor drew a design immediately on the body diagram. The last assessor first drew the design with a black alcohol marker on the skin of the participant then made pictures of the ventral and dorsal sides, and finally, drew the design on the body diagram.

Collection of data

The outcome parameters for the agreement between the two assessors were divided into four groups of parameters extracted at different phases of the procedure.

The first group was the **lymphatic transport out of the injection site**. This parameter was scored after three minutes of rest, after three minutes of activity, after five minutes of manual stimulation and after 60 minutes of break with a standardized activity program. The assessors scored the transport out of the ulnar and radial injection site and circled a ‘yes’ or a ‘no’ directly on the evaluation sheet. The timing of this transport after injection was noted.

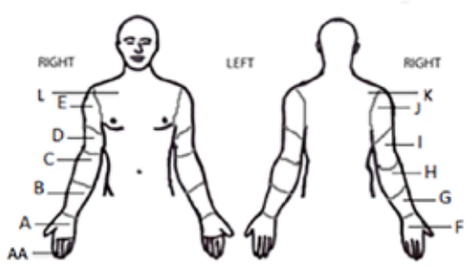
The second group was the amount of agreement concerning **the dermal backflow patterns**. This was evaluated before and after the 60-minute break. As shown in **figure 1**, for the evaluation of dermal backflow patterns, the affected arm was subdivided in thirteen zones. On the evaluation sheet, for each zone, the patterns were scored from 0-3 (0 = normal patterns, 1 = splash patterns, 2 = stardust patterns, 3 = diffuse patterns). If only a part of the zone had a score for a certain dermal backflow pattern, the whole zone received this score. If two patterns were seen in one arm zone, the worst dermal backflow pattern was scored. In addition, the total dermal backflow score comprised the sum of the dermal backflow scores from the thirteen zones (score between 0 and 39) of the upper limb.

The third group of the outcome parameters was based on the visualization of **the efferent superficial lymphatic vessels** leaving the dermal backflow region before the break and after the break.
If an efferent vessel departing from a dermal backflow region was noticed by the assessors, this was written on the evaluation sheet and a ‘yes’ was scored, if nothing was written a ‘no’ was scored.

The last group was based on the visualization of **the lymph nodes** before the break and after the break. The assessors evaluated if lymph nodes were visible in the axillary, humeral, retroclavicular and cubital region of the affected arm. If one or multiple lymph nodes were visible, a ‘yes’ was scored and if not, a ‘no’. The assessors wrote down the number of lymph nodes seen in each region.
The parameters were extracted from the standard evaluation sheet. If a parameter was unclear it was checked on the body diagram and on the data sheet. If a different parameter was seen, the data from the body diagram was used.

TABLE 1. Procedure of the NIRFL

Phase	*Step*	*Duration*	*Description of the procedure performed by the two assessors together*	*Reporting by the two assessors independently on the evaluation sheet */body diagram Δ*
Preparation	Dilution of Contrast Agent		Suspended ICG in 25 ml pure water and subsequently diluted with saline water to reach a final concentration of 0.20 mg/ml.	* Time of injection.
	Injection of Contrast Agent		Intradermal injection in the 1st (ulnar injection site) and the 4th (radial injection site) web space dorsum of the hand. 0.20 ml of the diluted solution is injected in each injection site.	
	Camera placement		The PDE camera (Hamamatsu) is held perpendicular to the observed skin at a distance of 15 cm (best focus).	
Phase 1	1.1. Rest	3 m	Hand in resting position on table. Observing the spreading lymph from the injection site. Focus camera on the injection site.	* Lymph transport out of the ulnar or radial injection site (yes/no). If yes, note the time post-injection.
	1.2. Activity	3 m	Place the hand of the patient over the border of the table. Ask the patient to perform flexion and extension of the hand, with a large range of motion while the lower arm is stable on the table.	* Increase of transport in the lymph collector out of the ulnar or radial injection site (yes/no). If yes, note time after the start of the activity.
	1.3. Stimulation	5 m	Stimulate lymphatic transport to spread the lymph through the superficial lymphatic network.	
	1.4. Perform a scan with the camera:	20 s	1) Of the arm and shoulder with hand in pronation: starting at hand up to the retroclavicular region. 2) Of the arm and axilla with hand in supination and abduction of the shoulder: starting at hand up to the axilla, together with the pectoral region: from the ipsilateral to the heterolateral axilla.	* - Number of lymph collectors (number), the length (in cm), location and dilated situation (normal vs dilated); -Number of lymph nodes;
Phase 1	1.4. Perform a scan with the camera:		3) Of the scapular region: from the ipsilateral to the heterolateral axilla.	- Presence of splash, stardust and diffuse pattern (yes/ no) and location (finger 1-5, hand dorsal/ ventral, lower arm ventral-distal/ ventral-proximal, dorsal-distal/dorsal-proximal, upper arm ventral-distal/ ventral-proximal, dorsal-distal/dorsal-proximal, breast and dorsal side).
	1.5 Close injection.		Place a piece of foam and cover it on the injection sites. Place a bandage around the hand to increase the pressure on the injection sites.	
	1.6 Design body diagram.			Δ Design on a body diagram of linear and dermal backflow pattern and lymph nodes.
Phase 2	2. Break	1 h	Break of 60 minutes: 5 minutes of squeezing, 10 minutes of rest, 5 minutes of circle motions with the wrist, 10 minutes of rest performed twice.	
Phase 3	3.1 Scan	20 s	Scan the same area as 1.4	* Repeat 1.4
	3.2		Design on a body diagram the lymphatic transport, rerouting and lymph nodes.	Δ First assessor draws a design on the body diagram. Last assessor first draws linear and dermal backflow pattern and lymph nodes on the skin of the patient. Then, makes pictures of ventral and dorsal side of arm and trunk. Finally, makes a design of the body diagram.



AA: Fingers
A: Hand, ventral side
B: Forearm, distal ventral side
C: Forearm, proximal ventral side
D: Upper arm, distal ventral side
E: Upper arm, proximal ventral side
F: Hand, dorsal side
G: Forearm, distal dorsal side
H: Forearm, proximal dorsal side
I: Upper arm, distal dorsal side
J: Upper arm, proximal dorsal side
K: Upper back (dorsal side)
L: Breast

FIGURE 1.
Diagram of the divided arm zones

Statistical analysis

For the statistical analyses SPSS version 26.0 was used for all analyses of all the parameters. To examine interrater reliability of nominal data (group 1,3 and 4), the percentage of agreement and Cohen's Kappa were established. For ordinal variables (group 2), the percentage of agreement and the linear Weighted Cohen's Kappa were determined. The continuous variables were analyzed using the Intraclass Correlation Coefficient (ICC), the mean and the standard deviation (SD). The Kappa coefficients were interpreted as follows: <0.40 was a minimal agreement, between 0.40 and 0.59 was a weak agreement between 0.60 and 0.79 was a moderate agreement, between 0.80 and 0.90 was a strong agreement and >0.90 was a very strong agreement.[17,19]

McHugh[17] stated that 'Low levels of interrater reliability (K < .60) are not acceptable in health care or in clinical research, especially when results of studies may change clinical practice in a way that leads to poorer patient outcomes.' The interpretation of Landis et al[20] was that in the healthcare studies 0.41 might lead to recommendations for changing practice based on incorrect evidence.[17,20,21] Any kappa below 0.60 indicates that there is only little confidence in the study results.[17] To be able to evaluate the interrater reliability of the measurements in a reliable way a Kappa of 0.60 or higher is considered as sufficient.

RESULTS

Study characteristics

Twenty patients participated in this study. Patient characteristics were described in **table 2**.

TABLE 2.
Patient characteristics (n=20)

Variables	*Outcome, mean (SD)*
Descriptive	
Age	60.5 (7.7)
Body mass index (kg/m^2)	28.3 (5.8)
Duration lymphedema (months)	63.5 (70.2)
Arm difference volume %	22.1 (14.9)
Arm + hand difference volume %	18.6 (13.9)
Hand difference volume %	14.9 (9.7)

Variables	*Outcome, N (%)*
Frequencies	
Lymphedema stage	
Stage I	5 (25)
Stage IIa	11 (55)
Stage IIb	4 (20)
Side lymphedema	
Right	6 (30)
Left	14 (70)
Location of lymphedema	
Arm	10 (50)
Arm + hand	9 (45)
Hand	1 (5)
Breast cancer	
IDA	16 (80)
ILA	2 (10)
Other	2 (10)
Breast surgery	
Mastectomy	16 (80)
Breast-conserving surgery	4 (20)
Amount of lymph nodes dissected	
0-9 lymph nodes	2 (10)
10-19 lymph nodes	11 (55)
20-29 lymph nodes	7 (35)
Surgery on the dominant side	6 (30)
Radiotherapy	20 (100)
Chemotherapy	16 (80)
Anti-hormonal therapy	6 (30)
Target therapy (Herceptin)	17 (85)
Measurement point	
At baseline	5 (25)
End intensive treatment	4 (20)
End maintenance treatment	10 (50)
After one year	1 (5)

Abbreviations: IDA = Invasive Ductal Adenocarcinoma, ILA = Invasive Lobular Adenocarcinoma, N = Number of participants in percentage, SD = Standard deviation.

Outcome transport out of injection sites

As shown in **table 3** and **figure 2**, there was for 7 out of 8 different outcomes a moderate (K = .643) to very strong (K = 1.000) agreement between both assessors regarding the lymphatic transport out of the injection sites at the different time intervals. Transport out of the radial injection site after rest was the only parameter showing a weak agreement (K = .459).

TABLE 3.
Transport out of injection site

Outcome	*Assessor 1*	*Assessor 2*	*Agreement*	*Kappa*	*p-value*
Transport out of injection site after rest	U = Yes: n=8 No: n=12 R = Yes: n=3 No: n=17	U = Yes: n=8 No: n=12 R = Yes: n=1 No: n=19	U = 90% (n=18) R = 90% (n=18)	U = .792 R = .459	U = 0.0001 R = 0.015
Transport out of injection site after activity	U = Yes: n=12 No: n=8 R = Yes: n=6 No: n=14	U = Yes: n=12 No: n=8 R = Yes: n=5 No: n=15	U = 100% (n=20) R = 95% (n=19)	U = 1.000 R = .875	U = 0.0001 R = 0.0001
Transport out of injection site after stimulation	U = Yes: n=16 No: n=4 R = Yes: n=15 No: n=5	U = Yes: n=16 No: n=4 R = Yes: n=15 No: n=5	U = 90% (n=18) R = 90% (n=18)	U = .688 R = 0.733	U = 0.002 R = 0.001
Transport out of injection site after break	U = Yes: n=18 No: n=2 R = Yes: n=17 No: n=3	U = Yes: n=19 No: n=1 R = Yes: n=17 No: n=3	U = 95% (n=19) R = 100% (n=20)	U = .643 R = 1.000	U = 0.002 R = 0.0001

Abbreviations: U = ulnar, R = radial, Yes = transport out of injection site present, No = no transport out of injection site, p = P value of Kappa.

Outcome of the dermal backflow patterns

The interrater reliability on the total score between the assessors was strong (ICC: 0.822, 95% CI: 0.562-0.929) before the break and very strong (ICC: 0.942, 95% CI: 0.852-0.977) after the break.

Concerning interrater reliability of the interpretation of the type of dermal backflow for each region, figure 2 shows before the break that 8 out of 13 different outcomes had a moderate to very strong agreement. This improved to 10 out of 13 different outcomes after break.

Table 4 shows the outcomes of dermal backflow patterns for the different regions. A minimal agreement was found for the fingers (WK = .352), dorsal proximal side upper arm (WK = .375) and the breast region (WK = .348) after the break.

Outcome of the efferent lymphatic vessels

As shown in **table 4**, the agreement related to the presence of draining pathways out of the region with dermal backflow was weak before the break (K = 0.571) and after the break (K = 0.490) as well.

Outcome of the lymph nodes

Before the break there was a very strong agreement of the visualization of the lymph nodes between both assessors, but there were no lymph nodes visualized (no variation). After the break for the axilla and the humeral region there was again a very strong agreement. For the retroclavicular region there was a moderate agreement (K = .608), with variation (3 lymph nodes were visualized). In the cubital region, the Cohen's Kappa statistic could not be measured due to the lack of data of one assessor.

FIGURE 2.

Overview agreement of the groups of parameters

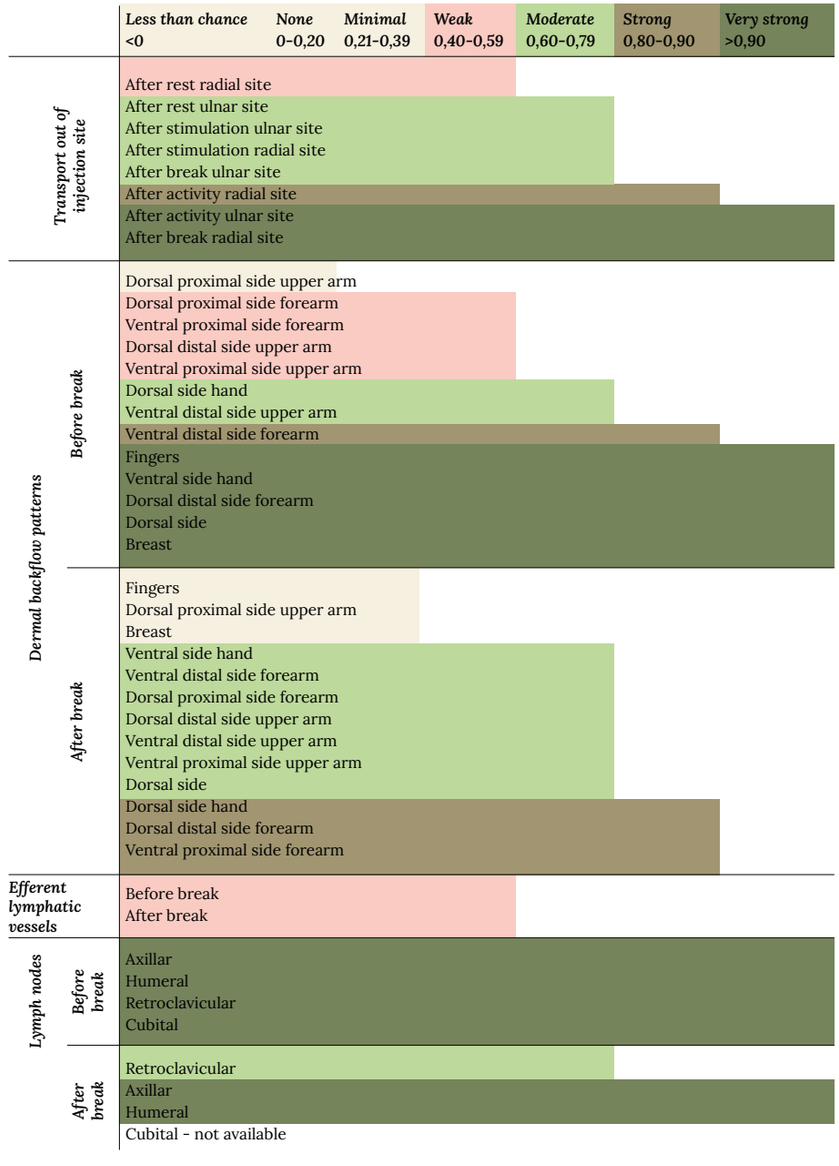


TABLE 4.

Outcome measurements of the parameters

	BEFORE BREAK					
Dermal backflow	*Dermal backflow patterns*	*Assessor 1 (n=)*	*Assessor 2 (n=)*	*Agreement*	*Kappa/ ICC*	*P-value*
Fingers	no: splash: stardust: diffuse:	18 2 0 0	18 2 0 0	100% (n=20)	1.000	.0001
Dorsal side hand	no: splash: stardust: diffuse:	15 4 1 0	16 3 1 0	85% (n=17)	.663	.0001
Ventral side hand	no: splash: stardust: diffuse:	19 1 0 0	19 1 0 0	100% (n=20)	1.000	.0001
Dorsal distal side forearm	no: splash: stardust: diffuse:	11 8 1 0	11 9 0 0	95% (n=19)	.908	.0001
Ventral distal side forearm	no: splash: stardust: diffuse:	10 10 0 0	10 10 0 0	90% (n=18)	.800	.0001
Dorsal proximal forearm	no: splash: stardust: diffuse:	8 11 1 0	8 11 1 0	70% (n=14)	.478	.013
Ventral proximal forearm	no: splash: stardust: diffuse:	6 11 3 0	7 9 4 0	65% (n=13)	.452	.007
Dorsal distal side upper arm	no: splash: stardust: diffuse:	11 9 0 0	12 8 0 0	75% (n=15)	.490	.028
Ventral distal side upper arm	no: splash: stardust: diffuse:	11 9 0 0	13 7 0 0	90% (n=18)	.794	.0001
Dorsal proximal side upper arm	no: splash: stardust: diffuse:	19 1 0 0	19 1 0 0	90% (n=18)	-.053	.814
Ventral proximal side upper arm	no: splash: stardust: diffuse:	12 8 0 0	16 4 0 0	80% (n=16)	.545	.006
Dorsal side	no: splash: stardust: diffuse:	20 0 0 0	20 0 0 0	100% (n=20)	1.000	.0001
Breast	no: splash: stardust: diffuse:	20 0 0 0	20 0 0 0	100% (n=20)	1.000	.0001
Efferent lymphatic vessels						
	Yes No	5 15	4 16	85% (n=17)	.571	.010
Lymph nodes						
Axillar	Yes No	0 20	0 20	100% (n=20)	1.000	.005
Humeral	Yes No	0 20	0 20	100% (n=20)	1.000	.005
Retroclavicular	Yes No	0 20	0 20	100% (n=20)	1.000	.005
Cubital	Yes No	0 20	0 20	100% (n=20)	1.000	.005

	AFTER BREAK					
Dermal backflow	*Dermal backflow patterns*	*Assessor 1 (n=)*	*Assessor 2 (n=)*	*Agreement*	*Kappa/ ICC*	*P-value*
Fingers	no: splash: stardust: diffuse:	13 7 0 0	14 5 0 1	75% (n=15)	.352	.052
Dorsal side hand splash:	no: stardust: diffuse:	13 1 4 2	12 2 5 1	80% (n=16)	.806	.0001
Ventral side hand	no: splash: stardust: diffuse:	18 1 0 1	14 5 0 1	80% (n=16)	.623	.0001
Dorsal distal side forearm	no: splash: stardust: diffuse:	6 10 4 0	8 7 5 0	85% (n=17)	.815	.0001
Ventral distal side forearm	no: splash: stardust: diffuse:	3 11 6 0	4 9 7 0	80% (n=16)	.726	.0001
Dorsal proximal forearm	no: splash: stardust: diffuse:	3 11 6 0	4 7 9 0	70% (n=14)	.610	.0001
Ventral proximal forearm	no: splash: stardust: diffuse:	4 6 10 0	5 5 10 0	85% (n=17)	.824	.0001
Dorsal distal side upper arm	no: splash: stardust: diffuse:	5 9 6 0	5 10 5 0	75% (n=15)	.677	.0001
Ventral distal side upper arm	no: splash: stardust: diffuse:	5 6 9 0	6 5 9 0	80% (n=16)	.721	.0001
Dorsal proximal side upper arm	no: splash: stardust: diffuse:	6 12 2 0	10 7 3 0	60% (n=12)	.375	.021
Ventral proximal side upper arm	no: splash: stardust: diffuse:	6 11 3 0	6 11 3 0	80% (n=16)	.704	.0001
Dorsal side	no: splash: stardust: diffuse:	18 2 0 0	18 1 1 0	95% (n=19)	.783	.0001
Breast	no: splash: stardust: diffuse:	18 2 0 0	18 1 1 0	85% (n=17)	.348	.047
Efferent lymphatic vessels						
	Yes No	11 9	12 8	70% (n=14)	.490	.028
Lymph nodes						
Axillar	Yes No	0 20	0 20	100% (n=20)	1.000	.005
Humeral	Yes No	0 20	0 20	100% (n=20)	1.000	.005
Retroclavicular	Yes No	3 17	3 17	90% (n=18)	.608	.007
Cubital	Yes No	0 20	1 19	95% (n=19)	-	-

DISCUSSION

The aim of this study was to investigate whether different assessors can evaluate the superficial lymphatic architecture and transport through NIRFLI in a reliable way in patients with BCRL. To our knowledge, this is the first study investigating interrater reliability of the interpretation of the images obtained by NIRFLI in BCRL.
Overall, there was a moderate to strong agreement for 31 out of 44 different outcomes scored by two assessors independently. Moreover, the reliability was better after the break, than before the break **(figure 2)**.

The evaluations were divided into four groups of parameters. The agreement for the evaluation for **the lymphatic transport out the injection sites** was the lowest for the radial injection site after the three minutes of rest (K = .459). This might be explained by the fact that the ICG fluid had just been injected and the lymphatic architecture is best visible after 20 minutes of the intradermal injection.[22]

Before the break six of the thirteen arm zones showed a strong to very strong agreement (K > .800) in the visualizations of the **dermal backflow patterns**. Another two regions showed a moderate agreement. Only three regions: fingers, dorsal proximal side of the upper arm and breast showed a weak agreement after the break. The reflection of the injected ICG fluid in the hand, could have made it more difficult to interpret the presence of a dermal backflow pattern at the fingers. This could have caused the difference in the interpretation of the dermal backflow patterns for the fingers. The weak agreement of the breast zone can be explained by the lack of boundary between the zone of the breast and the zone of the ventral upper arm. No cut-off point has been described for the boundary between those zones. For more reliable results a separate zone for the axilla could help. Also after the break, more dermal backflow patterns (i.e. abnormal patterns) were visible. This is due to the spreading of the ICG fluid during the break. The more abnormal images were seen, the higher the risk of variability in the interpretations of the images between the assessors.

The total score of the dermal backflow patterns gives an indication for the amount of disturbance of the superficial lymphatic transport. The higher the value, the larger the region with dermal backflow on the arm/trunk and/or the more severe the disturbance is. This total score showed a strong interrater reliability, even though it is possible that the patterns were sometimes scored in different zones. The risk of error was higher after the break, because more dermal backflow patterns were visible. Despite the higher risk of error, the reliability of the total score was stronger after the break.[22]

A possible explanation for the weak agreement of the visualization of the **efferent lymphatic vessels** could be that it is difficult to visualize the vessels leaving the dermal backflow patterns, because they could be overshadowed by a dermal backflow pattern or are situated too deep and cannot be visualized by the infrared camera.

All of our patients received a level 1 and 2 axillary lymph node dissection, no axillary **lymph nodes** were seen. In addition, in none of them, humeral lymph nodes were seen. A possible explanation is that these lymph nodes are often located >2cm under the skin and cannot be visualized by NIRFLI. The only lymph nodes seen after the break were the ones in the retroclavicular and cubital area. Since lymph nodes are only visible 20 minutes after intradermally injection of the ICG, they were not visible before the break. The agreement of the scoring of the retroclavicular lymph nodes was strong.

Strengths and limitations

This study had several strengths.

First of all, after breast cancer treatment swelling of the upper arm is reported more frequently (43%) than swelling limited to the hand only (34%).[22] In this study only one patient had lymphedema of the hand, therefore the patients selected for this sub-study were representative for all the patients with BCRL.

Secondly, all the patients were scored on the same day, by both assessors. Internal and external factors that can influence the fluctuation of lymphedema (e.g. temperature, activities,...) were comparable and ensured a decrease in measurement bias in the interrater reliability. If the assessors would have measured on different days, the result could have been different due to fluctuation of edema. Also, the results would not have been reliable due to the fact that part of the ICG fluid could have been absorbed.

Thirdly, in this study the patients were not evaluated on the same measurement point. For this sub-study of a large randomized controlled trial to determine the effectiveness of the fluoroscopy-guided manual lymph drainage (MLD) for the treatment of BCRL (EFforT-BCRL trial)[18], patients were randomly selected at any of the measurement points, so either at baseline, after three weeks of intensive treatment, after six months of maintenance treatment and after one year. The patients also had different stages of lymphedema ranging from stage I to IIb. This variety is a strength of the study, because it allows a more general statement.

Fourthly, as described in the procedure, all measurements and evaluations were strictly scored independently. Also, the time schedule was followed accurately. During the break a standardized activity program was performed. The fact that the squeezing of the hand was not standardized, could be a limitation of the study. Some participants could have probably applied more force while squeezing the hand than others.

A limitation was that after the break, the independent evaluation was not performed exactly in the same way. The first assessor drew the visualizations on the body diagram and the last assessor drew the visualizations first onto the skin of the patient before drawing on the body diagram. It is easier to score and measure the different parameters when this is drawn onto the skin of the patient; therefore the body diagrams could differ. It is not possible for both assessors to draw onto the skin first, because the marker can't be removed completely and the second assessor would not have been blinded. But despite this, the agreement after the break was better than before the break.

Another limitation is that the interrater reliability of the interpretation of the images was performed by two experienced assessors, who are performing NIRFLIs together for several years. Whether the interpretation of NIRFLI is reliable among persons who are not used to working together is unknown. Therefore, we advise to discuss cut-off points or standardized boundaries between all zones in advance, to make evaluation by other assessors also reliable.

Future research

The measurement of the reproducibility of the whole procedure of NIRFLI would be an interesting topic for future studies (as was done for the lymphoscintigraphy[23]). However this would be difficult, because the ICG fluid is visible for a long period of time after injection in the lymphatic system, resulting in a long delay in between two evaluations. And using a long period between both evaluation with NIRFLI is not reliable due to the fluctuations of lymphedema.
It would be interesting to investigate the change of the total score of dermal backflow after a decongestive lymphatic treatment.

Clinical implication

The evaluation of the superficial lymphatic architecture and function by two different assessors using the NIRFLI, can be performed in a reliable way. This means that NIRFLI can be used for the evaluation of the changes of the lymphatic architecture and the lymphatic function before and after the application of a physical or surgical treatment. The following outcomes can be used before and after application of the treatment: presence of lymphatic transport out the injection sites, presence and severity of dermal backflow and presence of lymph nodes.
This study has shown that the breast and dorsal zones are more difficult to assess due to unclear boundaries. Clear boundaries and separate zones for the axilla could make the interpretation of the dermal backflow of these zones easier. The measurements of the other zones are reliable.

CONCLUSION

The aim of this study was to investigate whether different assessors can evaluate the lymphatic architecture and transport through NIRFLI in a reliable way, in patients with BCRL. Overall, there was a moderate to strong agreement for 31 out of 44 outcomes scored when evaluating the lymphatic architecture and transport through NIRFLI. This means that NIRFLI can be used for the evaluation of the changes of the lymphatic architecture and the lymphatic function before and after the application of a physical or surgical treatment.

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3

Relation between early disturbance of lymphatic transport visualized with lymphofluoroscopy and other clinical assessment methods in patients with breast cancer.

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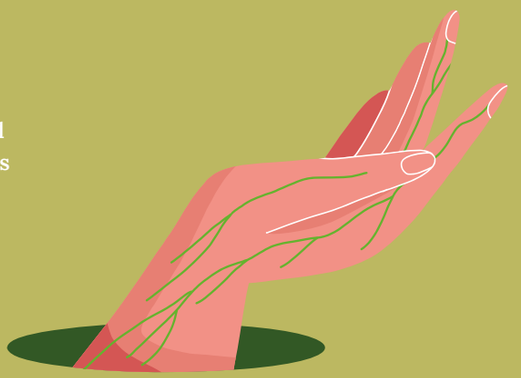


ABSTRACT

Introduction:
Lymphedema of the upper extremity is one of the most feared complications following breast cancer treatment. Lymphofluoroscopy is a sensitive instrument for detection of lymphedema and visualization of superficial lymphatic transport, thus suitable for early detection. Early detection of lymphedema is important as it can prevent lymphedema to progress into more severe stages and minimalize impact on quality of life and medical costs.

Objective:
To determine agreement between the presence of early disturbance of the lymphatic transport and outcome of clinical measurement tools evaluating the development of lymphedema.

Methods:
A prospective study was conducted in 128 breast cancer patients scheduled for breast cancer surgery. Patients were evaluated before surgery and 1, 3, 6, 9 and 12 months post-surgery. Cohen's Kappa was used to determine agreement between presence of early disturbance in lymphatic transport and presence of pitting/ increased skinfold thickness/increased Percentage Water Content ratio (PWC)/ increased arm-hand volume (circumference measures and water displacement).

Results:
For pitting status (Kappa 0.23), for skinfold thickness (Kappa 0.29) and the PWC ratio (Kappa 0.21) a minimal agreement was found. The circumference measurement had a minimal agreement for 5% volume difference (Kappa 0.22) and no agreement for 3% volume difference (Kappa 0.19). Sensitivity was weak for all clinical assessments. The specificity was excellent for pitting status, skinfold thickness, PWC ratio and for 5% volume difference. For 3% volume difference a high specificity was found.

Conclusion:
The clinical tools assessed in this study were not able to predict an early disturbance of the lymphatic transport seen on lymphofluoroscopy.

INTRODUCTION

Lymphedema of the upper extremity is a side-effect commonly seen following treatment for breast cancer. Although incidence rates vary among studies, likely due to different criteria and assessment of breast cancer-related lymphedema (BCRL), an overall incidence rate of 16.6% can be observed.[1]

BCRL has a profound impact on quality of life.[2-4] Since survival of breast cancer is currently increasing, so is the need for improving quality of life of these survivors.[5-6] Diagnosing a person with BCRL means the prospect of life-long treatment in order to control the condition, and prevent the lymphedema from developing into more severe stages. It would be desirable to detect the lymphedema as early as possible so treatment can start early. In addition, treatment and medical costs would be less extensive thus making the necessity of early detection even more important.[7-9]

There are many different methods to detect BCRL. Unfortunately there is no consensus about the best method.[10] Most measurement methods assess the water content, thickness of the skin (Stemmer sign test), amount of extracellular fluid (pitting test, tissue dielectric constant and bioelectrical impedance spectroscopy) or limb volume (circumference measurement, perometer and water displacement method).[11] The most commonly used imaging method to visualize the lymphatic system is lymphoscintigraphy.[12-14] After a radioactive tracer is injected into the tissue, the uptake and transport in the lymphatic system is visualized using a scintillation camera that provides an image of the superficial and deep lymphatic system. By repeated imaging over time, the intensity of the radioactive tracer is measured to assess the lymphatic transport.[15] Another method to visualize the superficial lymphatic transport system of the upper limb is near-infrared fluorescence imaging (e.g. lymphofluoroscopy). In this method, indocyanine green (ICG) is injected intradermally into the hand. The fluorescence of the ICG can be obtained by an infrared camera. The images are then classified into either a normal linear pattern or three dysfunctional backflow patterns progressing from splash, stardust to diffuse.[16] A dysfunctional backflow pattern may occur before the lymphedema becomes clinically detectable. This makes it possible to detect early abnormalities in lymphatic transport, enabling early intervention and prevent lymphedema progressing in more severe stages.[10,17,18] In contrast to the lymphoscintigraphy, lymphofluoroscopy is capable of giving a detailed mapping of the superficial lymphatic architecture. According to the study of Mihara et al lymphofluoroscopy is more sensitive than lymphoscintigraphy for the diagnosis of lymphedema as lymphofluoroscopy scored excellent on sensitivity and lymphoscintigraphy scored moderate. Both assessment methods scored 1.0 on specificity of detection of lymphedema of the upper limbs.[17]

A major concern is that currently, the equipment to evaluate lymphatic transport by injection of ICG is not often available in clinical practice and that the procedure is time-consuming. Therefore, it is interesting to know whether there is an agreement between the presence of early disturbance visualized by lymphofluoroscopy and clinical assessment tools. In addition, the second aim was to investigate the sensitivity and specificity of the clinical assessment tools compared to early disturbance of the lymphatic transport seen on lymphofluoroscopy.

MATERIAL AND METHODS

Study design and setting

A prospective cohort study part of the ongoing Dearly trial (Determining the role of pre-existing factors, early diagnostic options and early treatment in the development of BCRL) was performed.[19] Breast cancer patients who were scheduled for surgery were assessed. These patients underwent an axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB) for the treatment of breast cancer at the Multidisciplinary Breast Center of the University Hospitals Leuven, Belgium. The study was approved by the Ethical Committee of the University Hospitals Leuven (S-number 60382).

Patients

Recruitment started in November 2017 and ended in April 2019. Inclusion criteria were 1) age ≥18year, 2) women/men with breast cancer and scheduled for unilateral ALND or SLNB, 3) oral and written approval of informed consent, 4) understanding Dutch. Exclusion criteria were 1) age <18year, 2) edema of the upper limb from other causes, 3) cannot participate during the entire study period, 4) mentally or physically unable to participate in the study, 5) contra-indication for the use of ICG: allergy to ICG, iodine, hyperthyroidism, 6) metastatic disease. All patients received written as well as oral information. All included patients signed an informed consent document prior to the start of the study.

Assessment

All assessments were performed according to a standardized protocol by two assessors (ST and ND/NVL) at baseline and after 1, 3, 6, 9 and 12 months. Visits for the study were incorporated into the existing oncologic follow-up schedule. All patients were investigated with lymphofluoroscopy and clinical measurements at the different time points.

Lymphofluoroscopy

During lymphofluoroscopy, ICG was injected intradermally in the first and fourth webspace of the hand on the affected side. An infrared camera system (PDE, Hamamatsu®) captured the fluorescence. The procedure consisted of 3 consecutive phases **(Table 1)**: an early phase, a break and a late phase. All information about the lymphatic transport was documented in a standard evaluation document and in case of disturbance, this information was drawn on a body diagram according to the legend **(Figure 1)**.

TABLE 1.
Protocol near-infrared fluorescence imaging

Step		*description*	*reporting*
Preparation	0.1 Dilution of ICG	Suspended ICG in 25 ml pure water and subsequently diluted with saline water to reach a final concentration of 0.20 mg/ml	
	0.2 Camera	Camera is held perpendicular to the observed skin at distance of 15 cm (best focus)	
	0.3 Injection of ICG	Intradermal injection in 1st (ulnar injection point) and 4th web space (radial injection point) dorsally in the hand 0.2 ml of the diluted solution is injected in each injection point	Time of injection
Early phase	1.1 Rest: 1 min	Hand in resting position on table	Linear transport starting from ulnar injection point: Yes/No (if "yes", after ..... sec) Linear transport starting from radial injection point: Yes/No (if "yes", after ..... sec)
	1.2 Stimulation: 3 min	Lymph capillaries at the level of the injection points are filled and transport through the lymph collectors is stimulated by the assessor	
Early phase	1.3 Scan with camera and measuring	1) of the arm and shoulder with hand in pronation: starting at hand up to the retroclavicular region, 2) of the arm and axilla with hand in supination and abduction of the shoulder: starting at hand up to the axilla, together with the pectoral region: from the ipsilateral to the contralateral axilla, 3) of the scapular region: from the ipsilateral to the contralateral axilla, 4) of the pectoral region: from the ipsilateral to the contralateral axilla	After scan, reporting on an assessment form: - Number of lymph collectors - Of each lymph collector: length (measured with tapeline in cm), location and normal versus dilated situation - Presence of splash, stardust and diffuse pattern and location (fingers, hand, proximal/distal and ventral/dorsal lower or upper arm, breast and trunk) - Number of lymph nodes (cubital, humeral, axillary, retroclavicular)
Break	30 min		
Late phase	3.1 Scan with camera and measuring	See step 1.3	See step 1.3
	3.2 Drawing on skin and body diagram	If disturbance is seen lymph collectors and dermal backflow (splash, stardust and diffuse) are designed on a body diagram (see **figure 1**)	Design on body diagram if disturbance is seen

ICG: Indocyanine Green

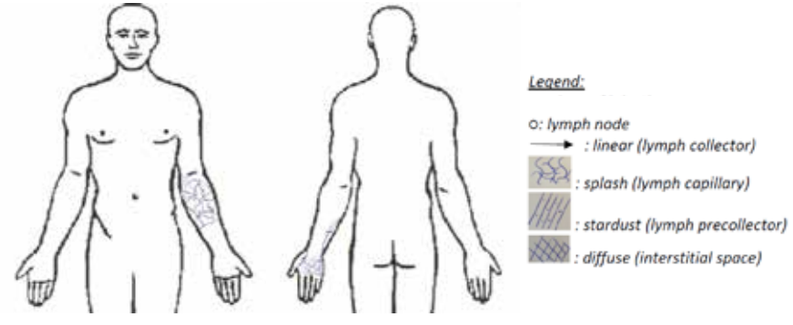


FIGURE 1.
Example of body diagram

Clinical assessments

The water content of the skin was evaluated by the pitting test and tissue dielectric constant. The thickness of the skin was evaluated by the Stemmer test. The change of volume in the arm was evaluated by the circumference measurement (after which the volume was calculated using a truncated cone formula) and the volume of the hand by the water displacement method. A 3% and 5% relative volume difference increase compared to preoperative measurement was used. **Table 2** discusses the procedure (i.e. position of the participant, the material, reference points used, cut-off values and the execution), the outcome and processing of the different clinical measurements: pitting status, skinfold thickness, Percentage Water Content (PWC), arm (including hand) volume.

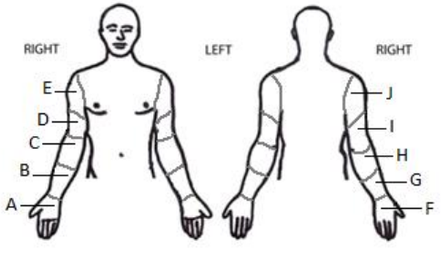
TABLE 2.
Description of clinical assessments

Clinical characteristic	*Clinical assessment method*	*Position participant*	*Material*	*Reference point/ domain*	*Measurement procedure*	*Outcome*	*Processing*
Pitting status (i.e. amount of free fluid in the superficial interstitial tissue space	**Pitting test**	Sitting, hand and elbow supported.	-	Seven locations on the arm **(Figure 3)**.	Prolonged sustained vertical pressure on skin and the superficial tissues with a thumb for 10 seconds. If, after releasing the pressure, a dent remains the test can be defined as pitting [20].	Pitting is present or not present	0 = no pitting 1 = pitting
Skinfold thickness	**Stemmer test**	Sitting, hand and elbow supported.	-	Seven locations on the arm **(Figure 3)**.	The assessor picks up the skinfolds between thumb and index finger [21].	Skinfold thickness operated side compared to the non-operated side [21].	0 = no increase in skinfold thickness 1 = increase in skinfold thickness.
Percentage Water Content (PWC)	**Tissue dielectric constant**	Sitting, hand and elbow supported.	Moisture meter D Compact® (Delfin Technologies)	Seven locations on the arm **(Figure 3)**.	Placement probe on the reference point with gentle pressure [22].	PWC operated side compared to PWC non-operated [23].	0 = ratio PWC < 1.2 1 = ratio PWC ≥1.2 [23,24].
Arm volume	**Circumference measurement**	Sitting, 90-degree anteflexion shoulder, hand supported, elbow stretched.	A stainless-steel bar (500x 20 x 0.8 mm) with fixed tape line every 4 cm and weighs of 20 grams at each end.	At the olecranon. 4, 8, 12, 16 and 20 cm proximal and distal of the olecranon[25].	The bar is placed on the dorsal side of the arm at the reference point at the upper border of the olecranon. At 11 reference points the circumference was taken on both arms.	Arm volume calculated by Truncated cone method in ml.	0 =<3% difference operated/non-operated side 1 = ≥3% difference operated/non-operated arm. 0 =<5% difference operated/non-operated side 1 = ≥5% difference operated/non-operated arm.
Hand volume	**Water displacement method**	Standing beside a cylinder filled with water. No touching of the border of the cylinder.	Cylinder filled with water of 20-30°C placed on a scale connected to a soft-ware program which calculates the change in volume.	Lower ventral fold wrist.	The amount of water displacement is deter-mined for both hands.	Hand volume in ml.	0 =<3% difference operated/non-operated side 1 = ≥3% difference operated/non-operated arm. 0 =<5% difference operated/non-operated side 1 = ≥5% difference operated/non-operated arm.

PWC= Water Content, ml=milliliter

Data processing

To be able to compare the outcomes the arm was divided in ten different zones **(Figure 2)**. Interpretation of the lymphofluoroscopy and the clinical assessments were gathered for each patient at five different time points (1, 3, 6, 9 and 12 months).



A: Ventral side hand
B: Distal ventral side forearm
C: Proximal ventral side forearm
D: Distal ventral side upper arm
E: Proximal ventral side upper arm
F: Dorsal side hand
G: Distal dorsal side forearm
H: Proximal dorsal side forearm
I: Distal dorsal side upper arm
J: Proximal dorsal side upper arm

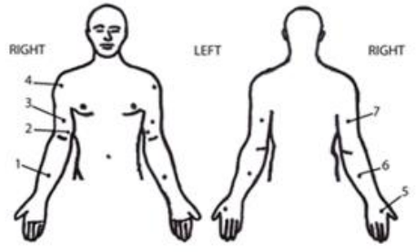
FIGURE 2.
Description of the zones for the lymphofluoroscopy

Lymphofluoroscopy

The presence of dermal backflow at the ten zones was scored 0 if a normal, linear pattern was seen; 1 if a splash pattern was seen; 2 if a stardust pattern was seen, 3 if a diffuse pattern and 4 if no transport was seen.

Clinical assessment

Pitting status, skinfold thickness and PWC were evaluated at seven reference points **(Figure 3)**. These seven reference points were matched with the ten zones of the lymphofluoroscopy: reference point 1 was matched to zone B, reference point 2 and 3 to zone D, reference point 4 to zone E, reference point 5 to zone F, reference point 6 to zone H and reference point 7 to zone I. To determine the agreement between the arm (including hand) volume measured by circumference measurement and the lymphofluoroscopy, the outcome of the circumference measurements was clustered into four segments to match with the different zones of the lymphofluoroscopy **(Table 3)**. For each segment the volume was calculated using the formula of the truncated cone ($V=4(C^2+Cc+c^2)/12\pi$; V: volume, C/c: circumference at each end of the segment).[26] If there was a difference in volume of ≥ 3% or ≥ 5% compared to preoperative measurement the outcome on the circumference measurement was scored positive for that particular clustered section. For the segment of the hand, the water displacement technique was used.



1: Ventral side forearm
2: Medial side upper arm
3: Ventral side upper arm
4: Shoulder
5: Dorsal side hand
6: Dorsal side forearm
7: Dorsal side upper arm

FIGURE 3.
Description of the reference points for the local clinical assessments

TABLE 3:
Matching regions between circumference measurement and lymphofluoroscopy

Circumference measurement sections	*Sections*	*Lymphofluoroscopy zones*
+20 cm +16 cm +12 cm +8 cm	Section 1	Upper arm proximal, ventral and dorsal (Zone E and J)
+8 cm +4 cm Olecranon	Section 2	Upper arm distal, ventral and dorsal (Zone D and I)
Olecranon -4 cm -8 cm -12 cm	Section 3	Forearm proximal, ventral and dorsal (Zone C and H)
-12 cm -16 cm -20 cm wrist	Section 4	Forearm distal, ventral and dorsal (Zone B and G)
hand		Hand (Zone A en F)

cm= centimetre

Statistical method

For each time point and each zone the presence of disturbance of the lymphatic transport and the presence of the clinical outcome measure was assessed.
When at a certain time point (1, 3, 6, 9 and 12M post-surgery) a disturbance of the lymphatic transport was seen, the clinical assessment at that time and in that zone was compared. In the statistical analysis, the data of the positive lymphofluoroscopy was compared to the outcome of the other clinical assessment methods at that same moment and same zone. For example, if a participant showed disturbance in lymphatic transport at 3 months post-surgery in zone D, the outcome of the other clinical measurement methods at 3 months post-surgery for zone D were evaluated to determine the agreement. Given the interest in early detection of lymphofluoroscopy, all data of a patient at a specific zone are discarded after the first positive lymphofluoroscopy (either splash, stardust or diffuse).

When no disturbance was seen at a certain time point/zone, the clinical assessment at that same time and in that same zone was assessed. The data of the zones where early disturbance was seen the most, were also assessed separately. The Cohen's Kappa was used to determine the agreement between the presence of early disturbance on lymphofluoroscopy and the other clinical assessment methods (presence of pitting/ increased skinfold thickness/ increased PWC ratio/ increased arm-hand volume). A Cohen's Kappa coefficient of <0.20 was interpreted as no agreement, 0.21-0.39 as a minimal agreement, 0.40-0.59 as a weak agreement, 0.60-0.79 as a moderate agreement, 0.80-0.90 as a strong agreement and >0.90 as an almost perfect agreement. Diagnostic accuracy is quantified by sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy, estimated as proportions with 95% confidence intervals.

Sensitivity is the proportion correctly identified positive fluoroscopy results, specificity is the proportion correctly identified negative fluoroscopy results, positive predictive value is the proportion of patients with positive screening (clinical assessment) that has a positive fluoroscopy, negative predictive value is the proportion of patients with negative screening (clinical assessment) that has a negative fluoroscopy, and total accuracy is the proportion of all cases where clinical assessment and fluoroscopy result coincide. The sensitivity and specificity were calculated for the lymphofluoroscopy compared to the other clinical measurement methods, using lymphofluoroscopy as the gold standard. The sensitivity and specificity of < 60% was interpreted as weak, between 60% and 74% as moderate, between 75% and 90% as high and >90% as an excellent sensitivity or specificity. Analyzes have been performed by the Leuven Biostatistics and Statistical Bioinformatics Centre, using SAS software (version 9.4 of the SAS System for Windows).

RESULTS

Descriptive data

Hundred twenty-eight patients were enrolled for this trial. Patients' ages ranged from 29 to 82 years (mean 56.7 SD 12.2). The body mass index had a mean of 25.9 (SD 4.9). Hundred twenty-seven patients were female, and one patient was male. For detailed information about the patient characteristics, see **table 4**.

TABLE 4.
Patient characteristics

	N	*Mean (SD)/Frequency (%)/ *Median (IQR)*
Age (y)	128	56.7 (12.2)
BMI (kg/m²)	128	25.9 (4.9)
Side of surgery	128	
- Left		70 (55%)
- Right		58 (45%)
Surgery on the dominant side	128	63 (49%)
Breast surgery	128	
- Mastectomy		89 (70%)
- Breast-conserving surgery		39 (30%)
Extent of LN dissection	128	
- SLNB		55 (43%)
- ALND		73 (57%)
Type of cancer	128	
- Ductal		101 (79%)
- Lobular		18 (14%)
- Other		9 (7%)
Tumor stage	128	
- is		2 (1%)
- T1		44 (34%)
- T2		52 (41%)
- T3		20 (16%)
- T4		10 (8%)
Node stage	128	
- N0		55 (43%)
- N1		44 (34%)
- N2		13 (10%)
- N3		16 (13%)
Number of LN removed	128	11 (2.00;21.00)*
Number of positive LN	128	0 (0.00;2.00)*
Radiotherapy	128	110 (86%)
Chemotherapy	128	74 (58%)
Endocrine therapy	128	20 (16%)

BMI: body mass index; LN: lymph node

Before surgery, none of the patients had a disturbance of the lymphatic transport (i.e. dermal backflow). **Table 5** shows the characteristics of the lymphatic transport after breast-cancer treatment. In total, 66 out of 115 patients (57.4%) showed early disturbance of the lymphatic transport on the lymphofluoroscopy during the 1-year follow-up. In thirteen patients (10.2%) no data was available as they discontinued participation in this study. In sixty-one patients a splash pattern was seen, in 4 patients a stardust pattern and in 1 patient no transport out of the injection sites was noticed. Fifteen patients showed disturbance of lymphatic transport at 1 month post-surgery, 17 at 3 months post-surgery, 13 at 6 months post-surgery, 12 at 9 months and 4 at 12 months. A dermal backflow pattern was seen in 104 different zones. The frequency of disturbance was the highest in the ventral site of the upper arm distal (zone D) and proximal part (zone E). No patients showed disturbance at the ventral side of the hand (zone A).
In 38 out of the 128 patients (29.6%) there was a ≥ 5% relative volume difference increase compared to preoperative measurement and in 32 patients (25%) we found a positive pitting test at any time point up to 12 months.

TABLE 5.
Characteristics lymphatic transport

	N	*Frequency (%)*
Fluoroscopic pattern	115	
- Linear		49 (42.6%)
- Splash		61 (53%)
- Stardust		4 (3.6%)
- Diffuse		0 (0%)
- No transport		1 (0.8%)
Time point early disturbance	66	
- P1		17 (26%)
- P3		18 (27%)
- P6		14 (21%)
- P9		12 (18%)
- P12		5 (8%)
Zones of early disturbance	104	
- A		0 (0%)
- B		13 (12.5%)
- C		12 (11.5%)
- D		36 (34.6%)
- E		17 (16.3%)
- F		4 (3.9%)
- G		8 (7.7%)
- H		9 (8.7%)
- I		4 (3.9%)
- J		1 (0.9%)

Outcome data

Results were presented over all locations and different time points **(table 6)**. For the pitting test a Kappa of 0.23 was found. Twenty-seven positive pitting tests were found out of the 140 positive lymphofluoroscopies leading to a sensitivity of 19.29%. The specificity was 98.27% as there were 2560 negative pitting tests out of the 2605 negative lymphofluoroscopies. For the Stemmer test (Kappa 0.29) and for the tissue dielectric constant (Kappa 0.21) minimal agreement was found. The circumference measurement had a minimal agreement for the 5 % volume difference (Kappa 0.22) and no agreement for the 3% volume difference (Kappa 0.19). Sensitivity was weak for the pitting test, for the Stemmer test and for the tissue dielectric constant. For the circumference measurement sensitivity was higher, but still weak. The specificity was excellent for the pitting test, Stemmer test, tissue dielectric constant and the 5% volume measurement. For the 3% volume measurement a high specificity was found. Early disturbance of the lymphatic transport was seen mostly at Zone D and E. The findings of Table 7 are similar to the findings of **Table 6**.

TABLE 6.
Overview of the agreement between the presence of early disturbance on lymphofluoroscopy and the other clinical assessments methods and the associated sensitivity, specificity, positive and negative predictive value and accuracy; for all regions and all time points

Clinical outcome	*Kappa*	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*Accuracy*
Pitting						
n/N		27/140	2560/2605	27/72	2560/2673	2587/2745
Estimate (95% CI)	0.23 (0.15;0.31)	19.29 (13.11;26.81)	98.27 (97.70;98.74)	37.50 (26.36;49.70)	95.77 (94.94;96.50)	94.24 (93.31;95.09)
Increased skinfold tickness						
n/N		40/140	2536/2605	40/109	2536/2636	2576/2745
Estimate (95% CI)	0.29 (0.21;0.37)	28.57 (21.26;36.81)	97.35 (96.66;97.93)	36.70 (27.67;46.47)	96.21 (95.40;96.90)	93.84 (92.88;94.71)
Ratio percentage water content (PWC) >1.2						
n/N		50/138	2370/2567	50/247	2370/2705	2420/2705
Estimate (95% CI)	0.21 (0.15;0.27)	36.23 (28.23;44.84)	92.33 (91.23;93.33)	20.24 (15.41;25.80)	96.42 (95.61;97.12)	89.46 (88.25;90.60)
Volume difference ≥3%						
n/N		111/186	3789/4408	111/730	3789/3864	3900/4594
Estimate (95% CI)	0.19 (0.15;0.23)	59.68 (52.25;66.79)	85.96 (84.90;86.97)	15.21 (12.68;18.02)	98.06 (97.57;98.47)	84.89 (83.82;85.92)
Volume difference ≥5%						
n/N		86/186	4040/4408	86/454	4040/4140	4126/4594
Estimate (95% CI)	0.22 (0.18;0.27)	46.24 (38.91;91.53)	91.65 (90.80;92.45)	18.94 (15.44;22.86)	97.58 (97.07;98.03)	89.81 (88.90;90.67)

PPV= positive predictive value, NPV= negative predictive value, CI=Confidence Intervals

DISCUSSION

To our knowledge this is the first prospective study investigating the agreement between early disturbance of the lymphatic transport seen on lymphofluoroscopy and commonly used clinical assessment tools for early signs of lymphedema in patients receiving treatment for breast cancer.

This study showed low rates of agreement and sensitivity for all the clinical assessments used. The pitting test, Stemmer test and tissue dielectric constant are weak predictors for early disturbance of the lymphatic transport because the sensitivity was lower than 40%. Specificity and negative predictive value for these clinical assessments were high to excellent, meaning that there is a high chance that a negative clinical test also means that there is a negative lymphofluoroscopy. Several studies have assessed the correlation between lymphofluoroscopy and some clinical measurements. However, these studies were not performed with a preventive purpose (i.e. to detect the development of lymphedema). In these studies, the correlation between disturbance of lymphatic transport (i.e. dermal backflow) and clinical outcomes was investigated in patients with clinical BCRL.[27,28] In one of our previous studies, a moderate to strong agreement was found for the clinical assessment pitting status, skinfold thickness and water content. Overall specificity was high for pitting status (83.4%) and moderate for skinfold thickness (61.6%) and water content (74.8%). So in patients with BCRL, in which the lymphatic disturbance is more pronounced, most of the common clinical assessments showed a good agreement with the presence of lymphatic disturbance.[27] Another study of Medina-Rodriguez et al[28] showed a correlation between the increase of arm circumference and the lymphatic disturbance in patients with BCRL. This was the case at 4 specific anatomical zones: the wrist, elbow, anterior and posterior upper arm.

TABLE 7.
Overview of the agreement between the presence of early disturbance on lymphofluoroscopy and the other clinical assessments methods and the associated sensitivity, specificity, positive and negative predictive value and accuracy; for zones ventral upper arm distal and proximal (zone D and E).

Clinical outcome	*Kappa*	*Sensitivity*	*Specificity*	PPV	NPV	*Accuracy*
Pitting						
n/N		10/73	764/775	10/21	764/827	774/848
Estimate (95% CI)	0.18 (0.07;0.29)	13.7 (6.77;23.75)	98.58 (97.47;99.29)	47.62 (25.71;70.22)	92.38 (90.36;94.10)	91.27 (89.17;93.09)
Increased skinfold tickness						
n/N		21/73	753/775	21/43	753/805	774/848
Estimate (95% CI)	0.32 (0.20;0.43)	28.77 (18.77;40.55)	97.16 (95.73;98.21)	48.84 (33.31;64.54)	93.54 (91.62;95.14)	91.27 (89.17;93.09)
Ratio percentage water content (PWC) >1.2						
n/N		27/71	693/763	27/97	693/737	720/834
Estimate (95% CI)	0.25 (0.15;0.34)	38.03 (26.76;50.33)	90.83 (88.55;92.78)	27.84 (19.21;37.86)	94.03 (92.07;95.63)	86.33 (86.81;88.59)
Volume difference ≥3%						
n/N		49/73	503/774	49/320	503/527	552/847
Estimate (95% CI)	0.13 (0.08;0.18)	67.12 (55.13;77.67)	64.99 (61.51;68.35)	15.31 (11.55;19.73)	95.45 (93.30;97.06)	65.17 (61.86;68.38)
Volume difference ≥5%						
n/N		37/73	608/774	37/203	608/644	645/847
Estimate (95% CI)	0.16 (0.09;0.23)	50.68 (38.72;62.60)	78.55 (75.49;81.40)	18.23 (13.17;24.24)	94.41 (92.34;96.05)	76.15 (73.13;78.99)

PPV= positive predictive value, NPV= negative predictive value, CI=Confidence Intervals

Since the aim was to detect early disturbance of lymphatic transport the cut-off of ≥3% and ≥5% relative volume increase were used in this study. The latter corresponds to the volume difference recommended for the diagnosis of lymphedema.[29,30] Specht et al found an increase of arm volume of ≥3% to be one of the risk factors for the development of lymphedema.[31] Hence, the cut-off for the definition of subclinical lymphedema or early disturbance in lymphatic transport is still unclear. In our study lower cut-off values may have resulted in an increase in false positive outcomes (lower specificity) and less agreement with the early detection on lymphofluoroscopy. Perhaps some of these changes in arm volume could be explained by the presence of transient edema, which can be present in a portion of the patients. According to a study by Hayes[32], 58% had transitory lymphedema and 23% in another study.[33]

It could be possible that some of the patients developed a dermal collateral flow pathway which will protect them from developing clinical lymphedema. Suami identified four different pathways of lymphatic drainage in BCRL and suggested that an alternative detour to the deep lymphatics may be created.[34] Perhaps these pathways can be sufficient to maintain the lymphatic drainage of the limb. According to Akita et al some of these early detected dermal backflow patterns can return to normal over time.18 Further research is needed to investigate if this early disturbance is indeed a risk factor for the development of BCRL.
Regarding the tissue dielectric constant several studies indicated that a threshold of 1.2 may not be applicable on all locations measured, as the forearm ratios in these studies ranged between 1.2635,36 and 1.29.37 Mayrovitz et al 2009 suggested that a threshold of 1.26 for the detection of early lymphedema should be used.[35] This may implicate that a threshold of 1.2 may lead to false positives.

Strengths

The study has several strengths.

A first strength is the number of analyzes. The extensive analyses of commonly used assessment methods with the use of many reference points (pitting test, Stemmer test, tissue dielectric constant) and segments (circumference measurement) is a strength. A total of 6400 analyzes were done.

A second strength is the use of segments to analyze the clinical outcomes. Local changes in the arm were assessed since several studies indicated that segmental variations in lymphatic transport is seen and segmental volume may change before apparent changes in total limb volume occur.[38,39]

A third strength is that in the zones of the ventral upper arm (zone D and E) the most disturbance was seen, corresponding to other studies where the elbow regions and proximal parts of the arm are first described to have a disturbance in dermal backflow.[8-10] In our study, splash pattern was seen in 53% of the patients this is also described in other studies as the splash pattern is considered to represent less severe dysfunction of the lymphatic transport and will appear first in most cases.[16,28,40]

A fourth strength is the timing of the postoperative changes in lymphatic transport. BCRL is a chronic disease developing after breast cancer treatment but in 75% of the patients BCRL will develop in the first year after breast cancer treatment.[41] In the study of Akita et al lymphatic disorder onset 5.2 (±3.0) months after surgery was seen.[18] This is comparable to the study by Stout where the average time to onset of BCRL was 6.9 months.[38] McDuff et al found a peak in lymphedema onset between 6-12 months in patients with ALND and without regional lymph node radiation and even a peak between 18-24 months in patients with ALND and regional lymph node radiation.[42] Our findings showed that the time point of seeing disturbance for the first time, ranged from one month to nine months. Only 5 (4%) patients had the first visualization of disturbance at 12 months.

Limitations

A first limitation is that our sample is not completely representative for all breast cancer patients. With a mean age of 56.68 years the population studied is younger than the average breast cancer population according to the Belgian Cancer Registry, which is 63 years of age.[43] As younger breast cancer patients (<40 years or premenopausal) seem to develop more aggressive cancer tumor subtypes, often more drastic treatments such as mastectomy, ALND or regional lymph node radiation are required.[44,45] This may explain why a higher percentage of participants (57%) had to undergo an ALND. More extensive surgery, higher number of lymph nodes removed, high body mass index, regional lymph node radiation and chemotherapy are known risk factors for the development of BCRL[1] and this may be the reason why in this population 57.4% of the patients developed disturbance in lymphatic transport. Furthermore, because people are more aware of the risk factors of BCRL, patients scheduled for ALND were probably more willing to participate in the study (selection bias).

A second limitation is that we matched the zones of the lymphofluoroscopy with the seven reference points. Another method could be to perform the clinical assessment at the exact same location of the disturbance of the lymphatic transport seen on lymphofluoroscopy. Possibly this would increase the agreement. However, in this way it was not possible to blind the assessor of the clinical measurements for the result of the lymphofluoroscopy.

A last limitation is that we did not analyze the results of the bioelectrical impedance spectroscopy in this study. This technique can assess extracellular fluid in the whole arm, but not in specific segments, therefore we decided not to incorporate this data. A study by Bundred et al[46] confirmed this underdiagnosis of segments of lymphedema such as hand or elbow by bioelectrical impedance spectroscopy.

Clinical implications

Early disturbance visualized by lymphofluoroscopy can't be predicted by the clinical assessment tools used in this study. If we want to detect early disturbance we will need to do a lymphofluoroscopy. Performing a lymphofluoroscopy as a screening tool in every patient after breast cancer treatment will not be feasible (high cost, time-consuming,...), but in high risk patients, such as more advanced cancer (positive lymph nodes), after radiotherapy of the axilla, after therapy with taxanes, screening with lymphofluoroscopy could be useful and cost-effective. Screening for lymphedema in these high risk patients in the first postoperative year and especially the first six months are recommended as 74% of the early disturbance is seen the first six months. This study also indicates that special attention should be taken in the assessment of the pericubital region and ventral upper arm as most of the disturbance appears in these zones.

CONCLUSION

The study results showed that there is no agreement between the pitting test, Stemmer test, tissue dielectric constant and water volume assessments (circumference measurement and water displacement method) and early disturbances in lymphatic transport as visualized by the lymphofluoroscopy. If we want to detect early disturbance we will need to do a lymphofluoroscopy. Therefore this lymphofluoroscopy can be used as a screening tool for early detection of abnormalities of the lymphatic transport, especially useful in high risk patients.

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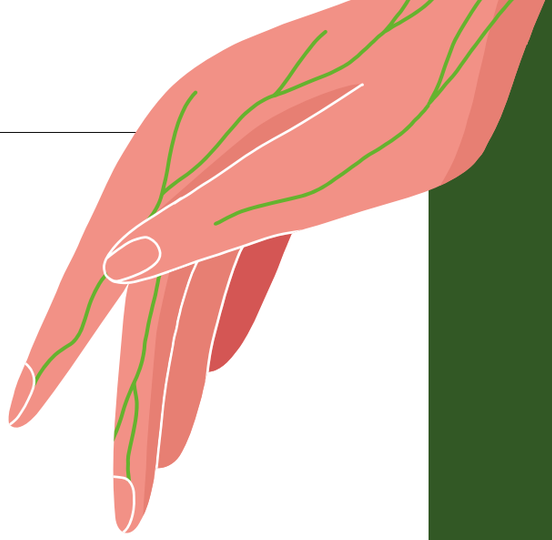

4
Risk factors for developing unilateral breast cancer-related lymphedema: a systematic review.

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ABSTRACT

Background:
As more patients survive breast cancer, long-term complications such as lymphedema of the arm gain importance. Numerous studies and reviews have identified possible risk factors for the development of breast cancer-related lymphedema. As treatment modalities for breast cancer have changed over the past years, we performed an extensive up-to-date systematic review of the literature.

Methods:
The search was performed in Web of Science, Pubmed, Embase and Cochrane library. All data until December 2020 was used. Papers were included if they studied patients with unilateral breast cancer both female and male, contained a follow-up of at least 1 year, assessed incidence/prevalence and risk factors, and used an objective diagnosis of lymphedema. Cross-sectional studies, cohort studies, case-control studies and randomized controlled trials were included in this review. All studies were assessed for level of evidence and risk of bias.

Results:
Hundred forty-one studies that met the inclusion criteria were identified. Risk factors with a strong level of evidence were axillary lymph node dissection, node stage and taxane-based chemotherapy. Body mass index, a greater number of excised lymph nodes, the presence of positive lymph nodes, radiotherapy, radiotherapy of the axilla and postoperative infections were risk factors with a moderate level of evidence.

Conclusion:
Factors related to more advanced breast cancer seem to increase the risk for development of breast cancer-related lymphedema the most. Still, even in the optic of evolution towards less invasive treatments, lymphedema remains an important issue in the postoperative phase.

INTRODUCTION

Breast cancer-related lymphedema (BCRL) is the swelling of the upper limb after treatment for breast cancer. Estimates of incidence rates of BCRL have varied over time especially since advances in treatment of breast cancer in the past 20-25 years have been realized. According to a review by DiSipio et al[1] the incidence rate of arm lymphedema was about four times higher in women who had an axillary lymph node dissection (19.9%) than in those who had sentinel lymph node biopsy (5.6%). Several risk factors have been suggested for the development of BCRL such as overweight, lack of mobility, extensive surgery (such as axillary lymph node dissection), radiation therapy and chemotherapy.[2-4]

These reviews are based on data from different types of studies and different types of methods to diagnose BCRL. Over the years even more different diagnostic tools and definitions for BCRL have been used. Using the right definitions of lymphedema will affect the identification of risk factors of BCRL, as will the choice of measuring.[5]

Although numerous review articles and meta-analyses have been written, an up-to-date review of the risk factors for the development of BCRL, taking into account the different and objective diagnostics tools as well as the different definitions for lymphedema, is lacking.[6] With this systematic review we want to fill this gap.

METHODS

Search strategy and selection criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyzes PRISMA statement was followed 7 and this review was registered in the Prospero database CRD42020211696.

The search was performed in Web of Science, Pubmed, Embase and Cochrane library. A first search of the databases was performed in November 2019, a second search was performed in January 2021 with December 2020 as a data cut-off. The search strategy can be found in Appendix 1. All articles were organized in Endnote and duplicates were removed manually.

Study selection

Covidence was used to import citations. During the first stage, articles were selected based on the in- and exclusion criteria, by reviewing abstracts. During a second stage, these articles were read in full text. This process was performed by two independent reviewers (ST, CV). Any discrepancy in the selection of articles was discussed between the two authors and if no consensus was reached, a third reader (IF) was consulted.

All titles and abstracts in English, French and Dutch were retrieved from the search and assessed for eligibility. There were five categories of inclusion criteria: 1) type of study: cross-sectional studies, cohort studies, case-control studies and randomized controlled trials; 2) patient characteristics: patients with unilateral breast cancer both female and male; 3) diagnosis of lymphedema: studies should use objective methods such as ultrasound, lymphofluoroscopy, lymphoscintigraphy, clinical assessment tools such as bio-electrical impedance spectroscopy (BIS), moisture meter and volume measurements such as circumference measurement, perometry and water displacement; 4) outcomes: studies should mention at least incidence, prevalence and risk factors; 5) follow-up: studies should report at least one year of follow-up.

Data extraction

Data extraction was performed independently by ST and CV. Following data was extracted: author, year of publication, origin of publication, risk factors, measurement techniques, definition of lymphedema used, sample size, follow-up time, type of study, level of evidence and risk of bias. The findings are displayed in the study characteristics table **(table 1)**.

Risk factors for BCRL were divided in demographic and general health related factors, treatment related factors and breast cancer related factors. For certain risk factors, different analyzes were mentioned. If the type of analyzis that was performed on the data was not mentioned in the study or another analyzis was performed than the one mentioned, these studies were listed under the title 'not specified'.

The studies were divided in two groups depending on the outcome of the assessment of the risk factor in the study (significant or non-significant). The ratio of the number of studies who found the risk factor significant to the total number of studies investigating the risk factor was calculated for risk factors with at least 5 studies investigating it. If this ratio was > 75% with at least 2 high quality studies included, then this was interpreted as a strong level of evidence that this factor was a risk factor for the development of BCRL. If this ratio was between 50 and 75%, the level of evidence to list the factor as a risk factor was moderate. If the ratio was less than 50%, it was considered as weak evidence. When less than 5 studies investigated the risk factor, we considered this as inconclusive.

Risk of bias assessment

The level of evidence of each study was determined, based on the method outlined by the National Health and Medical Research Council; in general the Aetiology column was used except for exercise or surgical intervention trials, for which the Intervention column was used.[8] Methodological quality of the included articles was assessed by two reviewers independently (ST, CV), any difference was solved by consensus. The Tool to assess Risk of Bias in Cohort Studies (https://methods.cochrane.org/bias/sites/methods.cochrane.org.bias/files/public/uploads/Tool%20to%20Assess%20Risk%20of%20Bias%20in%20Cohort%20Studies.pdf) was used for the cohort studies and the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials) was used for the randomized controlled trials.

RESULTS

Study selection

A total of 7393 abstracts were identified. After removal of the 117 duplicates by Covidence, 7276 remained for screening. Screening of these abstracts resulted in 416 full-text studies (6860 studies were found irrelevant). After screening the full-text articles, 275 articles were excluded. Hundred-forty-one articles were included in this review. **Figure 1** shows the flow diagram of the study selection.

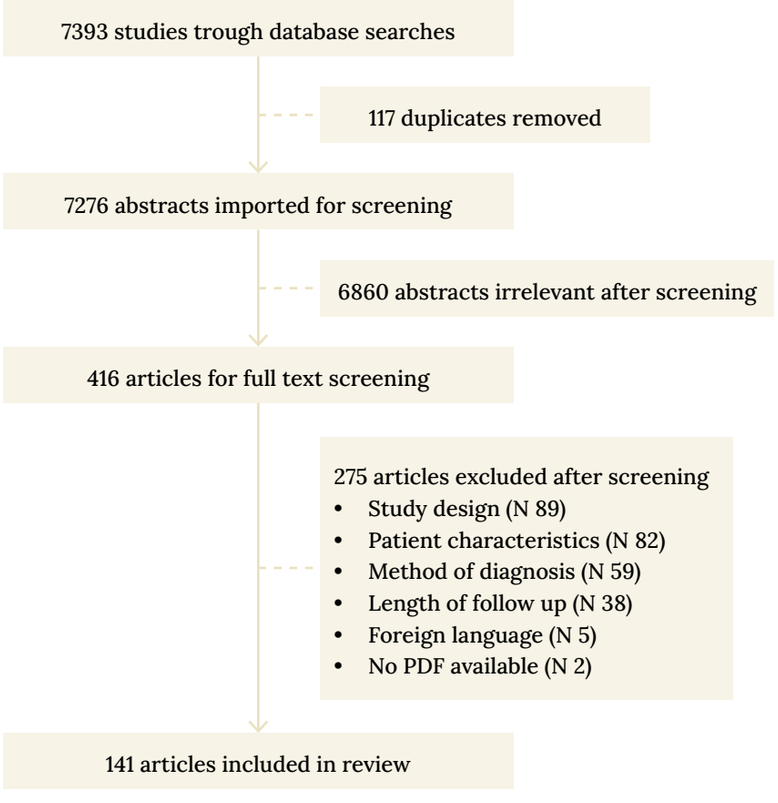

FIGURE 1.
Flow diagram of the study selection

Type of study

Table 1 shows the characteristics of the studies sorted by the measurement tool that was used. Most of the studies were prospective cohort studies (74) or retrospective cohort studies (32). A total of 18 randomized controlled trials were identified. There were 14 cross sectional studies and 3 case-control studies. Level of evidence was scored for each study and can be found in **Table 1**.
Most of the studies originated from North America (42), followed by United Kingdom (14), Turkey (9) and Australia (9). The publication dates ranged between 1981 and 2020. The sample size in the included studies varied between 38 and 5064. Length of the follow-up of patients was a maximum of 15 years.

TABLE 1.

Study characteristics sorted by the measurement tool that was used.

	Definition of BCRL	*Sample size*	*Length of follow-up (Y=years, M= months)*	*Level of evidence*	*Risk of bias*
Arm circumference					
Case control studies					
Honarvar et al. (2016); Iran [9]	≥ 2 cm between arms	400		Level III-3	Intermediate
Newman et al. (2012); Australia [10]	≥ 5 cm between arms	120	18M	Level III-3	Intermediate
Soran et al. (2006); USA [11]	≥ 2 cm increase from baseline	104	1990-2000	Level III-3	Intermediate
Cross sectional studies					
Ay et al. (2014); Turkey [12]	≥ 5% increase in circumference	5064	13M-12Y	Level III-3	Low
Ben Salah et al. (2012); Tunisia [13]	≥ 2 cm between arms	222	68M	Level III-3	Low
Bennet-Britton et al. (2007); UK [14]	≥ 10% increase in volume	50	39M-48M	Level III-3	Low
Deo et al. (2004); India [15]	≥ 3 cm between arms	300	1Y	Level III-3	Low
Graham et al. (2006); Australia [16]	≥ 200 ml increase in volume between arms	106	4.2Y	Level III-3	Low
Haddad et al. (2010); Iran [17]	≥ 10% increase in circumference	355	4Y	Level III-3	Low
Ikeda et al. (2014); Japan [18]	≥ 2 cm between arms	76	24M	Level III-3	Low
Kibar et al. (2015); Turkey [19]	≥ 2 cm between arms	190	12.7M	Level III-3	Low
Kodama et al. (2012); Japan [20]	≥ 3 cm between arms	1043	1Y	Level III-3	Low
Morcos et al. (2014); Jordan [21]	≥ 2 cm between arms	515	26.2M	Level III-3	Low
Nesvold et al. (2008); Norway [22]	≥ 10% increase in volume	340	47M	Level III-3	Low
Nielsen et al. (2017); Denmark [23]	≥ 2 cm between arms	277	3.3Y-4.3Y	Level III-3	Low
Querci della Rovere et al. (2003); UK [24]	> 5% increase in circumference between arms	198	21M	Level III-3	Low
Velloso et al. (2011); Brazil [25]	≥ 10% increase in circumference	45	21.3M	Level III-3	Low
Prospective cohort studies					
Akezaki et al. (2019); Japan [26]	Clinical stages of ISL	238	30M	Level II	Low
Armer et al. (2019); USA [27]	≥ 10% increase in volume	486	2.2Y-3Y	Level II	Low
Avraham et al. (2010); USA [28]	≥ 2 cm between arms	316	5Y	Level II	Low
Bevilacqua et al. (2012); Brazil [29]	≥ 200 ml increase in volume between arms	1054	41M	Level II	Low
Bland et al. (2003); USA [30]	≥ 1 cm between arms	90	3Y	Level II	Low
Blaney et al. (2015); UK [31]	≥ 5% increase in circumference	98	12M	Level II	Low
Bundred et al. (2020); UK [32]	≥ 10% increase in volume	1100	24M	Level II	Low
Burak et al. (2002); USA [33]	Absolute change of volume	96	15M	Level II	Low
Card et al. (2012); USA [34]		574	3Y	Level II	Intermediate
Chandra et al. (2015); USA [35]	≥ 10% increase in volume	1476	29.3M	level II	Low
Chen et al. (2009); China [36]	≥ 2 cm between arms	221	12M	Level II	Low
Clark et al. (2005); UK [37]	≥ 5% increase in volume	251	3Y	Level II	Low
De Groef et al. (2016); Belgium [38]	≥ 5% increase in volume	100	12M	Level II	Low
Fontaine et al. (2011); Belgium [39]	≥ 2 cm between arms	100	1Y-2Y	Level II	Low
Francis et al. (2006); USA [40]	≥ 5% increase in circumference	152	1Y	Level II	Low
Goldberg et al. (2011); USA [41]	≥ 2 cm between arms	600	5Y	Level II	Low
Gross et al. (2018); USA [42]	≥ 2,5 cm between arms	492	5.5Y	Level II	Low
Gross et al. (2019); USA [43]	≥ 2,5 cm between arms	265	3Y	Level II	Low
Helyer et al. (2010); Canada [44]	≥ 200 ml increase in volume between arms	137	24M	Level II	Low
Hidding et al. (2018); The Netherlands [45]	≥ 10% increase in volume	51	1M after completion of treatment	Level II	Low
Huang et al. (2012); China [46]	≥ 2 cm between arms	126	24M	Level II	Low
Iyigun et al. (2018); Turkey [47]	≥ 2 cm between arms	277	36M	Level II	Low
Johansen et al. (2000); Denmark [48]	≥ 2 cm between arms	266	6.6Y	Level II	Low
Jung et al. (2014); Korea [49]	≥ 5% increase in circumference	848	5.1Y	Level II	Low
Khan et al. (2017); India [50]	≥ 10% increase in circumference	216	42M	Level II	Low
Khanna et al. (2019); India [51]	≥ 2 cm between arms	98	12M	Level II	Intermediate
Kiel et al. (1996); USA [52]	≥ 1 cm between arms	402	20M	Level II	Low
Kim et al. (2013); Korea [53]	≥ 5% increase in circumference	772	5.1Y	Level II	Low
Kim et al. (2015); Korea [54]	≥ 5% increase in circumference	313	5.6Y	Level II	Low
Kim et al. (2016); Korea [55]	≥ 5% increase in circumference	1073	5.1Y	Level II	Intermediate
Kissin et al. (1986); UK [56]	≥ 200 ml increase in volume between arms	200	1Y	Level II	Low
Koca et al. (2020); Turkey [57]	Absolute volume difference between arms	67	36M	Level II	Low
Langer et al. (2007); Switzerland [58]	≥ 2 cm between arms	698	29.5M-31M	Level II	Low
McLaughlin et al. (2008); USA [59]	> 2 cm between arms	936	5Y	Level II	Low
McLaughlin et al. (2013); USA [60]	≥ 10% increase in volume	120	12M	Level II	Low
Menezes et al. (2016); Brazil [61]	≥ 200 ml increase in volume between arms	622	57M	Level II	Low
Meric et al. (2002); USA [62]	≥ 3 cm between arms	294	89M	Level II	Low

	Definition of BCRL	Sample size	Length of follow-up (Y=years, M= months)	Level of evidence	Risk of bias
Ozcinar et al. (2012); Turkey [63]	≥ 2 cm increase from baseline	218	64M	Level II	Low
Ozmen et al. (2019); USA [64]	≥ 2 cm between arms	380	15M	Level II	Low
Ribeiro Pereira et al. (2017); Brazil [65]	≥ 200 ml increase in volume between arms	1631	10Y	Level II	Low
Schmitz et al. (2012); USA [66]	≥ 5 cm between arms	182	6Y	Level II	Low
Segerstrom et al. (1992); Sweden [67]	≥ 150 ml increase in volume between arms	136	42M	Level II	Low
Sener et al. (2001); USA [68]	≥ 20% increase in volume	420	24M	Level II	Low
Shahpar et al. (2013); Iran [69]	≥ 2 cm between arms	410	3Y	Level II	Low
Tasmuth et al. (1996); Finland [70]	≥ 2 cm increase from baseline	93	12M	Level II	Low
Terada et al. (2020); Japan [71]	≥ 2 cm between arms	631	3.8Y	Level II	Low
Thompson et al. (1995); Australia [72]	≥ 200 ml increase in volume between arms	121	1Y	Level II	Intermediate
Wang et al. (2016); China [73]	≥ 2 cm between arms	358	12M	Level II	Low
Werner et al. (1991); USA [74]	≥ 2,5 cm between arms	282	37M	Level II	Low
Wojewoda et al. (2013); Poland [75]	≥ 10% increase in circumference	77	36M	Level II	Low
Yang et al. (2010); Korea [76]	≥ 1 cm increase from baseline	183	12M	Level II	Low
Zou et al. (2018); China [77]	≥ 2 cm increase from baseline	387	2Y	Level II	Low
Prospective randomized controlled trials					
Bland et al. (2019); USA [78]	≥ 10% increase in volume	119	3Y	Level II	Low
Box et al. (2002); Australia [79]	≥ 5 cm increase from baseline	65	24M	Level II	Low
Chetty et al. (2000); UK [80]	Absolute change of volume	466	3Y	Level II	Intermediate
Del Bianco et al. (2008); Italy [81]	Absolute change of volume	677	24M	Level II	Intermediate
Deutsch et al. (2008); USA [82]	≥ 2 cm between arms	1457	3Y	Level II	Intermediate
Devoogdt et al. (2011); Belgium [83]	≥ 2 cm between arms	160	1Y	Level II	Low
Goyal et al. (2008); UK [84]	Absolute change of volume	179	1Y	Level II	Low
Lacomba et al. (2010); Spain [85]	≥ 2 cm between arms	116	1Y	Level II	Intermediate
Lucci et al. (2007); USA [86]	≥ 2 cm between arms	468	12M	Level II	Intermediate
Mansel et al. (2006); UK [87]	Ratio of arm volume compared to volume at baseline	1031	12M	Level II	Low
Paskett et al. (2020); USA [88]	≥ 10% increase in volume	554	18M	Level II	Intermediate
Purushotham et al. (2005); UK [89]	Absolute change of volume	298	1Y	Level II	Low
Veronesi et al. (2003); Italy [90]	> 2 cm increase from baseline	516	46M	Level II	Low

	Definition of BCRL	Sample size	Length of follow-up (Y=years, M= months)	Level of evidence	Risk of bias
Retrospective cohort studes					
Aoishi et al. (2020); Japan [91]		1069		Level III-2	Intermediate
Ballal et al. (2018); Australia [92]	≥ 2 cm between arms	745	12M	Level III-2	Low
Belmonte et al. (2018); Spain [93]	Absolute change of volume	112	5Y	Level III-2	Low
Bhatt et al. (2018); Ireland [94]	≥ 2 cm between arms	141	3Y	Level III-2	Low
Coen et al. (2003); USA [95]	≥ 2 cm between arms	727	72M	Level III-2	Low
Delouche et al. (1987); France [96]	> 2 cm between arms	410	11Y	Level III-2	Intermediate
Herd-Smith et al. (2001); Italy [97]	≥ 5% increase in circumference	1278	5Y	Level III-2	Low
Hojris et al. (2000); Denmark [98]	≥ 200 ml increase in volume between arms	84	9Y	Level III-2	Low
Invernizzi et al. (2019); Italy [99]	≥ 2 cm between arms	368	6Y	Level III-2	Low
Kwan et al. (2002); USA [100]	≥ 200 ml increase in volume between arms	744	2Y	Level III-2	Low
Leidendius et al. (2005); Finland [101]	> 2 cm between arms	139	3Y	Level III-2	Low
Lorek et al. (2019); Poland [102]	≥ 10% increase in circumference	298	25.5M	Level III-2	Low
Lumachi et al. (2009); Italy [103]	≥ 2 cm between arms	205	22M	Level III-2	Low
Markowski et al. (1981); USA [104]	≥ 1,5 cm between arms	58	12M	Level III-2	Intermediate
Mathew et al. (2006); UK [105]	≥ 2 cm between arms	504	2Y	Level III-2	Intermediate
Monleon et al. (2015); Spain [106]	≥ 2 cm between arms	371	2Y-6Y	Level III-2	Intermediate
Nagel et al. (2003); The Netherlands [107]	≥ 2 cm increase from baseline	106	14.3M	Level III-2	Low
Ozaslan et al. (2004); Turkey [108]	≥ 2 cm between arms	240	30M	Level III-2	Low
Park et al. (2008); South-Korea [109]	≥ 2 cm between arms	450	12M-24M	Level III-2	Low
Pezner et al. (1986); USA [110]	≥ 2,5 cm between arms	74	14M	Level III-2	Low
Pillai et al. (2010); India [111]	≥ 5% increase in circumference	231	12M	Level III-2	Low
Powell et al. (2003); USA [112]	≥ 2 cm between arms	727	72M	Level III-2	Low
Soyder et al. (2014); Turkey [113]	≥ 2 cm between arms	101	12M	Level III-2	Low
Ugur et al. (2013); Turkey [114]	≥ 5% increase in volume	455	53M	Level III-2	Low
Van der Veen et al. (2004); Belgium [115]	≥ 2,5 cm between arms	108	59M	Level III-2	Low
Wernicke et al. (2013); USA [116]	≥ 1 cm between arms	226	9.9Y	Level III-2	Low
Yadav et al. (2020); India [117]	≥ 2 cm between arms	1770	12Y	Level III-2	Low
Yamamoto et al. (2012); Japan [118]	≥ 2 cm between arms	459	60M-79M	Level III-2	Low
Zhang et al. (2017); China [119]	≥ 2 cm between arms	2597	6M-60M	Level III-2	Low

	Definition of BCRL	*Sample size*	*Length of follow-up (Y=years, M= months)*	*Level of evidence*	*Risk of bias*
Bioelectrical impedance					
Prospective cohort studies					
Fu et al. (2015); USA [120]	Interlimb impedance ratio	136	12M	Level II	Low
Kilbreath et al. (2016); Australia [121]	Interlimb impedance ratio	450	18M	Level II	Low
Polat et al. (2017); Turkey [122]	Interlimb impedance ratio	67	3Y	Level II	Low
Schmitz et al. (2012); USA [66]	Interlimb impedance ratio	333	6Y	Level II	Low
Terada et al. (2020); Japan [71]	Interlimb impedance ratio	631	3.8Y	Level II	Low
Prospective randomized controlled trials					
Kilbreath et al. (2013); Australia [123]	Interlimb impedance ratio	143	15M	Level II	Intermediate
Retrospective cohort studies					
Hayes et al. (2008); Australia [124]	Interlimb impedance ratio	287	18M	Level III-2	Intermediate
Perometry					
Prospective cohort studies					
Bains et al. (2015); UK [125]	Excess volume in affected limb compared with healthy limb	38	3Y	Level II	Low
Cariati et al. (2015); UK [126]	≥ 10% increase in volume	273	2.67Y	Level II	Low
Duff et al. (2001); Ireland [127]	≥ 200 ml increase in volume between arms	100	1Y	Level II	Low
Ferguson et al. (2016); USA [128]	≥ 10% increase in volume	632	24M	Level II	Low
Jammallo et al. (2013); USA [129]	≥ 10% increase in volume	787	27M	Level II	Low
McDuff et al. (2019); USA [130]	≥ 10% increase in volume	4437	4Y	Level II	Low
Miller et al. (2014); USA [131]	≥ 10% increase in volume	627	22.8M	Level II	Low
Miller et al. (2016); USA [132]	≥ 10% increase in volume	616	22.2M	Level II	Low
Naoum et al. (2020); USA [133]	≥ 10% increase in volume	1850	52.7M	Level II	Low
Ridner et al. (2011); USA [134]	≥ 200 ml increase in volume between arms	138	30M	Level II	Low
Warren et al. (2014); USA [135]	≥ 10% increase in volume	1476	25.4M	Level II	Low
Retrospective cohort studies					
Lee et al. (2017); Korea [136]	Excess volume in affected limb compared with healthy limb	429	45.3M	Level III-2	Low
Water displacement					
Prospective cohort studies					
Celebioglu et al. (2007); Sweden [137]	≥ 10% increase in volume	60	2Y-3Y	Level II	Low
Johansson et al. (2001); Sweden [138]	≥ 10% increase in volume	90	2Y	Level II	Low
Pain et al. (2005); UK [139]	≥ 10% increase in volume	70	12M	Level II	Low
Sagen et al. (2014); Norway [140]	≥ 10% increase in volume	313	2.5Y	Level II	Low
Showalter et al. (2013); USA [141]	≥ 5% increase in volume	295	5Y-15Y	Level II	Low
Tausch et al. (2013); Switzerland [142]	≥ 10% increase in volume	114	19M	Level II	Intermediate
Tengrup et al. (2000); Sweden [143]	≥ 10% increase in volume	110	5Y	Level II	Low
Thompson et al. (1995); Australia [72]	≥ 200 ml increase in volume between arms	121	1Y	Level II	Intermediate
Prospective randomized controlled trials					
Ammitzboll et al. (2019); Denmark [144]	> 3% increase in volume	158	12M	Level II	Intermediate
Ashikaga et al. (2010); USA [145]	≥ 10% increase in volume	3983	36M	Level II	Intermediate
Sagen et al. (2009); Norway [146]	≥ 200 ml increase in volume between arms	204	2Y	Level II	Low
Schmitz et al. (2010); USA [147]	≥ 5% increase in interlimb volume	154	1Y	Level II	Low
Retrospective cohort studies					
Beaulac et al. (2002); USA [148]	≥ 200 ml increase in volume between arms	151	4.8Y	Level III-2	Low
Edwards et al. (2000); Australia [149]	≥ 10% increase in volume	201	37M	Level III-2	Low
Nagel et al. (2003); The Netherlands [107]	≥ 200 ml increase in volume between arms	106	14.3M	Level III-2	Low

Risk of bias

Table 1 shows the risk of bias. Hundred-nineteen studies (84%) had a low risk of bias, 22 studies (16%) had an intermediate risk. Some of the reasons for scoring intermediate risk were: lack of blinding details, assessments at different time points, lack of randomization details.

Tools for BCRL measurement and definition

A range of measurement tools were used in the selected studies. In 79% of the studies (111 studies) circumference measurement was used to diagnose lymphedema. Water displacement was used in 10% of the studies (15 studies), perometry in 8.5% of the studies (12 studies) and bioelectrical impedance spectroscopy in 5% of the studies (7 studies). In 4 studies two different measuring tools were used.
In the studies using measurement tools assessing the arm volume (circumference measurements, perometry and water displacement), different definitions for BCRL were used. Thirty-eight studies used the definition ≥ 2 cm between arms, 25 studies used ≥ 10% volume difference, 15 studies used ≥ 200 ml increase in volume between both arms and 9 studies used ≥ 5 cm increase in circumference. In 47 studies other definitions for BCRL were used.

Risk factors for the development of BCRL

A large variation was found in the factors being investigated in the studies and the different analyzes performed. **Table 2** shows the risk factors assessed in the different studies.

In the group of **demographic and general health related factors**, age and body mass index (BMI) were assessed the most. Fifteen studies identified higher age as a significant risk factor for the development of BCRL, 51 studies as a non-significant risk factor. Age is considered as a risk factor with weak level of evidence (15/66). Age was analyzed as a continuous variable in 4 studies. In 7 studies age was divided in two categories with different cut-offs (e.g. age < 40 years or age ≥ 40 years). In 4 studies more than two categories were used or the analyzes were performed using mean age.
Forty-seven studies identified BMI as a significant risk factor, in 25 studies as a non-significant risk factor. BMI is withheld as a risk factor with moderate level of evidence (47/72). In 9 studies BMI was analyzed as a continuous variable, in 17 studies categories were used. Different categories were made such as BMI under or above 24, 25, 28 or 30. In 23 studies different analyzes were done or the type of analyzes was not mentioned in the study.
Other risk factors such as previous history of trauma/infection, unemployment, education, race, presence of co-morbidity, smoking, diabetes, hypertension, and

menopause were found significant in a small number of studies. Dominance was found to be a significant risk factor in 4 studies and a non-significant risk factor in 11 studies, so a risk factor with weak level of evidence (4/15). A lack of physical activity was found to be a significant risk factor in 3 studies 9, 109, 124, and a non-significant factor in 3 studies as well. [17, 69, 121] A lack of physical activity is also a risk factor with moderate evidence (50/100).

In the group of **treatment related factors**, mastectomy was almost equally found to be a significant and a non-significant risk factor (21 studies versus 29 studies). Mastectomy is withheld as a risk factor with weak level of evidence (21/50). Axillary lymph node dissection (ALND) was found to be a significant risk factor in 65 studies and in 3 studies as a non-significant risk factor and therefore considered as a risk factor with strong level of evidence (65/68). In 52 studies radiotherapy was identified as a risk factor for the development of BCRL, in 26 studies as a non-significant risk factor. In some studies radiotherapy as such was not investigated but a subgroup such as radiotherapy of the axilla (6 studies) or radiotherapy of the supraclavicular area (4 studies) were investigated. Radiotherapy (52/78) as well as radiotherapy of the axilla (6/9) are risk factors with a moderate level of evidence. In 30 studies chemotherapy was an identified risk factor, while 34 studies reported it as a non-significant risk factor. Chemotherapy is a risk factor of weak level of evidence. Taxane-based chemotherapy was investigated separately in 7 studies and found significant [49, 51, 55, 99, 121, 123, 126], therefore, taxane-based chemotherapy is a risk factor with strong level of evidence (7/7). Hormone therapy was only significant in 3 studies and non-significant in 21 studies, being a risk factor with weak level of evidence.

Infection is an important postsurgical complication and was reported as a risk factor for the development of BCRL in 9 studies [11, 13, 59, 67, 69, 73, 114, 119, 128] while in 8 studies [21, 31, 51, 56, 65, 79, 106, 113] reported that it was not a risk factor, and was withheld as a risk factor with moderate level of evidence (9/17). Numerous other postsurgical complications were investigated, but were investigated in a small number of studies.

TABLE 2.
Overview of the risk factors

RF	Number of studies in which RF is significant reference	Number of studies in which RF is non-significant reference	Ratio of studies in which significant RF/all studies (%)
DEMOGRAPHIC AND GENERAL HEALTH RELATED FACTORS			
Age			
Not specified	4 [19, 29, 123, 145]	24 [15, 31, 36, 38, 40, 50, 51, 56, 59, 60, 62, 64, 74, 82, 97, 106, 108, 109, 113, 115, 122, 141, 148, 149]	
Continuous	4 [16, 32, 131, 132]	14 [22, 27, 35, 41, 42, 47, 69, 76, 79, 86, 91, 129, 135, 136]	
≥ 40 years		1 [119]	
≥ 44 years	1 [98]		
≥ 50 years	2 [54, 124]	5 [21, 49, 55, 71, 130]	
≥ 52.5 years	1 [121]		
≥ 55 years	1 [52]		
≥ 60 years	2 [95, 110]	5 [37, 46, 53, 73, 112]	
≥ 65 years		2 [65, 67]	
Total	15	51	23%
BMI			
Not specified	22 [11-13, 15, 29, 36, 40, 44, 47, 50, 59, 62, 67, 74, 82, 100, 108, 123, 128, 142, 148, 150]	12 [31, 38, 60, 64, 71, 99, 106, 110, 113, 115, 122, 141]	
Continuous	9 [22, 27, 35, 41, 42, 69, 79, 131, 135]	4 [16, 86, 91, 136]	
≥ 24	1 [77]		
≥ 25	9 [9, 19, 21, 34, 37, 46, 109, 114, 120]	7 [49, 53-55, 73, 119, 124]	
≥ 28	1 [121]		
≥ 30	6 [32, 65, 129, 130, 132, 134]	2 [51, 98]	
Total	47	25	65%
Weight	2 [59, 74]	1 [110]	
Weight gain		1 [59]	
Dominance	4 [11, 73, 124, 145]	11 [19, 37, 41, 59, 69, 79, 109, 113, 115, 122, 149]	27%
Previous history of trauma/infection	2 [9, 114]		
Lack of physical activity	3 [9, 109, 124]	3 [17, 69, 121]	50%
Unemployment	1 [12]		
Education	1 [69]	3 [19, 65, 141]	
Race			
Non-white	1 [148]		
Non-white and non-black	1 [141]		
Presence of co-morbidity	3 [15, 69, 111]	3 [11, 19, 122]	50%
Smoking	1 [50]	3 [64, 98, 108]	
Diabetes	1 [64]	2 [108, 141]	
Hypertension	2 [50, 73]	3 [17, 108, 141]	40%
Menopause		2 [73, 148]	
TREATMENT RELATED FACTORS			
Mastectomy	21 [9, 17, 19, 22, 37, 40, 51, 55, 65, 70, 71, 77, 102, 109, 114, 119, 124, 129, 130, 135, 149]	29 [13, 14, 21, 27, 31, 35, 38, 42, 53, 54, 56, 60, 69, 73, 75, 76, 97, 106, 113, 115, 121-123, 127, 128, 131, 136, 145, 148]	42%
Oblique surgical incision	1 [67]		
ALND	65 [14, 17, 20, 21, 23, 29, 31, 33, 35, 36, 40, 45, 48, 50, 56, 58-60, 62, 63, 65, 68, 71, 73, 76, 77, 80, 81, 87, 89-94, 96, 99-101, 105, 106, 109, 110, 112-114, 116, 118, 119, 122, 123, 128-137, 139, 140, 145, 149]	3 [64, 86, 103]	96%
Extent of LN dissection	1 [119]	3 [26, 74, 79]	
Chemotherapy			
Not specified	18 [12, 15, 19, 24, 29, 32, 42, 53, 65, 98, 106, 109, 129-132, 135, 136]	32 [16, 17, 21, 27, 31, 35, 38, 46, 50, 52, 54, 60, 62, 69, 73-77, 95, 97, 108, 110, 112, 113, 115, 119, 122, 124, 141, 142, 148]	
Adjuvant therapy	1 [91]		
Neo-adjuvant therapy		2 [91, 126]	
Taxanes	7 [49, 51, 55, 99, 121, 123, 126]		100%
Paclitaxel	1 [39]		
Docetaxel	1 [91]		
Neoadjuvant docetaxel and cyclophosphamide	1 [26]		
Adjuvant docetaxel and cyclophosphamide	1 [26]		
Total	30	34	47%
Length of neo-adjuvant therapy	1 [27]		
Radiotherapy			
Not specified	41 [9, 15-19, 21, 29, 32, 34, 42, 46, 48, 49, 56, 62, 63, 65, 67, 71-73, 77, 91, 96, 97, 106-109, 111-114, 129-132, 135, 136, 141]	23 [14, 22, 26, 27, 31, 35, 37, 38, 41, 52, 59, 60, 64, 69, 74-76, 79, 98, 99, 110, 124, 148]	
Axilla	6 [51, 100, 115, 121, 138, 145]	3 [12, 13, 149]	67%
Supraclavicular RT	4 [50, 53, 55, 115]		
Chest/breast wall + regional LN irradiation	1 [128]		
Total	52	26	67%
Extent of LN irradiation	1 [95]		
Dose of RT at axillary-lateral thoracic vessel juncture	1 [43]		
Duration		1 [56]	
Dose		2 [100, 106]	
Hormone therapy	3 [38, 98, 135]	21 [15, 16, 19, 21, 42, 49, 51, 65, 69, 73-75, 99, 106, 109, 121, 122, 129-132]	12.5%
Anti-HER2		2 [49, 122]	
Postsurgical complications		1 [19]	
Infections	9 [11, 13, 59, 67, 69, 73, 114, 119, 128]	8 [21, 31, 51, 56, 65, 79, 106, 113]	53%
Seroma	3 [41, 65, 91]	4 [21, 65, 69, 113]	43%
Injury	2 [59, 148]	2 [17, 41]	
Postop swelling	1 [135]		
Decreased range of motion	1 [148]		
Drainage	1 [63]	1 [79]	
Seroma duration	1 [51]		
Cording		2 [65, 79]	
Days drain in situ	1 [123]	1 [114]	
Wound complication		2 [51, 106]	
Hospital skin puncture/ blood draws/injections	1 [37]	2 [17, 128]	
Flights		1 [128]	
BREAST CANCER RELATED FACTORS			
Side operation	1 [24]	2 [106, 122]	
Type of cancer		7 [38, 41, 51, 60, 77, 106, 130]	0%
Tumor located in the upper outer quadrant	1 [68]		
Tumor stage	21 [15, 32, 40, 42, 49, 53, 55, 56, 65, 74, 97, 106, 109, 111, 113, 114, 131, 132, 135, 136, 149]	25 [21, 22, 31, 38, 41, 51, 54, 60, 62, 64, 69, 73, 75, 77, 82, 95, 98, 100, 108, 112, 115, 119, 122, 141, 145]	46%
Size of tumor		1 [121]	
Node stage	5 [46, 49, 55, 56, 100]	1 [55]	83%

RF	*Number of studies in which RF is significant reference*	*Number of studies in which RF is non-significant reference*	*Ratio of studies in which significant RF/all studies (%)*
Number of removed LN			
Not specified	19 [9, 13, 21, 22, 31, 40, 48, 50, 60, 72, 73, 78, 97, 98, 102, 117, 124, 141, 148]	15 [11, 19, 74, 75, 82, 100, 106, 108, 113, 115, 122, 127, 142, 145, 149]	
Continuous	8 [16, 27, 41, 42, 131, 132, 135, 136]	4 [35, 69, 79, 91]	
≥ 3 LN	1 [130]		
≥ 10 LN	4 [49, 53-55]		
≥ 15 LN	1 [52]	3 [46, 51, 65]	
≥ 16 LN		1 [77]	
≥ 22 LN	1 [64]		
Total	34	23	60%
Number of positive LN	29 [16, 19, 21, 22, 24, 27, 32, 34, 38, 47, 52, 56, 65, 73, 74, 77, 91, 98, 111, 113, 115, 119, 121, 122, 129, 131, 132, 135, 136]	17 [11, 35, 37, 41, 42, 46, 51, 64, 75, 78, 79, 82, 95, 105, 108, 112, 123]	63%
Volume of axillary tissue removed	1 [148]		
Capsular invasiveness of the lymph node	1 [47]		
Lymphovascular invasion	1 [21]		
Presence of cranial collectors (lymphatic ducts along or above the axillary vein)	1 [18]		

BMI: Body Mass Index; ALND: axillary lymph node dissection; RT: radiotherapy; LN: lymph node; RF: risk factor

In the group of **breast cancer related factors**, the number of removed lymph nodes and the number of positive lymph nodes were found to be a risk factor for the development of BCRL. The number of lymph nodes was found to be a significant risk factor in 34 studies, in 23 studies it was a non-significant risk factor. The number of removed lymph nodes was also analyzed in different ways: continuous in 8 studies or as a categorical variable in 7 studies. Most frequently, a cut-off of 10 or 15 number of removed lymph nodes was used. In 29 studies, the presence of positive lymph nodes was a risk factor for the development of BCRL, in 17 studies it was a non-significant risk factor. So, the number of lymph nodes removed (34/57) and the number of positive lymph nodes (29/46) are both risk factors with a moderate level of evidence. Tumor stage was found almost equally a significant and a non-significant risk factor. Node stage was found to be a significant risk factor in most of the studies investigating it and is therefore a risk factor with strong level of evidence.

DISCUSSION

This systematic review was carried out to perform an up-to-date review of the variety of risk factors related to the development of BCRL.

Demographic and general health related variables associated with BCRL

In this review we cannot conclude that age is a risk factor for the development of BCRL as it is only found significant in 23% of the studies (weak level of evidence). BMI was considered as a risk factor in a previous review article.[1] In this systematic review, 65% of the studies reporting BMI as a risk factor, found it to be significant. So BMI can be considered as a risk factor with moderate level of evidence. Perhaps not only the presence of obesity preoperatively but also the fluctuations in weight and/or the postoperative BMI can play a role in the development of BCRL.[129, 151] Additionally, when lymphedema patients lose weight, this can result in decrease of the arm volume.[152, 153] This all suggest that BMI can play a role in the development of BCRL.

For general health related factors, such as previous history of trauma/infection, race, unemployment, education, smoking, diabetes and menopause the evidence is inconclusive. The presence of co-morbidities, hypertension, dominance and lack of physical activity are risk factors with weak level of evidence. In the review by DiSipio, sedentary lifestyles were identified as a risk factor with moderate evidence.[1] Physical activity activates the muscle pump and can influence the lymphatic and

venous transport [154], so having a good physical activity level could be a protective factor for the development of BCRL, although this is not clear in this review.

Treatment related variables associated with BCRL

The present review shows that there is strong level of evidence that patients who underwent treatment with ALND are at increased risk for developing lymphedema. These findings were correlated to the findings of other reviews and meta-analyses.[1, 4] More and more strict guidelines are proposed to diminish this risk by narrowing the indications for ALND and evolving to less invasive treatment such as sentinel lymph node biopsy (SLNB) and axillary radiotherapy. For this last one, we have to be careful especially because the side effects of radiotherapy often appear later than the effects of surgery, so a longer follow-up is needed.[130]

Mastectomy is mentioned as a risk factor in 42% of the studies, so in this review it is considered as a factor with weak level of evidence. It is not clear if mastectomy has an impact on the development of BCRL, but it is suggested that if a more advanced cancer is present, a more invasive surgery, such as mastectomy and ALND is performed, and chances to develop BCRL will be increased.[55]

Chemotherapy is identified as a risk factor in 47% of the studies. Sometimes specifically a certain type of chemotherapy was found a risk factor such as taxanes. In other studies only the presence of chemotherapy in the treatment plan or the timing of the chemotherapy (adjuvant versus neo-adjuvant) was taken into account. In this review, taxane-based chemotherapy is a significant risk factor in 100% of the studies[39, 49, 51, 55, 91, 99, 121, 123, 126], resulting in a risk factor with strong level of evidence. The working mechanism of edema caused by taxanes is partially related to an increase of the capillary permeability. According to the study by Cariati[126] the influence of the taxane-based chemotherapy on lymphangiogenesis also plays a role. When taxanes are administrated in combination with axillary radiation, lymphedema will not only be caused by the capillary permeability increase but also by the damage to the lymphatic system due to the radiotherapy.[39] This result was also identified by the review of DiSipio.[1] In the review by Tsai, chemotherapy was not withheld as a risk factor for the development of BCRL. A possible reason for this is that taxane-based chemotherapy as such was not investigated. Further research is needed to establish the role of chemotherapy, specifically taxane-based chemotherapy, and the combination with other treatment modalities in the development of BCRL.

Radiotherapy is considered a risk factor with moderate level of evidence (67%). A large variety in variables was investigated, ranging from specific regions where radiotherapy was performed such as axillary and supraclavicular areas to the dose and extent of irradiation. In 100% of the studies investigating axillary radiotherapy, it was identified as a risk factor for the development of BCRL (strong level of evidence). Radiation of the axilla is indicated if the patient has ≥ 4 positive lymph nodes with capsular breakthrough, tumor is left in the axilla or if not enough lymph nodes are removed during a ALND (< 6 LN).[155] Another indication for radiotherapy of the axilla is 1 or 2 positive lymph nodes after SLNB. [156] Although axillary radiotherapy could be a risk factor, the AMAROS trial found significant less lymphedema in the radiotherapy and SLNB group versus the ALND group.[157] In the group of combined ALND and axillary radiation lymphedema risk was the highest. This finding is also confirmed by others.[62, 130, 157] Radiotherapy of the supraclavicular area is found significant in 4 studies, so inconclusive to draw a conclusion.

Postoperative complications such as infections are withheld as a risk factor with moderate level of evidence (53%). The other postoperative complications are withheld as either weak level of evidence or inconclusive.

Breast Cancer related variables associated with BCRL

Node stage is found to be a risk factor with strong level of evidence (83%). The number of lymph nodes removed and the number of positive lymph nodes are identified as a risk factor in many studies and therefore identified as risk factors with moderate level of evidence, the same as in the review by DiSipio.[1] The number of removed lymph nodes correlates with the fact that ALND is a risk factor. The node stage and the number of positive lymph nodes fits into the idea that more advanced disease has a higher risk to develop BCRL than less advanced disease.[4, 54] In summary risk factors with a strong level of evidence are axillary lymph node dissection, node stage and taxane-based chemotherapy. Risk factors with a moderate level of evidence are BMI, greater number of excised lymph nodes, presence of positive lymph nodes, radiotherapy, radiotherapy of the axilla and postoperative infections.

Strengths of this systematic review

This review has several strengths.

A first strength is a very broad search using search terms such as 'lymphedema' and 'breast cancer'. This made it possible to identify 7393 titles relevant to this topic. Hundred forty-one of the 7393 articles were included in this systematic review. A previous review by DiSipio [1] included only 79 articles and the review by Tsai [4] included 98 articles.

A second strength are the inclusion criteria. To avoid the presence of transient oedema [55, 158, 159], only articles that investigated the presence of lymphedema 1 year or more after the treatment of breast cancer were included. Moreover, only studies using objective measurement tools were included in the search; subjective measurement tools such as clinical assessment by the patient or questionnaires were, in contrast to other reviews, not included. In some studies validated questionnaires such as the Lymphedema Breast Cancer Questionnaire (LBCQ) [160] were used, but this was not the case in all studies. In some studies, only a few questions were asked by phone. In the review by DiSipio also subjective symptoms such as self-reported swelling was allowed.[1] We preferred not to use subjective assessments in this study, because most of these subjective measures lack specificity as a lot of the symptoms felt after treatment can be present due to other complications occurring after breast cancer treatment.[161] We also preferred only to consider studies dealing with unilateral breast cancer because bilateral disease is more difficult to measure in an objective way (no comparison possible). The risk of bias scored low in most cases, due to these strict inclusion criteria.

Limitations

A first limitation of this review is that the impact of preventive measures such as manual lymph drainage, compression therapy or preventive surgery such as a lymphovenous anastomosis on the development of BCRL was not taken into account in this review. We especially wanted to focus on the impact of the different treatment modalities for breast cancer and not on the impact of preventive measures.
Second, due to the diversity of analyzes being found in the studies, a meta-analysis was not performed in this study.

Impact on practice

Being up-to-date on risk factors related to the development of BCRL will be useful in setting up a surveillance program for the high risk patients, as setting up a surveillance program for all patients after breast cancer treatment will not be feasible and not cost-effective.[162]

CONCLUSION

Overall we can conclude that there is strong evidence that ALND, taxane-based chemotherapy and node stage are risk factors for the development of BCRL. BMI, high number of removed lymph nodes, the number of positive lymph nodes, radiotherapy, radiotherapy of the axilla and postoperative infections are risk factors with a moderate level of evidence. Although there is an evolution towards less invasive treatment, lymphedema remains an important issue in the postoperative phase.

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APPENDIX 1. SEARCH TERMS

Pubmed

"Breast Cancer Lymphedema"[Mesh] OR BCRL[tiab] OR (("Breast Neoplasms"[Mesh] OR breast-neoplasm*[tiab] OR breast-tumor*[tiab] OR breast-cancer*[tiab] OR mammary-cancer*[tiab] OR mamma-cancer*[tiab] OR mammary-carcinoma*[tiab] OR mammary-neoplasm*[tiab] OR breast-carcinoma*[tiab] OR breast-carcinoma-in-situ[tiab] OR lobular-carcinoma-in-situ[tiab] OR intraductal-carcinoma*[tiab] OR DCIS[tiab] OR ductal-carcinoma-in-situ[tiab] OR noninfiltrating-intraductal-carcinoma*[tiab] OR non-infiltrating-intraductal-carcinoma*[tiab] OR atypical-ductal-hyperplasia*[tiab] OR paget-disease-of-the-breast[tiab] OR paget's-disease-of-the-breast[tiab] OR paget's-disease-of-the-nipple-and-areola[tiab] OR paget's-disease-of-the-nipple[tiab] OR pigmented-mammary-paget-disease[tiab] OR mammary-paget-disease[tiab] OR mammary-paget's-disease[tiab] OR mammary-pagets-disease[tiab] OR mammary-ductal-carcinoma*[tiab] OR lobular-carcinoma*[tiab] OR hereditary-breast-and-ovarian-cancer-syndrome[tiab] OR HBOC-syndrome*[tiab] OR post-mastectomy[tiab] OR post-mastectomy[tiab]) AND ("Lymphedema"[Mesh:NoExp] OR lymphedema*[tiab] OR lymphoedema*[tiab] OR lymph-edema*[tiab] OR lymph-oedema*[tiab] OR lymphatic-edema*[tiab] OR lymphatic-oedema*[tiab] OR lymphooedema*[tiab] OR lymphostatic-edema*[tiab] OR lymphostatic-oedema*[tiab]))

Embase

'breast cancer-related lymphedema'/exp OR 'BCRL':ti,ab,kw OR (('breast cancer'/exp OR 'breast neoplasm*':ti,ab,kw OR 'breast tumor*':ti,ab,kw OR 'breast cancer*':ti,ab,kw OR 'mammary cancer*':ti,ab,kw OR 'mamma cancer*':ti,ab,kw OR 'mammary neoplasm*':ti,ab,kw OR 'breast carcinoma*':ti,ab,kw OR 'breast carcinoma in situ':ti,ab,kw OR 'lobular carcinoma in situ':ti,ab,kw OR 'intraductal carcinoma*':ti,ab,kw OR 'DCIS':ti,ab,kw OR 'ductal carcinoma in situ':ti,ab,kw OR 'non infiltrating intraductal carcinoma*':ti,ab,kw OR 'atypical ductal hyperplasia*':ti,ab,kw OR 'paget* disease of the breast':ti,ab,kw OR 'paget s disease of the breast':ti,ab,kw OR 'paget s disease of the nipple and areola':ti,ab,kw OR 'paget s disease of the nipple':ti,ab,kw OR 'pigmented mammary paget* disease':ti,ab,kw OR 'mammary paget* disease':ti,ab,kw OR 'mammary paget s disease':ti,ab,kw OR 'mammary ductal carcinoma*':ti,ab,kw OR 'lobular carcinoma*':ti,ab,kw OR 'hereditary breast and ovarian cancer syndrome':ti,ab,kw OR 'HBOC syndrome':ti,ab,kw OR 'post mastectomy':ti,ab,kw) AND ('lymphedema'/exp OR 'lymphedema*':ti,ab,kw OR 'lymph edema*':ti,ab,kw OR 'lymphatic edema*':ti,ab,kw OR 'lymphostatic edema*':ti,ab,kw OR 'lymphoedema*':ti,ab,kw OR 'lymph oedema*':ti,ab,kw OR 'lymphatic oedema*':ti,ab,kw OR 'lymphostatic oedema*':ti,ab,kw))

WoS

"breast cancer lymph$edema*" OR "BCRL" OR (("breast neoplasm*" OR "breast tumor*" OR "breast cancer*" OR "mammary cancer*" OR "mamma cancer*" OR "mammary carcinoma*" OR "mammary neoplasm*" OR "breast carcinoma*" OR "breast carcinoma in situ" OR "lobular carcinoma in situ" OR "intraductal carcinoma*" OR "DCIS" OR "ductal carcinoma in situ" OR "noninfiltrating intraductal carcinoma*" OR "non infiltrating intraductal carcinoma*" OR "atypical ductal hyperplasia*" OR "paget* disease of the breast" OR "paget s disease of the breast" OR "paget s disease of the nipple and areola" OR "paget s disease of the nipple" OR "pigmented mammary paget disease" OR "mammary paget* disease" OR "mammary paget s disease" OR "mammary ductal carc
inoma*" OR "lobular carcinoma*" OR "hereditary breast and ovarian cancer syndrome" OR "HBOC syndrome*" OR "postmastectomy" OR "post mastectomy") AND ("Lymphedema*" OR "lymph$edema*" OR "lymph $edema*" OR "lymphatic $edema*" OR "lymphostatic $edema*"))

Cochrane

#1: [mh "Breast Cancer Lymphedema"]
#2: (BCRL):ti,ab,kw
#3: #1 OR #2
#4: [mh "Breast Neoplasms"]
#5: ((breast NEXT neoplasm*) OR (breast NEXT tumor*) OR (breast NEXT cancer*) OR (mammary NEXT cancer*) OR (mamma NEXT cancer*) OR (mammary NEXT neoplasm*) OR (breast NEXT carcinoma*) OR (breast NEXT carcinoma NEXT in NEXT situ) OR (lobular NEXT carcinoma NEXT in NEXT situ) OR (intraductal NEXT carcinoma*) OR (DCIS) OR (ductal NEXT carcinoma NEXT in NEXT situ) OR (non NEXT infiltrating NEXT intraductal NEXT carcinoma*) OR (atypical NEXT ductal NEXT hyperplasia*) OR (paget* NEXT disease NEXT of NEXT the NEXT breast) OR (paget s NEXT disease NEXT of NEXT breast) OR (paget s NEXT disease NEXT of NEXT the NEXT breast) OR (paget s NEXT disease NEXT of NEXT the NEXT areola) OR (paget s NEXT disease NEXT of NEXT the NEXT nipple) OR (pigmented NEXT mammary NEXT paget NEXT disease) OR (mammary NEXT paget s NEXT disease) OR (mammary NEXT paget* NEXT disease) OR

(mammary NEXT ductal NEXT carcinoma*) OR (lobular NEXT carcinoma*) OR (hereditary NEXT breast NEXT cancer NEXT syndrome) OR (HBOC NEXT syndrome) OR (post NEXT mastectomy)):ti,ab,kw
#6: #4 OR #5
#7: [mh ^“Lymphedema”]
#8: ((lymph?edema*) OR (lymph NEXT ?edema*) OR (lymphatic NEXT ?edema*) OR (lymphooedema*) OR (lymphostatic NEXT ?edema*)):ti,ab,kw
#9: #7 OR #8
#10: #6 AND #9
#11: #3 OR #10

5

Early disturbance of the lymphatic transport as a risk factor for the development of breast-cancer related lymphedema.

Preliminary results. Final results will be submitted for publication when 3 years follow-up is reached.

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ABSTRACT

Introduction:
Breast-cancer related lymphedema (BCRL) is a frequently occurring and debilitating condition. When lymphedema is diagnosed late, treatment can be expected to be less effective. Lymphofluoroscopy visualizes the superficial lymphatic architecture in detail, giving the opportunity to detect an early disturbance in the lymphatic transport (i.e. dermal backflow) before the lymphedema is clinically visible. The main objective is to investigate if this early disturbance of the lymphatic transport visualized by lymphofluoroscopy is a risk factor for the development of BCRL.

Methodology:
All patients scheduled for breast cancer surgery with unilateral axillary lymph node dissection or sentinel node biopsy in the Multidisciplinary Breast Center of the University Hospitals Leuven were considered. Patients were assessed at baseline and at 1, 3, 6, 9 and 12 months postoperatively. At each visit a clinical assessment was performed determining the volume difference between both arms and hands (through circumference measurements and water displacement). Clinical lymphedema was defined as a ≥5% increase of relative arm volume difference compared to the baseline value. Variables related to 1) the disturbance of lymphatic transport, 2) the demographics and general health of the patient and 3) the breast cancer and treatment of the patient were investigated.

Results:
We included 128 patients in this study. Thirty-eight patients (29.7%) developed lymphedema at 12 months. Early disturbance visualized by lymphofluoroscopy was significantly more frequent in the group of patients developing lymphedema (p= 0.0180). Variables related to demographic and general health were not associated with a significant different incidence of BCRL. Breast cancer and treatment related variables such as axillary lymph node dissection (OR 55.468), tumor stage (OR 2.041), number of positive lymph nodes (OR 1.204), number of removed lymph nodes (OR 1.082), radiotherapy of the axilla (OR 20.085), adjuvant taxanes (OR 4.400) and postsurgical complications (OR 4.051) were identified as a significant risk factor for the development of BCRL.

Conclusion:
Lymphofluoroscopy can identify an impaired lymphatic transport early and is a good predictor for the development of BCRL. This study confirms that patients with more advanced breast cancer (mastectomy, high number of positive lymph nodes, high number of removed lymph nodes, postsurgical complications, high tumor stage, radiotherapy of the axilla and taxanes) have more risk to develop BCRL.

INTRODUCTION

Despite less invasive surgical techniques and treatment options, breast cancer-related lymphedema (BCRL) remains one of the most important complications after breast cancer treatment.[1] Breast cancer survivors have a lifelong risk of developing lymphedema, with the incidence rate ranging from 5.6% to 63.4%.[2] According to history and clinical examination, a clinical stage system can be used, based on the consensus document of the International Society of Lymphology (ISL).[1] Stage 0 refers to a subclinical state, where edema is not yet visible despite impaired lymphatic transport. Stage I refers to an early accumulation of fluid. This edema subsides with elevation of the limb. Stage IIa represents swelling that not subsides with limb elevation and pitting is manifest. In late stage II (IIb) no pitting is visible and fibrosis together with fat emerges. Stage III or 'lymphostatic elephantiasis' is the most advanced form, with skin abnormalities and further fibrosis of the tissue.
Clinical assessment tools such as tissue dielectric constant, bioelectrical impedance spectroscopy, circumference measurement, perometer and water displacement method can be used to detect lymphedema.[3,4] Preoperative and postoperative measurement at regular times are needed to detect lymphedema early, but there still is no consensus on the threshold defining subclinical lymphedema.[3] In some studies a threshold of ≥ 3% volume increase compared to preoperative values is defined as a subclinical lymphedema (19).[5] A threshold of ≥ 5% volume increase is used to define clinical lymphedema. Other measurement techniques can assess fluid in the tissue, either in the extracellular space (bioelectrical impedance spectroscopy) [6] or the skin (tissue dielectric constant).[7]
Lymphofluoroscopy or near-infrared fluorescence imaging is an imaging technique that visualizes the disturbance of the superficial lymphatic transport. Three patterns of dermal backflow (splash, stardust and diffuse) are described according to the severity of the disturbance.[8] This imaging technique can, according to Akita et al, be used for early detection of BCRL.[9] They included hundred ninety six patients planned for surgical treatment of breast cancer of which 25 % of developed a dermal backflow pattern within the first year after the surgery.

A number of risk factors for the development of BCRL have been investigated. These can be categorized in risk factors related to demographics and general health (such as body mass index (BMI), age, race or diabetes) and risk factors related to the treatment (such as type of surgery, type of lymph node dissection, chemotherapy, radiotherapy, tumor stage, number of positive lymph nodes). A higher age and a higher BMI are proven to be associated with a higher risk for the development of BCRL. In some studies a low level of physical activity[10], hypertension[11], black race11 and a low level of education[12] are associated with a higher risk as well. Modified radical mastectomy (versus breast-conserving surgery),

axillary lymph node dissection (ALND) versus sentinel lymph node dissection (SLND), radiotherapy, chemotherapy and postsurgical complications[13] are described as being treatment-related risk factors for the development of BCRL.[2,14-16] Higher tumor stage and higher number of positive lymph nodes are known risk factors related to the breast cancer.[2,16]
Whether early disturbance of the lymphatic transport visualized by lymphofluoroscopy is a risk factor for the development of BCRL has never been investigated yet. The primary aim of this study is to investigate if this early disturbance of lymphatic transport visualized by lymphofluoroscopy is a risk factor for the development of BCRL. The secondary aim is to investigate whether demographic, general health and treatment related variables found in the literature, can be confirmed by the present study.

METHODOLOGY

Trial design

The present study is a prospective cohort study which is part of the ongoing Dearly trial (Determining the role of pre-existing factors, early diagnostic options and early treatment in the development of BCRL).[17] The study was approved by the Ethical Committee of the University Hospitals Leuven (S-number 60382, EudraCT Number 2017-002306-12). The study has been registered in clinicaltrials.gov (NCT 03210311).

Participants

The recruitment of subjects started in November 2017 and ended May 2019. All consecutive breast cancer patients who were scheduled for surgery for primary breast cancer were asked to participate. All patients were recruited in the Multidisciplinary Breast Center of the University Hospitals Leuven, Belgium. Inclusion criteria were 1) age ≥18y, 2) women/men with primary breast cancer and scheduled for unilateral axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB), 3) oral and written approval of informed consent, 4) understanding Dutch. Exclusion criteria were 1) edema of the upper limb from other causes, 2) not being able to participate during the entire study period, 3) mentally or physically unable to participate in the study, 4) contra-indication for the use of Indocyanine Green (ICG): allergy to ICG, iodine, hyperthyroidism, or 5) metastatic disease.

All patients received written as well as oral information. All included patients signed an informed consent document prior to the start of the study.

Data Collection

All assessments were performed at baseline and at 1, 3, 6, 9 and 12 months postoperatively.

Development of BCRL

At the different follow-up visits, the presence of clinical lymphedema was scored. Circumference measurements at the olecranon and at 4, 8, 12, 16 and 20cm above and under the olecranon at the affected and healthy arms were performed.[18]
Clinical lymphedema was defined as a ≥5% increase of relative arm volume difference compared to the baseline value. The relative arm volume difference was calculated as the absolute arm volume difference between the affected side and the healthy side divided by the absolute arm volume of the healthy side and multiplied by 100, the absolute arm volume is the sum of the volumes of the different arm segments and the hand volume. The volume of the arm segments was calculated using the formula of the truncated cone ($V= 4 \times (C_1^2+C_1C_2+C_2^2)/12\pi$, where V is the volume, C_1 is the upper circumference and C_2 is the lower circumference of each segment).[19] The hand volume of both sides was determined by the water displacement method using the most distal skinfold at the wrist as the reference point.[20] Lymphedema was scored positive when observed at 12 months or earlier.

Lymphatic transport related variable

All lymphofluoroscopic assessments are performed by one person (ST) who was blinded to the participant's data.
During lymphofluoroscopy, ICG was injected intradermally in the first and fourth webspace of the hand on the affected side. An infrared camera system (PDE, Hamamatsu®) captured the fluorescence. The procedure consisted of three consecutive phases **(Table 1)**: an early phase, a break and a late phase. All information about the lymphatic transport was documented in a standard evaluation document and in case of disturbance, this information was drawn on a body diagram according to the legend **(Figure 1)**.

TABLE 1.
Protocol of lymphofluoroscopy

Step		*Description*	*Reporting*
Preparation	0.1 Dilution	Suspended ICG in 25 ml pure water and subsequently diluted with saline water to reach a final concentration of 0.20 mg/ml	
	0.2 Camera	Camera is held perpendicular to the observed skin at distance of 15 cm (best focus)	
	0.3 Injection of ICG	Intradermal injection in 1st (ulnar injection point) and 4th web space (radial injection point) dorsally in the hand 0.2 ml of the diluted solution is injected in each injection point	Time of injection
Early phase	1.1 Rest: 1 min	Hand in resting position on table	Linear transport starting from ulnar injection point: Yes / No (if "yes", after ..... sec) Linear transport starting from radial injection point: Yes / No (if "yes", after ..... sec)
	1.2 Stimulation: 3 min	Lymph capillaries at the level of the injection points are filled and transport through the lymph collectors is stimulated by the assessor	
	1.3 Scan with camera and measuring	1) of the arm and shoulder with hand in pronation: starting at hand up to the retroclavicular region, 2) of the arm and axilla with hand in supination and abduction of the shoulder: starting at hand up to the axilla, together with the pectoral region: from the ipsilateral to the contralateral axilla, 3) of the scapular region: from the ipsilateral to the contralateral axilla, 4) of the pectoral region: from the ipsilateral to the contralateral axilla	After scan, reporting on an assessment form: - Number of lymph collectors - Of each lymph collector: length (measured with tapeline in cm), location and normal versus dilated situation - Presence of splash, stardust and diffuse pattern and location (fingers, hand, proximal/ distal and ventral/ dorsal lower or upper arm, breast and trunk) - Number of lymph nodes (cubital, humeral, axillary, retroclavicular)
Break	30 min		
Late phase	3.1 Scan with camera and measuring	See step 1.3	See step 1.3
	3.2 Drawing on skin and body diagram	If disturbance is seen lymph collectors and dermal backflow (splash, stardust and diffuse) are designed on a body diagram (see **figure 1**)	Design on body diagram if disturbance is seen

The presence of dermal backflow was scored 0 if a normal (linear) pattern was seen; 1 if an abnormal pattern (splash, stardust or diffuse) was seen. Early disturbance was defined as present if there was at least one occurrence of lymphofluoroscopy abnormality before the first occurrence of clinical lymphedema or before 12 months (in lymphedema-negative cases).

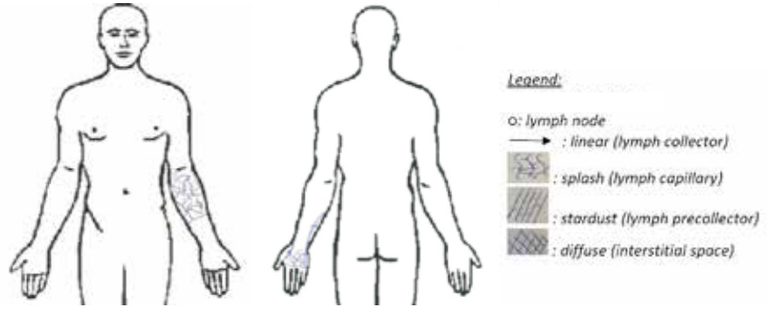

FIGURE 1.
Example of body diagram

Demographic and general health related variables

Demographic variables (age, dominance, BMI) and general health related variables (diabetes, hypertension, hypothyroidism, hyperthyroidism, chronic heart failure, chronic renal failure, and history of infection or trauma in affected limb) were collected by interview with the patients.
The physical activity level was assessed at baseline using the International Physical Activity Questionnaire (IPAQ long version). This questionnaire comprises a set of 5 activity domains asked independently.[21] According to the scoring, three levels of physical activity were given: low (< 600 metabolic equivalent (MET)-min/week), moderate (< 3000 MET-min/week) and high (> 3000 MET-min/week).

Breast cancer and treatment related variables

Data related to the breast cancer such as tumor stage, type of cancer, number of removed lymph nodes and number of positive lymph nodes were recorded according to the pathology report.
Treatment related variables consisting of the type of surgery, chemotherapy, radiotherapy, hormone therapy and postsurgical complications were identified by notes in the electronic medical file of the patient.

Statistical methods

Group comparisons were performed using a Fishers Exact test for nominal variables, or a Mann-Whitney U test for continuous or ordinal variables. Most of the variables were nominal variables. The variables age, BMI, physical activity level, number of removed lymph nodes and number of positive lymph nodes were analyzed as continuous variables. Tumor stage was analyzed as an ordinal variable.
Logistic regression analyses were applied to investigate the prognostic effect of possible risk factors on development of clinical lymphedema (yes/ no). The results were reported as odds ratio (OR) with 95% confidence intervals.
Thereafter, a forward stepwise model selection procedure was applied to develop a multivariable model of independent risk factors. A 5% significance level was used for model entry and exit.
All reported p-values are two-sided. Analyses have been performed using SAS software (version 9.4 of the SAS System for Windows).

RESULTS

Description participants

Hundred twenty-eight patients were enrolled for this trial. The mean age of the patients was 56.68 (SD 12.25), the mean BMI was 25.96 (SD 11.98). In 73 patients ALND (57%) was performed, 55 patients (43 %) underwent SLNB. Eighty-nine patients (70%) underwent a mastectomy, 39 patients (30%) a breast-conserving surgery. Detailed patient characteristics are summarized in **Table 2**.
Of the 128 patients in the study, 38 (29.6%) patients developed clinical lymphedema, after a follow-up time of 12 months. Nine patients developed BCRL at one month, seven at three months, eleven at six months, four at nine months and seven at twelve months. The mean relative arm volume difference was 197.31 ml (SD 138).

TABLE 2.
Variables of the study participants

Variable	*Without clinical lymphedema at 1 year*	*With clinical lymphedema at 1 year*	*p-value*
	N=90	**N=38**	
Age	56.10 (11.98)*	58.05 (12.94)*	0.443
BMI	25.82 (4.91)*	26.27 (4.96)*	0.470
Treatment on dominant side			
No	47 (52.22%)	18 (47.37%)	0.700
Yes	43 (47.78%)	20 (52.63%)	
Diabetes			
No	87 (96.67%)	36 (94.74%)	0.633
Yes	3 (3.33%)	2 (5.26%)	
Hypertension			
No	72 (80%)	29 (76.32%)	0.642
Yes	18 (20%)	9 (23.68%)	
Hypothyroidism			
No	84 (93.33%)	33 (86.84%)	0.301
Yes	6 (6.67%)	5 (13.16%)	
Hyperthyroidism			
No	85 (94.44%)	38 (100%)	0.321
Yes	5 (5.56%)	0 (0%)	
Chronic heart failure			
No	88 (96.67%)	37 (97.37%)	1.000
Yes	2 (2.22%)	1 (2.63%)	
Chronic renal failure			
No	90 (100%)	37 (97.37%)	0.297
Yes	0 (0%)	1 (2.63%)	
Previous injury/ infection			
No	83 (92.22%)	35 (92.11%)	1.000
Yes	7 (7.78%)	3 (7.89%)	
Type of cancer			
Ductal	72 (80%)	29 (76.32%)	0.673
Lobular	11 (12.22%)	7 (18.42%)	
Other	7 (7.78%)	2 (5.26%)	
Tumor stage			
Tis	2 (2.22%)	0 (0%)	0.010
T1	37 (41.11%)	7 (18.42%)	
T2	35 (38.89%)	17 (44.74%)	
T3	13 (14.44%)	7 (18.42%)	
T4	3 (3.33%)	7 (18.42%)	
Type of surgery			
Mastectomy	56 (62.22%)	33 (86.84%)	0.006
Breast-conserving surgery	34 (37.78%)	5 (13.16%)	
Extend of lymph node dissection			
ALND	36 (40%)	37 (97.37%)	**<.001**
SLNB	54 (60%)	1 (2.63%)	
Number removed LN	9.58 (10.92)*	18.11 (7.02)*	**<.001**
Number positive LN	1.10 (2.85)*	3.26 (3.98)*	**<.001**
Postsurgical complications			
No	43 (47.78%)	7 (18.42%)	**0.003**
Yes	47 (52.22%)	31 (81.58%)	
RT axilla			
No	89 (98.89%)	31 (81.58%)	**<.001**
Yes	1 (1.11%)	7 (18.42%)	
Taxanes			
No	55 (61.11%)	10 (26.32%)	**<.001**
Yes	35 (38.89%)	28 (73.68%)	
Tamoxifen			
No	72 (80%)	32 (84.21%)	0.631
Yes	18 (20%)	6 (15.79%)	
AI			
No	30 (33.33%)	9 (23.68%)	0.303
Yes	60 (66.67%)	29 (76.32%)	
	N=81	**N=37**	
Physical activity score			
Low	9 (11.11%)	5 (13.51%)	0.923
Moderate	37 (45.68%)	17 (45.95%)	
High	35 (43.21%)	15 (40.54%)	
	N=80	**N=26**	
Early disturbance lymphofluoroscopy			
No	55 (68.75%)	11 (42.31%)	**0.018**
Yes	25 (31.25%)	15 (57.69%)	

BMI: Body Mass Index; ALND: axillary lymph node dissection; SLNB: sentinel lymph node biopsy; LN: lymph nodes; RT: radiotherapy, AI: Aromatase inhibitor
* Mean (SD)

Lymphatic transport related variable

The results from the lymphofluoroscopy of 106 patients were recorded. In thirteen patients no data was available as they discontinued participation in this study, in another nine patients clinical lymphedema occurred before the first follow-up visit. Preoperative lymphofluoroscopy was normal in all patients. In the group with lymphedema 15 out of the 26 patients had early disturbance visualized with lymphofluoroscopy (58%) **(Table 2)**. In 11 patients no abnormal pattern was seen. In the group without lymphedema 55 of the 80 patients did not show any abnormal lymphatic transport. The presence of early disturbance was a significant predictor for the development of BCRL (P= 0.0180) **(Table 3)**.

Demographic and general health related variables

In this analysis, age and BMI was not significant different for the group with or without clinical lymphedema, respectively p= 0.4094 and p= 0.6362 **(Table 3)**. Univariate analysis showed that general health related variables such as diabetes, hypertension, hypothyroidism, hyperthyroidism, chronic heart failure, chronic renal failure and previous injury/infection did not significantly differ in the two groups **(Table 3)**. Dominance was in this study not a risk factor in the development of clinical lymphedema. Physical activity score before surgery (assessed in 118 patients) was not significantly different in de two groups (p= 0.7031).

TABLE 3.
Univariate analysis of variables

Variable	OR (95%CI)	*P-value*	*N patients*
Age, continuous	1.013 (0.982;1.045)	0.4094	128
BMI, continuous	1.019 (0.944;1.100)	0.6362	128
Treatment at dominant side versus non-dominant side	1.214 (0.568;2.595)	0.6160	128
Diabetes versus no diabetes	1.611 (0.258;10.053)	0.6096	128
Hypertension versus no hypertension	1.241 (0.500;3.081)	0.6410	128
Hypothyroidism versus no hypothyroidism	2.122 (0.606;7.429)	0.2395	128
Hyperthyroidism versus no hyperthyrodism	*	0.1383	128
Chronic heart failure versus no chronic heart failure	1.189 (0.105;13.521)	0.8889	128
Chronic renal failure versus no chronic renal failure	*	0.1223	128
Previous injury/infection versus no previous injury/infection	1.016 (0.248;4.159)	0.9820	128
Type of cancer		0.6059	128
Tumor stage	2.041 (1.326;3.143)	**0.0012**	128
BCS versus ME	0.250 (0.089;0.701)	**0.0084**	128
ALND versus SLNB	55.468 (7.285;422.35)	**0.0001**	128
Number removed LN, continuous	1.082 (1.040;1.126)	**< 0.0001**	128
Number positive LN, continuous	1.204 (1.063;1.363)	**0.0035**	128
Postsurgical complications versus no postsurgical complications	4.051 (1.617;10.151)	**0.0280**	128
RT axilla versus no RT axilla	20.085 (2.377;169.76)	**0.0059**	128
Taxanes versus no taxanes	4.400 (1.905;10.163)	**0.0005**	128
Tamoxifen versus no tamoxifen	0.750 (0.272;2.066)	0.5780	128
AI versus no AI	1.611 (0.677;3.833)	0.2810	128
Physical activity score, continuous	0.894 (0.502;1.592)	0.7031	118
Early disturbance lymphofluoroscopy versus no early disturbance lymphofluoroscopy	3.000 (1.207;7.456)	**0.0180**	106

OR: odds ratio; CI: confidence interval; ME: mastectomy; BCS: breast-conserving surgery; ALND: axillary lymph node dissection; SLNB: sentinel lymph node biopsy; LN: lymph nodes; RT: radiotherapy, AI: Aromatase inhibitor
OR>(<)1: higher (lower) risk with increasing predictor level/for first category
* OR cannot be estimated due to lack of events in one group
Categorical variables with >2 levels: the global p-value is given

Breast cancer and treatment related variables

When we look at the data from the pathology reports **(Table 3)**, type of cancer was not a risk factor for the development of lymphedema. Patients with a higher tumor stage were more prone to develop lymphedema (p= 0.0012) than patients with a lower tumor stage, also patients who received a mastectomy (70%) had a higher risk of development of BCRL than patients who received a breast-conserving surgery (30%) (p= 0.0084). The number of removed lymph nodes as well as the number of positive lymph nodes was significantly different in the group with clinical lymphedema compared to the group without lymphedema (respectively p< 0.0001 and 0.0035). The extend of lymph node dissection (ALND versus SLNB) was also significantly different in the group with clinical lymphedema (p= 0.0001) with a very high OR (55.468). Postsurgical complications such as infection had an influence on the development of lymphedema (p= 0.028). Lymphedema was more likely to occur in patients who received adjuvant taxanes (p= 0.0005) and radiotherapy of the axilla (p= 0.0005). Hormone therapy (Tamoxifen and Aromatase Inhibitors) did not differ significantly between the two groups.

Multivariate analysis

After multivariate analysis, the following variables were positively associated with BCRL: ALND, age and radiotherapy of the axilla **(Table 4)**. The remaining risk factors did not have additional prognostic value.

TABLE 4.
Multivariate analysis of variables

Variable	*OR (95%CI)*	*P-value*	*N patients*
ALND versus SLNB	70.462 (8.696;570.91)	<.0001	128
Age, continuous	1.056 (1.013;1.101)	0.0097	128
RT axilla versus no RT axilla	12.157 (1.265;116.86)	0.0305	128

ALND: axillary lymph node dissection; RT: radiotherapy
OR: odds ratio, CI: confidence interval
OR>(<)1: higher (lower) risk with increasing predictor level/for first category

DISCUSSION

This is the first trial investigating the role of early disturbance of the lymphatic transport in the development of BCRL.

Lymphatic transport related variable associated with BCRL

In this study early disturbance was visible in 40 out of the 106 patients (37.7%). The univariate analysis showed that early disturbance visualized by lymphofluoroscopy is a risk factor for the development of BCRL. In the multivariate analysis early disturbance was not identified as a risk factor.
Akita et al investigated the presence of dermal backflow in 189 patients. Fifty arms out of 196 arms (25.5%) showed an abnormal pattern within the first year after breast cancer treatment and no significant change in volume was seen before the presence of disturbance visualized by lymphofluoroscopy.[22] When comparing lymphofluoroscopy and clinical assessments, our previous study[23] and the study by Jørgensen showed that the early disturbance visualized by lymphofluoroscopy can't be assessed by another clinical measurement tool.[24] So this disturbance in the lymphatic transport visualized by lymphofluoroscopy is a predictor for BCRL. Other imaging techniques such as lymphoscintigraphy are until now not able to detect this early disturbance.[25,26]

Demographic and general health related variables associated with BCRL

Demographics such as BMI showed no significance in our study, this result can also be found in several other studies.[27,28] Our data did show that there was an OR>1, so a higher BMI gives a higher risk for development of BCRL. In the systematic review by DiSipio[2] a high BMI was one of the risk factors with a high level of evidence. One of the difficulties in analyzing the data is that in different studies, different variables are used, sometimes BMI is used as a continuous variable, sometimes grouped in categories, this could explain the discrepancy in the studies. Other variables such as age, education, employment were according to the review by DiSipio weak or inconclusive.[2] In our study age was not a risk factor in the univariate analysis, although in the multivariate analysis age was identified as an independent risk factor, the number of lymph nodes was a confounder, so the effect of age was concealed in the univariate analysis.
General health related factors such as diabetes, hypo- and hyperthyroidism, hypertension and previous injury/infection have been investigated in different studies but were not identified as significant risk factors.[29-32]

Physical activity was thought to have a negative impact on the development of lymphedema. However, recent studies have demonstrated that by activating the muscle pump, exercise promotes the lymphatic transport[33] and Baumann et al[34] also reported that exercise might have preventive effects on the development of lymphedema. In this study we could not find an association of a low physical activity preoperative and the development of lymphedema. This finding is similar to other authors.[35,36] According to the review by DiSipio, there is moderate level of evidence that not participating in regular physical activity is a possible risk factor for the development of BCRL.[2]

Breast cancer and treatment related variables associated with BCRL

More invasive surgical procedures are more prone to develop lymphedema than less invasive procedures such as breast conserving treatment. The reason for that is not totally clear, but perhaps the fact that a more advanced cancer needs a more invasive treatment such as a mastectomy combined with a ALND can explain this. This is also confirmed in other studies.[16] ALND and a higher number of removed lymph nodes was an important risk factor in this study. The severity of the cancer can also be expressed as a higher tumor stage, which also is confirmed as being a risk factor for the development of lymphedema. So patients with a more advanced breast cancer have the highest risk of developing clinical lymphedema.

Postsurgical complications such as seroma were significantly different between the two groups in the current study. Other studies have identified the duration of the seroma as an important risk factor.[37-39] But most often postsurgical infection is reported as a risk factor for the development of BCRL.[12,40,41]

Radiotherapy to the axilla was seen as a risk factor. Other studies who looked at the effect of radiotherapy on the development of lymphedema, specifically radiotherapy of the axilla, confirm this.[42,43] Radiotherapy not only blocks the lymph vessels but also compresses them by radiation fibrosis. The indications for radiation of the axilla can vary according to the center but generally high tumor burden in the axilla (such as ≥ 4 positive lymph nodes with capsule breakthrough or tumor is left in the axilla and if not enough lymph nodes removed during in ALND (< 6 LN)) and a positive sentinel lymph node are indications for radiation of the axilla. Therefore, the number of positive lymph nodes is also related to the development of BCRL, again confirming that more advanced cancers are at risk the most. Another indication for radiotherapy of the axilla is 1 or 2 positive lymph nodes after SLNB. The AMAROS trial found significant less lymphedema in the radiotherapy and SLNB group versus the ALND group.[44]

Chemotherapy is mentioned as a risk factor in several studies, specifically taxanes.[45-47] On stratification by timing of chemotherapy (adjuvant versus neoadjuvant), women receiving taxanes in the adjuvant setting were nearly twice as likely to develop BCRL than patients receiving non-taxane-based adjuvant chemotherapy, although this did not reach statistical significance in the study by Cariati.[46]

Hormone therapy was not identified as a risk factor for the development of BCRL and this is in line with different studies whom investigated this.[38,48,49]

Limitations

A first limitation is that this study analysed the data until 12 months postsurgery. In 75% of the cases lymphedema is established within the first year[50], but a follow-up of 3 years will perhaps reveal more information.

A second limitation is that physical activity was assessed at baseline and not at the follow-up points. Physical activity could have been diminished at a later time point, especially in patients whom still needed chemotherapy and/or radiotherapy or could have been increased if patients participated in an exercise program to reduce chemo symptoms.

Clinical implications

Previous study[23] analyzed the agreement between the early disturbance visualized by lymphofluoroscopy and other widely used clinical assessment tools. None of the clinical assessment tools could predict the early disturbance visualized by lymphofluoroscopy. This study shows that early disturbance visualized by lymphofluoroscopy is a risk factor for the development of BCRL. Screening patients with a high risk (e.g. more advanced breast cancers) with lymphofluoroscopy will make it possible to start treatment before clinical lymphedema is present.

CONCLUSION

In this prospective study 29.8% of the patients developed clinical lymphedema after a follow-up of 12 months. Early disturbance visualized by lymphofluoroscopy is a risk factor for the development of BCRL. More advanced breast cancer (ALND, high tumor stage, positive lymph nodes, RT axilla, adjuvant taxanes,...) is identified as an additional risk factor to develop lymphedema. Surveillance program of these patients with lymphofluoroscopy can be useful to identify lymphedema in a subclinical stage.

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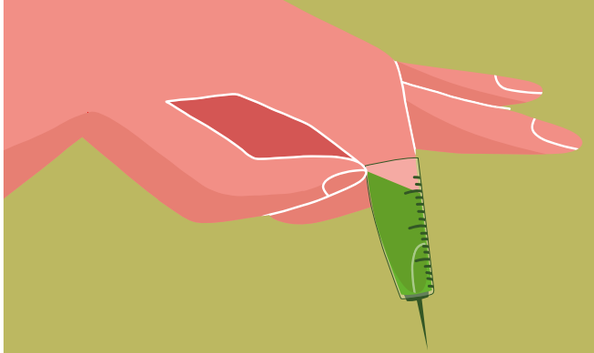

6

Impact of a compression garment, on top of the usual care, in breast cancer patients with early disturbance of the lymphatic transport: a protocol.

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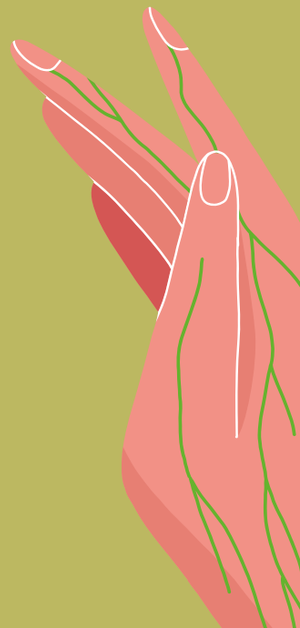

ABSTRACT

Introduction:
Breast-cancer related lymphedema (BCRL) is a common phenomenon. When lymphedema is diagnosed late, options for treatment are diminished. Therefore, early diagnosis and treatment are very important to alter the potential deleterious evolution. Lymphofluoroscopy visualizes the superficial lymphatic architecture in detail, giving the opportunity to detect a disturbance in the lymphatic transport (i.e. dermal backflow) before the lymphedema is clinically visible. The main objective is to investigate if there is an additional effect of a compression garment on top of the usual care (i.e. information and exercises) in patients with early disturbance of the lymphatic transport after breast cancer treatment. Development of clinical lymphedema and/or deterioration of the dermal backflow visualized by lymphofluoroscopy is investigated.

Methodology:
All patients scheduled for breast cancer surgery with unilateral axillary lymph node dissection or sentinel node biopsy in the Multidisciplinary Breast Clinic of the University Hospitals Leuven are being considered. Patients are assessed before surgery and at 1, 3, 6, 9, 12, 18, 24 and 36 months postoperatively. At each visit a clinical assessment is performed determining the volume difference between both arms and hands (through circumference measurements and water displacement), the water content, the extracellular fluid, the pitting status and the skinfold thickness. Quality of life questionnaires are filled in. At each visit a lymphofluoroscopy is performed as well. When a disturbance of the lymphatic transport is seen on lymphofluoroscopy, without the presence of clinical lymphedema, the patient is randomized in either a control group receiving usual care or a preventive treatment group receiving usual care and a compression garment (whether or not combined with a glove).

Conclusion:
The investigators hypothesize that development of clinical BCRL can be prevented and/or the dermal backflow can be stabilized or improved, if a preventive treatment with compression garment is started in the early phase of disturbance.

INTRODUCTION

Lymphedema is a chronic and debilitating disease caused by imbalance between lymph production and lymph transport. It reduces patient's quality of life by limb enlargement but also by other physical and psychosocial problems, e.g. decreased mobility, recurrent infections, stress and decreased ability to perform occupational activities.[1,2,3]

Breast cancer-related lymphedema (BCRL) is a secondary lymphedema of the upper limb that can occur after treatment for breast cancer. Incidence of BCRL vary in literature, especially since the introduction of less invasive techniques such as sentinel node procedures and radiotherapy. According to a review of DiSipio et al., the incidence of arm lymphedema was about four times higher in women who had an axillary lymph node dissection (19.9%) than after sentinel lymph node biopsy (5.6%).[4,5] A study by Rockson et al. suggested that in almost 75% of the cases, lymphedema is established within the first year after breast cancer treatment.[6] A volume difference between both limbs of 5 to 10% is normally used to define clinical lymphedema.[4,7]

Lymphedema can progress from a soft pitting edema to a hard fibrotic or soft fatty and non-pitting edema because of lipogenesis, fibrosis, inflammation, lymphangiogenesis and immunosuppression.[8,9]

There is no consensus concerning the best measuring tool to detect the development of BCRL.[10,11] Volume increase of the limb can be assessed with circumference measurements[12] or with the water displacement method.[13,14] A relative volume change between both arms is used, comparing preoperative measurements between the affected arm and the healthy arm, to the postoperative measurements.[7] In addition, the increase of water content in the edematous limb can be assessed by the pitting test,[15] by measuring the extracellular fluid (bioelectrical impedance spectroscopy)[16] or by measuring the water content of the skin (tissue dielectric constant).[17,18] Measurement of the skinfold thickness (Stemmer sign) can be performed, which is the typical sign for lymphedema.[19] Historically lymphangiography has been the technique to image the lymphatic system. This technique is difficult to perform and has become obsolete.[20] Lymphoscintigraphy has replaced lymphangiography and became the new standard for imaging the lymphatic system. With lymphoscintigraphy a radiopharmaceutical (^{99m}Tc-nanocolloid) is injected and followed by sequential gamma imaging.[21,22] This technique not only provides dynamic imaging of the lymphatics and the lymph nodes, but also provides semi-quantitative data of radionuclide transport and lymph node absorption. Near-infrared fluorescence imaging or lymphofluoroscopy is another minimally invasive technique. The injection of indocyanine green (ICG) intradermally allows

to visualize lymphatics in the upper 2 cm of the skin using an infrared camera system, capturing the fluorescence.[23,24] It provides real-time relatively high-resolution images and detailed information about the superficial lymphatic transport.[25] The images themselves are classified in different patterns: a normal linear lymph transport pattern and three dysfunctional dermal backflow (DB) patterns. The first dysfunctional pattern is the splash pattern, representing a dispersed tracer in tortuous lymphatic channels. The second is the stardust pattern, which demonstrates spotted fluorescent signals, representing the effusion of lymph fluid into the interstitium. The last type is the diffuse pattern wherein the tracer is widely distributed without identifiable spots. In this pattern, besides accumulation in the lymphatic capillaries and lymph precollectors, lymph stagnates in the interstitium.[25,26] Different studies have demonstrated that lymphofluoroscopy is a valid imaging technique to evaluate superficial lymphatic transport in patients with BCRL[27,28] and can be used for early detection of BCRL.[29]

To prevent further evolution to fibrous and fatty tissue, early start of BCRL treatment is recommended.[30,31] Previous studies demonstrated that early detection of BCRL with clinical measurement tools such as bioelectrical impedance spectroscopy and volume measurements and subsequently early start of manual lymph drainage and exercise, reduces the rate of clinical lymphedema.[32,33] Encouraging participation in regular exercise and maintaining healthy body weight as well as giving information such as avoiding infection, heat and tight clothing are guidelines to prevent lymphedema.[34] The previous studies investigated the effect of early treatment by using clinical assessments. The optimal tool to use remains unclear, and furthermore patient subjective symptoms and extremity volume can vary depending on the timing of measurement (morning and evening), the temperature, the activities performed by the patient during the day,...[35,36] thus not reliable for lymphedema diagnosis. Subclinical lymphedema should be diagnosed with lymphatic imaging.

Therefore, the aim of this study is to investigate the additional effect of wearing a compression garment on top of the usual care (i.e. exercise and information), on the incidence of clinical lymphedema and/or deterioration of the dermal backflow visualized by lymphofluoroscopy, in patients developing early disturbance after treatment for breast cancer.

METHODOLOGY

Trial design

This study is a prospective randomised controlled trial. Figure 1 gives an overview of the participant flow in the trial. All participants are assessed at the Department of Vascular Surgery of the University Hospitals Leuven. The trial started in November 2017 and will end in May 2023.
The trial has been approved by the Ethical Committee of the University Hospitals Leuven (CME reference S60382, EudraCT Number 2017-002306-12). The study has been registered in clinicaltrials.gov (NCT 03210311).

Patient and public involvement

The protocol was discussed extensively with the oncologists of the Multidisciplinary Breast Clinic. Patients with BCRL were involved in the trial design and the methods of assessing the lymphedema. They were informed through information sessions at the center for lymphedema. The results of the study will be communicated in a symposium organized for patients recruited in the study and the patients whom were involved in the trial design.

Participants

All patients scheduled for breast surgery combined with either unilateral axillary lymph node dissection (ALND) or sentinel node biopsy (SLNB) in the Multidisciplinary Breast Clinic Center at the University Hospitals Leuven are screened for participation in the study.
Recruitment started in November 2017. Inclusion criteria were 1) Age ≥18y, 2) women/men with breast cancer and scheduled for unilateral ALND or SLNB, 3) oral and written approval of informed consent, 4) understanding Dutch. Exclusion criteria were 1) edema of the upper limb from other causes, 2) cannot participate during the entire study period, 3) mentally or physically unable to participate in the study, 4) contra-indication for the use of ICG: allergy to ICG, iodine, hyperthyroidism, 5) metastatic disease.

All patients receives written as well as oral information. All included patients sign an informed consent document prior to the start of the study.

Assessments

Figure 1 gives an overview of the different assessments and their timing in the trial. All assessments are performed at baseline and at 1, 3, 6, 9, 12, 18, 24 and 36 months postoperatively.

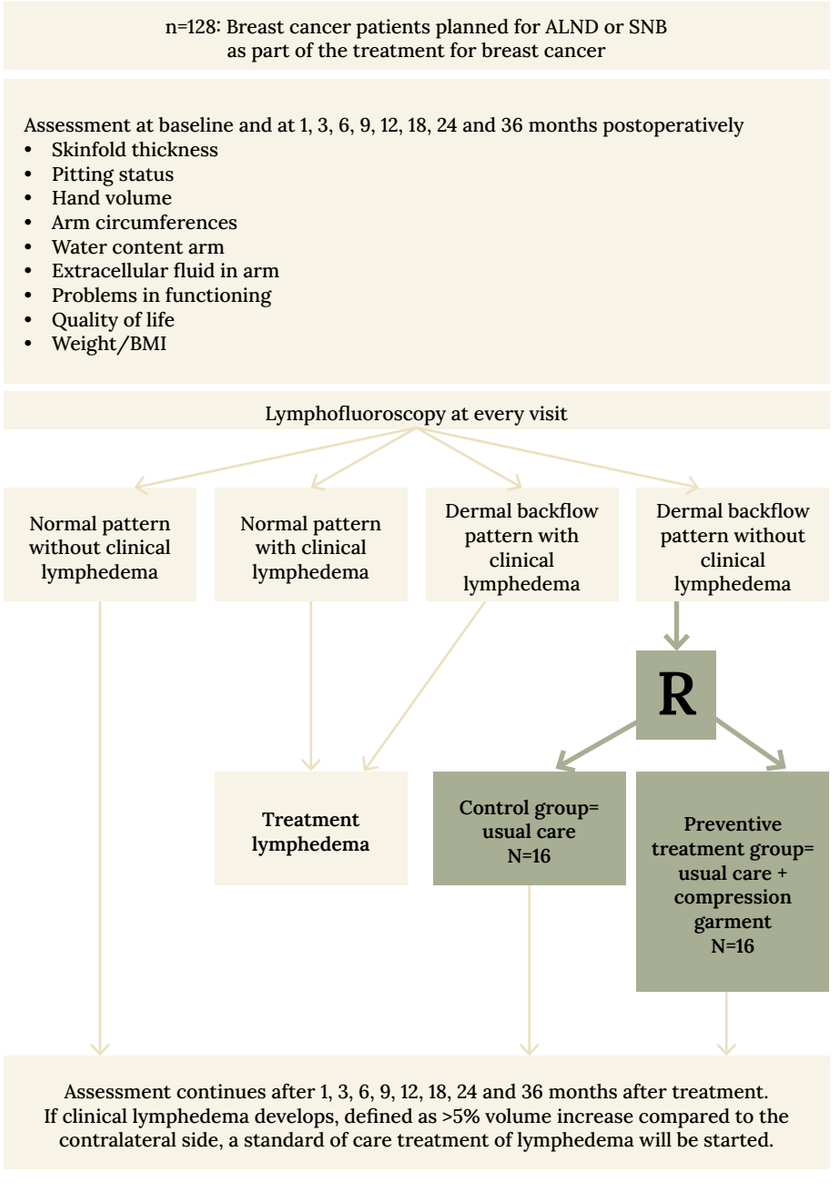

FIGURE 1.
Flow of participants

Near-infrared fluorescence imaging of the lymphatic system or lymphofluoroscopy

All lymphofluoroscopic assessments are performed by one person (ST) who is blinded to the participant's data as well as to the assigned group if relevant.
During lymphofluoroscopy, ICG is injected intradermally in the first and fourth webspace of the hand on the affected side. An infrared camera system (PDE, Hamamatsu®) captures the fluorescence. The procedure consists of three consecutive phases **(Table 1)**: an early phase, a break and a late phase. All information about the lymphatic transport is documented in a standard evaluation document and in case of disturbance, this information is drawn on a body diagram according to the legend **(Figure 2)**.

TABLE 1.
Protocol near-infrared fluorescence imaging

Step		*description*	*reporting*
Preparation	0.1 Dilution of ICG	Suspended ICG in 25 ml pure water and subsequently diluted with saline water to reach a final concentration of 0.20 mg/ml	
	0.2 Camera	Camera is held perpendicular to the observed skin at distance of 15 cm (best focus)	
	0.3 Injection of ICG	Intradermal injection in 1st (ulnar injection point) and 4th web space (radial injection point) dorsally in the hand 0.2 ml of the diluted solution is injected in each injection point	Time of injection
Early phase	1.1 Rest: 1 min	Hand in resting position on table	Linear transport starting from ulnar injection point: Yes/No (if "yes", after ..... sec) Linear transport starting from radial injection point: Yes/No (if "yes", after ..... sec)
	1.2 Stimulation: 3 min	Lymph capillaries at the level of the injection points are filled and transport through the lymph collectors is stimulated by the assessor	
	1.3 Scan with camera and measuring	1) of the arm and shoulder with hand in pronation: starting at hand up to the retroclavicular region, 2) of the arm and axilla with hand in supination and abduction of the shoulder: starting at hand up to the axilla, together with the pectoral region: from the ipsilateral to the contralateral axilla, 3) of the scapular region: from the ipsilateral to the contralateral axilla, 4) of the pectoral region: from the ipsilateral to the contralateral axilla	After scan, reporting on an assessment form: - Number of lymph collectors - Of each lymph collector: length (measured with tapeline in cm), location and normal versus dilated situation - Presence of splash, stardust and diffuse pattern and location (fingers, hand, proximal/distal and ventral/dorsal lower or upper arm, breast and trunk) - Number of lymph nodes (cubital, humeral, axillary, retroclavicular)

Step		*description*	*reporting*
Break	30 min		
Late phase	3.1 Scan with camera and measuring	See step 1.3	See step 1.3
	3.2 Drawing on skin and body diagram	If disturbance is seen lymph collectors and dermal backflow (splash, stardust and diffuse) are designed on a body diagram (see **figure 2**)	Design on body diagram if disturbance is seen

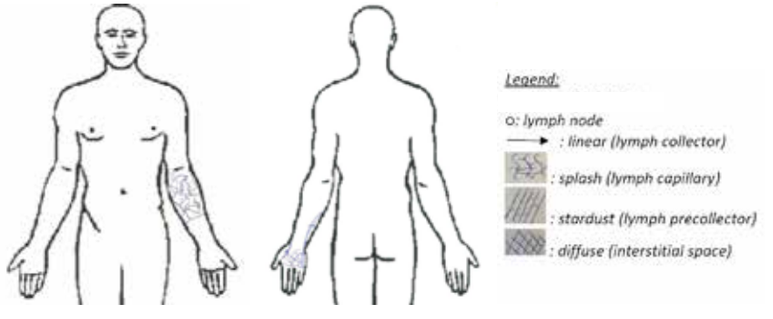

FIGURE 2.
Example of body diagram

Clinical assessments

The clinical assessments are performed by one assessor. In order to ensure blinding of the assessor, participants are asked not to share any information concerning their treatment (e.g. wearing compression garment or not) neither to wear their compression material during evaluations. In addition, the assessor is blinded to previous measurement data in order to avoid being influenced by previous results. **Table 2 and 3** provides a detailed overview of the clinical evaluation methods and procedures performed. Figure 3 shows the reference points used for the local clinical assessments.

TABLE 2.
Overview of measurement method and calculation of the primary outcomes

Outcome parameter	*Measurement time, method, material*	*Calculation*
Cumulative incidence of clinical lymphedema defined as:	Before surgery, at 12M, 18M, 24M and 36M.	
≥5% increase of relative arm volume difference compared to pre-surgical value	With perimeter Circumferences at olecranon and 4, 8, 12, 16 and 20cm above and under olecranon of arm at affected and healthy side[12] With volumeter, weighing balance and recipient Water displacement method hand[13,14]	0 = No clinical lymphedema 1 = Clinical lymphedema Relative arm volume difference compared to pre-surgical value = relative arm volume difference at assessment – relative arm volume difference at baseline Relative arm volume difference =(absolute arm volume difference/ arm volume healthy side) x 100 Absolute arm volume difference = arm volume affected side – arm volume healthy side Arm volume = sum of volume of different arm segments determined by circumference measurements + hand volume Arm segment = $4 \times (C_1^2+C_1C_2+C_2^2)/12\pi$, where C_1 is the upper circumference and C_2 is the lower circumference of each segment (formula of the truncated cone)[12] Hand volume = volume measured with volumeter
Proportion of subjects with deterioration of the dermal backflow	At 12M, 18M, 24M *and* 36M.	
	With lymphofluoroscopy: injecting ICG in the hand of the affected arm[26], protocol see **table 1**	0 = Stabilization or improvement 1 = Deterioration Stabilization: stable area of dermal backflow OR stable dermal backflow pattern Improvement: diminished area of dermal backflow OR diminished severity of dermal backflow pattern Deterioration: increased area of dermal backflow OR increased severity of dermal backflow pattern

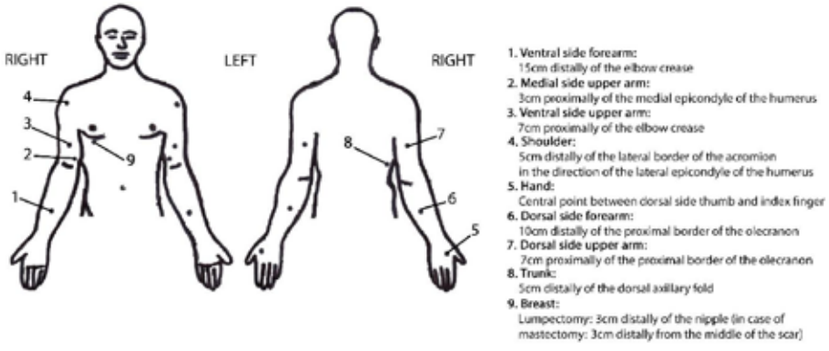

FIGURE 3.
Description of the reference points needed for the local clinical assessments

Randomization and allocation sequence generation

After visualization of an early disturbance of the lymphatic transport, without the presence of clinical lymphedema, patients are randomized in either the control group or the preventive treatment group. Randomization is performed according to 'www.randomization.com'. This generator randomizes each subject to a single treatment by using the method of randomly permuted blocks. Assessments are performed by a person blinded to the treatment allocation groups.

Interventions

During hospitalization all participants receive information about the prevention of lymphedema. They are advised to avoid lifting heavy objects, but to use the affected arm as normally as possible. Limb constriction and extremes of temperatures should be avoided. In case of heaviness the arm should be elevated. Skin care is recommended, and gain in body weight should be avoided to prevent lymphedema. Patients receive a brochure which outlines these guidelines.
Participants are prescribed exercise therapy, which is started during hospitalization with low level mobilizing exercises for the hand, elbow and shoulder. After hospitalization, these exercises are continued. Patients who underwent ALND are going to a physical therapist nearby to continue physical therapy such as passive mobilization of the shoulder, stretching and transverse strain of the breast muscles, scar tissue massage and active mobilizing and stabilizing exercises. This starts twice a week and frequency is gradually diminished. Exercises are continued until

a full range of motion is reached. When a seroma is present intensity of exercises is diminished. Patients who underwent SLNB are not routinely seen by a physical therapist after discharge. If functional shoulder problems are seen at discharge or at follow-up consultation, physical therapy is prescribed. Patients are encouraged to do exercises at home twice a day until full range of motion is reached.
If early disturbance is seen on lymphofluoroscopy at a control visit, the patient is randomized in either the preventive treatment group or the control group. In the control group, the usual care is continued consisting of preventive measures and exercises as described above. The participants in the preventive treatment group receive the usual care and a compression garment whether or not combined with a glove on top. The compression garment is measured by an experienced compression specialist. The first choice is a round knitted custom-made compression garment, compression class 2 (23 -32 mmHg). If patients are not comfortable with this garment, a flat-knitted garment is ordered. If the hand shows swelling after wearing the garment, a glove is measured. Patients need to wear the garment/glove at daytime during the remaining follow-up time of the trial. Written instructions for washing and maintenance of the garment and glove are given. Patients receive a new garment/glove every 6 months. A compression questionnaire is filled in at every visit to assess adherence and adverse events of the compression material.
If clinical lymphedema is established the patient receives the normal standard of care treatment for lymphedema with decongestive lymphatic therapy. Patients are referred to a specialized physical therapist or to the UZ Leuven center for lymphedema.

Primary outcomes

The primary outcomes are the incidence of clinical lymphedema of the arm/hand measured by circumference measurements and volume displacement defined as 5% volume increase compared to the contralateral side (first primary outcome) and the proportion of subjects with deterioration of the dermal backflow measured by lymphofluoroscopy (second primary outcome) (see **table 2**).

Secondary outcomes

Secondary outcome measures are: the incidence of clinical lymphedema of the arm/hand based on the extracellular fluid content, based on the water content, based on thickening of the skinfold, the relative change of arm volume, the severity of disturbance of lymphatic transport, the change in functional problems related to the lymphedema and the change in health-related quality of life (see **table 3**).

TABLE 3.
Overview of measurement method and calculation of the secondary outcomes

Outcome parameter	*Measurement time, method, material*	*Calculation*
Incidence of lymphedema based on pitting status	At 12M, 18M, 24M and 36M. The therapist gives a vertical pressure with the thumb for 5 seconds at the 7 reference points (see **figure 3**)[15]	0 = The skin immediately returns to starting position 1 = Pitting is present
Incidence of lymphedema based on skinfold thickness	At 12M, 18M, 24M and 36M. The examiner picks up the skinfolds between thumb and index finger at the 7 reference points (see **figure 3**).[19] The skinfold thickness of the edematous side is compared to the non-edematous side (Stemmer sign).	0 = No increase in skinfold thickness 1 = An increase in skinfold thickness
Incidence of lymphedema based on the amount of extracellular fluid	Before surgery, at 12M, 18M, 24M and 36M. Impedimed L-dex U400[16] Reference points On each hand, one double electrode is placed on the dorsum of the hand On the right foot, one double electrode is placed on the dorsum of the foot.	0= Patients with a score of <10 L-Dex units or with an increase of < 10 units from baseline 1 = Patients with a score of >10 L-Dex units or with an increase of ≥ 10 units from baseline[31]
Incidence of lymphedema based on the water content	At 12M, 18M, 24M and 36M. MoistureMeter D Compact® (Delfin Technologies) measured at the 7 reference points (see **figure 3**)[18]	Ratio PWC = PWC healthy side / PWC affected side 0 = ratio PWC < 1.2 1 = ratio PWC ≥ 1.2
Relative change of arm volume difference (in %)	Before surgery, at 12M, 18M, 24M and 36M.	Relative arm volume difference = relative volume difference at assessment – relative volume difference at baseline See **table 2** for further explanation.
Problems in functioning related to development of lymphedema (score 0-100)	At 12M, 18M, 24M and 36M. Using Lymf-ICF questionnaire[35] Filled out by patient	Total score and physical function score, mental function score, household activities score, mobility activities score and life and social activities score A lower score indicates less problems in functioning
Health related quality of life	At 12M, 18M, 24M and 36M. Using Mc Gill questionnaire[36] Filled out by patient	A lower score indicates a lower Quality of Life

Sample size calculation

For both hypotheses a sample size calculation is performed.
For the hypothesis that the incidence rate of clinical lymphedema will be lower in the preventive treatment group than in the control group, we estimate that 50% of the patients in the control group will develop clinical lymphedema in the first year after the randomization compared to 5% in the preventive treatment group (wearing a compression garment). The 5% is based on previous studies.[30-32] A study of Stout[30] treated patients, diagnosed with subclinical lymphedema, defined as a volume difference between both limbs of ≥ 3%, with a compression garment. The incidence of lymphedema (stage I/II) at 5 year was 5.6%. Another trial showed that the same type of treatment reduced the incidence of lymphedema to 4.4%.[31] The 50% incidence of clinical lymphedema in the control group is based on expert opinion.
The sample size calculation is based on the formula in Diggle for a longitudinal study for showing a time-averaged treatment effect for a binary outcome. Four time points per patient are foreseen (12m, 18m, 24m, 36m). Conservatively a high correlation of 0.90 between repeated measurements is assumed (higher correlation means larger sample size). Based on a power of 80% and 2.5% significance level (with a Bonferroni correction for multiple testing given that we test two primary outcomes, and keeping a family-wise alpha of 5%), we need a sample size of 14 patients per group. Taking into account a drop-out rate of 10%, 16 patient per group or a total of 32 randomized patients are needed.

For the hypothesis that patients in the preventive treatment group will have less deterioration of dermal backflow visualized by lymphofluoroscopy, we estimate that a deterioration of the dermal backflow can be expected in 40% of the cases in the preventive treatment group in contrast to 90% in the control group. There is one publication studying early detection with lymphofluoroscopy and the changes of the dermal backflow pattern in case of early treatment. Therapy consists of exercise, skin care, elevation and the use of a compression garment. This trial shows that only three out of 35 patients with dermal backflow deteriorate during the follow-up.[29] Deterioration was described as a change in severity of the dermal backflow pattern. In our study also the area of dermal backflow is taken into account, therefore we estimate a higher rate of deterioration. The 90% deterioration in the control group is based on expert opinion. The analysis is performed on a binary response (worsening versus stable condition/ improvement). Sample size calculation is completely analogous to the first outcome, leading to a total sample size of 30 patients after taking into account 10% of drop-out.

To calculate the total amount of patients to be included in the present trial two prospective observational studies about the incidence of subclinical lymphedema where considered[30-32] and one study about lymphofluoroscopic observations.[29] In the study by Akita, 196 patients are included in a 1-year follow-up study with lymphofluoroscopy. Twenty-five percent of the patients developed a dermal backflow pattern on lymphofluoroscopy.[29] The largest of both sample sizes, i.e. 32 patients, is adopted. We estimate that in 25% of the patients an early disturbance will be seen, hence 128 patients are included in the trial to have 32 patients that can be randomized.

Statistical methods

Logistic regression analysis will be used for both primary endpoints, studying the difference between the preventive treatment and control group over the follow-up period. Generalized estimating equations (GEE) are used to account for repeated measurement. Model covariates include time and treatment group. The main effect of the preventive treatment group is estimated and presented by odds ratios with 95% confidence intervals. Both analyses are tested at the 2.5% significance level.
All data is analyzed according the intention to treat principle. A 5% level of significance is applied for all secondary analyses.

Monitoring

There are no indications for setting up a data monitoring committee.
No adverse events (AE) are expected. AE will be reported during the entire trial period, i.e. 36 months. It will be specified that the investigator(s) and the institution(s) will permit trial-related monitoring, audits, EC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (i.e. patients' case files).

DISCUSSION

This is the first randomized controlled clinical trial investigating the additional effect of wearing a compression garment, to the usual care (i.e. information and exercises), on the incidence of clinical lymphedema and/or deterioration of the dermal backflow visualized by near infrared fluorescence imaging, in patients with early disturbance of the lymphatic transport (i.e. dermal backflow) after treatment for breast cancer. If treatment can start in this early phase of disturbance, further evolution to clinical lymphedema can perhaps be prevented.

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7
Impact of a compression garment, on top of the usual care, in breast cancer patients with early disturbance of the lymphatic transport: a randomized controlled trial.

Preliminary data. Final results will be submitted for publication when 3 years follow-up is reached

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ABSTRACT

Introduction:
Breast-cancer related lymphedema (BCRL) is a common condition. When lymphedema is diagnosed late, options for treatment are diminished. Therefore, early diagnosis and treatment are very important to alter the potential deleterious evolution. Lymphofluoroscopy visualizes the superficial lymphatic architecture in detail, giving the opportunity to detect a disturbance in the lymphatic transport (i.e. dermal backflow) before the lymphedema is clinically visible.The main objective is to investigate if there is an additional effect of a compression garment on top of the usual care (i.e. information and exercises) in patients with early disturbance of the lymphatic transport after breast cancer treatment. Development of clinical lymphedema and/or deterioration of the dermal backflow visualized by lymphofluoroscopy is investigated.

Methodology:
A prospective randomized controlled study was conducted in breast cancer patients scheduled for breast cancer surgery with unilateral axillary lymph node dissection or sentinel node biopsy in the Multidisciplinary Breast Clinic of the University Hospitals Leuven. Patients were assessed before surgery and at 1, 3, 6, 9, 12, 18, 24 and 36 months postoperatively. At each visit a clinical assessment determining the volume difference between both arms and hands (through circumference measurements and water displacement), the water content, the extracellular fluid, the pitting status and the skinfold thickness was performed as well as a lymphofluoroscopy. When a disturbance of the lymphatic transport was seen on lymphofluoroscopy within the first year of follow-up, without the presence of clinical lymphedema, the patient was randomized in either a control group receiving usual care or a preventive treatment group receiving usual care and a compression garment (whether or not combined with a glove).

Results:
Hundred twenty-eight patients were enrolled in the study. The mean age of the patients was 56.67 years and the mean BMI was 25.96. Within the first year after the last patient was included in the study, 39 patients developed an abnormal dermal backflow pattern visualized with lymphofluoroscopy and were randomized.

Conclusion:
The investigators hypothesized that development of clinical BCRL can be prevented and/or the dermal backflow can be stabilized or improved, if a preventive treatment with compression garment was started in the early phase of disturbance.

INTRODUCTION

Lymphedema is a chronic and debilitating disease caused by imbalance between lymph production and lymph transport. It reduces patient's quality of life by limb enlargement but also by other physical and psychosocial problems, e.g. decreased mobility, recurrent infections, stress and decreased ability to perform occupational activities.[1-3] Lymphedema can progress from a soft pitting edema to a hard fibrotic or soft fatty and non-pitting edema because of lipogenesis, fibrosis, inflammation, lymphangiogenesis and immunosuppression.[4]
Breast cancer-related lymphedema (BCRL) is a secondary lymphedema of the upper limb that can occur after treatment for breast cancer. The incidence of BCRL varies in literature, especially since the introduction of less invasive techniques such as sentinel node procedures and radiotherapy. According to a review of DiSipio et al., the incidence of arm lymphedema was about four times higher in women who had an axillary lymph node dissection (19.9%) than after sentinel lymph node biopsy (5.6%).[5,6] A study by Rockson et al. suggested that in almost 75% of the cases, lymphedema is established within the first year after breast cancer treatment.[7] To prevent further evolution to fibrous and fatty tissue, early start of BCRL treatment is recommended.[8,9]

Previous studies demonstrated that early detection of BCRL with clinical measurement tools such as bioelectrical impedance spectroscopy and volume measurements and subsequently early start of manual lymph drainage and exercise, reduces the rate of clinical lymphedema.[10,11] Encouraging participation in regular exercise and maintaining healthy body weight as well as giving information such as avoiding infection, heat and tight clothing are guidelines to prevent lymphedema.[12] The previous studies investigated the effect of early treatment by using clinical assessments. The optimal tool to use remains unclear, and furthermore patient subjective symptoms and extremity volume can vary depending on the timing of measurement (morning and evening), the temperature, the activities performed by the patient during the day,...[13,14] and thus are not reliable for lymphedema diagnosis.

Near-infrared fluorescence imaging or lymphofluoroscopy is used to assess the superficial lymphatic system.[15] The images themselves are classified in different patterns: a normal linear lymph transport pattern and three dysfunctional dermal backflow (DB) patterns: splash, stardust and diffuse.[16] Different studies have demonstrated that lymphofluoroscopy is a valid imaging technique to evaluate superficial lymphatic transport in patients with BCRL[17,18] and can be used for early detection of BCRL.[19] Dermal backflow patterns can be visualized before clinical lymphedema is present. This early disturbance of the lymphatic transport is not predictable with other clinical assessments tools such as the pitting test, Stemmer

sign test, tissue dielectric constant and water volume assessments (circumference measurement and water displacement method).[20]
The aim of this study was to investigate the additional effect of wearing a compression garment on top of the usual care (i.e. exercise and information), on the incidence of clinical lymphedema and/or deterioration of the dermal backflow visualized by lymphofluoroscopy, in patients developing early disturbance after treatment for breast cancer.

METHODOLOGY

Trial design and participants

This study was a prospective randomized controlled trial.[21]
All patients scheduled for breast surgery combined with either unilateral axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB) in the Multidisciplinary Breast Clinic Center at the University Hospitals Leuven were screened for participation in the study. Recruitment started in November 2017 and ended in May 2019. Inclusion criteria were 1) age ≥18y, 2) women/men with breast cancer and scheduled for unilateral ALND or SLNB, 3) oral and written approval of informed consent, 4) understanding Dutch. Exclusion criteria were 1) edema of the upper limb from other causes, 2) inability to participate during the entire study period, 3) mentally or physically inability to participate in the study, 4) contra-indication for the use of Indocyanine Green (ICG) such as allergy to ICG, iodine, hyperthyroidism, 5) metastatic disease.
All patients received written as well as oral information. All included patients signed an informed consent document prior to the start of the study. Patients were followed-up for a period of three years.

Assessments

All assessments were performed at baseline and at 1 month, 3 months, 6 months, 9 months, 12 months, 18 months, 24 months and 36 months after treatment. **Figure 1** shows the flow of the participants. An overview of these assessments were described in the protocol.[21]

After visualization of an abnormal dermal backflow pattern, without the presence of clinical lymphedema, patients were randomized in either the control group or the preventive treatment group.
In the control group, the usual care was continued consisting of preventive measures and exercises as described above. The participants in the preventive treatment group received the usual care and a compression garment. If there was a swelling of the hand when wearing the garment a glove was added.

If clinical lymphedema was established the patient received the normal standard of care treatment for lymphedema with decongestive lymphatic therapy.[22] Patients were referred to a specialized physical therapist or to the UZ Leuven center for lymphedema.

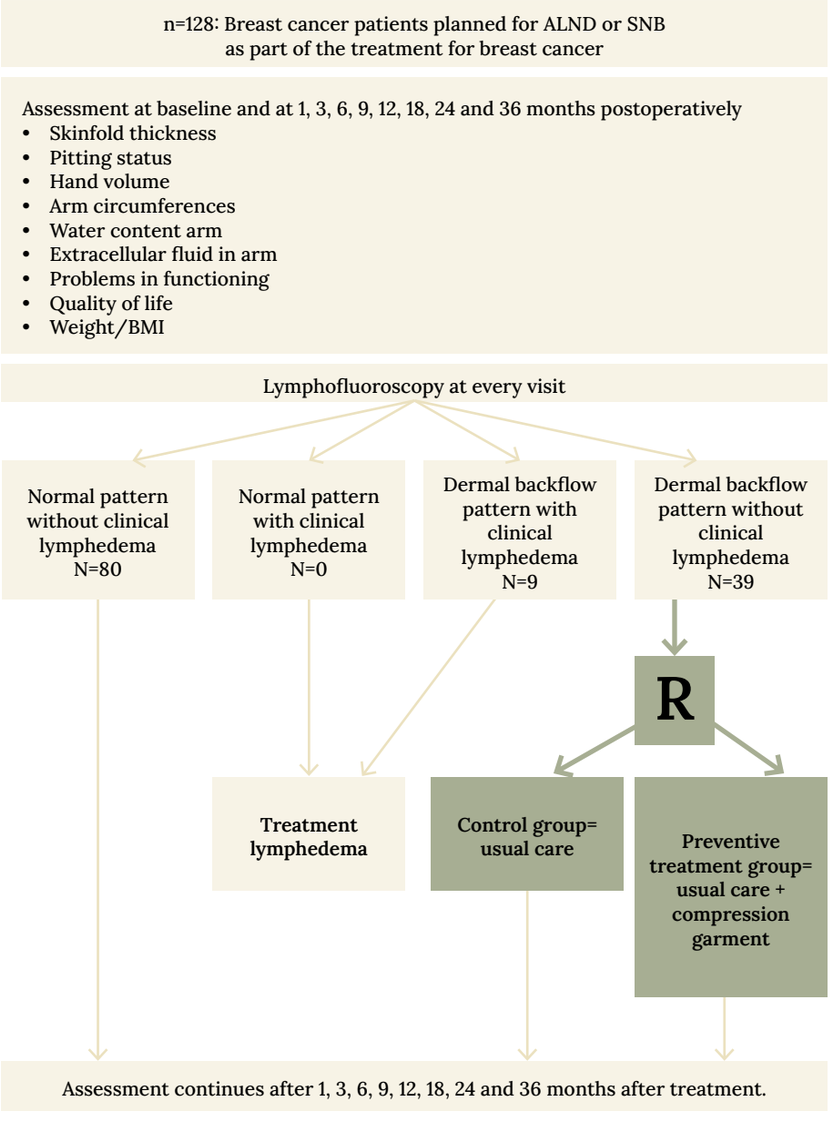

FIGURE 1.
Flow of the participants

RESULTS

Hundred twenty-eight patients were enrolled for this trial. The mean age of the patients was 56.7 years (SD 12.2) and the mean BMI was 25.96 (SD 4.9). In 73 patients ALND (57%) was performed, 55 patients (43 %) underwent SLNB. Eighty-nine patients (70%) underwent mastectomy and 39 patients (30%) breast-conserving surgery. Detailed patient characteristics are summarized in **Table 1**.

Within the first year after the last patient was included in the study, 39 patients developed an abnormal dermal backflow pattern visualized with lymphofluoroscopy and were randomized. This disturbance was seen in five patients at one month, sixteen patients at three months, nine patients at six months, five patients at nine months, one patient at twelve months and three patients at eighteen months. Splash pattern was present in 31 patients and stardust was seen in 8 patients. No diffuse pattern was visualized.

DISCUSSION

This is the first randomized controlled clinical trial investigating the additional effect of wearing a compression garment, to the usual care (i.e. information and exercises), on the incidence of clinical lymphedema and/or deterioration of the dermal backflow visualized by near infrared fluorescence imaging, in patients with early disturbance of the lymphatic transport (i.e. dermal backflow) after treatment for breast cancer. It is hypothesised that if treatment can start in this early phase of disturbance perhaps further evolution to clinical lymphedema can be prevented.

TABLE 1.
Patient characteristics (N=128)

	*Mean (SD)/Frequency (%)/ *Median (IQR)*
Age (y)	56.7 (12.2)
BMI (kg/m²)	25.9 (4.9)
Side of surgery	
- Left	70 (55%)
- Right	58 (45%)
Surgery on the dominant side	63 (49%)
Breast surgery	
- Mastectomy	89 (70%)
- Breast-conserving surgery	39 (30%)
Extent of LN dissection	
- SLNB	55 (43%)
- ALND	73 (57%)
Type of cancer	
- Ductal	101 (79%)
- Lobular	18 (14%)
- Other	9 (7%)
Tumor stage	
- is	2 (1%)
- T1	44 (34%)
- T2	52 (41%)
- T3	20 (16%)
- T4	10 (8%)
Node stage	
- N0	55 (43%)
- N1	44 (34%)
- N2	13 (10%)
- N3	16 (13%)
Radiotherapy	110 (86%)
- Axilla	8 (6.25%)
Chemotherapy	74 (58%)
- Neo-adjuvant	28 (22%)
- Adjuvant	33 (26%)
- Both	13 (10%)
- Taxanes	63 (49%)
Hormone therapy	108 (84%)
- Aromatase inhibitor	24 (19%)
- Tamoxifen	89 (70%)

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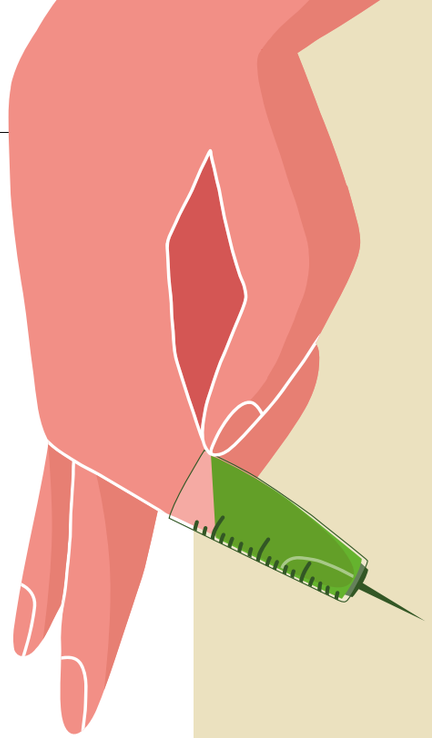

General discussion and future perspectives

Lymphofluoroscopy is the common theme of this doctoral thesis. In the first section of this general discussion we discuss the role of lymphofluoroscopy in the management of breast cancer-related lymphedema (BCRL) overall; in the second section we discuss the role of lymphofluoroscopy in the early phase of BCRL specifically. We conclude with a proposal for a preventive surveillance model and future research to optimize diagnostic and treatment modalities further.

The role of lymphofluoroscopy in the management of BCRL

Lymphedema is defined as the stasis of lymph fluid in the subcutaneous tissue. This condition occurs when there is a dysfunction of the lymphatic transport due to for instance breast cancer treatment. The incidence of BCRL can vary and is higher after axillary lymph node dissection (ALND) than after sentinel lymph node biopsy (SLNB), with a pooled incidence of 16.6 %.[1]

Studies on cadavers have identified that different alternative pathways for the lymphatic flow can develop.[2] Patients who develop enough alternative pathways to maintain the lymph flow and prevent lymph stasis, will not develop lymphedema. According to Suami[3] the different pathways seen after breast cancer treatment can be divided in four types. First a detour through the deep lymphatics, who can still be intact after treatment, and transport to the axillary region can develop. Second, a detour using the lateral pathway of the upper arm to the clavicular region can be seen. Third, a detour through the superficial lymphatics all the way up to the torso and then entering the parasternal region or fourth, a detour to the contralateral axillary region can develop. The body will try to bypass the obstructed lymph vessels towards intact lymph vessels, by either lymphangiogenesis or by transporting the lymph through the capillaries. This is confirmed through animal and clinical studies.[4] In most of the patients after breast cancer, this process of bypassing and using a detour, will be sufficient to maintain a good lymph flow. In the patients were this flow will not be sufficient, a stasis of lymph will appear.[3]

Lymphofluoroscopy was introduced as a novel imaging technique two decades ago. Gradually it gained a place in the clinical care of lymphedema patients. Lymphofluoroscopy can visualize the alternative pathways. Not only the remaining lymph vessels, but also the area where dermal backflow is present, can be visualized. This helps to understand the pathophysiology and alternative pathways and will enable to optimize the care for patients. This information can guide the treatment, not only by directing the manual lymph drainage, but also by optimizing the compression material. For instance, in patients with a difficult to treat arm lymphedema, having extra information on the details of the lymphatic transport can be useful. This is especially true in areas where treatment with compression material is difficult such as proximal to the garment or the shoulder region. Having information on which pathway is being used, can guide the manual lymph drainage in this specific direction.

In **chapter 1** we investigated if these lymphofluoroscopic findings of dermal backflow can also be perceived by other clinical assessment tools that are commonly used. These tools include assessing the volume with circumference measurements or water displacement, assessing the skinfold thickness, assessing the local water content with tissue dielectric constant (TDC) or pitting status, and assessing the extracellular fluid with a bioelectrical impedance spectroscopy (BIS).[5] We determined the presence of dermal backflow at 7 different reference points and the arm dermal backflow stage of the arm. The best overall agreement with dermal backflow was found for the clinical assessment tools of pitting status, skinfold thickness and local water content. Overall sensitivity was excellent for lymphedema volume (92.5%), high for skinfold thickness and local water content (86.6% and 75.0% respectively) and moderate for pitting status (67.7%). Overall specificity was excellent for skin elasticity (94.7%), high for pitting status (83.4%) and moderate for skinfold thickness (61.6%) and local water content (74.8%). In the evaluation of the whole arm, measurements of the excess volume were significantly greater for patients in an advanced stage of dermal backflow in comparison with patients in an earlier stage of dermal backflow ($p = 0.002$). Practically this means that if a lymphofluoroscopic evaluation is not available, measuring the skinfold thickness, local water content and lymphedema volume will be most accurate to detect the areas with dermal backflow according to lymphofluoroscopic images.

In **chapter 2** we evaluated the inter-rater reliability of the lymphofluoroscopy. Although lymphofluoroscopy has some advantages over lymphoscintigraphy and has been found to be more sensitive[6], up until now it is not possible to perform a quantification of lymphatic transport with lymphofluoroscopy. In contrast to lymphoscintigraphy, lymphofluoroscopy remains a subjective evaluation method as the evaluation of the images is based on the interpretation of the images by the assessor. Therefore it is important to know if different assessors interpret the imaging in the same manner. The study showed a moderate to strong agreement for 31 out of 44 outcomes scored when evaluating the lymphatic architecture and transport through lymphofluoroscopy. This means that lymphofluoroscopy can be used for the evaluation of the changes of the lymphatic architecture and the lymphatic function before and after the application of a physical or surgical treatment. For the breast and dorsal zones of the upper arm clear boundaries are necessary to make the interpretation of the dermal backflow of these zones easier.

Early treatment of patients with BCRL will lead to less complications and more stabilization of the disease[7, 8] being able to detect BCRL in an early stage of the disease will even be more beneficial. According to a 10 years cohort of breast cancer survivors, measuring lymphedema relative volume (LRV) by water displacement showed that the volume of the arm at the time of diagnosis is an important predictive factor. Patients with a large LRV at time of diagnosis evolve faster to a more severe lymphedema (LRV > 20%) than patients with a small LRV. A small volume can remain stable, even until 10 years after breast cancer treatment.[9]

The role of lymphofluoroscopy in the early phase of BCRL

Multiple clinical assessment tools have been described for early detection of BCRL, but it still remains unclear which tool is the most sensitive. It is also not clear yet, which threshold for early detection can be used for the different assessment tools. It is accepted that a ≥ 5% volume difference in comparison with the preoperative measurement, is a good indication for starting BCRL treatment.[10] A ≥ 3% volume difference in comparison to preoperative measurements within 3 months after surgery, has been suggested to use as a threshold for subclinical lymphedema.[7, 10] It is necessary that, besides the dominance and preoperative measurements, comparing volumes in both arms needs to be included in the assessments since changes in body weight can have an influence on arm volumes.[10] As edema often starts to develop only in a certain area, volume measurements can perhaps underestimate BCRL. This can also be the case for BIS as this method measures the amount of extracellular water in the whole arm. In contrast, TDC can be performed in certain areas where lymphedema is often present, such as around the elbow. Lahtinen et al performed a study comparing BIS and TDC in the assessment of early arm lymphedema 11 and confirmed that TDC was more sensitive than the BIS method.

According to Akita et al lymphofluoroscopy can also be used for early detection of BCRL.[12] The visualization of dermal backflow was seen in 35 out of the 196 patients after a mean of 5.2 months after breast cancer treatment. According to the clinical severity stages[13], stage 0 is defined as a subclinical stage where lymphatic disturbance is present, but that not clinically apparent. It is suggested that this term 'clinically apparent', means that it is not visible, but that it is detectable by clinical examination. We set up a comparative study to evaluate if the dermal backflow visualized by lymphofluoroscopy can be detected by clinical assessments tools **(chapter 3)**. This comparative trial was part of the DEARLY trial (Determining the role of pre-existing factors, EARly diagnostic options and early treatment in the development of breast cancer related LYmphedema). We found no agreement between the pitting status, skinfold thickness, local water content and 3% and 5 % relative volume difference increase compared to preoperative measurement, and early disturbance in lymphatic transport visualized by lymphofluoroscopy. According to this study, none of the clinical assessment tools, such as the pitting test or assessing the skinfold thickness were able to detect the dermal backflow area visualized by lymphofluoroscopy, concluding that lymphofluoroscopy can detect a disturbance of the lymphatic transport earlier. The high false negative ratio of these clinical assessment tools may suggest that lymphofluoroscopy is overestimating the diagnosis of BCRL. However, the early disturbance seen by lymphofluoroscopy is not equal to lymphedema. As already mentioned, it is not unusual that an alternative pathway of the lymphatic transport can be seen after breast cancer treatment. The question is, if this early disturbance seen by lymphofluoroscopy will end up being an early sign for BCRL or just part of an attempt to bypass the obstructed lymph vessels. Perhaps this dermal backflow pattern is a protective factor for the development of BCRL. According to the preliminary results of the risk factor assessment of the DEARLY trial **(chapter 5)**, this early disturbance is indeed a risk factor for the development of BCRL. In this study the presence of dermal backflow was a significant risk factor for the development of BCRL (P= 0.0180), meaning that this early disturbance will evolve to a clinical visible lymphedema in most patients. In the multivariate analysis of the data after 1 year of follow-up only age, ALND and radiotherapy of the axilla could be identified as independent risk factors.

To investigate which patients will evolve towards a clinical lymphedema, other risk factors were also investigated in this risk factor assessment of the DEARLY trial. Risk factors were divided into demographic and general health related factors, treatment related risk factors and breast cancer related risk factors. For the demographic and general health related factors, in the univariate analysis no risk factor was significant. In the multivariate analysis, age became an independent risk factor. Body mass index and physical activity tended to an increased risk, but this was not significant. For the breast cancer and treatment related risk factors, more invasive treatment such as ALND and mastectomy, high number of removed lymph nodes and high number of positive lymph nodes were found to be risk factors for the development of BCRL. Postsurgical complications, radiotherapy of the axilla and taxane-based chemotherapy were also found to be significant risk factors. The more advanced the breast cancer, resulting in a more invasive treatment, the higher the risk for the development of lymphedema. This conclusion, is in line with the results from the systematic review described in **chapter 4**.

After early detection, an intervention trying to prevent further evolution towards clinical lymphedema is needed. Several studies performed early detection and intervention. This will not only have an impact on the incidence of BCRL[14, 15], these studies could also confirm the hypothesis that early intervention can stabilize the disease in a subclinical stage[9, 16], simplify the treatment (easier measuring garments, less intensive physiotherapy, more self-management,...), and make it more

cost-effective, as advanced disease tends to more complications and needs more intensive physiotherapy.[8] Unfortunately these studies were not randomized and some didn't describe the specifics of the intervention, such as the type of compression garment or exercises prescribed. To address these shortcomings, we set up a randomized controlled trial (DEARLY trial) as described in **chapter 6 and 7**. Hundred twenty-eight patients scheduled for breast cancer treatment were included in this study. Within the first year, after the last patient was included in the study, 39 patients (30%) developed an abnormal dermal backflow pattern visualized with lymphofluoroscopy before a clinical lymphedema was present. These 39 patients were randomized into either the control group or the preventive treatment group. All patients received information concerning skin care and exercises. In the preventive treatment group patients received a compression garment on top of this. The first choice was a round knitted custom-made compression garment, compression class 2 (23 -32 mmHg). If patients were not comfortable with this garment, a flat-knitted garment was ordered. Patients will be followed-up for 3 years.

Preventive surveillance model

Intensive follow-up of patients after breast cancer treatment suggests that subclinical lymphedema can be detected early. Suggestions for a surveillance model have been described in several studies.[16–20] Most studies suggest a surveillance using BIS or volume measurements every 3 months the first year and then up to 3 to 5 years[15, 21] and to start intervention when the threshold for subclinical lymphedema is met. The type of intervention varies between the studies. Physical therapy with manual lymph drainage, garments, education or self-massage was prescribed.[7, 22] In some studies only patients with a high-risk are followed-up.[16]

Based on the literature and the findings in the DEARLY trial, we can suggest to start surveillance already preoperatively with preoperative measurements to be able to compare with postoperative findings and informing the patients of the risk of development of BCRL. Most of the patients are aware of this risk and are eager to participate in a surveillance program. The first month after breast cancer treatment, then every 3 months the first year and then every 6 months until at least 3 years (preferable 5 years) after breast cancer treatment, volume measurement and a complementary other tool such as measuring local water content or assessing skinfold thickness are necessary.

It is recommended to pay even more attention to patients with a higher risk for developing BCRL, especially patients with a more advanced cancer such as after ALND, after taxane-based chemotherapy and after radiotherapy of the axilla.

According to the preliminary results, lymphofluoroscopy is able to detect early disturbance of the lymphatic transport, before any of the other clinical assessment tools and is a risk factor for the development of BCRL. Therefore lymphofluoroscopy should be used as a screenings tool in these high risk patients enabling an earlier start of intervention. Limiting surveillance to this group of patients can be a way to optimize the cost-effectiveness of a preventive surveillance model.

It is also important that patients are well informed about potential reversible risk factors, such as level of physical activity or body mass index. This needs to be brought to the attention in the postoperative and aftercare programs.
Continuing the search for narrowing the number of risk factors and the search for an assessment tool to detect lymphedema early, remains important in order to diminish the burden of this disease.

FUTURE RESEARCH

The analyses of the 3 year follow-up of the DEARLY trial will be important to see if this early disturbance remains a risk factor for the development of BCRL or if these lymphatic abnormalities are just part of an attempt to reroute the lymph flow. Certain characteristics of the dermal backflow can also play a role, such as the size of the area of dermal backflow and the type of dermal backflow. In a previous study it is presumed that only a stardust pattern is a predictor for the development of BCRL and not the splash pattern.[12]

The final analyses will include assessments of the pre-existing risk factors, including different characteristics of the lymphofluoroscopy (aim 5), and the impact of wearing a compression garment, on top of usual care, in patients with an early disturbance visualized with lymphofluoroscopy on the development of BCRL (aim 6). We are currently working on a meta-analysis of the results of the systematic review regarding the risk factors for the development of breast cancer-related lymphedema.

The investigated risk factors represent only a part of the potential risk factors. Certain characteristics of the venous circulation (venous flow, thickness of the vessel wall, compressibility), and the amount of lymph nodes and vessels visualized by lymphofluoroscopy, are potential factors contributing to the development of BCRL. These factors were also registered in the DEARLY trial and will be analysed in the near future.

There are still some unresolved issues about lymphofluoroscopy. For example the measurement of the reproducibility of the procedure of lymphofluoroscopy could be an interesting topic for future studies (as was done for the lymphoscintigraphy[23]). It would also be of interest to investigate the change of lymphatic transport, visualized by lymphofluoroscopy (by describing the presence and location of the different pathways), after reconstructive surgery.

In collaboration with Prof. Dr. An Zwijsen, KU Leuven, department of Cardiovascular Sciences, research has started to correlate lymphatic vessel morphology and presence/absence of bone morphogenetic protein (BMP) signalling components and BMP target genes in tissue samples from patients participating in the DEARLY trial with the later development of BCRL. (FWO G0B48 "Misregulation of lymphatic valve development by impaired BMP signalling as potential risk factor for development of breast-cancer related lymphedema" C14/19/095: "BMP signalling in endothelial function and dysfunction"). Perhaps this vessel morphology can also play a role in the development of BCRL.

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SUMMARY

In this thesis the role of lymphofluoroscopy in the optimization of diagnostic and treatment modalities to influence the natural history of breast cancer-related lymphedema (BCRL) was investigated.

In the **introduction** the lymphatic system, pathophysiology of lymphedema, clinical evaluation, imaging techniques and treatment of BCRL was described.

In **the research hypothesis and specific aims** were described in the next section. The general hypothesis of this thesis is to examine the role of the lymphofluorscopy in the management of BCRL. Furthermore the role of lymphofluoroscopy in the early phase of BCRL will be evaluated.

In **chapter 1** we investigated the correlation between lymphofluoroscopic findings (dermal backflow) and other clinical assessment tools such as circumference measurements, water displacement, skinfold thickness, local water content; pitting status and extracellular fluid. Measuring the skinfold thickness, local water content and lymphedema volume will be most appropriate to detect the areas with dermal backflow according to lymphofluoroscopic images.

In **chapter 2** we evaluated the inter-rater reliability of the lymphofluoroscopy. The lymphofluoroscopic evaluations were scored before and after break separately by two assessors. The outcome parameters used to assess the agreement were presence of lymphatic transport out of the injection sites, of dermal backflow patterns, of efferent lymphatic vessels and of lymph nodes. Overall, there was a moderate to strong agreement for most of the outcomes scored when evaluating the lymphatic architecture and transport through lymphofluoroscopy.

In **chapter 3** the early disturbance visualized by lymphofluoroscopy was correlated with the clinical assessment tools used in chapter 1. We found that none of the assessment tools correlated with the early disturbances in lymphatic transport as visualized by the lymphofluoroscopy.

In **chapter 4** we performed a systematic review of the risk factors for the development of BCRL. Hundred forty-one studies were analysed. Risk factors with a strong level of evidence were axillary lymph node dissection, node stage and taxane-based chemotherapy. Risk factors with a moderate level of evidence were BMI, greater number of excised lymph nodes, presence of positive lymph nodes, radiotherapy, radiotherapy of the axilla and postoperative infections.

In **chapter 5** we performed a risk assessment of the patients included in our randomized controlled trial (RCT). Preliminary results after 1 year follow-up were reported. Lymphofluoroscopy was identified to be able to detect an impaired lymphatic transport early and was found to be a good predictor for the development of BCRL. This study confirmed that patients with more advanced breast cancer (mastectomy, high number of positive lymph nodes, high number of removed lymph nodes, postsurgical complications, high tumor stage, radiotherapy of the axilla and taxanes) have more risk to develop BCRL.

In **chapter 6** we described the protocol of the RCT. All patients scheduled for breast surgery combined with either unilateral ALND or sentinel node biopsy (SLNB) in the Multidisciplinary Breast Clinic Center at the University Hospitals Leuven were screened for participation in this study. At every visit (preoperative and 8 postoperative visits) several clinical assessments and a lymphofluoroscopic evaluation was performed. If a disturbance of the lymphatic transport was visualized with lymphofluoroscopy, patients were randomized in either the control group or the preventive treatment group. In the control group, patients received information concerning skin care and exercises. In the preventive treatment group patients received on top of this, a compression garment. Patients will be followed-up for 3 years.

In **chapter 7** preliminary data of the RCT were presented. A total of 128 patients were included in this study. The mean age of the patients was 56.68 years and the mean body mass index was 25.96. In 73 patients ALND (57%) was performed, 55 patients (43 %) underwent SLNB. Eighty-nine patients (70%) underwent mastectomy and 39 patients (30%) breast-conserving surgery. Thirty-nine patients showed early disturbance of the lymphatic transport visualized with lymphofluoroscopy and were randomized in the two groups described earlier.

In the **general discussion** the role of lymphofluoroscopy in the management of BCRL was discussed. Understanding the pathophysiology and alternative pathways will enable us to optimize the care of patients. This information can guide the treatment, not only by directing the manual lymph drainage, but also by optimizing the compression material. When lymphofluoroscopy can't be performed, measuring the skinfold thickness, local water content and lymphedema volume will be most accurate to detect the areas with dermal backflow according to lymphofluoroscopic images. The inter-rater reliability of the lymphofluoroscopic evaluations was good. In the second section the role of lymphofluoroscopy in the early phase of BCRL was evaluated. There was no correlation found between the early disturbance visualized by lymphofluoroscopy and other clinical assessment tools. If the goal is to detect early disturbance, lymphofluoroscopy needs to be performed. In the risk assessment, this early disturbance was found to be a predictor for BCRL.

After breast cancer treatment, a strict follow-up (until 5 years after breast cancer treatment) with preoperative measurements is necessary. Volume measurements and local measurements with TDC or skinfold thickness are being suggested.

From the multiple studies performed in this thesis, the conclusion that lymphofluoroscopy makes it possible to detect BCRL in an early stage, before any of the other clinical assessment tools, has been confirmed. In high risk patients, this technique even seems to be more beneficial.

Further research will be performed to investigate if these findings remain visible after 3 years of follow-up and if early treatment with a compression garment, on top of usual care, in patient with an early disturbance of the lymphatic transport visualized with lymphofluoroscopy, is more efficient in prevention of the development of BCRL than skin care and exercises alone.

SAMENVATTING

In dit proefschrift werd de rol van lymfofluoroscopie in de optimalisatie van diagnostische en therapeutische modaliteiten ter beïnvloeding van het natuurlijk beloop van borstkanker-gerelateerd lymfoedeem onderzocht.

In de **inleiding** werd het lymfestelsel, pathofysiologie van lymfoedeem, klinische evaluatie, beeldvorming en behandeling van borstkanker-gerelateerd lymfoedeem beschreven.

De **onderzoekshypothese en specifieke doelstellingen** werden hierna beschreven. De algemene hypothese van dit proefschrift is om de rol van de lymfofluoroscopie in de klinische zorg van patiënten met borstkanker-gerelateerd lymfoedeem te onderzoeken. Verder zal de rol van lymfofluoroscopie in de vroege fase van het borstkanker-gerelateerd lymfoedeem worden geëvalueerd.

In **hoofdstuk 1** werd de correlatie onderzocht tussen lymfofluoroscopische bevindingen (dermal backflow) en andere klinische evaluatiemethoden die in de dagelijkse praktijk worden gebruikt. Deze klinische evaluatiemethoden worden gebruikt om lymfoedeem te beoordelen: beoordeling van het volume met omtreksmetingen, waterverplaatsing, beoordeling van de huidplooidikte, beoordeling van het lokale watergehalte, beoordeling van de pitting status en beoordeling van de extracellulaire vloeistof. Het meten van de huidplooidikte, het lokale watergehalte en het lymfoedeemvolume is het meest geschikt om de gebieden met dermal backflow volgens lymfofluoroscopische beelden te detecteren.

In **hoofdstuk 2** werd de inter-beoordelaarsbetrouwbaarheid van de lymfofluoroscopie geëvalueerd. De lymfofluoroscopische evaluaties werden voor en na de pauze afzonderlijk gescoord door twee beoordelaars. De uitkomstparameters die werden gebruikt om de overeenkomst te beoordelen, waren de aanwezigheid van lymfatisch transport uit de injectieplaatsen, aanwezigheid van dermal backflow, aanwezigheid van efferente lymfevaten en aanwezigheid van lymfeklieren. Over het algemeen was er een matige tot sterke overeenstemming voor de meeste resultaten die werden gescoord bij het evalueren van de lymfatische architectuur en het transport door lymfofluoroscopie.

In **hoofdstuk 3** werd de vroege verstoring gevisualiseerd door lymfofluoroscopie gecorreleerd met de klinische evaluatiemethoden gebruikt in hoofdstuk 1. We vonden dat geen van de evaluatiemethoden correleerde met de vroege stoornissen in lymfatisch transport zoals gevisualiseerd door de lymfofluoroscopie.

In **hoofdstuk 4** werd een systematische review van de risicofactoren voor het ontstaan van borstkanker-gerelateerd lymfoedeem uitgevoerd. Honderdeenenveertig studies werden geanalyseerd. Meer gevorderde kanker (na okselklierevidement (OE), hoog aantal verwijderde lymfeklieren, hoog aantal positieve lymfeklieren) werd geïdentificeerd als een risicofactor voor het ontstaan van borstkanker-gerelateerd lymfoedeem. Radiotherapie van de oksel en taxanen verhoogden ook het risico.

In **hoofdstuk 5** werd een risicobeoordeling uitgevoerd van de patiënten die deelnamen aan onze gerandomiseerde gecontroleerde studie (RCT). Voorlopige resultaten na 1 jaar follow-up werden gerapporteerd. Lymfofluoroscopie kon een verstoord lymfetransport vroegtijdig detecteren en was een goede voorspeller voor het ontstaan van borstkanker-gerelateerd lymfoedeem. Deze studie bevestigde dat patiënten met meer gevorderde borstkanker (mastectomie, hoog aantal positieve lymfeklieren, hoog aantal verwijderde lymfeklieren, postoperatieve complicaties, hoog tumorstadium, radiotherapie van de oksel en taxanen) meer risico hebben om borstkanker-gerelateerd lymfoedeem te ontwikkelen.

In **hoofdstuk 6** werd het protocol van de RCT beschreven. Alle patiënten die ingepland waren voor een borstoperatie in combinatie met ofwel een OE of schildwachtklierbiopsie (SB) in het Multidisciplinaire Borstcentrum van UZ Leuven werden gescreend voor deelname aan deze studie. Bij elk bezoek (preoperatieve en 8 postoperatieve bezoeken) werden verschillende klinische beoordelingen en een lymfofluoroscopische evaluatie uitgevoerd. Indien een verstoring van het lymfetransport werd gevisualiseerd met lymfofluoroscopie, werden patiënten gerandomiseerd in ofwel de controlegroep ofwel de preventieve behandelgroep. In de controlegroep kregen patiënten informatie over huidverzorging en oefeningen. In de preventieve behandelgroep kregen patiënten daar bovenop een compressiekous. Patiënten worden gedurende 3 jaar gevolgd.

In **hoofdstuk 7** werden voorlopige gegevens van de RCT gepresenteerd. In totaal werden 128 patiënten geïncludeerd in deze studie. De gemiddelde leeftijd van de patiënten was 56,68 jaar en de gemiddelde body mass index was 25,96. Bij 73 patiënten werd OE (57%) uitgevoerd, 55 patiënten (43%) ondergingen SB. Negenentachtig patiënten (70%) ondergingen een borstamputatie en 39 patiënten (30%) een borstsparende operatie. Negenendertig patiënten vertoonden een vroege verstoring van het lymfatisch transport, gevisualiseerd met lymfofluoroscopie en werden gerandomiseerd in de twee eerder beschreven groepen.

De **algemene discussie** werd als laatste beschreven. In het eerste deel werd de rol van lymfofluoroscopie bij de klinische zorg van patiënten met borstkanker-gerelateerd lymfoedeem besproken. Door de pathofysiologie en alternatieve paden te begrijpen, kunnen we de zorg voor patiënten optimaliseren. Deze informatie kan

de behandeling aanpassen, niet alleen door de manuele lymfedrainage te sturen, maar ook door het compressiemateriaal te optimaliseren. In de dagelijkse praktijk waar lymfofluoroscopie niet kan worden uitgevoerd, is het meten van de huidplooidikte, het lokale watergehalte en het lymfoedeemvolume het meest nauwkeurig om de gebieden met dermal backflow te detecteren volgens lymfofluoroscopische beelden. De inter-beoordelaarsbetrouwbaarheid van de lymfofluoroscopische evaluaties was goed. In het tweede deel werd de rol van lymfofluoroscopie in de vroege fase van borstkanker-gerelateerd lymfoedeem besproken. Er werd geen correlatie gevonden tussen de vroege verstoring gevisualiseerd door lymfofluoroscopie en andere klinische evaluatiemethoden. Als het doel is om vroege verstoring te detecteren, zou lymfofluoroscopie moeten worden uitgevoerd. In de risico analyse bleek deze vroege verstoring een voorspeller te zijn voor BCRL.

Na borstkanker behandeling, is een strikte follow-up (tot 5 jaar na de behandeling van borstkanker) met preoperatieve metingen noodzakelijk. Dit kan gebeuren door volume metingen en een lokale meting zoals meting van het lokale watergehalte of meting van de huidplooidikte.

Uit de meerdere onderzoeken die in dit proefschrift zijn uitgevoerd, is de conclusie bevestigd dat lymfofluoroscopie het mogelijk maakt om borstkanker-gerelateerd lymfoedeem in een vroeg stadium te detecteren, nog voor een van de andere klinische evaluatiemethoden. Bij hoog risico patiënten lijkt deze techniek zelfs aangewezen.

Verder onderzoek van de resultaten van de RCT zal aantonen of deze bevindingen ook na 3 jaar follow-up zichtbaar blijven of vroege behandeling, naast de gebruikelijke zorg, bij patiënten met een vroege verstoring van het lymfestelsel gevisualiseerd door lymfofluoroscopie, efficiënter is in het voorkomen van de ontwikkeling van borstkanker-gerelateerd lymfoedeem dan huidverzorging en oefeningen alleen.

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Acknowledgments and personal contribution

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Chapter 1 and 2
These studies were sub-studies of a double-blind, multicenter, randomized controlled trial (EFforT-BCRL trial), which is registered in clinicaltrials.gov (NCT02609724), CME reference S58689, EudraCT number 2015-004822-33 and was financed by the Agency for Innovation by Science and Technology, applied Biomedical Research (IWT 150178).

ST conceptualized and designed these studies.

For chapter 1: LD and TD collected the data. LD wrote a first draft of the manuscript as part of her master's thesis under supervision of ST and ND. ST revised the manuscript. IF, PN, IN and NG critically revised the article for important intellectual content and approved the final article.

For chapter 2: MH, JK and TD collected the data. MH and JK wrote a draft of the manuscript as part of their master's thesis under supervision of ST and ND. ST revised the manuscript. IF, TD and AH critically revised the article for important intellectual content and approved the final article.

Chapter 3, 5, 6 and 7
ST was the principal investigator of the Dearly trial. This randomized controlled trial was financed by the Clinical Research Fund of the University Hospitals Leuven, KOOR 2017, S60382. ST conceptualized and designed the study. She recruited the study patients and obtained informed consent. She measured all the patients, acquired the data. ST and AL conducted the data analysis. ST wrote the manuscript and revised according to the remarks of the co-authors.

For chapter 3: IF, BBH, ND, TD and AH critically revised the article for important intellectual content and approved the final article.

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Chapter 4
ST and CV conducted the systematic review. ST analysed the results and wrote the manuscript. IF, BBH and ND critically revised the article for important intellectual content and approved the final article.

Conflict of interest

None of the authors mentioned in this doctoral thesis have any conflict of interest to declare.

List of contributors

AH, An-Kathleen Heroes; AL, Annouschka Laenen; BBH, Beate Bechter-Hugl; CV, Cedric Vanluyten; IF, Inge Fourneau; IN, Ines Nevelsteen; JK, Jantine Kleiman; LD, Lore Dams; MH, Melissa Helberg; ND, Nele Devoogdt; NG, Nick Gebruers; PN, Patrick Neven; ST, Sarah Thomis; TD, Tessa De Vrieze.

CURRICULUM VITAE

Sarah Thomis was born in Gent, Belgium on 12th of March 1977. She grew up around Leuven and went to school in Paridaens, Leuven. The last year of high school was spent at Cheshire Academy, Cheshire, Connecticut, in the USA. She had indicated an interest in studying Pharmacy, the same as what her parents had done. However, the class of Anatomy had her changed her mind and in 1995 she started studying Medicine at the KU Leuven, convinced that she wanted to become a surgeon. In 2001 unfortunately she was victim of a car crash during her internship in South-Africa. She lost some months in her training but graduated cum Laude in 2003. She started training in General Surgery under the supervision of Prof. Dr. Broos. She trained at Ziekenhuis Oost-Limburg Genk, Imelda Ziekenhuis Bonheiden and University Hospitals Leuven. During her training she developed a passion for vascular surgery, and found that especially the reconstructive nature of the surgery was very appealing. After the training for general surgery, she continued her fellowship at University Hospitals Leuven. During that period she visited Duke University to learn more about venous pathology and and went to Erasmus MC Rotterdam and Maastricht Hospital to learn the skills of endovenous treatment. In 2011 she became a staff member of the department of Vascular Surgery in University Hospitals specialized in venous pathology. In 2014 a collaboration with Prof. Nele Devoogdt led to the creation of a lymphovenous center which would become the only expert center of lymphedema in Flandres. Meanwhile in 2015 she decided to start a PhD in lymphedema under the supervision of Prof. Dr. Inge Fourneau. She is married to Joris Devroye and they have three children, Marie, Louise and Jules. They currently live in Herent, near Leuven.

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Ik denk aan jou

Mijn droom is als een wens
Dat ’t leven je moge geven
Een hart van goud, een mens
Een vriend om blij te leven.

Ik wens je ijverige handen,
Twee vaste voeten op de grond,
Veel liefde, die zonder banden
Geluk strooit alom in ’t rond.

Ik wens je heldere ogen
Een mond die lief kan zijn
En niet door tegenslag gebogen
Een hoofd dat dromen kan als ’t mijn.

Ik wens je weinig zorgen,
Gezondheid steeds te koop
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Dan blijf je steeds geloven
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En zal je weer beloven
Blij te zijn om ’t samenzijn.

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Maurice De Weghe, 1998