KU Leuven

Biomedical Sciences Group

Faculty of Rehabilitation and Movement Sciences

Department of Rehabilitation Sciences

Research Group for Rehabilitation in Internal Disorders

EFFECTIVENESS OF FLUOROSCOPY-GUIDED MANUAL LYMPH DRAINAGE FOR THE TREATMENT OF BREAST CANCER-RELATED LYMPHEDEMA

Tessa DE VRIEZE

Dissertation presented in partial fulfillment of the requirements for the joint degree of

Doctor in Biomedical Sciences (KU Leuven) and

Doctor in Medical Sciences (University of Antwerp)

2020

Jury

Supervisor KU Leuven:	*Prof. dr. Nele Devoogdt*
Supervisor University of Antwerp:	*Prof. dr. Nick Gebruers*
Co-supervisor:	*Prof. dr. Ines Nevelsteen, KU Leuven*
Chair examining committee:	*Prof. dr. Simon Brumagne*
Jury members:	KU Leuven
	Prof. dr. Inge Fourneau
	Prof. dr. Ann Smeets
	Prof. dr. Eric Van den Kerckhove
	University of Antwerp
	Prof. dr. Sigrid Stroobants
	External jury
	Dr. Robert Damstra

TABLE OF CONTENTS

ABBREVIATIONS

ALND	axillary lymph node dissection
BC	breast cancer
BCRL	breast cancer-related lymphedema
BIS	bio impedance spectroscopy
BRCA1	breast cancer 1 gene
BRCA2	breast cancer 2 gene
DLT	decongestive lymphatic therapy
ER	estrogen receptor
GPE	Global Perceived Effect of change
HER-2	human epidermal growth factor receptor 2
HGF	hepatocyte growth factor
ICC	intraclass correlation coefficient
ICG	indocyanine green
IPC	intermittent pneumatic compression
ISL	International Society of Lymphology
Lymph-ICF-UL	Lymphedema Functioning, Disability and Health Questionnaire for Upper limb Lymphedema
McGill-QoL	McGill Quality of Life Questionnaire
MCID	minimal clinical important difference
MLD	manual lymph drainage
MMDC	MoisturemeterD Compact
MRI	magnetic resonance imaging
NRS	numeric rating scale
PDE	photo dynamic eye
PgR	progesterone receptor
PWC%	percentage of water content
RCT	randomized controlled trial
RR	relative risk
SEM	standard error of measurement
SLNB	sentinel lymph node biopsy
TDC	tissue dielectric constant
VAS	visual analogue scale

GENERAL INTRODUCTION

This general introduction comprises six different topics. In topic 1, more information will be provided about diagnosing breast cancer and its therapeutic approaches. The second topic will further explain lymphedema after the treatment for breast cancer. Thereafter, the rationale for the evaluation of breast cancer-related lymphedema will be elaborated in topic 3. In topic 4, different treatment modalities for breast cancer-related lymphedema will be discussed. Subsequently, the role of manual lymph drainage as a treatment modality for breast cancer-related lymphedema, is discussed in topic 5. At last, the specific aims and outlines of this doctoral thesis will be pointed out in topic 6.

1. Breast cancer

1.1. Epidemiology and risk factors

Breast cancer (BC) results from uncontrolled proliferation of breast cells, due to genetic alterations and thereby giving normal cells the capability of invading the surrounding healthy tissue and spreading throughout the body.[1] One out of eight women, will be diagnosed with BC at some point during their life.[2] Worldwide, there were about 2.1 million women with newly diagnosed BC in 2018, accounting for almost 1 in 4 cancer cases among women and the leading cause of cancer death in over 100 countries.[3] In Belgium, about 10 627 women were diagnosed with BC in 2017.[4] However, due to combined screening programs and improved therapeutics, the number of long-term survivors is continuing to increase each year.[5,6] Less than 1% of all breast carcinomas are detected in men.[7,8]

Global variation in BC incidence is reflected by differences in opportunities for (early) detection with mammography as well as by risk factors.[9] Five to 10% of the BC cases are due to a hereditary or genetic factor (such as strong family history of breast or ovarian cancer and/or mutations in cancer susceptibility genes (e.g. BRCA1, BRCA2)).[3] However, nonhereditary risk factors are probably the main drivers to explain the international differences in incidence rates.[3] Various risk factors have been established. These factors include reproductive as well as hormonal factors such as a long menstrual history (early age at menarche, later age at menopause), long-term use of oral contraceptives (RR 1.24) and hormone replacement therapy (RR 1.35) and never having children (or later age at first birth).[10] In contrast, baring children before the age of 30 and breastfeeding tend to decrease the risk of BC.[10] Other patient-related risk factors are weight gain after the age of 18, obesity (for postmenopausal BC), a personal history of breast and/or ovarian carcinoma, lack of physical activity and alcohol consumption.[10,11] Since the last decades, the risk for secondary BC in childhood cancer survivors (e.g. Hodgkin lymphoma survivors), had become an emerging area of interest.[12] Chest radiation (i.e. mantle field, whole lung, as well as total body radiation) is the most important treatment-related risk factor for secondary BC in childhood cancer survivors, comparable to the risk for BC in women with a BCRA1

or BRCA2 gene mutation.[12] Especially in childhood cancer survivors, also the presence of thyroid disease has been identified as a risk factor (RR 1.70).[12]

1.2. Breast anatomy and locoregional lymphatic drainage

The breast consists of the mammary gland, imbued with blood vessels, lymph nodes and lymph vessels, and connective tissue, all surrounded by subcutaneous adipose tissue. The gland itself consists of lobules and ducts, responsible for producing and transporting milk to the nipple in response to hormonal signals. The breast's size and shape are defined by the amount of glandular tissue, fatty and connective tissue. The breast itself contains no muscle tissue (Figure 1).

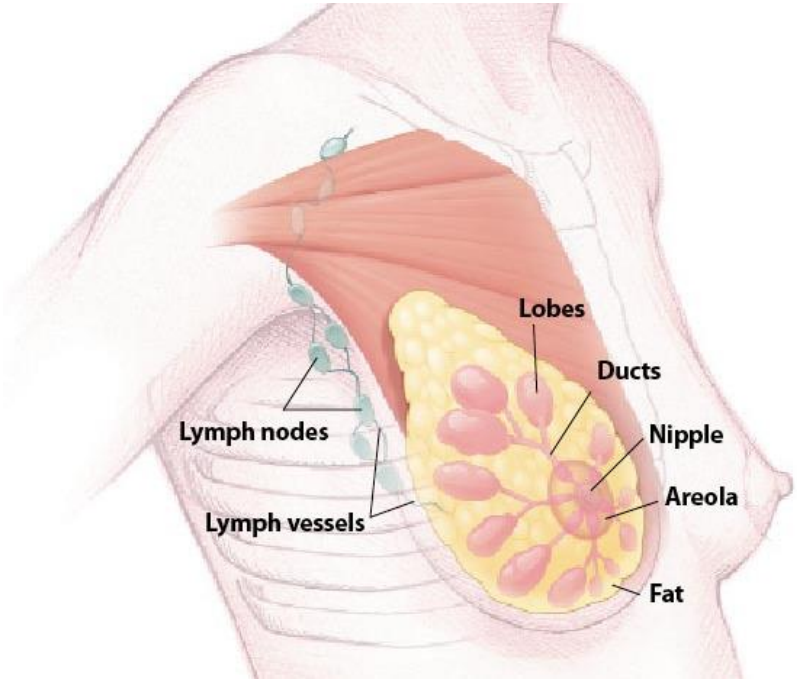


Figure 1. *Normal breast tissue (illustration adapted from web page[13])*

Different types of breast malignancies are defined, depending on which cell types (ductal versus lobular) grow out of control and whether they are invasive or not. When cancer cells remain within the basal membrane, they are classified as in situ or non-invasive e.g. ductal carcinoma in situ. In case there is dissemination of cancer cells outside this membrane, invading the adjacent normal tissue, it is called invasive.[14] Most common subtypes of invasive BC are ductal (75-80%) and lobular carcinoma (10-15%). BC can spread locally into the regional lymph nodes (e.g. axillary nodes, supra-, infraclavicular and internal mammary lymph nodes) or giving rise to distant metastases. As the stage of the disease determines the treatment, accurate diagnosis and staging of BC is needed.

In the breast region, there are three major lymphatic routes: axillary, internal mammary and supraclavicular (Figure 2). Furthermore, there are intramammary lymph nodes which are located within the breast.

1. Axillary: interpectoral nodes (Rotter's) and lymph nodes along the axillary vein and its branches are divided into following levels:
    a. Level I (low-axilla): lymph nodes located laterally to the lateral border of the pectoralis minor muscle.
    b. Level II (mid-axilla): lymph nodes between the medial and lateral borders of the pectoralis minor muscle and the interpectoral (Rotter's) lymph nodes.
    c. Level III (apical axilla): lymph nodes medially to the medial border of the pectoralis minor muscle and inferior to the clavicle. These are called apical of infraclavicular nodes.
2. Internal mammary: lymph nodes located in the intercostal spaces along the sternum in the endothoracic fascia.
3. Supraclavicular: lymph nodes located in the supraclavicular fossa (triangle defined by: omohyoid muscle and tendon – internal jugular vein – clavicle and subclavian vein).

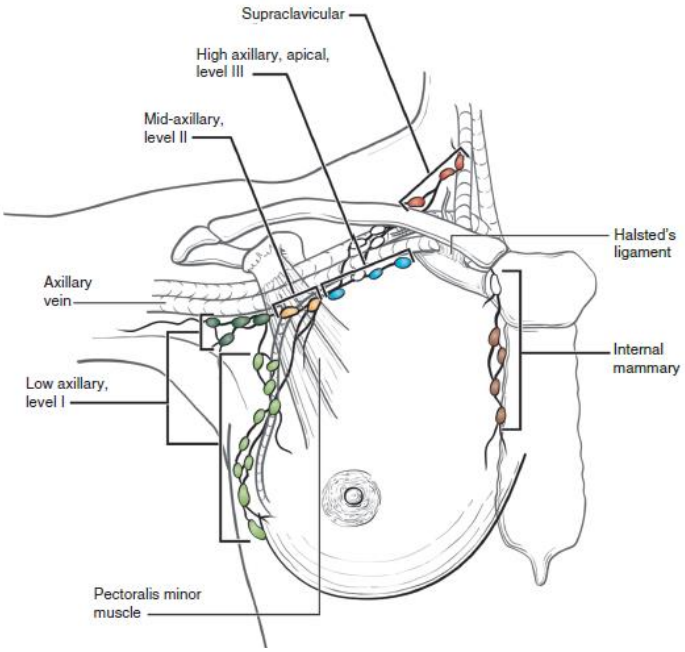


Figure 2. *Schematic diagram of the breast and regional lymph nodes (illustration with permission reprinted[15])*

1.3. Diagnosis and classification of breast cancer

BC diagnosis is based on triple diagnostics: physical examination, radiological investigations and biopsy with histology.

Physical examination includes inspection and palpation of both breasts and locoregional lymph nodes.[16] *Radiological investigation* includes primarily bilateral mammography and ultrasound of the breast and regional lymph nodes.[17] MRI of the breast is not routinely recommended, but should be considered in some cases (e.g. lobular subtype, suspicion of multifocality (particularly in lobular BC), familial BC associated with BCRA gene mutations, etc.).[16]

A *core needle biopsy* is needed to obtain information about the characteristics of the suspicious tissue. This core biopsy of tumoral breast tissue reports on several items, such as[16]:

- the type of breast malignancy (e.g. ductal, lobular, …)
- the immunohistochemical evaluation of estrogen receptor (ER) status and progesteron receptor (PgR) status (both for invasive as well as premalignant diseases)
- the human epidermal growth factor 2 receptor (HER-2) gene expression

Further staging of BC includes imaging for distant metastases (most often to bones, lungs, liver or the brain) and laboratory blood tests. After completion of these procedures, patients are assigned a globally accepted disease stage, preferably in terms of the TNM classification.[18] (Figure 3). This classification codes the extent of the primary tumor (T), regional lymph nodes (N) and distant metastases (M).[19] Prior to surgery, the classification contains a clinical staging system (cTNM). Once surgery has been performed, a histopathological examination of the dissected tumoral breast tissue and lymph nodes has to be accomplished in order to obtain a final pathological disease stage (pTN).[20,21]

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1(a,b,c)	Tumor is ≤ 2cm across
T2	Tumor is > 2cm but ≤ 5cm across
T3	Tumor is > 5 cm across
T4(a,b,c,d)	Tumor of any size, growing into chest wall or skin, includes inflammatory BC
Regional lymph nodes (N)	
Nx	Nearby lymph nodes cannot be assessed
N0	Cancer has not spread to nearby lymph nodes
N1(mi,a,b,c)	Cancer has spread to 1-3 axillary lymph node(s), and/or cancer is found in internal mammary lymph nodes (near to the breast bone) on sentinel lymph node biopsy
N2(a,b)	Cancer has spread to 4-9 lymph nodes under the arm, or cancer has enlarged the internal mammary lymph nodes
N3a	Cancer has spread to 10 or more axillary lymph nodes, with at least one area of cancer spread greater than 2mm, OR Cancer has spread to the infraclavicular lymph nodes, with at least one area of cancer spread greater than 2mm
N3b	Cancer has spread to at least one axillary lymph node (with at least one area of cancer spread greater than 2mm) and has enlarged the internal mammary lymph nodes, OR Cancer has spread to 4 or more axillary lymph nodes (with at least one area of cancer spread greater than 2mm) and cancer is found in internal mammary lymph nodes on sentinel lymph node biopsy
N3c	Cancer has spread to the supraclavicular lymph nodes with at least one area of cancer spread greater than 2mm
Metastases (M)	
Mx	Metastasis cannot be assessed
M0	No distant spread is found on imaging tests or by physical examination
cM0(i+)	Small numbers of cancer cells are found in blood or bone marrow, or tiny areas of cancer spread (≤0.2 mm) are found in lymph nodes away from the underarm, clavicular or in internal mammary areas
M1	Cancer has spread to distant organs (most often to the lungs, bones, liver or brain)

Figure 3. *TNM classification of the disease stage: codes the extend of the primary tumor (T), regional lymph nodes (N) and distant metastases (M)*

1.4. Treatment

BC treatment is multimodal and requires a multidisciplinary approach in order to tackle the disease and improve the disease-free and overall survival. In general, treatment consists of surgery, radiotherapy and/or systemic therapy, and can be combined in a neo-adjuvant or adjuvant setting. Neo-adjuvant therapy, in contrast to adjuvant therapy, is applied before surgery and is aimed to downstage tumor size and nodal state, to anticipate the risk of micro metastases, or to start treatment in case of inflammatory BC.[14]

Surgery

- Surgical procedures considering the breast contain two possibilities, depending on the clinical disease stage, breast volume and preference of the patient: *breast-conserving surgery* consisting of a wide excision of the tumor with (usually) limited surrounded healthy breast tissue, or *mastectomy* in which the whole breast (with or without the fascia of the pectoral muscles) is removed.[14]
- Initially based on the clinical disease stage (cTNM), surgical procedures considering the axilla contain two possibilities as well: *sentinel lymph node biopsy* (SLNB) and/or *axillary lymph node dissection* (ALND)

  In clinically node-negative patients (cN0), SLNB is proposed and preferred (except for some cases, e.g. a cT4d inflammatory BC). Alternatively, in node-positive patients, regarding the current state of the art, ALND is still proposed.

  By definition, the sentinel lymph node is the first node receiving direct lymphatic drainage from the tumor, which can be detected using a radioactive tracer (e.g. Tc99) or blue dye[22], or more recently, by using a magnetic tracer (e.g. Magtrace®)[23] (Figure 4). The identified (mostly one to three) biopsied sentinel lymph node(s) need(s) to be removed for histological examination, and according to the result, a further axillary lymph node clearance (ALND) is required.[22] During this dissection, lymph nodes from the different axillary levels can be removed (Figure 2, p. 9).

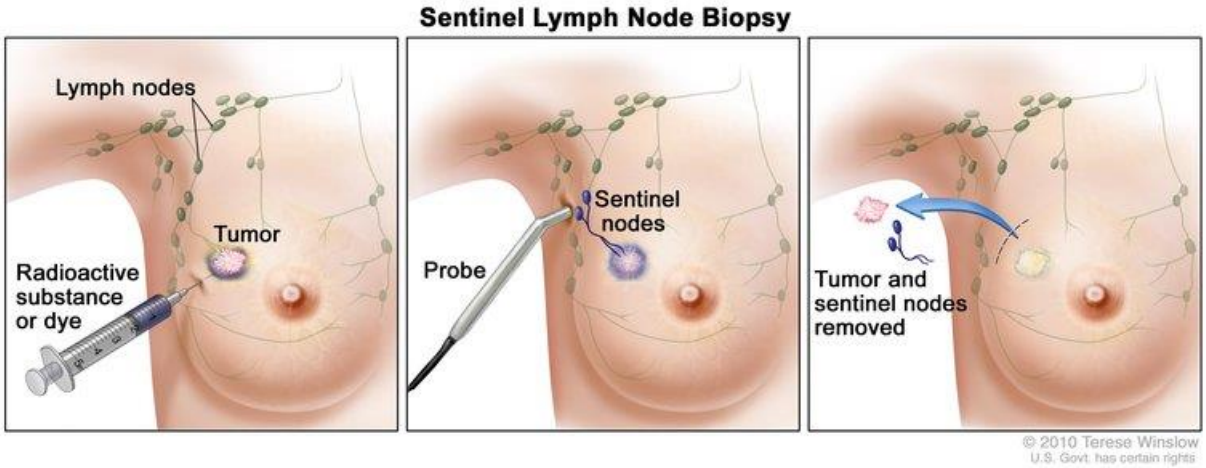


Figure 4. *Sentinel Lymph Node Biopsy (SLNB) procedure. For the National Cancer Institute © (2010) Terese Winslow LLC, U.S. Govt. has certain rights (illustration with permission of the author reprinted from web page[24])*

Radiotherapy

Adjuvant radiotherapy is used to eradicate remaining malignant cells after surgery in order to reduce the risk of locoregional recurrence. Depending on the pathological disease stage (pTN) and the type of surgery that has been applied, a decision can be made to administer adjuvant radiotherapy to the breast and tumor bed (*standard care after breast conserving therapy*), to the chest wall (*after mastectomy*), and/or to regional lymph nodes (axillary, periclavicular, internal mammary), if required.[14]

Systemic therapy

While surgery and radiation therapy promote locoregional control, systemic therapy uses substances that travel through the bloodstream, reaching cells all over the body. The aim of systemic therapy is to eradicate micro metastatic disease or to reduce the risk of BC recurrence.[25 ,26] Depending on the histopathology, different types of systemic treatment can be offered, e.g. chemotherapy, immunotherapy, endocrine therapy in case of hormone sensitive (ER and/or PgR) BC or targeted therapy (e.g. anti-HER2 in case of HER2-positivity).[16]

Thanks to advances in early diagnosis, more effective treatment modalities and more patient-tailored medicine, there is a steady increase in survival after BC treatment to a 5-year survival of 85% or more nowadays.[27] Therefore, healthcare practitioners should first recognize and thereafter manage the long-term morbidities and complications of treatment modalities.[27]

2. Breast cancer-related lymphedema (BCRL)

About 17% of the women treated for BC, develops lymphedema of the arm (nearly 20% after ALND and 6% after SLNB).[28] This is mainly due to an impaired or disrupted flow of lymph fluid through the lymphatic draining vessels and lymph nodes, usually as a consequence of surgery and/or radiation therapy.[29] Additionally, when remaining healthy lymphatic vessels are unable to accommodate the increased lymphatic load, lymph fluid will accumulate in the dependent tissues.[29] Research suggests that there may be a genetic predisposition for the development of lymphedema after treatment for BC, due to potential gene mutations in 'hepatocyte growth factor' (HGF) receptors.[30] Lymphedema is a progressive chronic condition which can have deleterious effects on patients' physical and psychological health.[31] Since untreated lymphedema can lead to progressive swelling, inflammation and tissue changes, early identification is essential in order to start appropriate treatment and to minimize complications.[29]

In this topic, the anatomy and physiopathology of lymphatics will be discussed first. Thereafter, the etiology and stages of lymphedema are addressed. Lastly, the occurrence of lymphedema after BC treatment is discussed.

2.1 Anatomy and physiopathology of lymphatics

Figure 5 presents a visualization of the lymphatic system in the human body including the different areas where lymph nodes are clustered.

In general, the lymphatic system is divided into a superficial system and a deep (including a visceral) system. The superficial system drains the skin and subcutaneous tissue, whereas the deep system drains organs and tissues (such as bones and muscles) underneath the fascia generalis.[29] The two systems are connected with each other via so called perforating vessels traversing the fascia. Some authors also consider another group of vessels, the communicating vessels, which communicate areas drained by different lymphatic bundles.[32]

Even though there is a close relationship between blood and lymphatic vessels (Figure 6), there are some important differences between both systems. Unlike blood vessels, the lymphatic system cannot be considered as a real circulatory system[32]: Lymph flow is unidirectional from peripheral tissues towards the venous system at the base of the neck, and is considered to be an open semicircular system.[32] Besides its role in the maintenance of tissue fluid homeostasis, additional essential lymphatic functions are gastrointestinal lipid absorption and the trafficking of immune cells.[33]

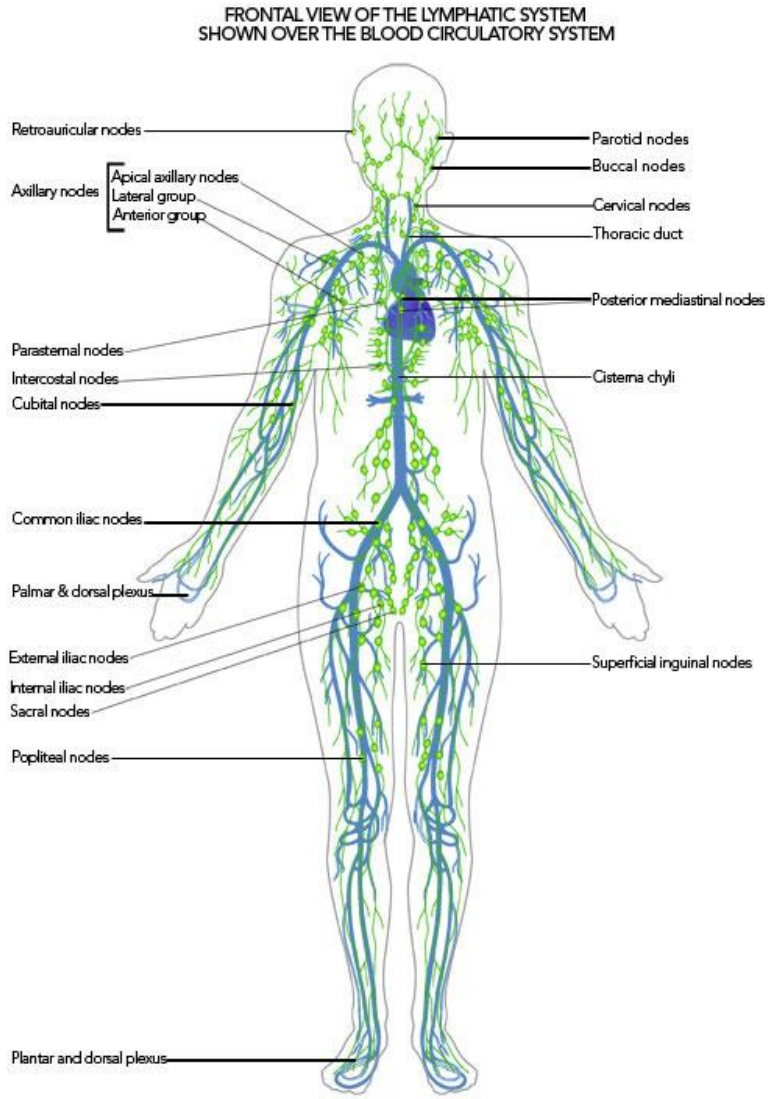


Figure 5. *The human lymphatic system (illustration with permission of the author reprinted from web page[34])*

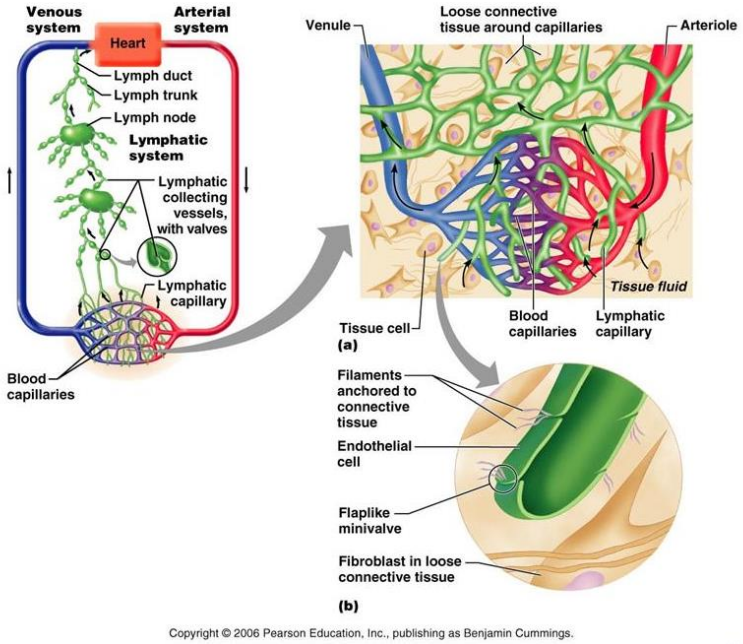


Figure 6. *Inter-relationship between the lymphatic system and blood circulatory system ©2019. Reprinted by permission of Pearson Education, Inc., New York[35]*

The drainage of the upper limbs comprises two components: a superficial lymphatic drainage and a less important deep lymphatic drainage. However, both systems anastomose and most of the upper limb lymph has a common destination: the axillary lymph nodes[32], after which it is further conducted towards the venous blood system nearby the heart.

After absorption of interstitial fluid by initial lymphatics, lymph is transported through progressively larger and structurally more complex vessels until its final destination to the venous blood system.[32] Along the way are lymph nodes located, responsible for filtering the lymph. According to Kubik, the lymphatic system can be classified (with a crescent order of size and complexity) in lymphatic capillaries (absorption of fluid and macromolecules), precollectors, collectors and trunks[32 ,36] (Figure 7).

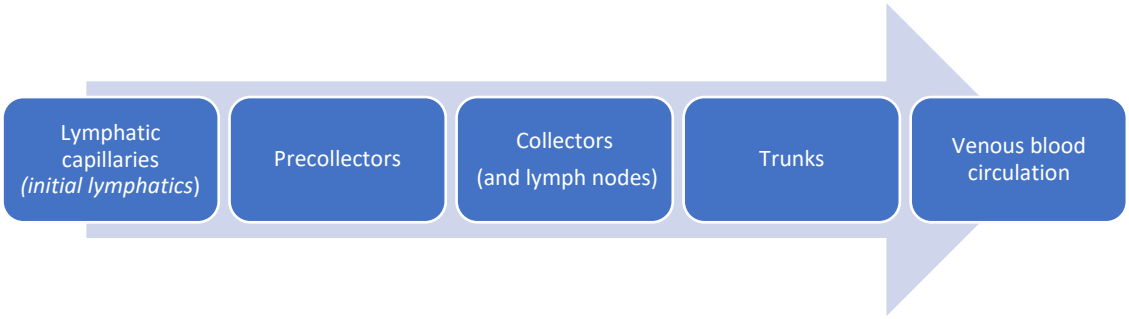


Figure 7. *Schematic visualization of the lymph flow in crescent order towards the heart*

Lymphatic capillaries are called 'initial lymphatics'.[32] They are structurally different from blood capillaries as they are larger and their endothelial junctions are more permeable, enabling them to absorb macromolecules and fluids from the interstitium.[29 ,36] Anchoring filaments provide a structural support network that connect the endothelium of the **lymphatic capillary** vessel with surrounding connective tissues[29 ,36] (Figure 6). This supporting network enables lymphatic vessels to remain open even under high interstitial tissue pressures.[29 ,36] As the anchoring filaments stretch, they open the lymphatic endothelial junctions, thereby allowing the interstitial fluid (which is fluid that entered the interstitium due to capillary leakage from the arteriovenous circulation) to enter the lower pressure lumen of the lymphatic vessels and subsequently into larger precollectors.[29 ,36] Once the fluid is caught in the lymphatic system and has passed a lymphatic valve, it is called lymphatic fluid.[36] Lymph primarily consists of water, proteins, fatty acids, salts, white blood cells, micro-organisms and foreign debris.[36]

Precollectors connect the lymph capillaries with the collectors, and unlike the capillaries, some of the precollectors contain valves.[29 ,36]

Collectors have valves and contain contractile smooth muscle cells to actively promote unidirectional flow towards the lymph nodes and lymphatic trunks[29,36,37]:

- The *superficial* lymphatic drainage system of the arm has 10 bundles (comprising one to many lymph collectors each): 6 proximal bundles in the arm (3 anterior: cephalic, basilic and prebicipital; and 3 posterior: posteromedial, posterolateral and posterior) and 4 distal bundles in the forearm and hand (2 anterior: anterior radial and anterior ulnar; and 2 posterior: posterior radial and posterior ulnar), according to their drainage area[32] (Figure 8).

  Superficial lymph nodes are located in the arm and in the deltopectoral sulcus, called deltoideopectoral lymph nodes.[32]
- The *deep* lymphatic drainage system of the arm has 6 bundles (2 proximal in the arm and 4 distal) of which the proximal are denominated (deep) brachial due to their anatomical relation with the homonymous arteries[32] (Figure 8). Deep lymph nodes are situated in the arm and forearm, close to vessels.[32] Lymph nodes in the axilla are organized as chains and receive lymph from the upper limb, supra-umbilical area up to the clavicle, and dorsal region.[32,36]

(a) (b)

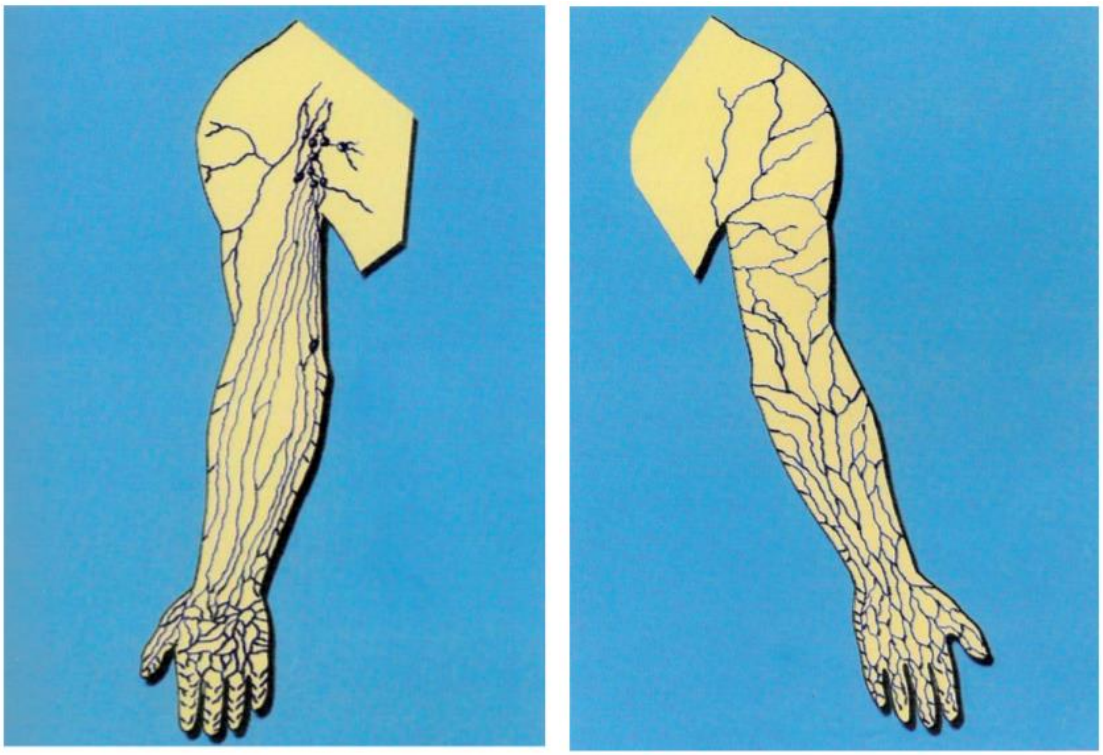


Figure 8. *The anterior (a) and posterior (b) view of the upper limb: Distribution of the superficial bundles of the forearm and arm including cubital and axillary lymph nodes (illustrations with permission reprinted[32])*

The major **lymphatic trunks** drain the lymph directly into the venous system: the jugular trunk (draining the head and neck), subclavian trunk (draining the upper extremities, chest wall, upper back, shoulders and breasts), and bronchomediastinal trunks enter the thoracic duct ipsilaterally[29,36] (Figure 9). This **thoracic duct** is the largest lymphatic trunk, which is responsible for emptying approximately 3 liters of lymph per day into the left **venous angle.**[29,36] The bilateral lower quadrants of the body also drain in the left venous angle via the thoracic duct, whereas the right upper quadrant of the body drains into the right venous angle via the right lymphatic duct (formed by the right jugular, supraclavicular, subclavian, and parasternal trunks).[29,36]

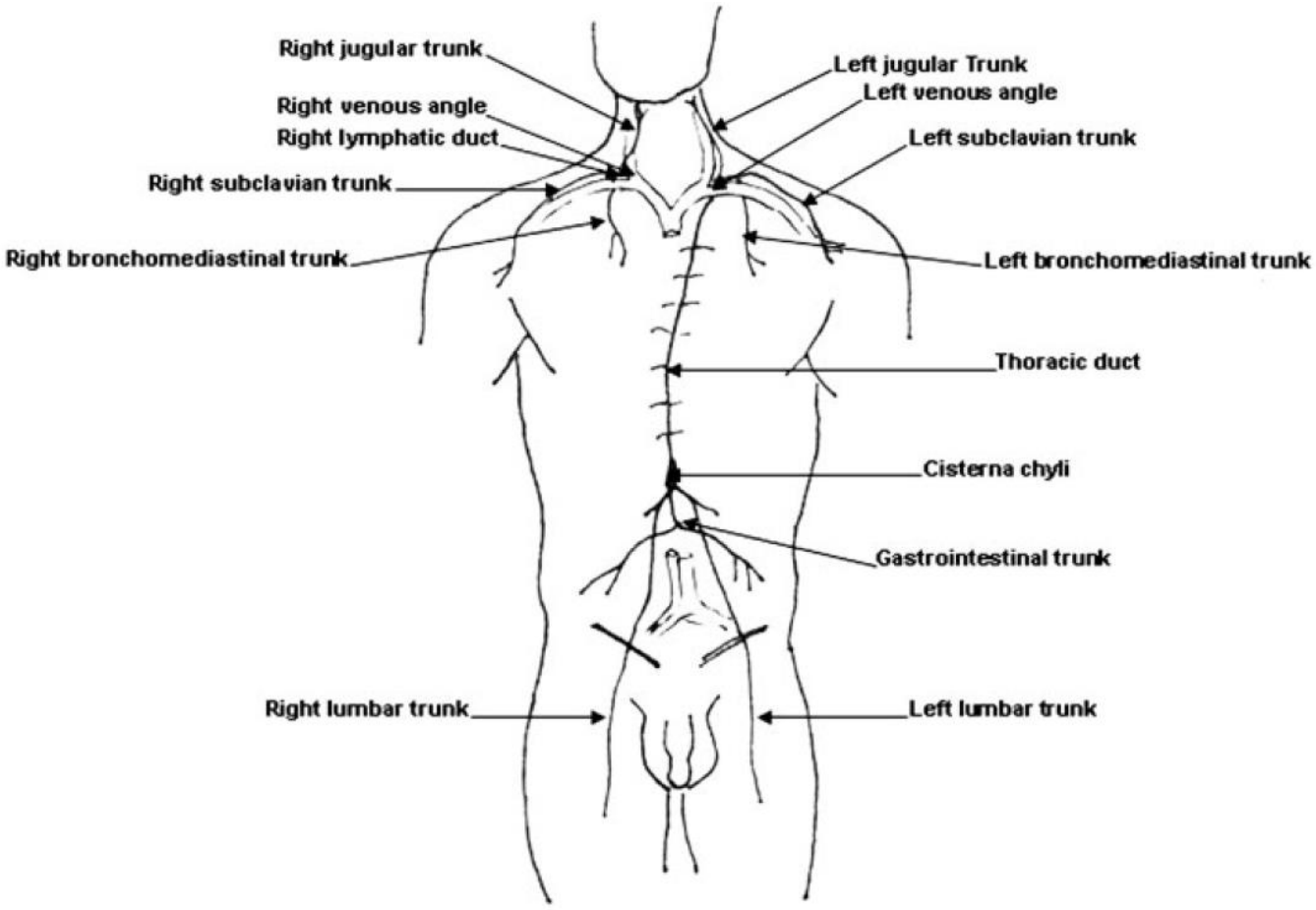


Figure 9. *Visualization of lymphatic trunks (illustration reprinted from: Lymphedema: A Primer on the Identification and Management of a Chronic Condition in Oncologic Treatment[29])*

Lymph nodes consist in an agglomerate of lymphoid tissue surrounded by a capsule of dense connective tissue and some smooth muscle fibers.[32] Their inner structure is formed by trabeculae, extensions of the inner aspect of the capsule that limit lymph follicles[32] (Figure 10). After reaching the lymph node, lymph flows through its subcapsular space and is filtered in the network formed by the trabecular and medullar sinuses.[32] The total number of lymph nodes in humans is estimated to be around 600–700.[36] The shape of the lymph nodes is usually spherical or round and can vary considerably in size. Structurally, they have a small depression called the hilus and an opposite convex surface. Efferent lymph vessels and nodal arteries and veins are found in the hilus whereas afferent lymph vessels reach the lymph node in many points along its convex surface.

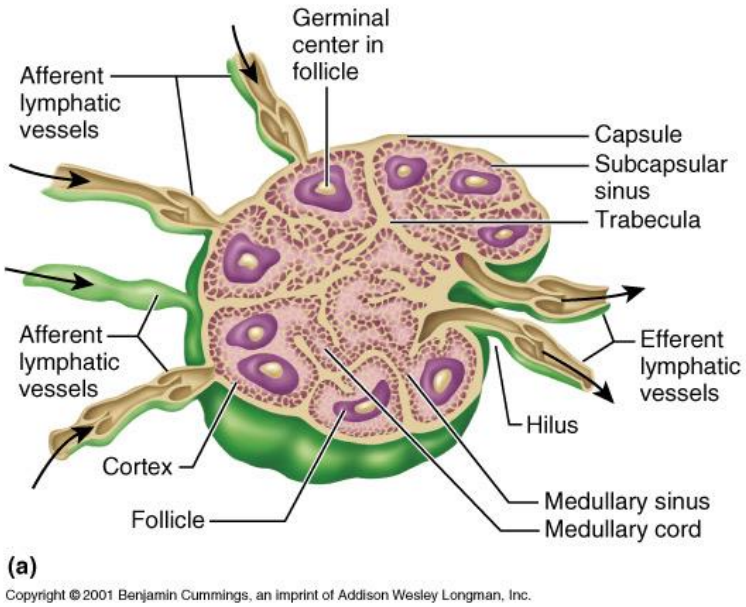


Figure 10. *The inner structure of a lymph node ©2001. Reprinted by permission of Pearson Education, Inc., New York[38]*

The ability of lymphatics to transport the lymphatic fluids, is depending on the lymphatic load (i.e. the volume of lymph fluid) and transport capacity (i.e. the maximum amount of lymph fluid that can be transported during a given period of time).[36] An imbalance between load and capacity will result in edema. In case the lymphatic load surpasses the transport capacity of an intact and functional lymphatic system, '**dynamic insufficiency or high-output failure'** occurs.[36] Reasons for an increase in lymphatic load could be an increased oncotic/venous pressure or capillary permeability. On the other hand, functional or anatomic abnormality in the lymphatic system (e.g. after a trauma/ surgery, or in case of a congenitally less developed lymphatic system) can result in a reduced transport capacity for the normal lymphatic load and is called '**mechanical insufficiency or low-output failure**'.[36] The last

mentioned is considered as the most common etiology for breast cancer-related lymphedema (BCRL), whether or not combined with an increased load on the lymphatic system.

2.2 Etiology and stages of lymphedema

Generally, lymphedema can be classified into two types: primary and secondary lymphedema. Primary (or hereditary) lymphedema develops as a consequence of a pathologic and/or hereditary etiology.[29,36] Secondary (or acquired) lymphedema is caused by mechanical insufficiency due to surgery, radiation, trauma, infection, tumoral blockage, chronic venous insufficiency or immobility.[29,36]

Lymphedema is a chronic condition, as it cannot be cured due to the permanent damage or absence of certain lymphatic components. A subclinical phase of lymphedema may exist after surgery or radiotherapy, and will be clinically noticed once the lymphatic load exceeds the reduced lymphatic transport capacity.[29] Lymphedema can occur in different stages and without proper treatment, it might aggravate from one stage to another. There are several staging systems for classifying the severity of lymphedema, including the staging system devised by the International Society of Lymphology (ISL).[39]

Stage 0 (Ia)	A latent of sub-clinical condition where swelling is not yet evident despite impaired lymphatic transport, subtle changes in tissue fluid, and changes in subjective symptoms.
Stage I	Early accumulation of fluid relatively high in protein content which subsides with limb elevation. Pitting may occur.
Stage II (a, b)	IIa. Pitting is manifest and limb elevation alone rarely reduces tissue swelling. IIb. In a late phase, pitting may or may not be present as fat tissue and fibrosis supervenes.
Stage III	Lymphostatic elephantiasis were pitting can be absent and trophic skin changes can occur and further deposition of fat and fibrosis have developed.

2.3 Lymphedema as a consequence of breast cancer treatment

In developed countries, the most common causes of secondary lymphedema are surgery and irradiation[40] due to damage to the lymphatics, wherein BC treatment is most referred to. However, lymphedema can also result from treatment for cervical, endometrial, prostate, vulvar and head or

neck cancers, as well as sarcomas and melanomas.[29] Once the lymphatic system has been damaged, the transport capacity is permanently diminished in that region, thereby predisposing that area to lymphedema.[29]

Regarding the development of BCRL, most important risk factors include the extent of the ALND[41-44], mastectomy[41 ,43 ,44], presence[41] and number of positive axillary lymph nodes[43 ,44], (supraclavicular lymph node) radiotherapy[42-44], increased body mass index and post-operative weight gain[42-44] and (taxane-based) chemotherapy.[42 ,44 ,45] Establishment of these risk factors has encouraged clinicians and researchers in their search for de-escalating cancer therapy in order to reduce treatment-related morbidity without oncological compromises. In addition, a better understanding of patients who are at risk for developing BCRL, and enhanced awareness to recognize (and treat/monitor) early signs and symptoms[46] has occurred.

Previous research has shown that in established BCRL, radiocontrast lymphangiography demonstrated dilated and tortuous lymph vessels, dermal backflow of the lymph and extravasation of contrast fluid.[47 ,48] These alterations were attributed to axillary obstruction (due to local surgery and/or radiotherapy) because the epifascial vessels (draining the skin and subcutis) mainly drain to the axilla (although some of them also anastomose with a scapular collateral pathway[49]) and the subfascial vessels (draining the muscles) exclusively drain to the axilla.[48] More recent insights suggest that it is likely that women who progress to BCRL have a greater capillary filtration rate that overwhelms vulnerable lymphatics.[48] As a consequence, it is proposed that the first abnormality in the pathogenesis of BCRL is not the lymphatic obstruction, but high fluid filtration into both arms in a subgroup of women with subsequently, due to the chronically elevated lymph load, lymphatic failure and the development of edema in the ipsilateral arm.[48] However, for areas such as anatomic and genetic predisposition for BCRL, research towards potential risk factors is still evolving.[46] Stanton highlighted in his studies that there are two types of women with BCRL: those with hand edema and those without.[46 ,50] Results from their studies suggested that hand edema might result from failure of peripheral lymphatics in the wrist and forearm, rather than as a result of axillary intervention.[46 ,50] Nevertheless, an early detection and treatment of lymphedema is crucial as it can both reduce lymphatic swelling and maintain the reduced arm volume over time.[51 ,52] To date, there is no evidence that genetic alterations in primary breast tumors are directly linked to BCRL pathogenesis either.[53] However, the association between somatic mutations and higher rates of nodal involvement could indirectly involve more aggressive therapeutic schemes, such as ALND and axillary irradiation, increasing the risk of developing BCRL.[53]

Patients having undergone locoregional treatment for BC are not only at risk for developing lymphedema at level of the **arm/hand**, but also for edema at the ipsilateral quadrant including the

breast[54] and **trunk**[55] (or posterior axillary fold), owing to the shared lymph drainage route in the axilla.

3. Evaluation of breast cancer-related lymphedema

In patients with a suspicion of lymphedema, a thorough causal examination is required to exclude any other reasons of swelling.[56] Additionally, an accurate diagnosis of lymphedema is crucial for an appropriate therapy plan. It is recommended that, in case there is a volume difference or change of >5% to 10%[28,57] of the arm compared to the non-affected arm or preoperative volumetric values, appropriate treatment should start.[58] When swelling presents in areas where volumetric measurements are not possible (e.g. in case of breast or trunk lymphedema), alternative assessment methods should be used.[58]

Once lymphedema has been diagnosed, the procedure to intermediately **evaluate treatment effects** starts with a (basic) patient interview and should be accompanied with a physical and psychosocial assessment. If necessary, it can be complemented by lymphofluoroscopy (also called near infrared fluorescent lymphatic imaging) to evaluate changes in the superficial lymphatic architecture and function over time.

3.1 Physical and psychosocial assessment

Different characteristics of the lymphedema and edematous limb can be evaluated, such as arm size (arm volume), amount of extracellular fluid, water content in the skin, and hardness and elasticity of the skin.

A plethora of different measurement methods determining **arm size** is available, such as several methods for water displacement[59,60], opto-electronic volumetry[61] and circumference measurements[62], which all have shown to be effective and valid, but are not interchangeable.[56] For evaluating swelling, the water displacement method and circumference measurements are the most frequently used volumetric methods[39] and are recommended as best practice for measuring lymphedema in extremities.[56] In general, water displacement by measuring the overflow of water is considered as the gold standard.[39,60] Circumference measurements can be performed by tape, or by using a perimeter. This is a special designed, reliable and accurate device which consists of a steel bar with tape fixed at every four centimeters and a 20 gram weight at the end of each tapeline.[62] Afterwards, based on circumference measurements of the arm, the total arm volume can be calculated by using geometric formulas, such as the truncated cone formula.[63]

Opto-electronic volumetry, or perometry, is another valid evaluation method that has proven to be accurate and reproducible, using an optical-electronic infrared device to detect volume differences.[61] In daily practice, evaluation of lymphedema volume is mostly performed at the moment of diagnosis, after an intensive treatment phase, and during follow-up.[31] In case preoperative measurements are lacking, prediction formulas can be applied to calculate the normal volume of the edematous arm/hand.[44 ,60 ,64] It is important to determine the volume of both arms and consequently the excessive arm volume, in order to adjust for changes in muscle size and subcutaneous fat.[44]

The amount of (and change in) **extracellular fluid** can be assessed with Bio Impedance Spectroscopy (BIS). In this technique, not only the amount of total body water, but also the differentiation between the extracellular and intracellular water extent is measured in terms of resistance to the flow of an electric current through the body or a body part.[65]
To evaluate the **water content** in the skin, the MoistureMeterD® Compact (MMDC) device can be applied to measure the percentage of water under the skin in terms of the Tissue Dielectric Constant value, making use of a probe with 300 MHz signal.[66] Also the pitting test can be applied to assess local tissue water in the skin by firmly pressing on the area of interest and evaluating the skin indentation that remains afterwards.[67]
Fibrotic alterations in **skin elasticity** and accumulation of adipose/fibrotic tissue can be assessed with tonometry or by using a SkinFibrometer® device. This is a relatively recently developed device which consists of a 1-mm-long intender and records the resistance to 50 gram of pressure by using its reference plate and related built-in force sensors. The resistance from the skin to deformation when an external force is applied, is expressed in Newton (N) and represents the induration of the skin.[68] Also, both the presence of fibrosis or hardness and of increased skin fold thickness can be evaluated manually by palpation.

Additionally, lymphedema does not only induce physical and functional impairments such as swelling, or heaviness, but also **psychosocial problems**.[69] Given the large role on subjective complaints in lymphedema, paying attention to only physical edema characteristics such as swelling is not enough to outline a holistic, patient-centered follow-up with tailored treatment and support.[58] To investigate the impact of lymphedema on a person's quality of life, or to monitor long-term treatment effects on functioning, activities and participation problems, valid and reliable health-related quality of life questionnaires (such as the McGill Quality of Life questionnaire[70]) and/or lymphedema-specific questionnaires (such as the Lymphedema Functioning, Disability and Health questionnaire for Upper limb Lymphedema (Lymph-ICF-UL)[71]) should be used.[31]

3.2 Near infrared fluorescent lymphatic imaging or lymphofluoroscopy

Lymphoscintigraphy is currently reported as the golden standard for the diagnosis of lymphedema.[39] However, due to its time-invasive character and ionizing effects, it is not desirable for repeated use over time at follow-up evaluations. Nevertheless, recent advances in imaging techniques have led to new and even improved approaches for evaluating the (superficial) lymphatic system.[72] This newer technique is called near infrared fluorescent imaging or lymphofluoroscopy and is increasingly being used over the past years.

3.2.1 Lymphoscintigraphy versus lymphofluoroscopy

More than 200 years ago, researchers started their quest for an appropriate and useful contrast agent that could be used for imaging the lymphatic network. Developed in the 1950's, lymphoscintigraphy became the ultimate technique showing not only the topography of lymphatics, but also their (patho)physiology.[73] In this technique, a radio-tracer such as Tc99 agglutinated to human albumin, is injected intradermally or in the subcutaneous (epifascial) space, where it binds to plasma proteins in lymph. Because of its molecular weight, it is mainly transported through the lymphatic network.[74] Lymphoscintigraphy has also been used (both quantitatively and qualitatively) in the assessment of therapeutic interventions for lymphedema.[75] However, some drawbacks concerning this technique are reported, impeding repeatedly use of this technique over time for evaluating treatment effects: It entails some ionizing effects, radio-colloids are expensive and the examination requires the competence of a nuclear physician (who needs to obey the legislation on nuclear substances).[74] Furthermore, the tracer moves relatively slowly, hence it may not reach the regional lymph nodes during the limited scanning period.[76] Also it produces low resolution imaging without anatomical landmarks, hampering mapping of the exact anatomical position of lymphatics unless a SPECT scan is also used.[76] Since a few decades ago, a new fluorescent-based tracer "Indocyanine green" (ICG) has been applied, allowing to visualize the superficial lymphatic system under microscope without the use of radio-isotopes. At first it was introduced into diagnostic medicine for cardiac output measures, liver functioning, and ophthalmic angiography.[77] After its use for detecting sentinel lymph nodes in BC patients was successfully explored[78], the implementation of ICG as a lymphatic imaging technique was a fact.[77] A new and less expensive technique, rapid binding to protein, with very high sensitive fluorescence properties and low toxicity[77] was arisen for examining and evaluating the superficial lymphatic network and its (patho)physiology.

3.2.2 Principles of lymphofluoroscopy

A lymphofluoroscopic investigation of the arm starts when ICG is injected intradermally in the first and fourth web space of the hand, thereby temporarily creating high pressure in the interstitial space.[77]

ICG emits fluorescence in the near-infrared spectrum (785 nm) and the signal is acquired by a camera with a Photo Dynamic Eye (PDE) system to visualize the superficial lymphatic system from a distance of ± 15 cm (Figure 11). As soon as ICG is being injected, it binds to local free albumin, subsequently resorbed and transported exclusively by lymphatics.[79] Up to a depth of ± 2 cm underneath the skin surface, the progression of the ICG uptake and transport through the superficial lymphatic network, can be observed.

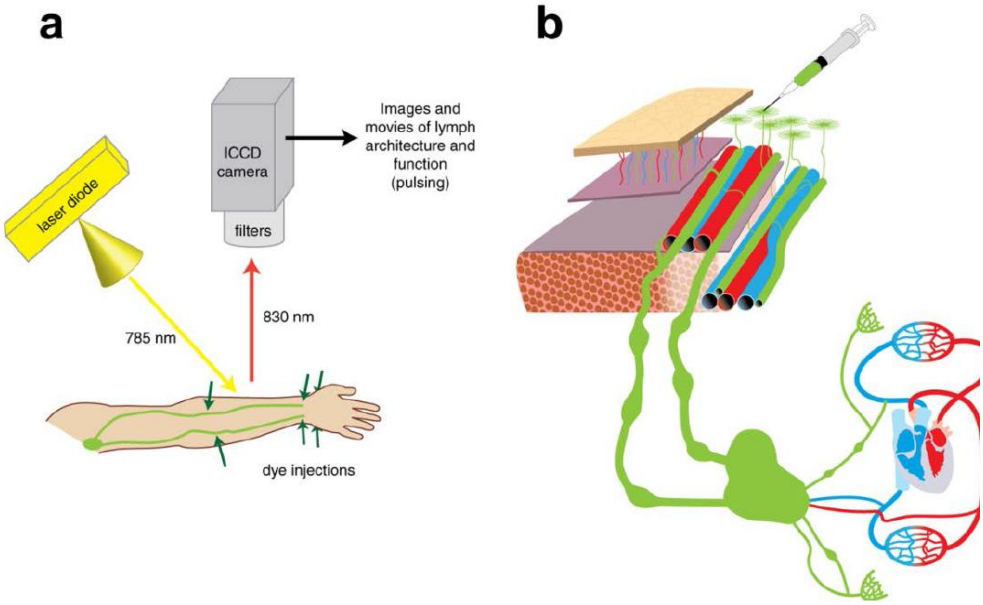


Figure 11. *(a) Presentation of the system used for near infrared lymphatic mapping. (b) ICG is injected intradermally, absorbed by dermal lymphatic capillaries, and transported to lymphatic precollectors and collector vessels. (Illustration adapted from: Lymphatic abnormalities in the normal contralateral arms of subjects with breast cancer-related lymphedema as assessed by near-infrared fluorescent imaging[80])*

3.2.3 Pathophysiology of the lymphatic system

There are numerous superficial lymph collectors running parallel to the skin surface. They drain the precollectors coming from the initial lymph capillaries and are organized like links in a chain (see figure 12[81] and section *2.1. "Anatomy and physiopathology of lymphatics"* – p.14). In normal conditions, the initial or primary lymphatic network is not visible on lymphofluoroscopy. In case of lymphatic impairment, dermal rerouting or dermal backflow can occur. In case of dermal rerouting/ backflow, the lymphatics are trying to find alternative pathways to access the deeper lymphatics, due to the obstruction in upstream lymphatic vasculature. Dermal rerouting or dermal backflow patterns can be subdivided into three categories: splash, stardust and diffuse, consecutively representing the progression of lymphedema[82] (Figure 13). Splash represents lymph that is rerouting towards the initial lymphatic capillaries, enlarging the vessels.[81] In stardust there is a lymphatic reflux, which leads to lymph accumulation in the precollectors, or leakage out of the lymphatic collector valves, with fluid

located in the interstitium.[81] In a diffuse pattern, the lymph is widely distributed along the interstitium. Consequently, findings on a lymphofluoroscopy alter from a linear (or normal) pattern to a diffuse pattern as the severity of lymphedema increases.[82]

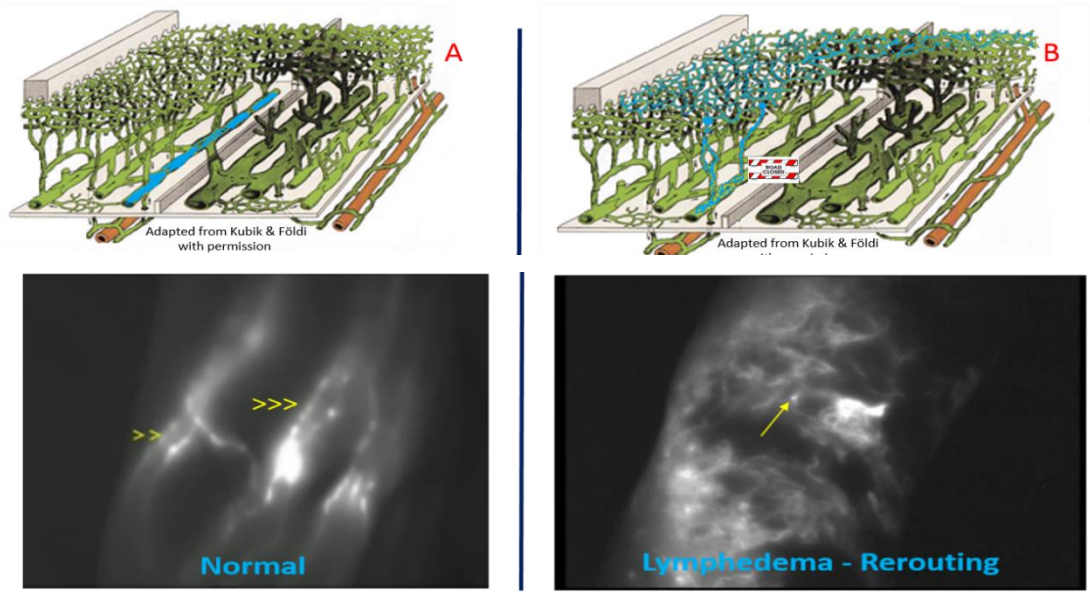


Figure 12. *Fluoroscopic image of the superficial lymphatic network and its schematic architecture. (A) represents a normal condition, in which the lymph fluid is being transported by the superficial lymph collectors. (B) represents an edematous condition, in which the lymph is rerouted through the lymph capillary network. (Illustrations adapted from: Near Infrared Fluorescence Lymphatic Imaging to Reconsider Occlusion Pressure of Superficial Lymphatic Collectors in Upper Extremities of Healthy Volunteers[81])*

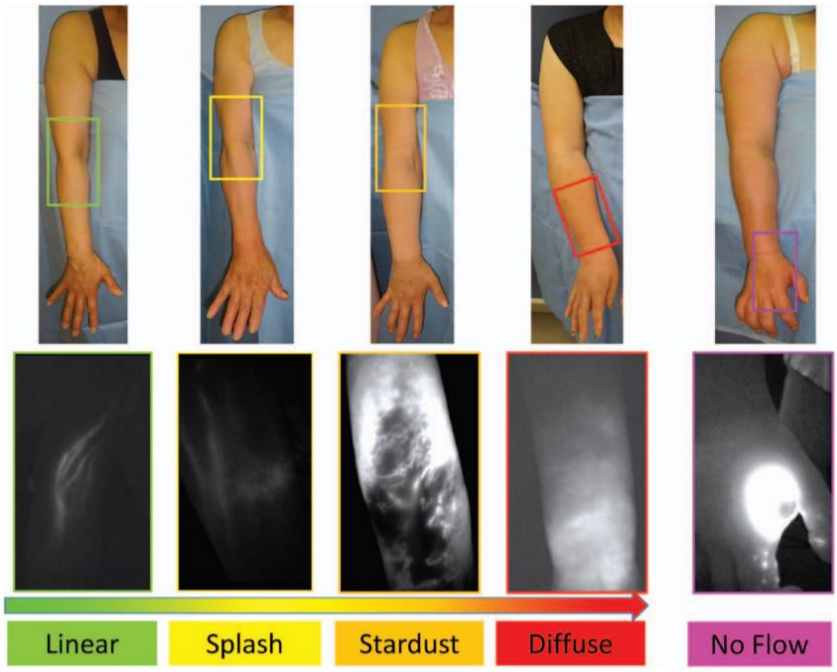


Figure 13. *Fluoroscopic images of a normal pattern, linear pattern, three dermal backflow patters (i.e. splash, stardust, diffuse) and no flow. (Illustration adapted from: Early Detection of Lymphatic Disorder and Treatment for Lymphedema following Breast Cancer[83])*

4. Treatment modalities for breast cancer-related lymphedema

Treatment modalities for BCRL comprise conservative (non-operative) and non-conservative (operative) treatment methods. As chapters 2, 8 and 9 of this doctoral thesis investigate the effectiveness and economic burden related to the conservative treatment of BCRL, the next sections will focus on the non-operative treatment modalities.

4.1 Conservative treatment

According to the recommendations of the International Society of Lymphology, lymphedema needs to be treated with decongestive lymphatic therapy (DLT) (also known as complex decongestive therapy or combined/ complete decongestive therapy).[39] This golden standard consists of a two-stage treatment program. During the first or intensive phase, lymphedema is maximally reduced. This phase consists of skin care and education, manual lymphatic therapy (MLD), multi-layer bandaging and exercise therapy. The second or maintenance phase aims to preserve and optimize the obtained results from the first phase. It consists of skin care, compression by a low-stretch compression sleeve, exercises and MLD (Figure 14).

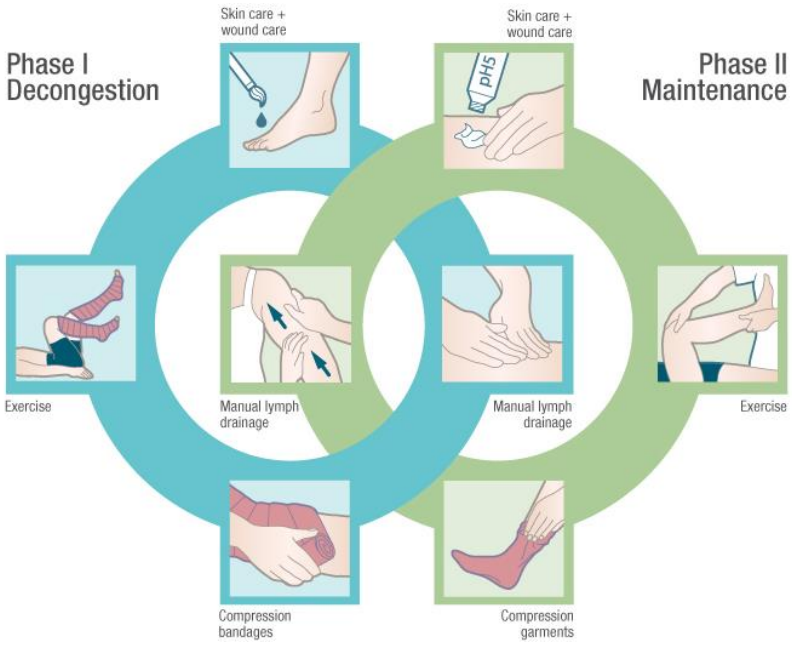


Figure 14. *Decongestive lymphatic therapy (DLT) consisting of two phases, including multiple treatment modalities: skin care, manual lymph drainage (MLD), compression therapy and exercises (illustration adopted from web page[84])*

The intensive treatment phase generally lasts 2 to 4 weeks. During this time, the patient ideally receives daily treatment for approximately 1 hour, preferably 5 times a week. Circumference measurements should be performed on a daily basis to determine whether the edema has been reduced or a plateau has been reached.[39] During this phase, treatment adherence to all the different treatment modalities is very important (although the additional value of MLD is controversial, see section 5 *"Unravelling the role of MLD: is an alternative approach warranted?"* – p. 32). In addition, wearing the compression bandages for 24 hours per day is important.[58] Once the edema volume has reached a plateau and maximal benefit has been achieved, phase 2, or the maintenance phase, starts. This phase consists of life-long self-care in order to control the size of the limb. Therefore, adherence is essential to maintain the results achieved during the treatment phase.[29] DLT has shown to be an effective treatment for reducing lymphedema volume.[85 ,86]

The different treatment modalities that are involved in the DLT are outlined below, ensued by a brief presentation of other (additional) conservative treatment options.

a. Skin care and education

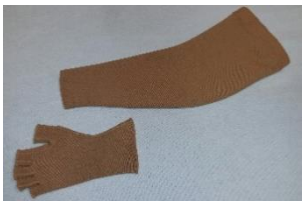
Skin and nail care consists of inspection of the limb to examine whether there are cuts or wounds, scratches, areas with irritation or signs of infection.[31] If these are present, wounds or scratches should be properly disinfected and infection should be combated with antibiotics. Furthermore, it is important to apply a pH-balanced moisturizer to the limb before application of the bandages. The patient is also educated about this skin and nail care during the intensive phase, in order to be able to continue this handling during the maintenance phase.[58] Randomized controlled trials (RCT's) investigating the effect of skin care in patients with BCRL are lacking.

b. Manual lymph drainage (MLD)

MLD is a manual technique to stimulate the smooth muscle sheath of superficial lymph vessels and thereby enhancing their pumping rate.[29] MLD aims to move excessive fluid from congested areas by: 1) increasing the activity of normal lymphatics, and 2) bypassing ineffective or damaged lymphatic vessels.[31] Literature shows a lot of controversy about the required application force for this drainage, as well as the effectiveness of this technique in general. For a long time it was told that a light application of pressure is needed to the location of the superficial lymphatic

vessels just below the skin. If the pressure is too high (i.e. higher than 40 mmHg), it could result in a spasm of the smooth muscle sheath of the superficial lymphatic vessels, or it could lead to damage of the thin anchoring filaments.[87 ,88] However, recent research revealed that the mean lymphatic occlusion pressure in the upper limb of 30 healthy volunteers, was 86 mmHg.[81] Generally, MLD is performed for 30 to 60 minutes, and is not only applied on the affected limb but also includes drainage of other body parts such as lymph node stations in adjacent areas. The aim of this technique is to improve the lymphatic flow, and in order to do so, the direction of MLD is always distal to proximal. The sequence and type of manual techniques should be determined for each patient separately, depending on certain aspects such as the area and stage of the lymphedema presented.[29]

c. Compression therapy



During the intensive treatment phase, compression bandaging is applied to the limb after performing MLD.[39] This is a multilayer, short-stretch bandage comprising of padding materials that should be worn 24h per day.[29] Inelastic bandages are preferred, since they have a low extensibility and produce high working pressures.[58] This stimulates the superficial lymphatics during movements via the muscle-joint pump. Additionally, these bandages show low resting pressures which increases the comfort for the patients.[31] Compression garments can be used as initial treatment in patients who have mild upper limb lymphedema (stage I) with minimal subcutaneous tissue changes.[31] However, when there is evidence of soft pitting edema, inelastic bandaging will be required to reduce and stabilize the swelling prior to the application of compression garments in the maintenance phase.[31] Once the volume reduction is stabilized, the intensive treatment phase can be continued with the maintenance phase and consequently, a custom-made flat knit (for preference) compression sleeve and/or gauntlet is fabricated.[58] This needs to be worn daily during the awake (and active) hours as it proved to prevent additional swelling.[89]

d. Exercises

Traditionally, patients with lymphedema have been recommended not to perform repetitive exercises, however, the consensus throughout numerous recent studies indicates that various types of exercise involving the affected extremity are not associated with exacerbation of lymphedema.[90] In addition, research showed that active exercises reduce lymphedema volume in BCRL.[89] Conventionally, it is advised that exercises need to be performed with the compression bandages (during the intensive treatment phase) and compression garment (during the maintenance treatment phase) worn, to facilitate the muscle-joint pump.[29] It is important that exercises (mobilizing exercises, circulation exercises, and stretching techniques) are being performed at regular time intervals during the day to stimulate this pumping mechanism. Additionally, associated diaphragmatic breathing during exercises can enhance the lymphatic pumping rate.[91]

e. Other treatment modalities

Additional conservative treatment modalities are available and may be applied as an adjunct to DLT.

<u>Intermittent pneumatic compression (IPC)</u>

IPC is a device that consists of an electrical air compression pump, attached to an inflatable plastic garment that is being placed over the affected limb.[31] The garment is inflated and deflated cyclically for a preset period of time and the produced pressure can vary.[31] IPC is thought to reduce edema by decreasing capillary filtration, rather than accelerating lymph return.[31] Although a systematic review and meta-analysis indicated no significant differences in the percentage of volume reduction and subjective symptoms (heaviness, pain, paresthesia, or tension) between patients receiving DLT with or without additional IPC[92], IPC as an adjunct to DLT seems to be beneficial in helping to reduce the edema volume during the intensive treatment phase.[89]

<u>Kinesio taping</u>

Lymphedema taping involves the application of elastic tape to the edematous or affected area, and can be used in combination with bandaging or compression garments.[31] By lifting the skin, it causes subcutaneous pressure fluctuations improving the lymph flow. However, convincing high-quality evidence regarding its effectiveness in reducing lymphedema volume, is lacking.

Laser therapy

Low level laser therapy has shown some potential for the treatment of lymphedema. For the upper limb in particular, it showed to provide reduction of limb volume and tissue hardness.[93] However, further research is warranted to investigate the optimal regimen.[31]

Drug therapy

In literature, two main types of drugs are described as a treatment for lymphedema: benzopyrones and diuretics.[31] Benzopyrones are based on a variety of naturally occurring substances (e.g. flavonoids and coumarin). There is some evidence that flavonoids may stabilize swelling by reducing the microvascular filtration, however little data is available to support the use of these drugs as a treatment modality.[31 ,94] Diuretics enhance the excretion of salt and water, thereby reducing the blood volume. Although diuretics are not standardly recommended for treatment of lymphedema, some patients might benefit from (short use) diuretics, depending on the etiology of the edema (i.e. in combination with congestive heart failure or high blood pressure).[31]

4.2 Non-conservative treatment

Surgery

There are three main categories in surgical procedures to treat lymphedema: lymphatic bypassing procedures (lymphovenous shunts and lymph node transplantations), liposuction, and surgical reduction.[31]

In lymphatic bypass operations, the aim is to restore the lymphatic function by creating lymphovenous anastomoses, lymphatic or venous vessel grafting, or by lymphatic lymph node transplantations.[95] However, convincing and supporting evidence-based results from prospective, randomized and controlled studies with long-term follow-up are currently missing.

Liposuction is a surgical technique removing excessive fat tissue that can be applied in patients with non-pitting, primarily non-fibrotic BCRL not responding to conservative treatment.[31] After surgery, long-term postsurgical compression therapy is required to maintain any improvement resulting from the procedure.[31] This can give rise to questions whether the described beneficial (short-term) effects are actually related to surgery, rather than to the intense conservative 'post-surgery' edema management.

In surgical reduction or debulking, excessive subcutaneous tissue and skin are removed. This procedure may be useful as a symptomatic treatment of severe (fibro sclerotic) lymphedema.[31]

An adequate patient-tailored treatment of the edema needs to be determined based on the location, stage, severity and complexity of the edema, according to the patient's psychosocial situation.[31]

5. Unravelling the role of manual lymph drainage: is an alternative approach warranted?

Although MLD is being performed since several decades, research data conclusively supporting its use, is lacking.[96-99] Nevertheless, almost all lymphedema patients in Belgium receive MLD as part of the physical treatment, which is time-consuming and entails a big financial cost for the patient as for the Health Care system.[100] As previously mentioned, the effectiveness of MLD in DLT is still controversial due to the lack of consistent and convincing results in literature.[58] A meta-analysis, including 6 RCT's, and a Cochrane systematic review have questioned the effectiveness of MLD.[52 ,101] The meta-analysis showed an overall additional benefit of MLD to the treatment of BCRL of 75ml on volume reduction, while the systematic review revealed that the individual contribution of MLD was limited to 7%.[52 ,101] Additionally, three RCT's were unable to demonstrate a surplus effect of MLD to DLT.[102-104]

A *first possible explanation* why MLD, according to the method applied in previous studies, has a rather small benefit (in addition to the other parts of DLT), might be that MLD is being applied in an inefficient or 'blind' way, and moreover, according to a 'normal' anatomy of the superficial lymphatic system. This method of MLD is further called 'traditional MLD'. However, after dissection of the axillary lymph nodes, whether or not combined with radiotherapy, the lymphatic system of the upper limb is damaged. Lymph nodes are removed, often resulting in fibrosis of the superficial lymphatic system.[105] As a consequence, dermal backflow can occur[106] and has been described in patients with lymphedema.[107 ,108] This rerouting is patient-specific (see section 3.2.3. *"Pathophysiology of the lymphatic system*" - p. 25). Therefore, it is proposed that the traditional MLD needs to be improved and a tailored approach needs to be established, as this might be more beneficial. By visualizing the superficial transport of lymph from the hand up to the axilla and thereby unravelling patient-specific alternative pathways towards other lymph nodes, near infrared fluorescence imaging or lymphofluoroscopy can contribute to a more efficient MLD (= fluoroscopy-guided MLD).[73 ,109]

A *second possible explanation* why traditional MLD has not proven to be effective, might be that, currently, the therapist does not optimally stimulate lymphatic transport. For that reason, in the fluoroscopy-guided MLD technique, hand maneuvers are tailored as well. Gliding techniques at higher pressure are performed instead of lower-pressure pumping techniques. Gliding (compared to no gliding) is hypothesized to be more effective to enhance lymphatic transport.[81] Additionally, the resorption of lymph capillaries has to be facilitated with the thumb (instead of with the hand in the traditional MLD, which gives a lower pressure).

A positive, short-term, physiological effect of one session of fluoroscopy-guided MLD has already been demonstrated in healthy volunteers as well as in patients with BCRL.[81,110] Whether the application of different sessions of fluoroscopy-guided MLD has a clinical and long-lasting effect on the lymphedema, superior to the traditional MLD and/or to a placebo MLD, has yet to be established.

6. Objectives of the research

BCRL is a dreaded morbidity affecting about 17% of the patients being treated for BC. Post-treatment management of BCRL becomes more and more important since improved screening and treatment modalities for BC have led to increased survival rates. Therefore, patients are increasingly confronted with long-term side effects of the treatment, such as the presence of lymphedema. BCRL is not only associated with feelings of discomfort, heaviness and limitations in functioning and participation due to the swelling, but also with a negative effect on a person's quality of life and psychological distress such as feelings of anxiety and depression. In Belgium, almost all lymphedema patients receive MLD as part of the physical treatment, which can be time-consuming for patients and entails a big financial cost for the patient as for the Health Care system. However, convincing scientific evidence regarding the effectiveness this MLD, is lacking. As mentioned before (see section 5 *"Unravelling the role of MLD: is an alternative approach warranted?"* – p. 32), a first explanation for this rather small therapeutic benefit from MLD, might be found in an inefficient or 'blind' way of drainage, according to a normal lymphatic anatomy. Second, it is hypothesized that the therapist does not optimally stimulate lymphatic transport whilst performing MLD, since it is applied using relatively lower pressure pumping techniques.

Therefore, the main research aim of this PhD was to investigate in a multi-center RCT, the effectiveness of fluoroscopic-guided MLD, as part of the DLT to treat BCRL. This research aim was subdivided into two parts: the development of the protocol of this RCT (**Chapter I**), and reporting the actual study results and conclusions (**Chapter II**).

In addition to this RCT, five studies were performed regarding the evaluation of lymphedema. First of all, since an overview is lacking regarding the best method to evaluate excessive arm volume over time in patients with BCRL, a comparison between five different and commonly used volume measurements was made regarding reliability, time-efficiency and clinical feasibility (**Chapter III**). Additionally, since this information is missing in literature, reliability of the MoisturemeterD® Compact device and the pitting test were investigated, in order to evaluate local tissue water in the skin over time in patients with BCRL (**Chapter IV**).

These methods are all measurement tools used to objectively assess the amount and characteristics of the lymphedema. However, BCRL does not only affect patients physically, but also psychosocially. A decade ago, the Lymph-ICF questionnaire for Upper limb Lymphedema has been developed to assess problems in functioning, activity limitations and participation restrictions in patients with BCRL. This questionnaire showed to be valid and reliable, however: 1) the scoring system was a VAS scale instead of a numeric rating scale which is preferred by patients; 2) responsiveness has not yet been investigated; and 3) the questionnaire has not yet been translated and validated into French and therefore could not be applied in a clinical or scientific setting in which French-speaking patients were involved. As a result, the scoring system was adapted into a numeric rating scale and consequently, reliability and validity of the revised Lymph-ICF-UL questionnaire were investigated (**Chapter V**). Next, further scrutiny continued regarding the responsiveness of this questionnaire (**Chapter VI**). Additionally, a cross-cultural translation into French was achieved and validated (**Chapter VII**).

Lastly, to have an overview of the extent of the economic impact of BCRL and its sequelae, two additional studies were conducted. A systematic review was carried out on the amount of direct and indirect costs related to the treatment of BCRL (**Chapter VIII**). Due to an existing knowledge gap regarding the economic hardships associated with BCRL in Belgium, a longitudinal financial evaluation of direct costs spent on DLT in patients with BCRL, was executed (**Chapter IX**). Table 1 provides an overview of the different studies.

6.1 Aims

Research objectives of this doctoral project were:

1) To examine in patients with BCRL the additional effect of fluoroscopy-guided MLD vs. traditional MLD vs. placebo MLD to the other components of the DLT on different clinical outcomes. A multi-center, double-blind, placebo-controlled and standardized trial was performed, with the primary outcomes change in excessive arm volume at the level of the arm/hand and change in fluid accumulation at level of the shoulder/trunk, and secondary outcomes change in amount of problems in functioning and change in quality of life.
2) To compare five volumetric measurement methods in terms of reliability, time-efficiency, and clinical feasibility for assessing excessive arm volume in patients with BCRL: traditional volumetry with overflow, volumetry without overflow, inversed volumetry, opto-electronic volumetry and calculated volume based on circumferences.
3) To investigate and compare reliability of the MoistureMeterD® Compact device and the pitting test as clinical assessment tools for evaluating the water content and composition of edema, in patients BCRL.

4) To assess the clinimetric properties (validity, reliability and responsiveness) of the Dutch Lymph-ICF-UL questionnaire in patients with BCRL.
   Additionally, to translate the Dutch version of the Lymph-ICF-UL questionnaire into French, and to assess its clinimetric properties (validity and reliability) accordingly, in a cohort of French-speaking patients with BCRL.
5) To make a systematic review on the financial impact of BCRL treatment. Furthermore, to make a financial analysis of the direct costs related to BCRL and its sequelae, in a European setting.

These five research aims were investigated through nine different studies representing nine chapters, which are outlined below.

6.2 Outlines

In **Chapter I** the protocol of the RCT regarding the additional effect of fluoroscopy-guided MLD, is presented.

Chapter II investigates the effect of fluoroscopy-guided MLD (vs. traditional MLD and vs. placebo MLD) in addition to the other parts of DLT, and provides the resulting findings and conclusions.

Chapter III reports which measurement method is best to evaluate excessive arm volume in patients with BCRL in terms of reliability, time efficiency and clinical feasibility.

In **Chapter IV** reliability of the MoisturemeterD® Compact device and the pitting test in order to evaluate local tissue water in patients with BCRL, is examined.

In **Chapter V** reliability and validity of the Lymph-ICF-UL questionnaire with revised scoring system is investigated.

Chapter VI provides knowledge regarding a third clinimetric property i.e. responsiveness, of the Lymph-ICF-UL questionnaire.

In **Chapter VII** the cross-cultural translation and validation process of the Lymph-ICF-UL questionnaire into French is reported.

Chapter VIII presents a systematic review on the economic burden associated with the treatment of BCRL.

At last, **Chapter IX** shows a longitudinal evaluation of derived direct healthcare costs associated with BCRL and its sequelae in Belgium.

Table 1. Overview of the characteristics of the nine different studies

Aim	Chapter	Design	Participants	Intervention	Outcomes
1	1: Protocol of the randomized controlled trial regarding efficiency of fluoroscopy-guided MLD for the treatment of BCRL	Protocol study			
	2: Randomized controlled trial regarding efficiency of fluoroscopy-guided MLD for the treatment of BCRL	Randomized, placebo-controlled, double-blind, multi-center trial	194 patients with objective unilateral hand and/or arm lymphedema after treatment for breast cancer	- 3 weeks (14 sessions) of intensive DLT (60min/session) - 6 months (18 sessions) of maintenance DLT (30min/session) - 6 months of follow-up	Primary: - Lymphedema reduction at level of the arm and/or hand(%) OR - Reduction in stagnation of fluids at the level of the shoulder and trunk (PWC%) Secondary: - Problems in functioning (Lymph-ICF-UL) - Quality of Life (McGill QoL)
2	3: Reliability, time-efficiency and clinical feasibility of five different volume measurements to evaluate excessive arm volume	Intra- and inter-rater reliability study; cross-sectional design	30 patients with objective unilateral arm lymphedema after treatment for breast cancer		1. Intra- and inter-rater reliability (intraclass correlation coefficients, measurement variability) 2. Time-efficiency (set-up, execution, total time) 3. Clinical feasibility (practical limitations) Methods: - traditional volumetry with overflow, - volumetry without overflow, - inversed volumetry, - opto-electronic volumetry - calculated volume based on circumferences
3	4: Reliability of the MMDC and pitting test	Intra- and inter-rater reliability study; cross-sectional design	30 patients with objective unilateral arm lymphedema		Intra- and inter-rater reliability (intraclass correlation coefficients, measurement variability): - MMDC device - Pitting test

			after treatment for breast cancer		
4	5: Reliability and validity Lymph-ICF-UL	PART I: Test retest reliability PART II: Face, content and construct validity; cross-sectional design	57 patients with objective unilateral hand and/or arm lymphedema after treatment for breast cancer		1. Reliability: Intra- and inter-rater reliability (intraclass correlation coefficients) internal consistency (Cronbach's alpha coefficients), measurement variability (SEM, SRD) 2. Validity: Face and content validity (questionnaire), construct validity (Spearman rank correlations)
	6: Responsiveness Lymph-ICF-UL	Prospective longitudinal cohort study	95 patients with objective unilateral hand and/or arm lymphedema after treatment for breast cancer	- <u>Intensive group:</u> 3 weeks (14 sessions) of intensive DLT (60min/session) and 1 month (8 sessions) of maintenance DLT (30min/session) - <u>Stable group:</u> 3 months (5 sessions) of maintenance DLT (30min/session)	Internal responsiveness: 1. Change in mean scores before and after intensive DLT (intensive group) 2. Change in mean scores before and after maintenance DLT (stable group) 3. SRM External responsiveness: 4. Change in mean Lymph-ICF-UL total score before and after intensive treatment between responders and non-responders 5. Correlation between the change in scores (before and after intensive/maintenance treatments) and the GPE 6. MCID
	7: Translation and cross-cultural validation French Lymph-ICF-UL	PART I: Translation PART II: Test retest reliability PART III:	50 patients with objective unilateral hand and/or arm lymphedema after treatment for breast cancer		1. Reliability: Intra- and inter-rater reliability (intraclass correlation coefficients) internal consistency (Cronbach's alpha coefficients), measurement variability (SEM, SRD)

		Face, content and construct validity; cross-sectional design			2. Validity: Face and content validity (questionnaire), construct validity (Spearman rank correlations)
5	8: Systematic review costs related to BCRL treatment	Systematic review			Direct and indirect patient-borne or society-borne treatment costs for the treatment of BCRL
	9: Evaluation direct costs related to DLT	Prospective longitudinal cohort study	170 patients with objective unilateral hand and/or arm lymphedema after treatment for breast cancer	Collection of costs during: - 3 weeks (14 sessions) of intensive DLT (60min/session) - 6 months (18 sessions) of maintenance DLT (30min/session) - 6 months of follow-up (= continuation maintenance DLT)	Direct costs: - Bandaging equipment - Compression material (sleeves, gauntlets, assisting aids) and accessories (moisturizing lotion, …) - Medication - Medical imaging - Blood investigation - Human resources

Abbreviations: MLD = manual lymph drainage, BCRL = breast cancer-related lymphedema, DLT = decongestive lymphatic therapy, MMDC = MoisturemeterD Compact device, SEM = standard error of measurement, SRD = smallest real difference, SRM = standardized response mean, MCID = minimal clinical important difference

References

1. Majeed W, Aslam B, Javed I, et al. Breast cancer: major risk factors and recent developments in treatment. Asian Pacific journal of cancer prevention : APJCP 2014;**15**(8):3353-8 doi: 10.7314/apjcp.2014.15.8.3353[published Online First: Epub Date]|.
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA: a cancer journal for clinicians 2009;**59**(4):225-49 doi: 10.3322/caac.20006[published Online First: Epub Date]|.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians 2018;**68**(6):394-424 doi: 10.3322/caac.21492[published Online First: Epub Date]|.
4. Stichting Kankerregister. Cancer Fact Sheets. Secondary Cancer Fact Sheets 2019 2016. http://kankerregister.org/media/docs/CancerFactSheets/2017/Cancer_Fact_Sheet_FemaleBreastCancer_2017.pdf.
5. Parry C, Kent EE, Mariotto AB, Alfano CM, Rowland JH. Cancer survivors: a booming population. Cancer Epidemiol Biomarkers Prev 2011;**20**(10):1996-2005 doi: 10.1158/1055-9965.epi-11-0729[published Online First: Epub Date]|.
6. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet 2015;**385**(9972):977-1010 doi: 10.1016/s0140-6736(14)62038-9[published Online First: Epub Date]|.
7. Giordano SH, Cohen DS, Buzdar AU, Perkins G, Hortobagyi GN. Breast carcinoma in men: a population-based study. Cancer 2004;**101**(1):51-7 doi: 10.1002/cncr.20312[published Online First: Epub Date]|.
8. Yalaza M, İnan A, Bozer M. Male Breast Cancer. J Breast Health 2016;**12**(1):1-8 doi: 10.5152/tjbh.2015.2711[published Online First: Epub Date]|.
9. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians 2015;**65**(2):87-108 doi: 10.3322/caac.21262[published Online First: Epub Date]|.
10. Colditz GA BH, Tamimi RM. *Breast cancer*. 3rd edition ed. New York: Oxfort University Press, 2006.
11. Chlebowski RT, Manson JE, Anderson GL, et al. Estrogen plus progestin and breast cancer incidence and mortality in the Women's Health Initiative Observational Study. J Natl Cancer Inst 2013;**105**(8):526-35 doi: 10.1093/jnci/djt043[published Online First: Epub Date]|.
12. Wijnen M, van den Heuvel-Eibrink MM, Medici M, Peeters RP, van der Lely AJ, Neggers SJ. Risk factors for subsequent endocrine-related cancer in childhood cancer survivors. Endocrine-related cancer 2016;**23**(6):R299-321 doi: 10.1530/erc-16-0113[published Online First: Epub Date]|.
13. NIH. Normal breast tissue. Secondary Normal breast tissue 2010. https://commons.wikimedia.org/wiki/File:Lymph-ill-lg.jpg.
14. Sainsbury JR, Anderson TJ, Morgan DA. ABC of breast diseases: breast cancer. Bmj 2000;**321**(7263):745-50
15. Amin M.B ES, Greene F, Byrd D.R, Brookland R.K, Washington M.K, Gershenwald J.E, Comptom C.C, Hess K.R, Sullivan D.C, Jessup J.M, Brierley J.D, Gaspar L.E, Schilsky R.L, Balch C.M, Winchester D.P, Asare E.A, Madera M, Gress D.M, Meyer L.R. *AJCC Cancer Staging Manual*. Chicago, Illinois: Springer International Publishing, 2017.
16. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;**26 Suppl 5**:v8-30 doi: 10.1093/annonc/mdv298[published Online First: Epub Date]|.
17. Perry N, Broeders M, de Wolf C, Tornberg S, Holland R, von Karsa L. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. Ann Oncol 2008;**19**(4):614-22 doi: 10.1093/annonc/mdm481[published Online First: Epub Date]|.
18. Yalcin B. Staging, risk assessment and screening of breast cancer. Exp Oncol 2013;**35**(4):238-45

19. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Annals of surgical oncology 2010;**17**(6):1471-4 doi: 10.1245/s10434-010-0985-4[published Online First: Epub Date]|.
20. Giuliano AE, Connolly JL, Edge SB, et al. Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA: a cancer journal for clinicians 2017;**67**(4):290-303 doi: 10.3322/caac.21393[published Online First: Epub Date]|.
21. Stages of breast cancer. Secondary Stages of breast cancer. https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/stages-of-breast-cancer.html.
22. Gherghe M, Bordea C, Blidaru A. Sentinel lymph node biopsy (SLNB) vs. axillary lymph node dissection (ALND) in the current surgical treatment of early stage breast cancer. J Med Life 2015;**8**(2):176-80
23. Karakatsanis A, Christiansen PM, Fischer L, et al. The Nordic SentiMag trial: a comparison of super paramagnetic iron oxide (SPIO) nanoparticles versus Tc(99) and patent blue in the detection of sentinel node (SN) in patients with breast cancer and a meta-analysis of earlier studies. Breast cancer research and treatment 2016;**157**(2):281-94 doi: 10.1007/s10549-016-3809-9[published Online First: Epub Date]|.
24. Winslow T. Sentinel Lymph Node Biopsy. Secondary Sentinel Lymph Node Biopsy 2010. https://visualsonline.cancer.gov/details.cfm?imageid=9094.
25. Hassan MS, Ansari J, Spooner D, Hussain SA. Chemotherapy for breast cancer (Review). Oncology reports 2010;**24**(5):1121-31 doi: 10.3892/or_00000963[published Online First: Epub Date]|.
26. Teven CM, Schmid DB, Sisco M, Ward J, Howard MA. Systemic Therapy for Early-Stage Breast Cancer: What the Plastic Surgeon Should Know. Eplasty 2017;**17**:e7-e7
27. Bodai BI, Tuso P. Breast cancer survivorship: a comprehensive review of long-term medical issues and lifestyle recommendations. The Permanente journal 2015;**19**(2):48-79 doi: 10.7812/tpp/14-241[published Online First: Epub Date]|.
28. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 2013;**14**(6):500-15 doi: 10.1016/S1470-2045(13)70076-7[published Online First: Epub Date]|.
29. Lawenda BD, Mondry TE, Johnstone PA. Lymphedema: a primer on the identification and management of a chronic condition in oncologic treatment. CA: a cancer journal for clinicians 2009;**59**(1):8-24 doi: 10.3322/caac.20001[published Online First: Epub Date]|.
30. Finegold DN, Schacht V, Kimak MA, et al. HGF and MET mutations in primary and secondary lymphedema. Lymphatic research and biology 2008;**6**(2):65-8 doi: 10.1089/lrb.2008.1524[published Online First: Epub Date]|.
31. International Lymphoedema Framework I. *Best Practice for the Management of Lymphoedema: International Consensus*, 2006.
32. Andrade M, Jacomo, A;. Anatomy of the human lymphatic system. Cancer Metastasis and the Lymphovascular System: Springer, 2007:p.69-91.
33. Jiang X, Nicolls MR, Tian W, Rockson SG. Lymphatic Dysfunction, Leukotrienes, and Lymphedema. Annual review of physiology 2018;**80**:49-70 doi: 10.1146/annurev-physiol-022516-034008[published Online First: Epub Date]|.
34. Berry C. The Lymphatic System. Secondary The Lymphatic System 2019. https://www.alholistichealth.com/?s=lymph.
35. Marieb E, N. ; Hoehn, Katja, N. . *Human Anatomy & Physiology*. 11 ed: Pearson, 2018.
36. Michael F. *Földi's Textbook of Lymphology*. Munich: Elsevier, 2012.
37. Aukland K. Arnold Heller and the lymph pump. Acta physiologica Scandinavica 2005;**185**(3):171-80 doi: 10.1111/j.1365-201X.2005.01470.x[published Online First: Epub Date]|.
38. Marieb E, N. ; Hoehn, Katja, N. *Human Anatomy & Physiology*. 5 ed: Pearson, 2001.
39. The Diagnosis and Treatment of Peripheral Lymphedema: 2020 Consensus Document of the International Society of Lymphology. Lymphology 2020;**53**(1):3-19

40. Lacovara JE, Yoder LH. Secondary lymphedema in the cancer patient. Medsurg Nurs 2006;**15**(5):302-6; quiz 07
41. Tsai RJ, Dennis LK, Lynch CF, Snetselaar LG, Zamba GK, Scott-Conner C. The risk of developing arm lymphedema among breast cancer survivors: a meta-analysis of treatment factors. Annals of surgical oncology 2009;**16**(7):1959-72 doi: 10.1245/s10434-009-0452-2[published Online First: Epub Date]|.
42. Zhu YQ, Xie YH, Liu FH, Guo Q, Shen PP, Tian Y. Systemic analysis on risk factors for breast cancer related lymphedema. Asian Pacific journal of cancer prevention : APJCP 2014;**15**(16):6535-41
43. Zou L, Liu FH, Shen PP, et al. The incidence and risk factors of related lymphedema for breast cancer survivors post-operation: a 2-year follow-up prospective cohort study. Breast cancer (Tokyo, Japan) 2018;**25**(3):309-14 doi: 10.1007/s12282-018-0830-3[published Online First: Epub Date]|.
44. Gebruers N, Verbelen H, De Vrieze T, et al. Current and future perspectives on the evaluation, prevention and conservative management of breast cancer related lymphoedema: A best practice guideline. European journal of obstetrics, gynecology, and reproductive biology 2017;**216**:245-53 doi: 10.1016/j.ejogrb.2017.07.035[published Online First: Epub Date]|.
45. Cariati M, Bains SK, Grootendorst MR, et al. Adjuvant taxanes and the development of breast cancer-related arm lymphoedema. Br J Surg 2015;**102**(9):1071-8 doi: 10.1002/bjs.9846[published Online First: Epub Date]|.
46. Brunelle CL, Swaroop MN, Skolny MN, Asdourian MS, Sayegh HE, Taghian AG. Hand Edema in Patients at Risk of Breast Cancer-Related Lymphedema: Health Professionals Should Take Notice. Physical therapy 2018;**98**(6):510-17 doi: 10.1093/ptj/pzy007[published Online First: Epub Date]|.
47. Abe R. A study on the pathogenesis of postmastectomy lymphedema. The Tohoku journal of experimental medicine 1976;**118**(2):163-71 doi: 10.1620/tjem.118.163[published Online First: Epub Date]|.
48. Stanton AW, Modi S, Bennett Britton TM, et al. Lymphatic drainage in the muscle and subcutis of the arm after breast cancer treatment. Breast cancer research and treatment 2009;**117**(3):549-57 doi: 10.1007/s10549-008-0259-z[published Online First: Epub Date]|.
49. Kubik S. The role of the lateral upper arm bundle and the lymphatic watersheds in the formation of collateral pathways in lymphedema. Acta biologica Academiae Scientiarum Hungaricae 1980;**31**(1-3):191-200
50. Stanton AW, Modi S, Mellor RH, et al. A quantitative lymphoscintigraphic evaluation of lymphatic function in the swollen hands of women with lymphoedema following breast cancer treatment. Clinical science (London, England : 1979) 2006;**110**(5):553-61 doi: 10.1042/cs20050277[published Online First: Epub Date]|.
51. Hayes SC, Johansson K, Stout NL, et al. Upper-body morbidity after breast cancer: incidence and evidence for evaluation, prevention, and management within a prospective surveillance model of care. Cancer 2012;**118**(8 Suppl):2237-49 doi: 10.1002/cncr.27467[published Online First: Epub Date]|.
52. Ezzo J, Manheimer E, McNeely ML, et al. Manual lymphatic drainage for lymphedema following breast cancer treatment. Cochrane Database Syst Rev 2015(5):Cd003475 doi: 10.1002/14651858.CD003475.pub2[published Online First: Epub Date]|.
53. Invernizzi M, Lopez G, Michelotti A, et al. Integrating Biological Advances Into the Clinical Management of Breast Cancer Related Lymphedema. Frontiers in oncology 2020;**10**:422 doi: 10.3389/fonc.2020.00422[published Online First: Epub Date]|.
54. Verbelen H, Gebruers N, Beyers T, De Monie A-C, Tjalma W. Breast edema in breast cancer patients following breast-conserving surgery and radiotherapy: a systematic review. Breast cancer research and treatment 2014;**147**(3):463-71
55. Roberts CC, Levick JR, Stanton AW, Mortimer PS. Assessment of truncal edema following breast cancer treatment using modified Harpenden skinfold calipers. Lymphology 1995;**28**(2):78-88

56. Hidding JT, Viehoff PB, Beurskens CH, van Laarhoven HW, Nijhuis-van der Sanden MW, van der Wees PJ. Measurement Properties of Instruments for Measuring of Lymphedema: Systematic Review. Physical therapy 2016;**96**(12):1965-81 doi: 10.2522/ptj.20150412[published Online First: Epub Date]|.
57. Stout Gergich NL, Pfalzer LA, McGarvey C, Springer B, Gerber LH, Soballe P. Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. Cancer 2008;**112**(12):2809-19 doi: 10.1002/cncr.23494[published Online First: Epub Date]|.
58. Damstra RJ, Halk AB. The Dutch lymphedema guidelines based on the International Classification of Functioning, Disability, and Health and the chronic care model. Journal of vascular surgery. Venous and lymphatic disorders 2017;**5**(5):756-65 doi: 10.1016/j.jvsv.2017.04.012[published Online First: Epub Date]|.
59. Damstra RJ, Glazenburg EJ, Hop WC. Validation of the inverse water volumetry method: A new gold standard for arm volume measurements. Breast cancer research and treatment 2006;**99**(3):267-73 doi: 10.1007/s10549-006-9213-0[published Online First: Epub Date]|.
60. Gebruers N, Truijen S, Engelborghs S, De Deyn PP. Volumetric evaluation of upper extremities in 250 healthy persons. Clinical physiology and functional imaging 2007;**27**(1):17-22 doi: 10.1111/j.1475-097X.2007.00708.x[published Online First: Epub Date]|.
61. Tierney S, Aslam M, Rennie K, Grace P. Infrared optoelectronic volumetry, the ideal way to measure limb volume. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 1996;**12**(4):412-7
62. Devoogdt N, Lemkens H, Geraerts I, et al. A new device to measure upper limb circumferences: validity and reliability. International angiology : a journal of the International Union of Angiology 2010;**29**(5):401-7
63. Taylor R, Jayasinghe UW, Koelmeyer L, Ung O, Boyages J. Reliability and validity of arm volume measurements for assessment of lymphedema. Physical therapy 2006;**86**(2):205-14
64. van Velze CA, Kluever I, van der Merwe CA, Mennen U.
65. Cornish BH, Thomas BJ, Ward LC, Hirst C, Bunce IH. A new technique for the quantification of peripheral edema with application in both unilateral and bilateral cases. Angiology 2002;**53**(1):41-7 doi: 10.1177/000331970205300106[published Online First: Epub Date]|.
66. Mayrovitz HN, Arzanova E, Somarriba S, Eisa S. Reference Values for Assessing Localized Hand Lymphedema Using Interhand Tissue Dielectric Constant Ratios. Lymphatic research and biology 2018;**16**(5):442-45 doi: 10.1089/lrb.2017.0065[published Online First: Epub Date]|.
67. Sanderson J, Tuttle N, Box R, Reul-Hirche HM, Laakso EL. THE PITTING TEST; AN INVESTIGATION OF AN UNSTANDARDIZED ASSESSMENT OF LYMPHEDEMA. Lymphology 2015;**48**(4):175-83
68. Sun D, Yu Z, Chen J, Wang L, Han L, Liu N. The Value of Using a SkinFibroMeter for Diagnosis and Assessment of Secondary Lymphedema and Associated Fibrosis of Lower Limb Skin. Lymphatic research and biology 2017;**15**(1):70-76 doi: 10.1089/lrb.2016.0029[published Online First: Epub Date]|.
69. Pusic AL, Cemal Y, Albornoz C, et al. Quality of life among breast cancer patients with lymphedema: a systematic review of patient-reported outcome instruments and outcomes. Journal of cancer survivorship : research and practice 2013;**7**(1):83-92 doi: 10.1007/s11764-012-0247-5[published Online First: Epub Date]|.
70. De Vrieze T, Coeck D, Verbelen H, Devoogdt N, Tjalma W, Gebruers N. Cross-cultural Psychometric Evaluation of the Dutch McGill-QoL Questionnaire for Breast Cancer Patients. Facts Views Vis Obgyn 2016;**8**(4):205-09
71. De Vrieze T, Vos L, Gebruers N, et al. Revision of the Lymphedema Functioning, Disability and Health Questionnaire for Upper Limb Lymphedema (Lymph-ICF-UL): Reliability and Validity. Lymphatic research and biology 2019 doi: 10.1089/lrb.2018.0025[published Online First: Epub Date]|.
72. Suami H, Heydon-White A, Mackie H, Czerniec S, Koelmeyer L, Boyages J. A new indocyanine green fluorescence lymphography protocol for identification of the lymphatic drainage pathway for

patients with breast cancer-related lymphoedema. BMC cancer 2019;**19**(1):985 doi: 10.1186/s12885-019-6192-1[published Online First: Epub Date]|.

73. Sage HH, Gozun BV. Lymphatic scintigrams: a method for studying the functional pattern of lymphatics and lymph nodes. Cancer 1958;**11**(1):200-3 doi: 10.1002/1097-0142(195801/02)11:1<200::aid-cncr2820110131>3.0.co;2-n[published Online First: Epub Date]|.
74. Modi S, Stanton AW, Mortimer PS, Levick JR. Clinical assessment of human lymph flow using removal rate constants of interstitial macromolecules: a critical review of lymphoscintigraphy. Lymphatic research and biology 2007;**5**(3):183-202 doi: 10.1089/lrb.2007.5306[published Online First: Epub Date]|.
75. Hwang JH, Kwon JY, Lee KW, et al. Changes in lymphatic function after complex physical therapy for lymphedema. Lymphology 1999;**32**(1):15-21
76. Suami H, Koelmeyer L, Mackie H, Boyages J. Patterns of lymphatic drainage after axillary node dissection impact arm lymphoedema severity: A review of animal and clinical imaging studies. Surgical oncology 2018;**27**(4):743-50 doi: 10.1016/j.suronc.2018.10.006[published Online First: Epub Date]|.
77. Pallotta OJ, van Zanten M, McEwen M, Burrow L, Beesley J, Piller N. Development and validation of a custom made indocyanine green fluorescence lymphatic vessel imager. Journal of biomedical optics 2015;**20**(6):066003 doi: 10.1117/1.jbo.20.6.066003[published Online First: Epub Date]|.
78. Kitai T, Inomoto T, Miwa M, Shikayama T. Fluorescence navigation with indocyanine green for detecting sentinel lymph nodes in breast cancer. Breast cancer (Tokyo, Japan) 2005;**12**(3):211-5 doi: 10.2325/jbcs.12.211[published Online First: Epub Date]|.
79. Giacalone G. BJP, Bourgeois P., Bracale P., Röh N., Moraine J.J. A new dynamic imaging tool to study lymphoedema and associated treatments. The European Journal of Lymphology 2011;**22**(62):10-14
80. Aldrich MB, Guilliod R, Fife CE, et al. Lymphatic abnormalities in the normal contralateral arms of subjects with breast cancer-related lymphedema as assessed by near-infrared fluorescent imaging. Biomed Opt Express 2012;**3**(6):1256-65 doi: 10.1364/boe.3.001256[published Online First: Epub Date]|.
81. Belgrado JP, Vandermeeren L, Vankerckhove S, et al. Near-Infrared Fluorescence Lymphatic Imaging to Reconsider Occlusion Pressure of Superficial Lymphatic Collectors in Upper Extremities of Healthy Volunteers. Lymphatic research and biology 2016;**14**(2):70-7 doi: 10.1089/lrb.2015.0040[published Online First: Epub Date]|.
82. Yamamoto T, Matsuda N, Doi K, et al. The earliest finding of indocyanine green lymphography in asymptomatic limbs of lower extremity lymphedema patients secondary to cancer treatment: the modified dermal backflow stage and concept of subclinical lymphedema. Plast Reconstr Surg 2011;**128**(4):314e-21e doi: 10.1097/PRS.0b013e3182268da8[published Online First: Epub Date]|.
83. Akita S, Nakamura R, Yamamoto N, et al. Early Detection of Lymphatic Disorder and Treatment for Lymphedema following Breast Cancer. Plast Reconstr Surg 2016;**138**(2):192e-202e doi: 10.1097/prs.0000000000002337[published Online First: Epub Date]|.
84. LymphCare. Complete Decongestive Therapy. Secondary Complete Decongestive Therapy 2020. https://www.lymphcareusa.com/patient/therapy-solutions/complete-decongestive-therapy.html.
85. Devoogdt N, Van Kampen M, Geraerts I, Coremans T, Christiaens MR. Different physical treatment modalities for lymphoedema developing after axillary lymph node dissection for breast cancer: a review. European journal of obstetrics, gynecology, and reproductive biology 2010;**149**(1):3-9 doi: 10.1016/j.ejogrb.2009.11.016[published Online First: Epub Date]|.
86. Lasinski BB, McKillip Thrift K, Squire D, et al. A systematic review of the evidence for complete decongestive therapy in the treatment of lymphedema from 2004 to 2011. PM & R : the journal

of injury, function, and rehabilitation 2012;**4**(8):580-601 doi: 10.1016/j.pmrj.2012.05.003[published Online First: Epub Date]|.
87. Foldi E. Massage and damage to lymphatics. Lymphology 1995;**28**(1):1-3
88. Eliska O, Eliskova M. Are peripheral lymphatics damaged by high pressure manual massage? Lymphology 1995;**28**(1):21-30
89. Rogan S, Taeymans J, Luginbuehl H, Aebi M, Mahnig S, Gebruers N. Therapy modalities to reduce lymphoedema in female breast cancer patients: a systematic review and meta-analysis. Breast cancer research and treatment 2016;**159**(1):1-14 doi: 10.1007/s10549-016-3919-4[published Online First: Epub Date]|.
90. Ha KJ, Lee SY, Lee H, Choi SJ. Synergistic Effects of Proprioceptive Neuromuscular Facilitation and Manual Lymphatic Drainage in Patients with Mastectomy-Related Lymphedema. Frontiers in physiology 2017;**8**:959 doi: 10.3389/fphys.2017.00959[published Online First: Epub Date]|.
91. Moseley AL, Piller NB, Carati CJ. The effect of gentle arm exercise and deep breathing on secondary arm lymphedema. Lymphology 2005;**38**(3):136-45
92. Shao Y, Qi K, Zhou QH, Zhong DS. Intermittent pneumatic compression pump for breast cancer-related lymphedema: a systematic review and meta-analysis of randomized controlled trials. Oncology research and treatment 2014;**37**(4):170-4 doi: 10.1159/000360786[published Online First: Epub Date]|.
93. Carati CJ, Anderson SN, Gannon BJ, Piller NB. Treatment of postmastectomy lymphedema with low-level laser therapy: a double blind, placebo-controlled trial. Cancer 2003;**98**(6):1114-22 doi: 10.1002/cncr.11641[published Online First: Epub Date]|.
94. Badger C, Preston N, Seers K, Mortimer P. Benzo-pyrones for reducing and controlling lymphoedema of the limbs. Cochrane Database Syst Rev 2004(2):Cd003140 doi: 10.1002/14651858.CD003140.pub2[published Online First: Epub Date]|.
95. Campisi C, Boccardo F, Zilli A, Maccio A, Napoli F. The use of vein grafts in the treatment of peripheral lymphedemas: long-term results. Microsurgery 2001;**21**(4):143-7
96. Badger C, Preston N, Seers K, Mortimer P. Physical therapies for reducing and controlling lymphoedema of the limbs. Cochrane Database Syst Rev 2004(4):Cd003141 doi: 10.1002/14651858.CD003141.pub2[published Online First: Epub Date]|.
97. Woods M. The experience of manual lymph drainage as an aspect of treatment for lymphoedema. Int J Palliat Nurs 2003;**9**(8):336-42; discussion 42 doi: 10.12968/ijpn.2003.9.8.11524[published Online First: Epub Date]|.
98. Williams AF, Vadgama A, Franks PJ, Mortimer PS. A randomized controlled crossover study of manual lymphatic drainage therapy in women with breast cancer-related lymphoedema. European journal of cancer care 2002;**11**(4):254-61
99. McNeely ML, Magee DJ, Lees AW, Bagnall KM, Haykowsky M, Hanson J. The addition of manual lymph drainage to compression therapy for breast cancer related lymphedema: a randomized controlled trial. Breast cancer research and treatment 2004;**86**(2):95-106 doi: 10.1023/B:BREA.0000032978.67677.9f[published Online First: Epub Date]|.
100. Karki A, Anttila H, Tasmuth T, Rautakorpi UM. Lymphoedema therapy in breast cancer patients: a systematic review on effectiveness and a survey of current practices and costs in Finland. Acta oncologica (Stockholm, Sweden) 2009;**48**(6):850-9 doi: 10.1080/02841860902755251[published Online First: Epub Date]|.
101. Huang TW, Tseng SH, Lin CC, et al. Effects of manual lymphatic drainage on breast cancer-related lymphedema: a systematic review and meta-analysis of randomized controlled trials. World J Surg Oncol 2013;**11**:15 doi: 10.1186/1477-7819-11-15[published Online First: Epub Date]|.
102. Bergmann A, da Costa Leite Ferreira MG, de Aguiar SS, et al. Physiotherapy in upper limb lymphedema after breast cancer treatment: a randomized study. Lymphology 2014;**47**(2):82-91
103. Gradalski T, Ochalek K, Kurpiewska J. Complex Decongestive Lymphatic Therapy With or Without Vodder II Manual Lymph Drainage in More Severe Chronic Postmastectomy Upper Limb Lymphedema: A Randomized Noninferiority Prospective Study. J Pain Symptom Manage

2015;**50**(6):750-7 doi: 10.1016/j.jpainsymman.2015.06.017[published Online First: Epub Date]|.
104. Tambour M, Holt M, Speyer A, Christensen R, Gram B. Manual lymphatic drainage adds no further volume reduction to Complete Decongestive Therapy on breast cancer-related lymphoedema: a multicentre, randomised, single-blind trial. Br J Cancer 2018;**119**(10):1215-22 doi: 10.1038/s41416-018-0306-4[published Online First: Epub Date]|.
105. Kwon S, Price RE. Characterization of internodal collecting lymphatic vessel function after surgical removal of an axillary lymph node in mice. Biomed Opt Express 2016;**7**(4):1100-15 doi: 10.1364/boe.7.001100[published Online First: Epub Date]|.
106. Weissleder H, Weissleder R. Lymphedema: evaluation of qualitative and quantitative lymphoscintigraphy in 238 patients. Radiology 1988;**167**(3):729-35 doi: 10.1148/radiology.167.3.3363131[published Online First: Epub Date]|.
107. Moshiri M, Katz DS, Boris M, Yung E. Using lymphoscintigraphy to evaluate suspected lymphedema of the extremities. AJR Am J Roentgenol 2002;**178**(2):405-12 doi: 10.2214/ajr.178.2.1780405[published Online First: Epub Date]|.
108. Rasmussen JC, Tan IC, Marshall MV, et al. Human Lymphatic Architecture and Dynamic Transport Imaged Using Near-infrared Fluorescence. Transl Oncol 2010;**3**(6):362-72
109. Tomson D, Lessert C, Luthi I, Mazzolai L, Depairon M. [Lymphatic vascular pathologies: contribution of lympho-fluoroscopy]. Rev Med Suisse 2015;**11**(460):362-5
110. Tan IC, Maus EA, Rasmussen JC, et al. Assessment of lymphatic contractile function after manual lymphatic drainage using near-infrared fluorescence imaging. Archives of physical medicine and rehabilitation 2011;**92**(5):756-64.e1 doi: 10.1016/j.apmr.2010.12.027[published Online First: Epub Date]|.

CHAPTER 1

Chapter 1

PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL REGARDING THE EFFECTIVENESS OF FLUOROSCOPY-GUIDED MANUAL LYMPH DRAINAGE FOR THE TREATMENT OF BREAST CANCER-RELATED LYMPHEDEMA (EFFORT-BCRL TRIAL)

Eur J Obstet Gynecol Reprod Biol. 2018 Feb; 221:177-188.

Tessa De Vrieze
Lore Vos
Nick Gebruers
Ines Nevelsteen
Wiebren A.A. Tjalma
Sarah Thomis
Patrick Neven
An De Groef
Liesbeth Vandermeeren
Jean-Paul Belgrado
Nele Devoogdt

Abstract

Objectives: Lymphedema is a dreadful complication following breast cancer therapy. According to the International Society of Lymphology, the consensus treatment for breast cancer-related lymphedema (BCRL) is the decongestive lymphatic therapy. This is a two-phase treatment and combines different treatment modalities including skin care, manual lymphatic drainage (MLD), compression therapy and exercise. However, the additional effect of MLD is debated since pooled data only demonstrated a limited non-significant additional value. A possible explanation is that in previous studies MLD has been applied blind, without knowledge of patient-specific lymphatic routes of transport. In addition, the MLD hand maneuvers used by the therapists in previous studies, possibly did not optimally stimulate lymphatic transport. Recently, near-infrared fluorescence imaging has been introduced to visualize the superficial lymphatic network which allows MLD at the most needed location. The aim of the present study is to determine the effectiveness of the fluoroscopy-guided MLD, additional to the other parts of the decongestive lymphatic therapy and compared to the traditional or a placebo MLD, in the treatment of BCRL.

Study Design: A three-arm double-blinded randomized controlled trial will be conducted in different university hospitals in Belgium. Based on a sample size calculation, 201 participants with chronic BCRL stage 1 or 2 of the arm or hand, with at least 5% difference between both sides (corrected for hand dominance) need to be recruited. All participants receive the standard treatment: skin care, compression therapy and exercises. The intervention group additionally receives fluoroscopy-guided MLD. One control group additionally receives the traditional 'blind' MLD and a second control group receives a placebo MLD. All subjects receive 3 weeks of daily intensive treatments and 6 months of maintenance treatment. Follow-up period is 6 months. The primary outcomes are the reduction in lymphedema volume of the arm/ hand and the change in stagnation of lymph fluid at level of the shoulder/ trunk.

Introduction

Lymphedema is an embarrassing and dreadful morbidity after breast cancer treatment. The incidence of breast cancer-related lymphedema (BCRL) of the arm is 16%.[1] Lymphedema does not only induce physical impairments such as swelling, heaviness and problems with performing household activities and mobility [2], but also psychosocial problems.[3]

According to the recommendations of the International Society of Lymphology (ISL), lymphedema needs to be treated with decongestive lymphatic therapy.[4] This is a two-stage treatment program. During the first or intensive phase, lymphedema is maximally reduced. This phase consists of skin care, manual lymph drainage (MLD), multi-layer bandaging and exercise therapy. The second or maintenance phase aims to conserve and optimize the results obtained in the first phase. It consists of skin care, compression by a low-stretch compression sleeve, exercises and MLD.

Due to the significantly improved screening and treatment modalities for breast cancer over the last few years, survival rates are growing resulting in a prevalence rate of BCRL which is still increasing as well.[5] In Belgium, almost all lymphedema patients receive MLD as part of the physical treatment, which can be time-consuming for patients and entails a big financial cost for the patient as for the Health Care system.[6] However, a meta-analysis, including 6 randomized controlled trials (RCT's), and a Cochrane systematic review have questioned the effectiveness of MLD.[7, 8] The meta-analysis showed an overall additional benefit of MLD to the treatment of BCRL of 75ml on volume reduction, while the systematic review revealed that the individual contribution of MLD was limited to 7%.[7, 8] Two recent RCT's were unable to demonstrate an additional effect of MLD to decongestive lymphatic therapy.[9, 10]

A possible explanation why MLD according to the method applied in previous studies, has a rather small benefit in addition to the other parts of decongestive lymphatic therapy, is that MLD is applied in an inefficient or 'blind' way. This method of MLD is further called 'traditional MLD'. After dissection of the axillary lymph nodes, whether or not in combination with radiotherapy, the lymphatic system of the upper limb is damaged. Lymph nodes are removed and often fibrosis of the superficial lymphatic system follows.[11, 12] As a result, reverse flow of lymph fluid coming from collecting vessels and going through precollecting vessels in direction of the dermal capillaries, can occur. This dysfunctional phenomenon is called dermal backflow.[13] Moreover, rerouting of lymphatic drainage via lymph collaterals and dermal capillaries, also called dermal rerouting, has been described in patients with lymphedema.[14, 15] This rerouting is patient-specific. Therefore, it is proposed that the traditional or 'blind' MLD needs to be abandoned and a tailored approach needs to be established. Near-infrared fluorescence imaging or lymphofluoroscopy can aid to apply a more efficient MLD.

During this investigation, diluted Indocyanine Green (ICG) is injected intradermally in the hand; it visualizes the superficial transport of lymph from the hand up to the axilla and it demonstrates alternative pathways towards other lymph nodes.[16]

A second possible explanation why traditional MLD has not proven to be effective, is that the therapist does not optimally stimulate lymphatic transport. The resorption of lymph capillaries has to be performed with the thumb (instead of with the hand in the traditional MLD, which gives a lower pressure). In addition, gliding (compared to no gliding) is hypothesized to be more effective to enhance lymphatic transport.[17] The physiological effect of one session of fluoroscopy-guided MLD was demonstrated in patients with BCRL.[17, 18] Whether the application of different sessions of fluoroscopy-guided MLD has a clinical and long-lasting effect on the lymphedema, superior to the traditional MLD, has yet to be established.

Further, clinical experience revealed that patients report a positive subjective feeling after MLD. Whether this is a real effect rather than a placebo-effect, needs to be investigated as well.

The objective of this trial is to examine the effectiveness of fluoroscopy-guided MLD versus traditional MLD and versus placebo MLD, applied as part of the decongestive lymphatic therapy, for the treatment of BCRL.

Methods

The RCT protocol used the recommended CONSORT guideline to report on the following items.[19]

Trial design

The EFforT-BCRL trial is a multi-center double-blind three groups RCT. Figure 1 gives an overview of the participant flow. All participants (n=201) receive an intensive treatment lasting 3 weeks and a maintenance treatment for 6 months. Additionally, they are followed up for another 6 months. All participants receive a standard treatment consisting of skin care, compression therapy, exercises and information. Only the MLD differs among the three groups: the intervention group receives a fluoroscopy-guided MLD, control group one receives the traditional MLD and control group two receives a placebo MLD. The participants are assessed before the start of the trial, after 3 weeks of intensive treatment, after 1, 3 and 6 months of maintenance treatment and after 6 months of additional follow-up.

All treatments and assessments are performed at the department of Physical Medicine and Rehabilitation (treatment and clinical assessment) and at the department of Vascular Surgery

(lymphofluoroscopy) of the University Hospitals of Leuven, at the Multidisciplinary Breast Clinic in the Antwerp University Hospital, at the Lymphology Clinic in Saint-Pierre University Hospital in Brussels and at the Centre of Oncology in General Hospital Groeninge in Kortrijk.

The EFforT-BCRL trial has been approved by the Ethical Committee of the University Hospitals of Leuven (main Ethical Committee) and received positive advise from the Ethical Committees of all other participating centers (CME reference S58689, EudraCT Number 2015-004822-33). The study has been registered in clinicaltrials.gov (NCT02609724).

Randomization and allocation sequence generation

All participants are allocated to one of the three groups. The random allocation sequence is computer-generated. Randomization is performed by using 6-size permuted blocks. The allocation to the groups is concealed and performed by an independent physical therapist. The sequence of randomization is determined by the participant's identification number, which he/ she receives after inclusion in the study.

Blinding

All participants are blinded for the allocation to one of the three MLD groups. Additionally, all clinical as well as fluoroscopic assessments are performed by investigators who are blinded for the allocation of the patients to the treatment groups. The therapists are blinded to participants' data, but are aware of the treatments provided to the three different groups.

Participants

Participants are recruited from three university hospitals and one general hospital in Belgium: University Hospitals of Leuven (n=90), Saint-Pierre University Hospital in Brussels (n=20), Antwerp University Hospital (n=51) and General Hospital Groeninge in Kortrijk (n=40). The recruitment of participants started in February 2016. Eligibility criteria for the EFforT-BCRL trial are 1) patients with unilateral lymphedema of the arm and/ or hand, developed after treatment for breast cancer, 2) chronic lymphedema stage I to IIb (duration of >3 months), 3) at least 5% difference between both arms, adjusted for hand dominance, and/ or between both hands, and 4) no active metastases. Patients are excluded when one of the following criteria are present 1) age <18y, 2) edema of the upper limb from another cause than breast cancer treatment, 3) cannot participate during the entire study

period, 4) mentally or physically unable to participate in the study, 5) allergy for iodine, sodiumiodine, Indocyanine Green, 6) increased activity of the thyroid gland; benign tumors of the thyroid gland, 7) lymph node transplantation or lymphovenous shunt in the past, 8) bilateral axillary lymph node dissection. All patients receive written as well as oral information. Only patients who signed the informed consent document prior to the start of the study, were included.

Assessments

Figure 1 gives an overview of the different assessments and their timing in the EFforT-BCRL trial.

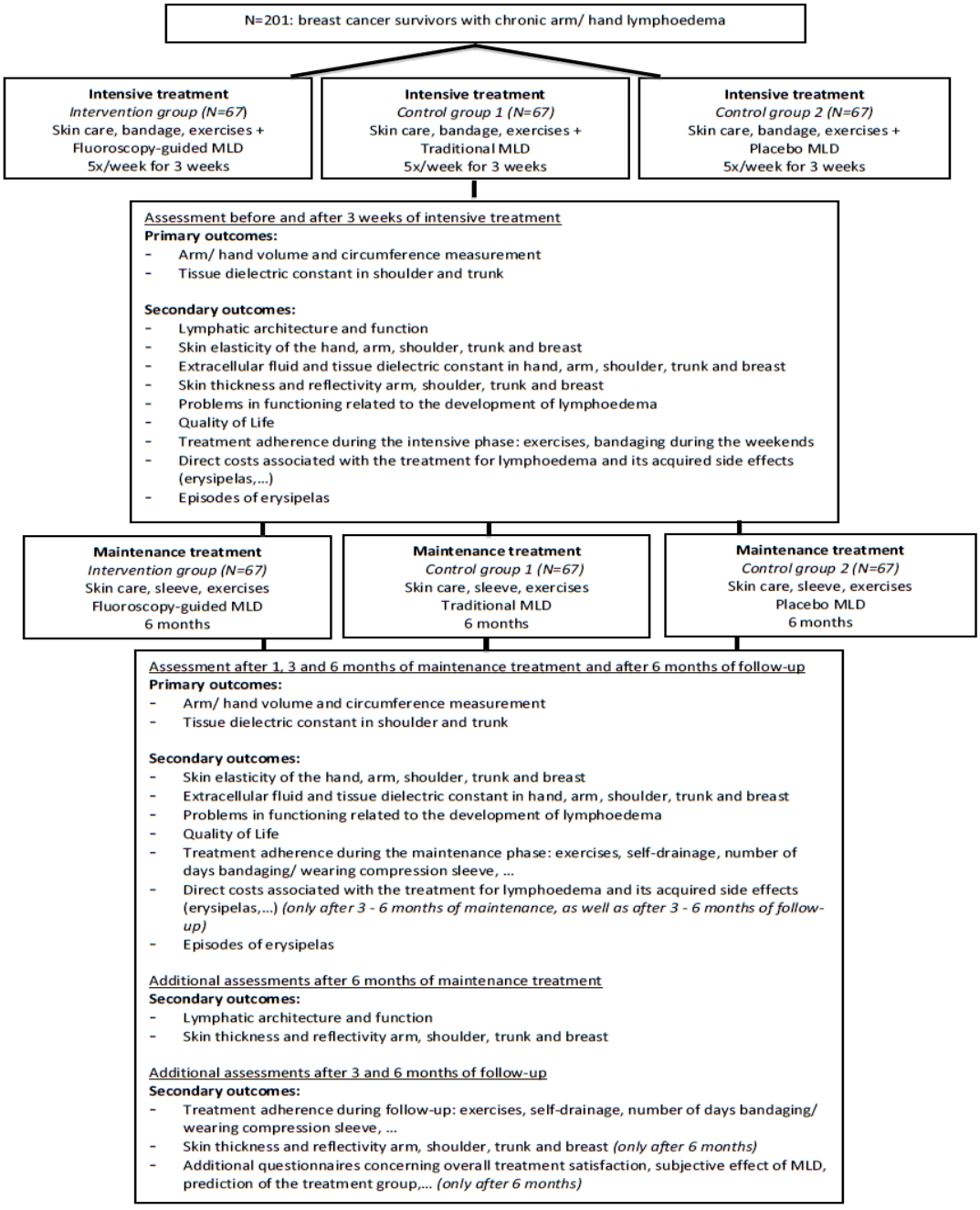


Figure 1. *Flow chart of the EFforT-BCRL trial*

Near-infrared fluorescence imaging or Lymphofluoroscopy

All lymphofluoroscopic assessments are performed by a vascular (ST) and plastic (LV) surgeon (the same surgeon for every patient) and assisted by a physical therapist (ND, NG, KD), who are experienced in performing this investigation. Both the surgeon and physical therapist are blinded to the participant's data as well as to the assigned therapy.

During a lymphofluoroscopy, Indocyanine Green (ICG) is injected intradermally in the first and fourth web space of the hand on the affected side. ICG emits fluorescence in the near-infrared spectrum (760 nm) and the signal is acquired using a camera with a Photo Dynamic Eye (PDE, Hamamatsu) system to visualize the superficial lymphatic system. The procedure consists of three consecutive phases. During the first part of the investigation, lymph flow is being evaluated at rest (3 min), after activity (3min of dorsiflexion of the wrist) and after stimulating lymph transport with MLD (5 min). Phase two consists of a 60min break in which exercise and rest are alternated. Last, in phase three, a scan of the limb (including arm, axilla, supraclavicular and scapular region) is performed with the PDE camera. Afterwards, pictures are taken of the ventral, lateral and dorsal side of the arm and trunk, and functional lymph nodes together with active lymphatic transport as well as dysfunctional rerouting patterns are designed on a body diagram. In Figure 2 an example is shown.

All the information about the lymphatic transport is documented in a standard evaluation document. For a detailed description of the procedure and protocol of this investigation, see Table 1.

Lymphofluoroscopic assessments occur at baseline, post-intensive (3 weeks) and post-maintenance phase (6 months) in all participants to assess the lymphatic transport (i.e. a secondary outcome parameter). In addition, baseline lymphofluoroscopy is used to determine the procedure of MLD (i.e. which hand movements at which location[17]) in the group receiving fluoroscopy-guided MLD.

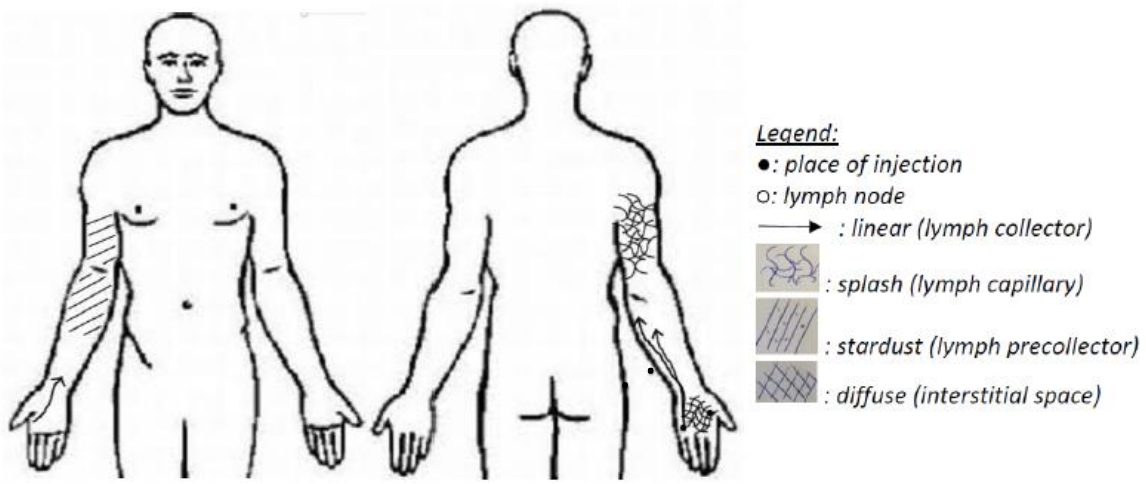


Figure 2. *Example of body diagram*

Table 1. Protocol near-infrared fluorescence imaging

	STEP	DURATION	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	3 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 Activity	3 min	Subject performs flexion/ extension of the hand, with a large range of motion and lower arm stable on table Lymph flow and spreading pattern is observed from the injection point	- Fill of lymph collector, starting from injection point : Yes / No (if "yes", after …… min) - Fill-in lymph collector after activity, starting from injection point : Yes / No (if "yes", after …… min)
	1.3 Stimulation	5 min	Lymph capillaries at the level of the injection points are filled and transport through the lymph collectors and dermal rerouting is stimulated by therapist	

	1.4 Scan with camera	20sec	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: - 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)
	1.5 Measuring		Length of each lymph collector is measured	Length of each lymph collector
Break		1h	Piece of foam is placed on the injection points Elastic bandage (Mollelast L&R) is placed around the hand to increase the pressure on the injection points Subject performs exercises: alternatively 5 minutes of squeezing with hand, 10 minutes of rest, 5 minutes of circumduction with hand, 10 minutes of rest, etc.	
Late phase	3.1 Scan with camera	20sec	See step 1.4	
	3.2 Drawing on skin and body diagram	+/- 10min	Clinician draws, under fluorescence feedback, the main lymph collectors and regions with dermal rerouting on the skin of the subject Pictures are taken of ventral, dorsal and lateral side of arm and trunk Lymph collectors and dermal rerouting (splash, stardust and diffuse) is designed on a body diagram	Reporting at the end of late phase: See step 1.4
	3.3 Measuring		Length of each lymph collector is measured Assessment document to score the lymphatic transport is filled out Recommendations for manual lymphatic drainage are made	Length of each lymph collector

Clinical assessments

The clinical assessments are performed by three assessors (KD, LV, TDV), according to the institution of participation. Each assessor is assigned to a particular institution and every participant is being evaluated by the same assessor. A standardized protocol consisting of the consecutive measurements and procedures has been developed, in order to maintain standardization between the different assessors. Multiple training sessions were performed to make the assessors familiar with the procedure. Participants are told not to mention information concerning their treatment during the evaluations, to ensure blinding of the assessor. In addition, the assessor is blinded to previous measurement data in order to avoid being influenced by previous results.

Clinical assessments occur at baseline, after 3 weeks of intensive treatment, after 1, 3 and 6 months of maintenance treatment and after 6 months follow-up. Tables 2 and 3 provide a detailed overview of the clinical evaluation methods and procedures performed in the EFforT-BCRL trial.

Primary outcomes

A first primary outcome measure is the change in lymphedema volume at the level of the whole arm, hand, distal and proximal lower arm and upper arm. The volume of the arm is determined with the water displacement method on the one hand and is calculated from circumference measurements on the other hand. A second primary outcome measure is the change of stagnation of lymph at the level of the shoulder or trunk. Table 2 gives an overview of the measurement method and the procedure to determine the outcome and the measurement method is shown in Figure 3.

Secondary outcomes

Secondary outcome measures are: change of extracellular fluid in the arm and trunk; change of thickness and reflectivity of cutis and subcutis at the level of hand, arm, shoulder and trunk; change of elasticity of skin and subcutaneous tissue at the level of hand, arm, shoulder and trunk; change of problems in functioning related to the lymphedema; change of quality of life; change of lymphatic architecture and function; change in number of episodes of erysipelas and direct costs related to the lymphedema and its treatment. Additionally, treatment adherence during the intensive and maintenance phase as well as during and after the follow-up period is investigated. At the last clinical evaluation, at 6 months follow-up, overall outcome satisfaction and prediction of group allocation is assessed by means of a survey.

Table 2. Overview of measurement method and procedure of the primary outcomes

Outcome	Measurement method	Procedure
Change of lymphedema volume of whole arm/ hand/ distal lower arm/ proximal lower arm/ upper arm	Water displacement method (ICC 0.99; SEM% 0.7%)[20] (see Figure 3) Material Cylinder filled with water of 20-30°C, placed on weighing balance with 0.1g accuracy (KERN 572); both are placed on top of a platform of 25 cm height Weighing balance is connected with software program on laptop; software program performs 10 volume measurements and calculates mean volume (Volume of upward displaced water = Mass of water/ density of water, density of water with T° between 20-30°C is 1); a signal is given if mean volume or its standard deviation is outside of preset range Reference points Lower ventral fold at level of wrist; middle between reference point at wrist and elbow; middle of elbow crease; at upper arm 10cm above the elbow reference point Method Jewelry at level of hand or arm is removed Subject is positioned in standing beside the cylinder Subject is drawn attention not to touch the border of the cylinder Arm is put in the cylinder with axis perpendicular to water surface; first up to the most distal reference point at the wrist, thereafter up to the midpoint of lower arm, than up to point at elbow crease and finally up to reference point at upper arm; Once the subject holds the arm stable, the assessor clicks on the assessment button on the program and the volume is determined	Volume whole arm = volume up to point on upper arm Volume of hand = volume up to point at wrist Volume of distal lower arm = volume up to midpoint lower arm – volume of hand Volume of proximal lower arm = volume up to point at elbow – volume hand – volume distal lower arm Volume of upper arm = volume up to point on upper arm - volume hand – volume distal lower arm – volume proximal lower arm Relative lymphedema volume of whole arm/ hand/ distal lower arm/ proximal lower arm/ upper arm = [(volume on affected side – volume on healthy side)/ volume on healthy side] × 100 Relative lymphedema volume of whole arm/ hand/ distal lower arm/ proximal lower arm/ upper arm is corrected with -3.3% for subjects with surgery on dominant side and with +3.3% for subjects operated on non-dominant side[21] Change of (relative) lymphedema volume of whole arm/ hand/ distal lower arm/ proximal lower arm/ upper arm = Relative lymphedema volume time 2 – relative lymphedema volume time 1
Change of lymphedema volume of whole arm	Circumference measurements (ICC 0.99; SEM% 1.2%)[20, 22] (see Figure 3) Material	Volume of whole arm = sum of volumes of all segments of arm

	Perimeter, which is a flexible stainless steel bar with a tapeline fixed every 4cm and a weight of 20g at the end Reference points Upper border of olecranon Method Jewelry at level of hand or arm is removed Subject is in sitting position with 90° anteflexion of the arm, straight elbow and hand supported on table Arm circumferences measured at olecranon and at 4, 8, 12, 16 and 20 cm proximal and distal of olecranon	Volume of 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 Relative lymphedema volume whole arm = cfr. supra Change of (relative) lymphedema volume of whole arm = cfr. supra
Change of stagnation of lymph at level of shoulder and trunk	Measurement of % water content (PWC) (ICC 0.92)[20] (see Figure 3) Material MoistureMeterD Compact (Delfin Technologies)[23-25] Reference points Deltoid, 5cm below lateral border of acromion Side of trunk, 5cm below axillary crease Method If skin is recently hydrated, dehydrate skin Sensor is placed perpendicular on the reference points with a pressure that is indicated by the device High electromagnetic wave is sent through the skin which will only be absorbed by water Degree of reflection/ water content can be read on the display of MoistureMeterD	Ratio PWC = PWC affected side / PWC healthy side Change of stagnation of lymph at level of shoulder and trunk = Ratio PWC time 2 – Ratio PWC time 1

Abbreviations: ICC= Intraclass Correlation Coefficient, SEM= Standard Error of Measurement, PWC= Percentage of Water Content

Table 3. Overview of measurement method and procedure of the secondary outcomes

Outcome	Measurement method
Change of extracellular fluid in arm/ shoulder/ trunk	Bio-impedance Spectroscopy (ICC 0.95)[20, 26, 27] 1. Bio-impedance Spectroscopy determining L-Dex value Material Impedimed L-Dex U400 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 Method Subject is in lying position; arms and legs spread Measurements are generated by a low frequency electrical signal transmitted to the patient (3-1000 kHz frequency range) Subject's gender, side at risk and dominant side are entered into the L-Dex software; according to this information, patient-specific instructions concerning the attachment of the color-coded leads are provided by the software program One measurement at each side is performed 2. Bio-impedance Spectroscopy determining phase angle, impedance (5kHz, 50kHz, 100kHz, 200kHz), resistance (50kHz), reactance (50kHz) Material BodyStat Quadscan 4000 Reference points On each hand, two electrodes are placed on the dorsum of the hand On each foot, two electrodes are placed on the dorsum of the foot On the trunk, two electrodes are placed on the sternum

	Method Subject is in lying position; arms and legs spread Two measurements according to two different measurement procedures (including the whole body versus only the arm) of both sides are performed
Change of thickness and reflectivity of cutis and subcutis of arm/ shoulder/ trunk	Measurement of thickness and reflectivity of cutis and subcutis Material Sonoscape S8 Portable ultrasound device Reference points See infra (annex I) Method Subject is seated according to which reference point is being evaluated (see annex I) A high frequency linear probe (10-5 MHz) is used Probe is placed perpendicular to the skin; reference point is located in the middle of the probe Minimal amount of pressure needs to be given Thickness of the cutis and subcutis is determined in mm Images of every reference point are saved with its indicated thicknesses at both sides using a patient-specific code Afterwards, assessment of reflectivity is made based upon the saved images
Change of elasticity of skin and subcutaneous tissue of arm/ shoulder/ trunk	Measurement of induration of skin and subcutaneous tissue Material SkinFibrometer (Delfin Technologies) Device consists of a 1-mm-long intender and records the resistance to 50g of pressure using its reference plate and related built-in force sensors Reference points See infra (annex I)

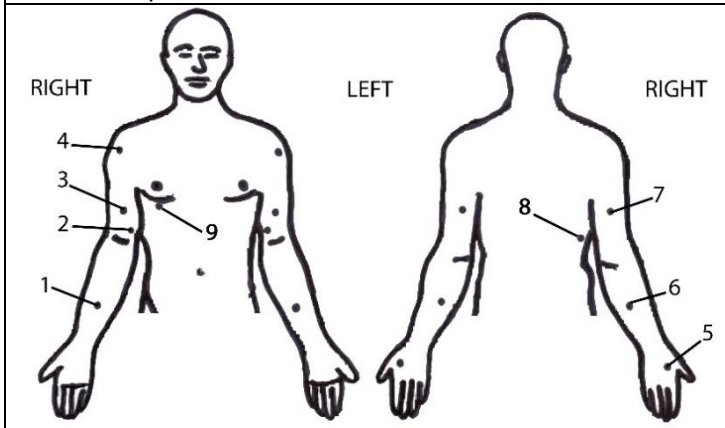
	Method First, the grey button is pressed to activate the device; if the display shows 'ready', the measurement can start Sensor is placed perpendicular on 1 of the 9 indicated points, in order to obtain maximal skin contact a light vertical pressure is applied; the device gives immediately feedback about the pressure and velocity Each measurement is repeated 5 times at each reference point The skin and subcutis resist deformation and induration and the induration force in Newton is determined by calculating the average resistance of 5 measurements A lower value indicates less resistance or softer tissue
Change of problems in functioning	Investigation of % of problems in functioning related to the development of arm lymphedema (ICC Total score: 0.93, SEM Total score: 4.8)[28] Material Lymph-ICF- Questionnaire with Numeric Rating Scale (Dutch and French version) Method At the end of each assessment, subjects are asked to fill in the questionnaire individually Questionnaire consists of 29 questions, divided into 5 domains: physical function, mental function, household activities, mobility activities, and life and social activities A numeric rating scale with 11 possibilities (0-10) is used onto a visual analogue scale Each of the 29 questions corresponds to a score between 0 and 100; a total score and 5 different domain scores are calculated A lower score indicates less problems in functioning
Change of Quality of Life (QoL)	Investigation of Quality of Life of patients with a chronic disease (ICC Total score: 0.93, SEM Total score: 0.44)[29] Material McGill-Quality of Life Questionnaire (Dutch version) Method At the end of each assessment, subjects are asked to fill in the questionnaire individually Questionnaire counts 16+1 questions, which relate to the following 5 domains: physical symptoms; physical wellbeing, psychological symptoms; existential wellbeing and support A Likert scale with 11 possibilities (0-10) is used for the 16 questions and part D is an open question Each question corresponds to a score between 0 (very bad) and 10 (excellent); a total score and 5 different domain scores are calculated

	A lower score indicates a lower Quality of Life
Change of lymphatic architecture and function	Near-infrared fluorescence imaging or lymphofluoroscopy for investigation of superficial lymphatic system (≤2 cm)[30-32] Material Near-infrared fluorescence imaging device with PDE camera Indocyanine Green (IGC) Method Subject is in sitting position with 90° anteflexion of the arm, straight elbow and hand supported on table A tracer (ICG) is injected in the subject's hand into the 1st and the 4th webspace Tracer is excited by near-infrared light and disseminates a fluorescent photon which makes observation of the lymphatic architecture and function possible by visualizing fluorescence of near-infrared light of the injected tracer For a detailed description of the procedure and protocol, see Table 1
Number of episodes of erysipelas	Investigation of the number of episodes of erysipelas in between two assessments Method The number of episodes of erysipelas is directly asked to the patient and noted down at the beginning of every clinical evaluation
Costs	Investigation of direct costs related to the treatment of (side effects of) lymphedema Material Self-developed questionnaire Method Investigation of the amount of direct costs is conducted in all subjects regarding following levels: ○ Compression material (i.e. bandaging material, stockings, gloves, accessories,…) ○ Medication related to the treatment of (the acquired side effects of) lymphedema (i.e. diuretics, antibiotics,…) ○ Diagnostics: imaging procedures related to the disease, blood examination (i.e. infection,…) ○ Human recourses: ▪ Admissions to the hospital/ surgery

	▪ Consultation(s) with a general practitioner or medical doctor/ physiotherapist/ psychologist/ nutrition specialist/ nurse/ other due to the disease, inside or outside the hospital. ▪ …

Annex I

Reference points



1. **Ventral side forearm:**
   15cm distally of the elbow crease
2. **Medial side upper arm:**
   3cm proximally of the medial epicondyle of the humerus
3. **Ventral side upper arm:**
   7cm proximally of the elbow crease
4. **Shoulder:**
   5cm distally of the lateral border of the acromion
   in the direction of the lateral epicondyle of the humerus
5. **Hand:**
   Central point between dorsal side thumb and index finger
6. **Dorsal side forearm:**
   10cm distally of the proximal border of the olecranon
7. **Dorsal side upper arm:**
   7cm proximally of the proximal border of the olecranon
8. **Trunk:**
   5cm distally of the dorsal axillary fold
9. **Breast:**
   Lumpectomy: 3cm distally of the nipple (in case of mastectomy: 3cm distally from the middle of the scar)

Measurement position

- Ventral side forearm (1), medial side upper arm (2), ventral side upper arm (3):
  - Sitting position with forearm partly supported on the table
  - Elbow slightly flexed, supination of forearm, arm slightly abducted
- Shoulder (4), hand (5), dorsal side forearm (6), dorsal side upper arm (7):
  - Sitting position with forearm partly supported on the table
  - Pronation of forearm
  - Fingers slightly abducted
- Trunk (8): Standing position, arms relaxed beside the body

Breast (9): Supine position

Abbreviations: ICC= Intraclass Correlation Coefficient, SEM= Standard Error of Measurement

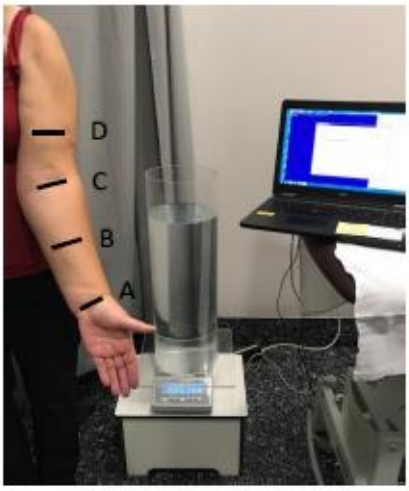
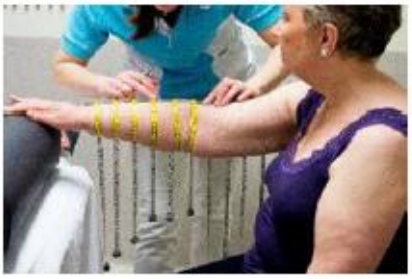
Primary outcome	Picture
Change of lymphoedema volume of whole arm/ hand/ distal lower arm/ proximal lower arm/ upper arm	Water displacement method  Reference points A: Ventral side wrist/ distal crease, B: Middle between reference point A and C, C: Middle elbow crease, D: 10 cm proximal of elbow crease
Change of lymphoedema volume of whole arm	Circumference measurements  Reference points Proximal border olecranon
Change of stagnation of lymph at level of shoulder and trunk	Measurement of % water content (PWC)  Reference points See Table 3 annex I

Figure 3. *Illustration of primary outcome measurement devices*

Interventions

The treatments in both phases are shown in the study flow chart (see Figure 1) and different treatment modalities are described in Table 4.

Treatments are provided by three different physical therapists in the University Hospitals of Leuven (RVH, LB, LV), two in Saint-Pierre University Hospital in Brussels as well as in General Hospital Groeninge in Kortrijk (LV, TDV) and one in Antwerp University Hospital (TDV), all experienced in the treatment of BCRL. Same therapists give the standard therapy as well as the MLD, but to limit any subjective influences of the therapist, a standardized treatment protocol has been developed. Multiple training and evaluation sessions are performed to make the therapists familiar with the procedure and to ensure that the treatments given by each therapist are identical. Therapists are blinded to the participant's data collected during clinical evaluations.

All participants receive a standard treatment for lymphedema consisting of information, skin care, compression therapy (bandage/ compression stocking) and exercise; referred to as decongestive lymphatic therapy[4]. The only treatment modality that differs among the three groups is the application of MLD (fluoroscopy-guided MLD versus traditional MLD versus placebo MLD). Participants receive 14 sessions during the three weeks of intensive treatment for lymphedema. Thereafter they receive during 6 months a maintenance treatment with 18 sessions in decreasing frequency (i.e. 2 weekly sessions during month 1; 1 weekly session during month 2; 2 two-weekly sessions during months 3-4; 1 monthly session during months 5-6).

Each intensive treatment session lasts for 60 minutes: 30 minutes of standard treatment (skin care, bandaging, exercises) and 30 minutes of MLD. Treatment starts with drainage of the shoulder and trunk, is followed by removal of the bandage and circumference measurements of the arm using a perimeter[22]. Afterwards, drainage of the arm (and hand), shoulder and trunk is continued. After MLD, skin care and bandaging is applied and the session ends with performing exercises. In the maintenance phase, therapeutic sessions last for 30 minutes as they only consist of skin care and manual lymph drainage. Additionally, participants perform exercises at home as they are wearing compression garment during daytime (sleeve and glove).

Table 4. Treatment modalities

	Modality	Duration	Intensive treatment		
Standard treatment	Information		Patient receives a leaflet with information about the lymphatic system and lymphedema, clinical evaluation and conservative treatment of lymphedema. During the treatments, this information is provided orally as well.		
	Skin care	5min	Skin is hydrated during the session. If wounds are present, the wound is cared for.		
	Multi-layer bandaging	15min	The bandage consists of different layers: a cotton tube embraces the limb and protects the skin; the cotton wool decreases the pressure under the bandage or protects the skin against injuries from the bandages; padding with structure creates a massage-effect under the bandage; inelastic (low-stretch) bandages, also applied from distal to proximal and in a crisscross pattern, provide an axial rotation of the whole bandage and an improvement of the lymphatic transport. At the start of the treatment, MLD is applied on the shoulder/ trunk in a first phase (with bandage), and on the arm/ hand in a second phase (without bandage). After MLD, hydration of the skin is performed. The bandage is applied again after hydrating the skin; than the patient performs the exercises. Patients have to wear the multi-layer bandage daily during day and night. Patients are also taught to bandage themselves. In case of slipping down of the bandage or in case of pain, the patient has to change the bandage her-/himself.		
	Exercise therapy	10min	Patients have to perform upper limb exercises while wearing the multi-layer bandage. They have to perform these exercises a second time at home and twice daily during the weekend. They are advised to use the arm as normal as possible. <u>Exercises:</u> - Mobilizing and stretching exercises - Lymphatic transport-enhancing exercises - Breathing exercises		
Experimental treatment	MLD	30min	<u>Fluoroscopy-guided MLD:</u> Therapist applies hand movements of higher pressure (up to 80 mmHg) which consist of following techniques: - Cleaning techniques to empty the lymph nodes at the level of	<u>Traditional MLD:</u> Therapist applies hand movements of lower pressure (up to 40 mmHg) which consists of following techniques: - Cleaning techniques to empty the lymph nodes at the level of	<u>Placebo MLD:</u> Deep massage by performing relaxing transverse movements on the muscles of the ipsilateral neck, back, shoulder, arm and hand. Following explanation to the patient about the effect of

			the clavicula, axilla, humerus and elbow; - Resorption technique with the thumb to create resorption of lymph by the lymph capillaries; - Gliding technique alongside the skin to stimulate transport of lymph through the lymph collectors or to stimulate transport of lymph through the rerouting. - Above mentioned techniques are described in the same way to the patient in order to explain this irregular ('new') type of MLD. MLD is also based on the assessment by fluoroscopy. During the drainage session, the therapist has to consider the photo of the patient (= the lymph mapping) and her/him lymphatic transport obtained by the lymphofluoroscopy.	the clavicula, axilla, humerus and elbow; - Drainage of the jugular and occipital region, stimulating lymph collectors on the trunk, shoulder, arm and hand; - 'Pumping' technique while stretching the skin to stimulate lymphatic transport through the lymph collaterals. - Above mentioned techniques are in the same way described to the patient to support the purpose of this applied drainage. MLD is performed based on 'normal' anatomy of the lymphatic system, without knowledge of the patient-specific lymphatic architecture.	the treatment is given to prevent suspicion for this irregular type of MLD: 'After axillary lymph node dissection, the superficial lymphatic network partially disappears (i.e. axillary web syndrome). Lymph transport mainly happens through the deep lymphatic network that is surrounded by the muscles. By relaxing the muscles lymphatic transport through the deep lymphatic network will improve.'
	Modality	**Duration**	**Maintenance treatment**		
Standard treatment	Skin care	5min	Skin is hydrated during the session. If wounds are present, the wound is cared for.		
	Compression garment	All day	Patients have to wear a custom-made compression sleeve and glove at daytime.		
	Exercise therapy	At home (2x10min)	Patients have to perform upper limb exercises twice daily at home, while wearing the compression garment.		
Experimental treatment	MLD	30min	Fluoroscopy-guided MLD	Traditional MLD	Placebo MLD
			Patients are taught to perform a self-drainage daily at home, except the days patients are visiting the therapist.		

Sample size calculation

The required sample size for the study is 201 subjects or 67 subjects per group to detect a difference of 15% in the reduction of lymphedema volume at the level of the arm or hand (primary outcome) or at the level of the shoulder or trunk (primary outcome) between the three groups. This is based on an alpha of 0.0125, a power of 80% and a two-way ANOVA for repeated measures analysis. The effect size is determined from clinical results of the Leuven Lymphovenous Centre and by consulting experts in the field of lymphology. 73 patients with unilateral BCRL were followed in the Leuven Lymphovenous Centre between November 2011 and November 2013. All patients received decongestive lymphatic therapy. Lymphedema volume of the arm reduced 36% (±28%) on average. According to different experts in the field of lymphology, an additional reduction of the lymphedema volume of 15% is clinically relevant. This can be a reduction of the lymphedema volume at the level of the arm/ hand OR at the level of the shoulder/ trunk. Consequently, the estimated reduction after the intensive phase is 35% (±25%) for the traditional MLD group, 50% (±25%) for the fluoroscopy guided MLD group, and 20% (±25%) for the placebo MLD group. Based on a previous longitudinal study with breast cancer patients [33], a drop-out rate of 5% is estimated (or 9 patients). The group with fluoroscopy-guided MLD is compared to the group with traditional MLD, and the group with fluoroscopy-guided MLD is compared to placebo MLD. This explains why an alpha level of 1.25% was chosen (and not 5%) (= 2 times Bonferroni correction). In literature, data on change of lymphedema volume at the level of the shoulder/ trunk is missing.

Statistical methods

The statistical analysis plan was developed under supervision of a statistician of Leuven Biostatistics and Statistical Bioinformatics Centre (L-BioStat). Following hypotheses will be tested:

Patients receiving fluoroscopy-guided MLD additional to decongestive lymphatic therapy will have a significantly 1) greater reduction of lymphedema volume at the level of the hand or arm OR 2) less stagnation of lymph at the level of the shoulder or trunk; than patients receiving traditional MLD or placebo MLD. To test the hypotheses a two-way ANOVA for repeated measures will be applied, assisted with post hoc analyses for further evaluation. Data will be analyzed according the intention-to-treat principle.

Discussion

This will be the first multi-center double-blind RCT to investigate the effectiveness of lymphofluoroscopy-guided MLD, in addition to the other parts of the decongestive lymphatic therapy, for the treatment of BCRL. If the current trial is able to demonstrate a significant improvement in change of lymphedema volume at the level of the arm/ hand or in stagnation of lymph at the level of the shoulder/ trunk, due to the application of fluoroscopy-guided MLD, a clear answer to the question 'do we need to implement fluoroscopy-guided MLD in the conservative decongestive treatment of BCRL' can be stated. If the current study fails to prove an additional value of fluoroscopy-guided MLD or traditional MLD to placebo MLD, then MLD may be omitted from the decongestive lymphatic therapy. If MLD is omitted, a large reduction in therapy burden and a large reduction in social services costs can be achieved. If fluoroscopy-guided MLD is equally effective than traditional MLD and both are more effective than placebo MLD, traditional MLD has to be continued. Less expenses have to be made for the reimbursement of lymphofluoroscopic investigations.

Acknowledgements

The authors are very grateful to the hospitals and research teams collaborating in this study. The authors also extend very grateful thanks to the study participants.

All authors critically revised the manuscript for important intellectual content and approved the final manuscript. This protocol is published on behalf of the EFforT-BCRL study group.

References

1. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol. 2013;14(6):500-15.
2. Ashikaga T, Krag DN, Land SR, Julian TB, Anderson SJ, Brown AM, et al. Morbidity results from the NSABP B-32 trial comparing sentinel lymph node dissection versus axillary dissection. Journal of surgical oncology. 2010

102(2):111-8.
3. Pusic AL, Cemal Y, Albornoz C, Klassen A, Cano S, Sulimanoff I, et al. Quality of life among breast cancer patients with lymphedema: a systematic review of patient-reported outcome instruments and outcomes. J Cancer Surviv. 2013;7(1):83-92.
4. ISL. The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology. Lymphology. 2013;46(1):1-11.
5. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet. 2015;385(9972):977-1010.
6. Karki A, Anttila H, Tasmuth T, Rautakorpi U. Lymphedema therapy in breast cancer patients -- a systematic review on effectiveness and a survey of current practices and costs in Finland. Acta Oncologica 2009 Aug;48(6):850-859. 2009.
7. Huang TW, Tseng SH, Lin CC, Bai CH, Chen CS, Hung CS, et al. Effects of manual lymphatic drainage on breast cancer-related lymphedema: a systematic review and meta-analysis of randomized controlled trials. World J Surg Oncol. 2013;11:15.
8. Ezzo J, Manheimer E, McNeely ML, Howell DM, Weiss R, Johansson KI, et al. Manual lymphatic drainage for lymphedema following breast cancer treatment. Cochrane Database Syst Rev. 2015(5):Cd003475.
9. Bergmann A, da Costa Leite Ferreira MG, de Aguiar SS, de Almeida Dias R, de Souza Abrahao K, Paltrinieri EM, et al. Physiotherapy in upper limb lymphedema after breast cancer treatment: a randomized study. Lymphology. 2014;47(2):82-91.
10. Gradalski T, Ochalek K, Kurpiewska J. Complex Decongestive Lymphatic Therapy With or Without Vodder II Manual Lymph Drainage in More Severe Chronic Postmastectomy Upper Limb Lymphedema: A Randomized Noninferiority Prospective Study. J Pain Symptom Manage. 2015;50(6):750-7.
11. Kwon S, Price RE. Characterization of internodal collecting lymphatic vessel function after surgical removal of an axillary lymph node in mice. Biomed Opt Express. 2016;7(4):1100-15.
12. Ahmed RL, Schmitz KH, Prizment AE, Folsom AR. Risk factors for lymphedema in breast cancer survivors, the Iowa Women's Health Study. Breast cancer research and treatment. 2011;130(3):981-91.
13. Weissleder H, Weissleder R. Lymphedema: evaluation of qualitative and quantitative lymphoscintigraphy in 238 patients. Radiology. 1988;167(3):729-35.
14. Moshiri M, Katz DS, Boris M, Yung E. Using lymphoscintigraphy to evaluate suspected lymphedema of the extremities. AJR Am J Roentgenol. 2002;178(2):405-12.
15. Rasmussen JC, Tan IC, Marshall MV, Adams KE, Kwon S, Fife CE, et al. Human Lymphatic Architecture and Dynamic Transport Imaged Using Near-infrared Fluorescence. Transl Oncol. 2010;3(6):362-72.
16. Tomson D, Lessert C, Luthi I, Mazzolai L, Depairon M. [Lymphatic vascular pathologies: contribution of lympho-fluoroscopy]. Rev Med Suisse. 2015;11(460):362-5.
17. Belgrado JP, Vandermeeren L, Vankerckhove S, Valsamis JB, Malloizel-Delaunay J, Moraine JJ, et al. Near-Infrared Fluorescence Lymphatic Imaging to Reconsider Occlusion Pressure of Superficial Lymphatic Collectors in Upper Extremities of Healthy Volunteers. Lymphatic research and biology. 2016;14(2):70-7.

18. Tan IC, Maus EA, Rasmussen JC, Marshall MV, Adams KE, Fife CE, et al. Assessment of lymphatic contractile function after manual lymphatic drainage using near-infrared fluorescence imaging. Archives of physical medicine and rehabilitation. 2011;92(5):756-64.e1.
19. Moher D, Schulz KF, Altman D. The CONSORT Statement: revised recommendations for improving the quality of reports of parallel-group randomized trials 2001. Explore (NY). 2005;1(1):40-5.
20. Hidding JT, Viehoff PB, Beurskens CH, van Laarhoven HW, Nijhuis-van der Sanden MW, van der Wees PJ. Measurement Properties of Instruments for Measuring of Lymphedema: Systematic Review. Physical therapy. 2016;96(12):1965-81.
21. Gebruers N, Truijen S, Engelborghs S, De Deyn PP. Volumetric evaluation of upper extremities in 250 healthy persons. Clinical physiology and functional imaging. 2007;27(1):17-22.
22. Devoogdt N, Lemkens H, Geraerts I, Van Nuland I, Flour M, Coremans T, et al. A new device to measure upper limb circumferences: validity and reliability. International angiology : a journal of the International Union of Angiology. 2010;29(5):401-7.
23. Nuutinen J, Ikaheimo R, Lahtinen T. Validation of a new dielectric device to assess changes of tissue water in skin and subcutaneous fat. Physiological measurement. 2004;25(2):447-54.
24. Czerniec SA, Ward LC, Kilbreath SL. Assessment of breast cancer-related lymphedema: a comparison of moisture meter and spot bioimpedance measurement. Lymphatic research and biology. 2015;13(1):10-9.
25. Mayrovitz HN, Weingrad DN, Davey S. Local tissue water in at-risk and contralateral forearms of women with and without breast cancer treatment-related lymphedema. Lymphatic research and biology. 2009;7(3):153-8.
26. Shah C, Arthur DW, Wazer D, Khan A, Ridner S, Vicini F. The impact of early detection and intervention of breast cancer-related lymphedema: a systematic review. Cancer Med. 2016;5(6):1154-62.
27. Shah C, Vicini FA, Arthur D. Bioimpedance Spectroscopy for Breast Cancer Related Lymphedema Assessment: Clinical Practice Guidelines. Breast J. 2016;22(6):645-50.
28. Devoogdt N, Van Kampen M, Geraerts I, Coremans T, Christiaens MR. Lymphedema Functioning, Disability and Health questionnaire (Lymph-ICF): reliability and validity. Physical therapy. 91. United States2011. p. 944-57.
29. De Vrieze T, Coeck D, Verbelen H, Devoogdt N, Tjalma W, Gebruers N. Cross-cultural Psychometric Evaluation of the Dutch McGill-QoL Questionnaire for Breast Cancer Patients. Facts Views Vis Obgyn. 2016;8(4):205-9.
30. Unno N, Nishiyama M, Suzuki M, Tanaka H, Yamamoto N, Sagara D, et al. A novel method of measuring human lymphatic pumping using indocyanine green fluorescence lymphography. J Vasc Surg. 2010;52(4):946-52.
31. Marshall MV, Rasmussen JC, Tan IC, Aldrich MB, Adams KE, Wang X, et al. Near-Infrared Fluorescence Imaging in Humans with Indocyanine Green: A Review and Update. Open Surg Oncol J. 2010;2(2):12-25.
32. Mihara M, Hara H, Araki J, Kikuchi K, Narushima M, Yamamoto T, et al. Indocyanine green (ICG) lymphography is superior to lymphoscintigraphy for diagnostic imaging of early lymphedema of the upper limbs. PloS one. 2012;7(6):e38182.
33. Devoogdt N, Christiaens MR, Geraerts I, Truijen S, Smeets A, Leunen K, et al. Effect of manual lymph drainage in addition to guidelines and exercise therapy on arm lymphedema related to breast cancer: randomised controlled trial. Bmj. 2011;343:d5326.

CHAPTER 2

Chapter 2

EFFECTIVENESS OF FLUOROSCOPY-GUIDED MANUAL LYMPH DRAINAGE, IN ADDITION TO DECONGESTIVE LYMPHATIC THERAPY, FOR THE TREATMENT OF BREAST CANCER-RELATED LYMPHEDEMA: A MULTI-CENTER RANDOMIZED CONROLLED TRIAL (EFFORT-BCRL TRIAL)

Draft – in preparation for submission

Tessa De Vrieze
Nick Gebruers
Ines Nevelsteen
Steffen Fieuws
Sarah Thomis
Wiebren A.A. Tjalma
Jean-Paul Belgrado
Liesbeth Vandermeeren
Chris Monten
Marianne Hanssens
Nele Devoogdt

Abstract

Background: Manual lymph drainage (MLD) is widely applied to treat breast cancer-related lymphedema (BCRL), but its effectiveness and true merit remains unclear. Pooled data demonstrated a limited non-significant additional effect. Near-infrared fluorescence imaging has been introduced to visualize the superficial lymphatic architecture which allows MLD at the most needed location.

Objective: To investigate the effectiveness of fluoroscopy-guided manual lymph drainage (MLD) additional to a standardized decongestive lymphatic therapy (DLT) and compared to a traditional as well as a placebo MLD, for the treatment of breast cancer-related lymphedema (BCRL).

Design: Multi-center, three-arm, double-blinded randomized controlled trial with concealed allocation and intention-to-treat analysis.

Setting: Four university hospitals and one general hospital in Belgium.

Participants: 194 participants (1 man and 193 women; mean age 61 years) with unilateral BCRL were enrolled. Five patients dropped-out during the intensive treatment phase of which 4 were lost to follow-up, leaving 190 participants in the analyses set (63 fluoroscopy-guided MLD, 63 traditional MLD, 64 placebo MLD).

Interventions: Participants were randomized into one of the three treatment groups, receiving standard treatment (education, skin care, compression therapy and exercises) either including fluoroscopy-guided MLD, traditional MLD or placebo MLD. Participants daily received 60 minutes of treatment during the 3-week intensive phase. Afterwards they received 18 sessions of 30 minutes during the 6-months maintenance phase. Follow-up comprised 6 months.

Main outcome measures: Primary outcomes were 1) change in excessive volume reduction at the level of the arm and/or hand, and 2) change in excessive volume accumulation at level of the shoulder/trunk. Primary endpoint was post-intensive phase. Secondary outcomes were 1) change in amount of problems in functioning, and 2) change in overall quality of life. Measurements were performed at baseline, at the end of the intensive phase, after 1, 3 and 6 months of maintenance treatments, and after 6 months of follow-up.

Results: In all three groups, excessive lymphedema volume was significantly decreased after three weeks of intensive treatment ($p<0.001$). No differences between the fluoroscopy-guided MLD group (relative reduction of 23.3%) and the traditional MLD group (20.9%) ($p= 0.890$), or between the fluoroscopy-guided MLD group and the placebo MLD group (24.8%) ($p= 0.826$) were found. An increased fluid accumulation at the level of the shoulder/trunk was present in all three treatment groups, with a post-intensive statistically significant increase in the fluoroscopy-guided MLD group

(p<0.001). No significant differences were present between the groups (a relative increase of 95.6% in the fluoroscopy-guided MLD group, 15.7% in the traditional MLD group, and 35.1% in the placebo MLD group). There were no statistically significant differences between the groups with respect to any of the secondary outcomes.

Conclusions: An additional benefit of MLD in general, as an adjunct to the other components of decongestive lymphatic therapy, could not be demonstrated. There is no indication to still include time-consuming MLD in the standard treatment of BCRL.

Trial registration: clinicaltrials.gov identifier: NCT02609724, EudraCT Number 2015-004822-33

Introduction

According to the recommendations of the International Society of Lymphology (ISL), lymphedema needs to be treated with decongestive lymphatic therapy (DLT) (also known as combined/complex physical therapy) and is a two-stage treatment.[1] During the first or intensive phase, lymphedema is maximally reduced. This phase consists of skin care, manual lymph drainage (MLD), multi-layer bandaging and exercise therapy. The second or maintenance phase aims to conserve and optimize the results obtained in the first phase. It consists of skin care, a compression sleeve, exercises and MLD.

Due to significantly improved screening and early treatment modalities for breast cancer over the last few years, survival rates are growing.[2] As a result, also the impact of breast cancer-related lymphedema (BCRL) becomes more apparent. Worldwide, almost all lymphedema patients receive MLD as part of their treatment, which can be time-consuming for patients and entails a big financial cost for the patient as well as for the Health Care system.[3] However, a meta-analysis, including six randomized controlled trials (RCT's), and a Cochrane systematic review have questioned the effectiveness of MLD.[4, 5] The meta-analysis showed an overall additional benefit of MLD to the treatment of BCRL of 75ml on volume reduction, while the systematic review revealed that the individual contribution of MLD was limited to 7%.[4, 5] Moreover, three RCT's were unable to demonstrate an additional effect of MLD to DLT in reducing lymphedema volume.[6-8] Also the improvement in other outcome parameters such as quality of life[7], patient experience of heaviness and tension[8], and health status[8] did not significantly differ between groups receiving DLT with or without additional MLD. The lack of unambiguous and convincing results from the current literature has contributed to the fact that more recent guidelines no longer prime MLD as a first-line treatment, but suggest to rather nuance its indication according to the etiology of the edema and to the patient's treatment phase.[9, 10] Indications that MLD during the maintenance phase is effective, are absent.[9, 10]

A possible explanation why MLD as applied in previous studies has a rather limited benefit in addition to the other parts of DLT, is that MLD was applied in an inefficient or 'blind' way, and according to the normal lymphatic anatomy. This method of MLD is called 'traditional MLD' throughout this paper. However, after dissection of axillary lymph nodes, whether or not in combination with irradiation, the lymphatic system of the upper limb is damaged. Lymph nodes are removed and often fibrosis of the superficial lymphatic system ensues.[11, 12] As a result, reverse flow of lymph fluid coming from collecting vessels and going through precollecting vessels in direction of the dermal capillaries, called dermal backflow[13], can occur. Moreover, rerouting of lymphatic drainage via lymph collaterals and dermal capillaries, also called dermal rerouting, has been described in patients with lymphedema.[14, 15] This rerouting is patient-specific. Therefore, it is proposed that traditional MLD needs to be

abandoned for a tailored approach. Near-infrared fluorescence imaging or lymphofluoroscopy can aid to apply a more efficient MLD. During this investigation, diluted Indocyanine Green (ICG) is injected intradermally in the hand. It visualizes the superficial transport of lymph from the hand up to the axilla and it demonstrates alternative pathways towards other lymph nodes.[16]

A second explanation why traditional MLD has not proven to be effective, might be that the therapist does not optimally stimulate lymphatic transport. Resorption of lymph capillaries performed with the thumb gives a higher pressure than when performed with the hand like in the traditional MLD. In addition, gliding (compared to no gliding) is hypothesized to be more effective to enhance lymphatic transport.[17] The adapted maneuvers in combination with the knowledge of the fluoroscopic findings, is throughout this paper referred to as fluoroscopic-guided MLD.

Promising findings regarding the use of a lymphofluoroscopic investigation to aid in the therapeutic management of BCRL in order to allow a personal approach to MLD, have already been established.[18] Furthermore, the physiological effect of one session of fluoroscopy-guided MLD has already been demonstrated in healthy volunteers and patients with BCRL.[17, 19] More recently, also other studies have demonstrated a positive, albeit short-term, physiological effect (enhanced lymphatic transport) after a single session of traditional MLD according to Vodder[20] and Leduc MLD schools[21]. However, whether the application of different sessions of fluoroscopy-guided MLD has a clinical and long-lasting effect on lymphedema, superior to traditional MLD, has yet to be established. Additionally, experiences in clinical practice revealed that patients report a positive subjective feeling after MLD. Whether this is a real effect rather than a (subjective) placebo-effect, needs to be investigated as well. Therefore, a three-arm RCT was conducted to examine the effectiveness of fluoroscopy-guided MLD versus traditional MLD and versus placebo MLD, applied as part of the DLT, for the treatment of BCRL.

Methods

Study design and setting

The EFforT-BCRL trial is a multi-center, double-blind, three-groups RCT. The design of the RCT is described in detail elsewhere.[22] Participants received an intensive treatment lasting 3 weeks and a maintenance treatment for 6 months. Additional follow-up of another 6 months was established. All participants received a standard treatment consisting of skin care, education, compression therapy, and exercises. Only MLD differed among the three groups: the intervention group received a fluoroscopy-guided MLD, control group one received the traditional MLD and control group two received placebo MLD. The participants were assessed before the start of the trial, after 3 weeks of

intensive treatment, after 1, 3 and 6 months of maintenance treatment and after 6 months of follow-up.

Participants were recruited in four university hospitals and one general hospital in Belgium. Accordingly, all treatments and assessments were performed at the department of Physical Medicine and Rehabilitation (treatment and clinical assessment) and at the department of Vascular Surgery (lymphofluoroscopy) of the University Hospitals of Leuven (UH Leuven), at the Edema Clinic (treatment and clinical assessment) and Multidisciplinary Breast Clinic (lymphofluoroscopy) of the Antwerp University Hospital (UH Antwerp), at the Lymphology Clinic in Saint-Pierre University Hospital in Brussels (UH Saint-Pierre), at the Center for Radiotherapy (treatment and clinical assessment) and the Department of Plastic Surgery (lymphofluoroscopy) of Ghent University Hospital (UH Ghent) and at the Center of Oncology of General Hospital Groeninge (GH Groeninge) in Kortrijk.

This trial had been approved by the Ethical Committee of the UH Leuven (main Ethical Committee) and received positive advise from the Ethical Committees of all other participating centers (CME reference number S58689, EudraCT Number 2015-004822-33). The trial has been registered in clinicaltrials.gov (NCT02609724). The paper used the recommended CONSORT guideline to report on the following items.[23]

Participants

Participants were recruited between February 2016 and September 2019. Eligibility criteria for the EFforT-BCRL trial were: 1) patients with unilateral lymphedema of the arm and/or hand, developed after treatment for breast cancer, 2) chronic lymphedema stage I to IIb (duration of >3 months), 3) at least 5% difference between both arms and/or between both hands, adjusted for limb dominance, and 4) no active metastases. Patients were excluded when one of the following criteria were present: 1) age <18y, 2) edema of the upper limb from another cause than breast cancer treatment, 3) cannot participate during the entire study period, 4) mentally or physically unable to participate in the study, 5) allergy for iodine, sodiumiodine, Indocyanine Green, 6) increased activity of the thyroid gland; benign tumors of the thyroid gland, 7) lymph node transplantation or lymphovenous shunt in the past, 8) bilateral axillary lymph node dissection.

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

Intervention

All participants received a standard treatment for lymphedema consisting of education regarding self-management, skin care, compression therapy (multilayer bandaging followed by a compression sleeve and hand glove) and exercises; referred to as DLT.[1] The only treatment modality that differed among the three groups was the application of MLD (fluoroscopy-guided MLD vs. traditional MLD vs. placebo MLD). Participants were planned to receive 14 individual sessions during the three weeks of intensive treatment. Thereafter they received during 6 months a maintenance treatment with 18 individual sessions in decreasing frequency (i.e. 2 weekly sessions during month 1; 1 weekly session during month 2; 2 two-weekly sessions during months 3-4; 1 monthly session during months 5-6).

Each intensive treatment session lasted for 60 minutes: 30 minutes of standard treatment (education, skin care, bandaging, exercises) and 30 minutes of MLD. Treatment started with drainage of the shoulder and trunk, was followed by removal of the bandages and circumference measurements of the arm using a perimeter.[24] Afterwards, drainage of the arm (and hand), shoulder and trunk was continued. After MLD, skin care and multilayer bandages were applied and the session ended with performing exercises. In the maintenance phase, therapeutic sessions lasted for 30 minutes as they only consisted of skin care and MLD. Additionally, participants performed exercises twice per day at home as they were wearing compression garment during daytime (sleeve and glove). Also patients needed to perform a daily self-MLD, except for the days treatment was provided by the therapist. During the entire study period, treatment adherence per patient was evaluated by means of a diary that patients needed to fill in. For all details regarding the treatment and the different treatment modalities, we refer to the publication of the trial's protocol.[22]

Treatments were provided by four different physical therapists in UH Leuven (RVH, LB, LV, AKH), two in UH Saint-Pierre (LV, TDV), GH Groeninge (LV, TDV) and UH Ghent (LV, TDV) and one in UH Antwerp (TDV); all specialized in edema therapy and trained in DLT prior to the start of this study. Same therapists gave the standard therapy as well as the MLD, but to limit any subjective influences of the therapist, a standardized treatment protocol had been developed. Multiple training and evaluation sessions were performed to make the therapists familiar with the procedure and to ensure that the treatments given by each therapist were identical. Therapists were blinded to the participant's data collected during clinical evaluations.

Assessments

All participants received a **lymphofluoroscopic assessment** at baseline (B0), post-intensive (P) and post-maintenance phase (P6). The baseline lymphofluoroscopy was used to determine the procedure of MLD (i.e. which hand maneuvers at which location[17]) in the group receiving fluoroscopy-guided MLD. **Clinical assessments** occurred at baseline (B0), after intensive treatment (P), after 1 (P1), 3 (P3) and 6 (P6) months of maintenance treatment and after 6 months follow-up (P12). For a detailed description regarding the fluoroscopic and different clinical assessments, see the protocol of the EFforT-BCRL trial.[22]

All lymphofluoroscopic assessments were standardized and performed by a vascular surgeon (ST), plastic surgeon (LV) or radiation oncologist (CM) (the same doctor for every patient) and each time assisted by the same physical therapist (ND, NG, KD), all of them experienced in performing this investigation. Both the doctor and physical therapist were blinded to the participant's data as well as to their assigned therapy.

The clinical assessments were standardized and performed by four assessors (KD, LV, TDV, SVDB), according to the institution of participation. Each assessor was assigned to one or more study center(s) and participants were evaluated by the same assessor. Participants were told not to mention information concerning their treatment during the evaluations, to ensure blinding of the assessor. In addition, the assessor was blinded to previous measurement data in order to avoid being influenced by previous results.

Outcome measures

Details of the primary and secondary outcome measures, their measurement methods and procedures are presented in Table 1.

A **first primary outcome** measure was the change in excessive lymphedema volume (analyzed by means of the inter-limb ratio) at the level of the arm and/or hand. In case patients were included in the trial because of the *presence of arm lymphedema* (based on a relative excessive volume of at least 5% at the level of the whole arm), the change in total excessive arm (including hand) volume was considered as outcome measure by calculating the volumes using a perimeter.[24] Although, as the volume of the hand is not included in this calculation, the hand volume (separately determined using the ValGrado® water displacement method[25]) was added to the calculated arm volumes afterwards. In case patients were included in the trial because of the *presence of only hand lymphedema* (based on a relative excessive volume of at least 5% at the level of the hand), only the excessive hand volume (also determined using the ValGrado® water displacement method), was considered as outcome measure. A **second primary outcome** measure was the change in excessive fluid accumulation at the

level of the shoulder and trunk (average between both inter-limb ratios), which was assessed using the MoistureMeterD® Compact (MMDC) device (Delfin Technologies, Kuopio, Finland).[26]

The two **secondary outcome** measures being examined were the change in amount of problems in functioning due to the lymphedema (measured using the Lymph-ICF-UL questionnaire[27]), and change in overall quality of life (measured using the McGill QoL questionnaire[28]).
Additionally, during the entire study period, episodes of erysipelas and adverse effects related to the treatment or fluoroscopic examinations were recorded. At the last clinical evaluation after 6 months follow-up (P12), the overall treatment and outcome satisfaction as well as the prediction of group allocation were assessed by means of a survey.

Table 1. Overview of the measurement methods and procedures of the primary and secondary outcomes

PRIMARY OUTCOME MEASURES			
Outcome		Measurement method	Procedure
1	Change of excessive lymphedema volume at the level of the **hand** => for patients included in the trial because of the *presence of only hand lymphedema*, (based on an relative excessive volume of at least 5% at the level of the hand), this was the only outcome measure.	**Water displacement method** (ICC 0.99; SEM% 0.7%)[29] Material Cylinder filled with water of 20-30°C, placed on weighing balance with 0.1g accuracy (KERN 572); both are placed on top of a platform of 25 cm height Weighing balance is connected with software program on laptop; software program performs 10 volume measurements and calculates mean volume (Volume of upward displaced water = Mass of water/ density of water, density of water with T° between 20-30°C is 1); a signal is given if mean volume or its standard deviation is outside of preset range Reference point Lower ventral fold at level of wrist Method Jewelry at level of hand or arm is removed Subject is positioned in standing beside the cylinder Subject is drawn attention not to touch the border of the cylinder Hand is put in the cylinder with axis perpendicular to water surface; up to reference point at the wrist; Once the subject holds the hand stable, the assessor clicks on the assessment button on the program and the volume is determined	Volume of hand = volume up to reference point at wrist The volume of the non-dominant hand/arm is on average 3.3% smaller than the dominant hand/arm.[30, 31] Therefore, the volume of the hand at the healthy side is corrected for hand dominance: - Multiplied by 0.967 if the affected side is the dominant side - Divided by 0.967 if the affected side is the non-dominant side Relative excessive lymphedema volume of hand (ratio) = (volume affected side) / (corrected volume healthy side) Change of relative excessive lymphedema volume of hand = Comparison between ratio time 1 and ratio time 2 in analysis
	Change of excessive lymphedema volume at the level of the **arm** => for patients included in the trial because of the *presence of arm lymphedema (*based on a relative excessive	**Circumference measurements** (ICC 0.99; SEM% 1.2%)[24, 29] Material Perimeter, which is a flexible stainless steel bar with a tapeline fixed every 4cm and a weight of 20g at the end Reference points Upper border of olecranon	Volume of whole arm = sum of volumes of all segments of arm Volume of 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 The volume of the non-dominant hand/arm is on average 3.3% smaller than the dominant hand/arm.[30, 31] Therefore, the volume of the hand at the healthy side is corrected for hand dominance:

	volume of at least 5% at the level of the whole arm), hand volume was added to arm volume.	Method Jewelry at level of hand or arm is removed Subject is in sitting position with 90° anteflexion of the arm, straight elbow and hand supported on table Arm circumferences measured at olecranon and at 4, 8, 12, 16 and 20 cm proximal and distal of olecranon	- Multiplied by 0.967 if the affected side is the dominant side - Divided by 0.967 if the affected side is the non-dominant side Relative excessive lymphedema volume of arm and hand (ratio) = [(volume arm + volume hand (cfr. supra) affected side) / (corrected volume arm + corrected volume hand (cfr. supra) healthy side)] Change of relative excessive lymphedema volume of arm and hand = Comparison between ratio time 1 and ratio time 2 in analysis
2	Change of excessive fluid accumulation at level of shoulder and trunk	**Measurement of % water content** (PWC%) (ICC 0.92)[29] Material MoistureMeter D Compact (Delfin Technologies)[32-34] Reference points Deltoid, 5cm below lateral border of acromion Side of trunk, 5cm below axillary crease Method If skin is recently hydrated, dehydrate skin Sensor is placed perpendicular on the reference points with a pressure that is indicated by the device High electromagnetic wave is sent through the skin which will only be absorbed by water Degree of reflection/ water content can be read on the display of MoistureMeter D Compact	Relative excessive fluid accumulation (ratio PWC%) = PWC% affected side / PWC% healthy side At both locations (shoulder and trunk) where after a mean ratio PWC% is calculated Change of excessive fluid accumulation at level of shoulder and trunk = Comparison between mean ratio PWC% time 1 and mean ratio PWC% time 2 in analysis

SECONDARY OUTCOME MEASURES		
Outcome		Measurement method
1	Change of problems in functioning	Investigation of % of problems in functioning related to the development of arm lymphedema (ICC Total score: 0.93, SEM Total score: 4.8)[35] Material Lymph-ICF-UL Questionnaire (Dutch[27, 36] and French[37] version) Method At the end of each assessment, subjects are asked to fill in the questionnaire individually Questionnaire consists of 29 questions, divided into 5 domains: physical function, mental function, household activities, mobility activities, and life and social activities A numeric rating scale with 11 possibilities (0-10) is used onto a visual analogue scale Each of the 29 questions corresponds to a score between 0 and 100; a total score and 5 different domain scores are calculated A lower score indicates less problems in functioning
2	Change of quality of life (QoL)	Investigation of quality of life of patients with a chronic disease (ICC Total score: 0.93, SEM Total score: 0.44)[28] Material McGill-QoL Questionnaire (Dutch version) Method At the end of each assessment, subjects are asked to fill in the questionnaire individually Questionnaire counts 16+1 questions, which relate to the following 5 domains: physical symptoms; physical wellbeing, psychological symptoms; existential wellbeing and support A Likert scale with 11 possibilities (0-10) is used for the 16 questions and part D is an open question Each question corresponds to a score between 0 (very bad) and 10 (excellent); a total score and 5 different domain scores are calculated A lower score indicates a lower quality of life

Abbreviations: ICC= Intraclass Correlation Coefficient, SEM= Standard Error of Measurement, PWC%= Percentage of Water Content

Hypotheses

Regarding the primary outcome measures, following hypotheses were tested:

Patients receiving **fluoroscopy-guided MLD,** additional to DLT, will have:

1) a significantly greater reduction of lymphedema volume at the level of the hand/arm; OR

2) significantly less accumulation of lymph at the level of the shoulder/trunk,

than patients receiving **traditional MLD** or **placebo MLD**, after three weeks of intensive treatment.

Regarding the secondary outcome measures, following hypotheses were tested:

Patients receiving **fluoroscopy-guided MLD,** additional to DLT, will have:

1) a significantly greater reduction in amount of problems in functioning;

2) a significantly greater improvement in quality of life,

than patients receiving **traditional MLD** or **placebo MLD**.

Sample size calculation

Based on an alpha of 0.0125 and power of 80%, the required sample size for the study was 201 subjects or 67 subjects per group (taking into account potential drop-outs) to detect a difference of 15% in the reduction of lymphedema volume at the level of the arm or hand or at the level of the shoulder or trunk (primary outcomes) between the three groups.[22] Based on a previous longitudinal study with breast cancer patients[38], a drop-out rate of 5% was estimated (or 9 patients).

Randomization and allocation sequence generation

All participants were allocated to one of the three groups. The random allocation sequence was computer-generated. Randomization was performed by using 6-size permuted blocks. The allocation to the groups was concealed and performed by an independent physical therapist. The sequence of randomization was determined by the participant's identification number, which he/she received after inclusion in the study.

Blinding

All participants were blinded for the allocation to one of the three MLD groups. When patients (after the final clinical evaluation) were asked to denote the treatment group they believed they were allocated to, results showed that only 23% (n=38/168) of the patients indicated (knew it or made a right guess) the correct treatment group (of them, 7% were patients from the fluoroscopy-guided MLD group, 11% were patients from the traditional MLD group, and 5% were patients from the placebo MLD group). Alternatively, 77% (n=130/168) of the patients claimed not to have any idea to which group they were allocated to (n=69/168), or indicated a wrong treatment group (n=60/168). Furthermore, all clinical as well as fluoroscopic assessments were performed by investigators who were blinded for the allocation of the patients to the treatment groups. The therapists were blinded to participants' data, but were aware of the treatments provided to the three different groups.

Statistical methodology

Statistical analyses were performed by S.F. of the Leuven Biostatistics and Statistical Bioinformatics Centre (L-BioStat). Baseline participant characteristics were reported descriptively whereby continuous data were presented as mean and standard deviation (SD) for normally distributed data, and as median and inter quartile range (IQR) for non-normally distributed data. Frequencies were reported in numbers and percentages. Findings concerning treatment and outcome satisfaction were reported descriptively as well.

The *primary outcome* used in the statistical analyses refers to two ratios of volume measurements:

- Ratio of the volume of the edematous arm (including hand volume) versus the volume of the contralateral side. For patients with hand edema as reason for inclusion, only the hand volume was used in this calculation.
- Ratio of mean PWC% in the shoulder/trunk region at the edematous side versus the mean PWC% at the contralateral side.

The analysis was performed on log-transformed ratios and not on (excess) percentages (reflected by the untransformed ratios). The calculation of the mean of the ratio in the shoulder region and the ratio in the trunk region was therefore also done on the log-scale.

To compare the evolution of the log-ratios between the three groups, a multivariate linear model for longitudinal measures was used. An unstructured covariance matrix was used for the 6x6 covariance matrix of the repeated measures over time (B0, P, P1, P3, P6, P12). Given that a likelihood procedure

was used, also subjects with incomplete outcome information were included in the analysis. Results for the edema/normal log-ratios were back transformed to the original scale (ratio) with a 95% confidence interval (CI). Changes versus baseline were calculated at each time point and compared between the three groups. Primary endpoint was at the end of the intensive treatment phase (P). Since the primary analysis concerns comparisons of the fluoroscopy-guided MLD group with the traditional MLD group, and the fluoroscopy-guided MLD group with the placebo MLD group, the alpha level for the primary analysis was set at 0.0125 (two comparisons with the fluoroscopy-guided MLD group, 2 outcomes).

Outcomes of the first two *secondary parameters* were:

- Total score (and domain scores) of the Lymph-ICF-UL questionnaire
- Total score (and domain scores) of the McGill QoL questionnaire

Similarly as for the primary outcomes, a multivariate linear model for longitudinal measures was used to compare the evolution of the scores between the three groups. Mean values with a 95% CI were reported at each time point. Changes versus baseline were calculated and compared between the three groups. Alpha level was set at 5%. No corrections for multiple testing were considered for the secondary outcomes, hence a single significant p-value should be interpreted with caution.

All analyses have been performed using SAS software, version 9.4 of the SAS System for Windows.

Results

Flow of participants and participant characteristics

Of the 391 patients that were screened, 194 were included in the present study (UH Leuven; n=112, UH Saint-Pierre; n=10, UH Antwerp; n=35, UH Ghent; n=14 and GH Groeninge; n=23). Among these, 65 patients were randomized to the fluoroscopy-guided group (intervention group), 64 patients were subjected to the traditional MLD group (control group 1), and 65 patients to the placebo MLD group (control group 2). Of all 194 included patients, 5 participants dropped-out during the intensive treatment phase. Of them, 4 were lost to follow-up. The flow of participants during the trial is presented in Figure 1. Mean age of the included participants was 61 years, mean BMI was 28, and all participants were female except 1 male (0.5%). Median absolute/relative excessive arm volume at baseline was 441 ml/ 21.7%, respectively (Table 2). Other treatment-related characteristics not reported in the table (i.e. number of patients that received neo-adjuvant therapy, type of cancer, levels of axillary clearance and type of hormonal therapy) were comparable between the groups as well.

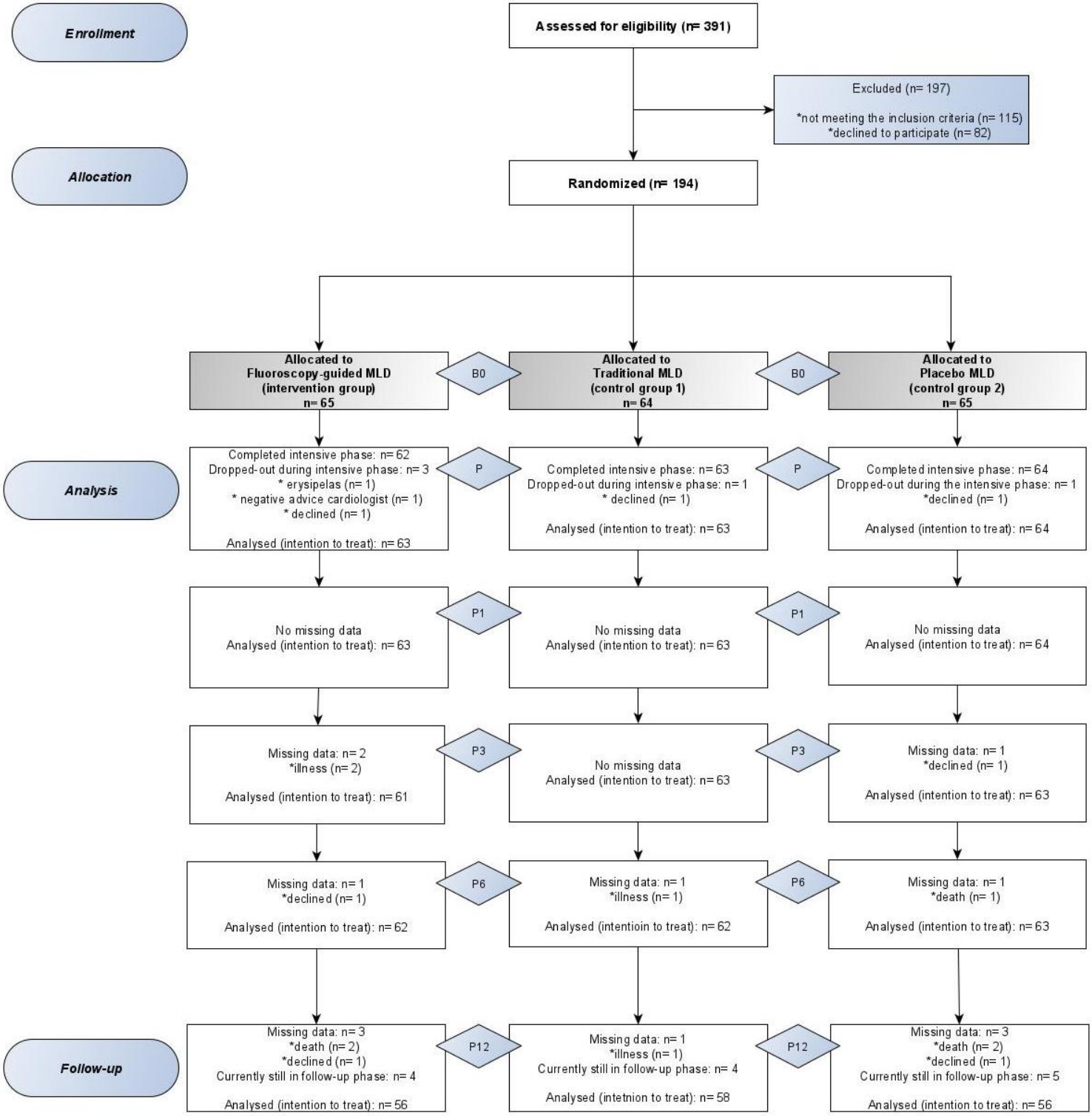


Figure 1. *Flow chart of the EFforT-BCRL trial according to the Consort 2010 Flow diagram[39]*

Abbreviations: MLD = manual lymph drainage, B0 = baseline assessment, P = post-intensive assessment, P1 = 1 month post-intensive assessment, P3 = 3 months post-intensive assessment, P6 = 6 months post-intensive assessment (= end of maintenance phase), P12 = 12 months post-intensive phase (= after 6 months of follow-up)

Table 2. Characteristics of the included participants

Variable	*Fluoroscopy guided MLD group (n=65)*	*Traditional MLD group (n=64)*	*Placebo MLD group (n=65)*	*Total (n=194)*
	N; mean (SD)	*N; mean (SD)*	*N; mean (SD)*	*N; mean (SD)*
Body Mass Index (kg/m²)	65; 27.6 (5.3)	64; 28.8 (5.6)	64; 27.8 (6.1)	194; 28.1 (5.7)
Age at baseline measurement (years)	65; 60 (10.8)	64; 62 (9.5)	65; 61 (9.0)	194; 61 (9.8)
Duration of lymphedema (months)*	65; 29 (49)	64; 28 (73)	65; 16 (50)	194; 24 (58)
Absolute excessive lymphedema arm volume (ml)*	65; 456.7 (390.5)	64; 441.8 (464.4)	64; 430.0 (510.8)	194; 441.0 (442.3)
Relative excessive lymphedema arm volume (%)*	65; 22.8 (24.2)	64; 21.9 (20.5)	65; 21.0 (18.9)	194; 21.7 (19.9)
Total pitting score[a] (/18) at baseline*	65; 5 (4)	64; 5 (5)	65; 4 (6)	194; 5 (5)
	n/N (%)	*n/N (%)*	*n/N (%)*	*n/N (%)*
Patient enrolment				
UH Leuven	39/65 (60%)	36/64 (56.3%)	37/65 (56.9%)	112/194 (57.7%)
UH Antwerp	9/65 (13.8%)	10/64 (15.6%)	16/65 (24.6%)	35/194 (18%)
UH Saint Pierre Brussels	6/65 (9.2%)	2/64 (3.1%)	2/65 (3.1%)	10/194 (5.2%)
GH Groeninge Kortrijk	7/65 (10.8%)	7/64 (10.9%)	7/65 (10.8%)	23/194 (11.9%)
UH Ghent	4/65 (6.2%)	9/64 (14.1%)	3/65 (4.6%)	14/194 (7.2%)
Gender				
Male	0/65 (0.0%)	1/64 (1.6%)	0/65 (0.0%)	1/194 (0.5%)
Female	65/65 (100.0%)	63/64 (98.4%)	65/65 (100.0%)	193/194 (99.5%)
Edema on dominant side				
No	34/65 (52.3%)	43/64 (67.2%)	32/65 (49.2%)	109/194 (56.2%)
Yes	31/65 (47.7%)	21/64 (32.8%)	33/65 (50.8%)	85/194 (43.8%)
Reason Inclusion				
Arm lymphedema	61/65 (93.9%)	62/64 (96.9%)	61/65 (93.9%)	184/194 (94.9%)
Hand lymphedema	4/65 (6.2%)	2/64 (3.1%)	4/65 (6.2%)	10/194 (5.2%)
Lymphedema Stage				
Stage I	10/65 (15.4%)	10/64 (15.6%)	12/65 (18.5%)	32/194 (16.5%)

Variable	*Fluoroscopy guided MLD group (n=65)*	*Traditional MLD group (n=64)*	*Placebo MLD group (n=65)*	*Total (n=194)*
Stage IIa	34/65 (52.3%)	40/64 (62.5%)	35/65 (53.8%)	109/194 (56.2%)
Stage IIb	21/65 (32.3%)	14/64 (21.9%)	18/65 (27.7%)	53/194 (27.3%)
Type of surgery				
Mastectomy	36/65 (55.4%)	40/64 (62.5%)	39/65 (60%)	115/194 (59.3%)
Breast conserving surgery	29/65 (44.6%)	24/64 (37.5%)	26/65 (40%)	79/194 (40.7%)
Number of positive lymph nodes (p)				
0	12/65 (18.5%)	19/64 (29.7%)	17/65 (26.2%)	48/194 (24.7%)
1-3	35/65 (53.8%)	24/64 (37.5%)	28/65 (43.1%)	87/194 (44.8%)
4-10	13/65 (20.0%)	11/64 (17.2%)	14/65 (21.5%)	38/194 (19.6%)
>10	5/65 (7.7%)	9/64 (14.1%)	6/65 (9.2%)	20/194 (10.3%)
pT				
1	20/65 (30.7%)	20/64 (31.3%)	17/65 (26.2%)	58/194 (29.9%)
2	32/65 (49.2%)	29/64 (45.3%)	43/65 (66.2%)	104/194 (53.6%)
3	6/65 (92%)	9/64 (14.1%)	3/65 (4.6%)	18/194 (9.3%
4	7/65 (10.8%)	6/64 (9.3%)	2/65 (3.1%)	14/194 (7.2%)
pN				
0	12/65 (18.5%)	16/64 (25%)	15/65 (23.1%)	45/194 (23.2%)
1	36/65 (55.4%)	32/64 (50%)	34/65 (52.3%)	99/194 (51.5%)
2	11/65 (16.9%)	8/64 (12.5%)	7/65 (10.8%)	26/194 (13.4%)
3	6/65 (9.2%)	8/64 (12.5%)	9/65 (13.8%)	23/194 (11.9%)
cM				
0	64/65 (98.5%)	64/64 (100.0%)	63/65 (96.9%)	191/194 (98.5%)
1	1/65 (1.5%)	0/64 (0.0%)	2/65 (3.1%)	3/194 (1.5%)
Radiotherapy				
No	2/65 (3.1%)	1/64 (1.6%)	2/65 (3.1%)	5/194 (2.6%)
Yes	63/65 (96.9%)	63/64 (98.4%)	63/65 (96.9%)	189/194 (97.4%)
Chemotherapy				
No	11/65 (19.6%)	12/64 (18.8%)	4/65 (6.2%)	27/194 (13.9%)
Yes	57/65 (83.1%)	52/64 (81.2%)	61/65 (93.8%)	167/194 (86.1%)
Hormonal therapy				
No	14/65 (21.5%)	11/64 (17.2%)	17/65 (26.2%)	42/194 (21.6%)
Yes	51/65 (78.5%)	53/64 (82.8%)	48/65 (73.8%)	152/194 (78.4%)
Targeted therapy				
No	52/65 (80.0%)	52/64 (81.3%)	51/65 (78.5%)	155/194 (79.9%)
Yes	13/65 (20.0%)	12/64 (18.8%)	14/65 (21.5%)	39/194 (20.1%)

Descriptives are depicted as N; mean (standard deviation), except when indicated with * where N; median (interquartile range) is shown. *MLD = manual lymph drainage, SD = standard deviation*. *[a] Calculated as a total score resulting from nine individual pitting test scores (between 0-2) on the edematous limb and trunk.[26] After application of a sustained thumb pressure during 5 seconds on the skin and superficial tissue at nine different locations of the edematous limb, the indentation of the tissue at the test site was evaluated. By palpation, each point was scored on a 3-point ordinal scale, where 0 = no clinical pitting edema, 1 = slight/doubtful pitting and 2 = noticeably pitting. Finally, a total score (/18) resulting from the nine locations was calculated for each patient. (p)TNM: T= tumor stage, N= nodal stage , M= metastasis*

Adherence to the study protocol

Generally, the intensive treatment phase lasted for 18 (±3) days (including the weekends with daily self-management treatment sessions consisting of skin care, bandaging and exercises). During this period, patients received 13 (±2) treatment sessions on average (60 min) of the 14 sessions that were initially planned. If a patient attended less than 80% (or 11 sessions) of the scheduled treatments during the intensive treatment phase (= primary endpoint), she/he was considered a drop-out. At the evaluation moment after the intensive treatment phase, 5 patients dropped-out of which 4 patients (2%) were lost to follow-up. Consequently, 97.4% of the participants attended at least 80% of the intensive treatment sessions. The maintenance treatment phase lasted for 6 months, in which patients received 17 (±4) treatment sessions on average (30 min) of the 18 sessions that were initially planned. At the end of the maintenance phase, only 3 additional patients (1.5%) were lost to follow-up. At this moment, 13 patients are still in the follow-up phase.

For more details regarding the patients' adherence to the self-management protocol during the maintenance treatment phase, see Table 3.

Primary outcomes

Figure 2 and Table 4 display the results regarding the two primary outcome measures: 1) change in excessive lymphedema volumes at the level of the arm/hand by means of the inter-limb ratio, and 2) change in excessive fluid accumulation at the level of the shoulder/trunk by means of the average inter-limb PWC% ratio of both locations.

As reported in Table 4, after the intensive treatment phase, the excessive lymphedema volume decreased significantly in all three groups ($p<0.001$). However, no statistical significant differences in volume reduction were found between the fluoroscopy-guided MLD group (5.3% [95% CI 3.2% - 5.4%] absolute excessive volume reduction or a relative reduction of **23.3%**) and the traditional MLD group (5.2% [95% CI 3.1% - 5.3%] absolute reduction or **20.9%** relative reduction) ($p= 0.890$), or between the fluoroscopy-guided MLD group and the placebo MLD group (5.4% [95% CI 3.4% - 5.5%] absolute reduction or **24.8%** relative reduction) ($p= 0.826$).

As also reported in Table 4, after the intensive treatment phase, an increased fluid accumulation at the level of the shoulder/trunk was present in all three treatment groups, whereby the change between baseline and the end of the intensive treatment phase was statistically significant in the fluoroscopy-guided MLD group ($p<0.001$). However, no statistical significant difference in excessive fluid accumulation was present between the fluoroscopy-guided MLD group (an absolute increase in excessive fluid accumulation of 4.3% [95% CI 2.3% - 6.2%], which is a relative increase of **95.6%**) and the traditional MLD group (0.8% [95% CI -1.1% - 2.6%] absolute increase, or **15.7%** relative increase)

(p= 0.0130), or between the fluoroscopy-guided MLD group and the placebo MLD group (2% [95% CI -0% - 3.8%] absolute increase, or **35.1%** relative increase) (p= 0.101).

Table 3. Adherence to the self-management protocol during the maintenance treatment phase

Number of complete diaries	147/189 (78%)			
Incomplete diaries	42/189 (22%)			
- *Lost diaries*	*32/189 (17%)*			
- *Partially filled-in diaries*	*6/189 (3%)*			
- *Diaries still needing to be delivered*	*4/189 (2%)*			
Self-MLD	***Total group***	***Fluoroscopy-guided MLD group***	***Traditional MLD group***	***Placebo MLD group***
- Average number of self-MLD's per week	5 days	*5 days*	*5 days*	*5 days*
- Number of patients having performed a self-MLD every day of the week (incl. days on which MLD was provided by the therapist)	21/148 (14%)	*6/44 (14%)*	*6/51 (12%)*	*9/53 (17%)*
- Number of patients never having performed self-MLD's	3/148 (2%)	*0/44 (0%)*	*3/51 (6%)*	*0/53 (0%)*
Compression therapy	***Total group***	***Fluoroscopy-guided MLD group***	***Traditional MLD group***	***Placebo MLD group***
- Number of patients having worn compression material (custom-made compression sleeve/glove or a bandage) each day	61/146 (42%)	*18/44 (41%)*	*21/48 (44%)*	*22/54 (41%)*
- Average number of days patients wore compression material per week	6 days	*6 days*	*7 days*	*6 days*
- Number of patients having worn compression material less than 2 days per week	8/146 (5%)	*4/44 (9%)*	*1/48 (2%)*	*3/54 (6%)*
- Number of patients that indicted to have worn multi-layer bandages for certain days during the maintenance phase	14/146 (10%), 14 days on average in total	*3/44 (7%), 12 days on average in total*	*5/48 (10%), 24 days on average in total*	*6/54 (11%), 6 days on average in total*
Exercise therapy	***Total group***	***Fluoroscopy-guided MLD group***	***Traditional MLD group***	***Placebo MLD group***
- Number of patients having performed exercises once or twice each day	33/149 (22%)	*12/44 (24%)*	*14/51 (27%)*	*7/54 (13%)*
- Average number of days per week on which patients performed exercises at least once per day	6 days	*6 days*	*6 days*	*6 days*
- Number of patients having performed their exercises less than 2 times per week	17/149 (11%)	*5/44 (11%)*	*4/51 (8%)*	*8/54 (15%)*

Table 4. Mean excessive lymphedema volume ratios (first primary outcome) and mean PWC% inter-limb ratios (second primary outcome) in each treatment group at the different time points, relative change versus baseline in each treatment group separately, and comparisons of changes between the treatment groups

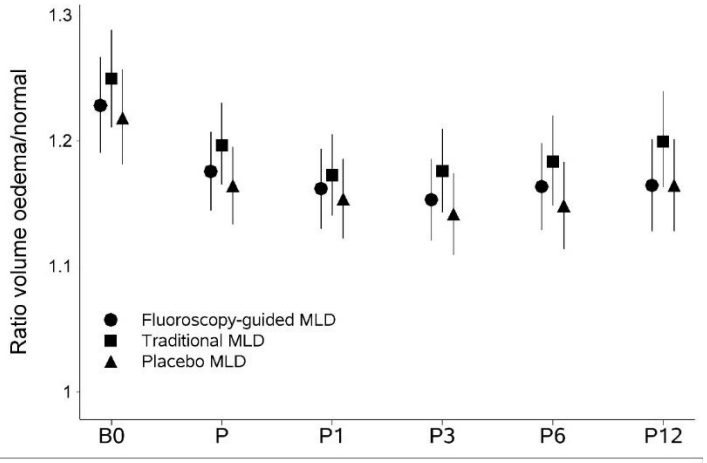
Change in excessive lymphedema volume at level of the arm/hand									
	Fluoroscopy-guided MLD		***Traditional MLD***		***Placebo MLD***		***P-values for the comparison of the changes between groups***		
Time	*Estimate (CI)*	*P-value (relative change versus B0)*	*Estimate (CI)*	*P-value (relative change versus B0)*	*Estimate (CI)*	*P-value (relative change versus B0)*	***Fluoroscopy-guided MLD vs Traditional MLD***	***Fluoroscopy-guided MLD vs Placebo MLD***	*Traditional MLD vs Placebo MLD*
B0	1.228 (1.190;1.266)		1.249 (1.211;1.288)		1.218 (1.181;1.256)				
P	1.175 (1.144;1.207)	<.0001	1.197 (1.165;1.229)	<.0001	1.164 (1.133;1.195)	<.0001	0.8898	0.8259	0.7198
P1	1.161 (1.129;1.194)	<.0001	1.172 (1.140;1.205)	<.0001	1.153 (1.122;1.185)	<.0001	0.3748	0.9138	0.3183
P3	1.152 (1.120;1.185)	<.0001	1.175 (1.142;1.209)	<.0001	1.141 (1.109;1.173)	<.0001	0.7976	0.8516	0.6897
P6	1.163 (1.128;1.198)	<.0001	1.183 (1.148;1.220)	<.0001	1.148 (1.113;1.183)	<.0001	0.9813	0.6726	0.6556
P12	1.164 (1.127;1.201)	<.0001	1.200 (1.162;1.239)	<.0001	1.164 (1.127;1.201)	<.0001	0.3284	0.5630	0.6897

Change in excessive fluid accumulation at level of the shoulder/trunk									
	Fluoroscopy-guided MLD		***Traditional MLD***		***Placebo MLD***		***P-values for the comparison of the changes between groups***		
Time	*Estimate (CI)*	*P-value (relative change versus B0)*	*Estimate (CI)*	*P-value (relative change versus B0)*	*Estimate (CI)*	*P-value (relative change versus B0)*	***Fluoroscopy-guided MLD vs Traditional MLD***	***Fluoroscopy-guided MLD vs Placebo MLD***	*Traditional MLD vs Placebo MLD*
B0	1.045 (1.024;1.065)		1.051 (1.030;1.072)		1.057 (1.036;1.078)				
P	1.088 (1.069;1.108)	<.0001	1.059 (1.040;1.077)	0.4418	1.077 (1.058;1.096)	0.0461	0.0130	0.1005	0.3872
P1	1.075 (1.054;1.096)	0.0037	1.060 (1.040;1.081)	0.3702	1.065 (1.044;1.085)	0.4474	0.1508	0.1229	0.9193
P3	1.053 (1.033;1.073)	0.4288	1.041 (1.022;1.060)	0.3277	1.053 (1.034;1.072)	0.7150	0.2113	0.4129	0.8866
P6	1.044 (1.025;1.063)	0.9320	1.040 (1.022;1.059)	0.2679	1.046 (1.028;1.065)	0.2649	0.4685	0.4675	0.9990
P12	1.057 (1.036;1.078)	0.2628	1.042 (1.022;1.062)	0.3955	1.045 (1.025;1.066)	0.2960	0.1640	0.1264	0.8866

Changes versus baseline (estimated mean ratio (95% confidence interval)). These are ratios of the edema/normal ratio. These changes are compared between the groups. Log-ratios are back transformed to the original scale (ratios). For the comparisons with the fluoroscopy-guided MLD group should be smaller than 0.0125 to be statistical significant.

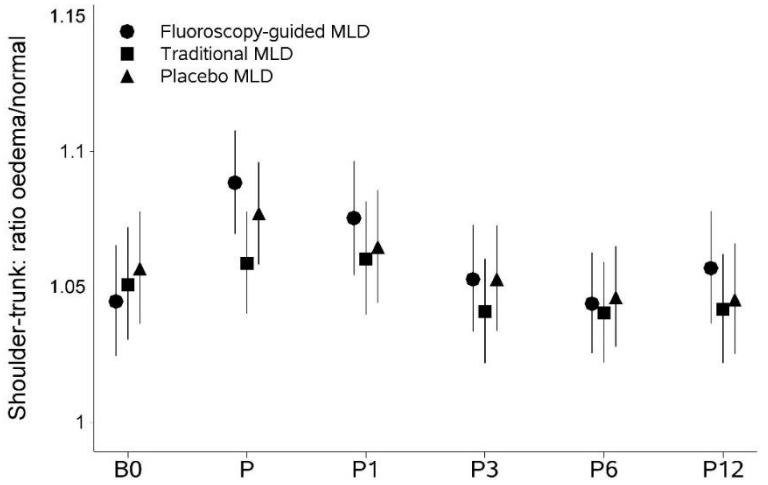
Abbreviations: MLD = manual lymph drainage

A)



Fluoroscopy-guided MLD (N)	65	63	63	61	62	56
Traditional MLD (N)	64	63	63	63	62	58
Placebo MLD (N)	65	64	64	63	63	56

B)



Fluoroscopy-guided MLD (N)	65	63	63	61	62	56
Traditional MLD (N)	64	63	63	63	62	58
Placebo MLD (N)	65	64	64	63	63	56

Figure 2.

A) *The ratio of relative lymphedema volume at the level of the arm/hand (first primary outcome) over different time points*

B) *The mean PWC% inter-limb ratio at the levels of the shoulder/trunk (second primary outcome) over different time points*

Secondary outcomes

Figure 3 and Tables 5-6 display the results regarding the secondary outcome measures: reduction in amount of problems in functioning by means of the Lymph-ICF-UL total and domain scores (Table 5), and improvement in overall quality of life by means of the McGill-QoL total and domain scores (Table 6).

As reported in Table 5, after the intensive treatment phase, the Lymph-ICF-UL total score decreased significantly in all three groups ($p<0.05$). However, no statistical significant difference in reduction of problems in general functioning between the fluoroscopy-guided MLD group (mean change (95% CI) = -9% (-12.8 ; -5.3)) and the traditional MLD group (mean change (95% CI) = -8% (-11.7 ; -4.2)) ($p= 0.696$), or between the fluoroscopy-guided MLD group and the placebo MLD group (mean change (95% CI) = -6% (-9.7 ; -2.2)) ($p= 0.254$) were found.

As reported in Table 6, after the intensive treatment phase, there was no improvement of quality of life in any of the three treatment groups. Hence, there was no significant difference in change of improvement between the fluoroscopy-guided MLD group (mean change (95% CI) = 0.09 (-0.35 ; 0.54)) and the traditional MLD group (mean change (95% CI) = 0.04 (-0.41 ; 0.48)) ($p= 0.858$) or the placebo MLD group (mean change (95% CI) = -0.05 (-0.50 ; 0.39)] ($p= 0.645$).

Table 5. Mean Lymph-ICF-UL total score and different domain scores in each treatment group at the different time points, significance of relative changes versus baseline in each treatment group separately, as well as comparisons of changes between the treatment groups

Lymph-ICF-UL Total score								
	Fluoroscopy-guided MLD		***Traditional MLD***		***Placebo MLD***	*P-values for the comparison of the changes between groups*		
	Estimate (CI)		*Estimate (CI)*		*Estimate (CI)*	***Fluoroscopy-guided MLD vs Traditional MLD***	***Fluoroscopy-guided MLD vs Placebo MLD***	*Traditional MLD vs Placebo MLD*
B0	38.0 (32.9;43.1)	B0	35.7 (30.6;40.8)	B0	38.1 (33.0;43.1)			
P	29.0** (24.3;33.6)	P	27.7** (23.0;32.4)	P	32.1* (27.5;36.7)	0.6962	0.2542	0.4553
P1	27.8** (23.3;32.3)	P1	24.6** (20.0;29.1)	P1	28.8** (24.3;33.3)	0.7496	0.7547	0.5286
P3	23.3** (18.8;27.8)	P3	25.4** (20.8;29.9)	P3	25.2** (20.7;29.8)	0.1440	0.5323	0.4749
P6	25.3** (20.5;30.0)	P6	24.5** (19.7;29.3)	P6	27.5** (22.8;32.3)	0.5945	0.4554	0.8324
P12	22.1** (17.3;27.0)	P12	23.4** (18.5;28.3)	P12	23.5** (18.7;28.4)	0.2504	0.6628	0.4749
Lymph-ICF-UL Physical functioning score								
	Fluoroscopy-guided MLD		***Traditional MLD***		***Placebo MLD***	*P-values for the comparison of the changes between groups*		
	Estimate (CI)		*Estimate (CI)*		*Estimate (CI)*	***Fluoroscopy-guided MLD vs Traditional MLD***	***Fluoroscopy-guided MLD vs Placebo MLD***	*Traditional MLD vs Placebo MLD*
B0	44.4 (38.7;50.0)	B0	40.1 (34.4;45.9)	B0	43.0 (37.3;48.7)			
P	29.5** (24.6;34.4)	P	24.2** (19.3;29.2)	P	29.7** (24.8;34.6)	0.7742	0.6423	0.4537
P1	26.8** (22.0;31.6)	P1	23.5** (18.7;28.3)	P1	25.7** (21.0;30.5)	0.8030	0.9431	0.8584
P3	21.1** (16.3;25.8)	P3	23.6** (18.8;28.4)	P3	22.8** (18.0;27.5)	0.0718	0.4122	0.1957
P6	23.4** (18.4;28.3)	P6	23.5** (18.5;28.5)	P6	24.8** (19.8;29.8)	0.2455	0.4566	0.6736
P12	21.2** (16.0;26.4)	P12	24.0** (18.8;29.3)	P12	21.7** (16.5;26.9)	0.0807	0.6465	0.1957
Lymph-ICF-UL Mental functioning score								
	Fluoroscopy-guided MLD		***Traditional MLD***		***Placebo MLD***	*P-values for the comparison of the changes between groups*		

	Estimate (CI)		*Estimate (CI)*		*Estimate (CI)*	***Fluoroscopy-guided MLD vs Traditional MLD***	***Fluoroscopy-guided MLD vs Placebo MLD***	*Traditional MLD vs Placebo MLD*
B0	33.4 (26.0;40.7)	B0	29.9 (22.5;37.3)	B0	24.6 (19.0;30.3)			
P	22.7** (16.3;29.2)	P	21.7* (15.2;28.2)	P	32.4* (25.0;39.8)	0.4530	0.1640	0.5231
P1	22.3** (16.1;28.5)	P1	21.0* (14.7;27.3)	P1	26.3* (19.8;32.7)	0.5504	0.4530	0.8811
P3	15.2** (9.4;21.1)	P3	19.9* (14.0;25.8)	P3	24.1** (17.9;30.3)	0.0417	0.0863	0.5694
P6	18.8** (12.4;25.2)	P6	18.7** (12.2;25.1)	P6	21.1* (15.2;26.9)	0.3855	0.0746	0.3609
P12	14.8** (8.8;20.8)	P12	19.1* (13.0;25.1)	P12	24.7** (18.3;31.1)	0.0582	0.1816	0.5694
Lymph-ICF-UL Household activities score								
	Fluoroscopy-guided MLD		***Traditional MLD***		***Placebo MLD***	*P-values for the comparison of the changes between groups*		
	Estimate (CI)		*Estimate (CI)*		*Estimate (CI)*	***Fluoroscopy-guided MLD vs Traditional MLD***	***Fluoroscopy-guided MLD vs Placebo MLD***	*Traditional MLD vs Placebo MLD*
B0	38.9 (32.2;45.5)	B0	35.6 (28.8;42.4)	B0	38.8 (32.0;45.6)			
P	33.4 (26.6;40.1)	P	37.1 (30.3;44.0)	P	40.1 (33.3;46.9)	0.1250	0.1370	0.9597
P1	32.1* (26.1;38.2)	P1	29.2* (23.0;35.4)	P1	36.5 (30.4;42.7)	0.9450	0.2804	0.3191
P3	27.5** (21.4;33.6)	P3	30.5 (24.3;36.7)	P3	30.6* (24.4;36.8)	0.1281	0.4488	0.4256
P6	28.7* (22.3;35.0)	P6	28.2* (21.7;34.6)	P6	31.8* (25.4;38.3)	0.5538	0.4828	0.9133
P12	27.1** (20.7;33.5)	P12	26.3* (19.8;32.8)	P12	26.0** (19.5;32.5)	0.5725	0.8087	0.4256
Lymph-ICF-UL Mobility activities score								
	Fluoroscopy-guided MLD		***Traditional MLD***		***Placebo MLD***	*P-values for the comparison of the changes between groups*		
	Estimate (CI)		*Estimate (CI)*		*Estimate (CI)*	***Fluoroscopy-guided MLD vs Traditional MLD***	***Fluoroscopy-guided MLD vs Placebo MLD***	*Traditional MLD vs Placebo MLD*
B0	38.9 (32.2;45.5)	B0	35.6 (28.8;42.4)	B0	38.8 (32.0;45.6)			
P	33.4* (26.6;40.1)	P	37.1* (30.3;44.0)	P	40.1 (33.3;46.9)	0.7276	0.3447	0.1978
P1	32.1* (26.1;38.2)	P1	29.2* (23.0;35.4)	P1	36.5* (30.4;42.7)	0.2937	0.8368	0.3978
P3	27.5* (21.4;33.6)	P3	30.5* (24.3;36.7)	P3	30.6* (24.4;36.8)	0.8760	0.9747	0.9342
P6	28.7* (22.3;35.0)	P6	28.2* (21.7;34.6)	P6	31.8* (25.4;38.3)	0.5120	0.8118	0.3723

P12	27.1** (20.7;33.5)	P12	26.3** (19.8;32.8)	P12	26.0** (19.5;32.5)	0.8922	0.9578	0.9342
Lymph-ICF-UL Social functioning score								
	Fluoroscopy-guided MLD		***Traditional MLD***		***Placebo MLD***	*P-values for the comparison of the changes between groups*		
	Estimate (CI)		*Estimate (CI)*		*Estimate (CI)*	***Fluoroscopy-guided MLD vs Traditional MLD***	***Fluoroscopy-guided MLD vs Placebo MLD***	*Traditional MLD vs Placebo MLD*
B0	33.9 (27.7;40.2)	B0	32.8 (26.5;39.1)	B0	35.6 (29.3;41.8)			
P	28.3* (22.7;33.9)	P	30.0 (24.4;35.6)	P	32.0 (26.4;37.6)	0.4925	0.6048	0.8641
P1	26.7* (21.4;32.0)	P1	24.7* (19.4;30.0)	P1	31.7 (26.4;36.9)	0.8127	0.4103	0.2911
P3	24.5* (18.9;30.0)	P3	24.8* (19.2;30.4)	P3	27.3* (21.8;32.9)	0.7588	0.7895	0.4118
P6	25.1* (19.9;30.4)	P6	25.8* (20.5;31.1)	P6	28.4* (23.1;33.6)	0.6725	0.6999	0.9695
P12	21.9** (16.2;27.6)	P12	20.9** (15.2;26.7)	P12	27.1* (21.4;32.8)	0.9756	0.3928	0.4118

Estimated mean(95% confidence interval). Changes of the estimated mean versus baseline that are statistically significant are annotated with ** (p<.0001) or * (p<.05). These changes are compared between the groups.

Abbreviations: MLD = manual lymph drainage

Table 6. Mean McGill-QoL total score and different domain scores in each treatment group at the different time points, significance of relative changes versus baseline in each treatment group separately, as well as comparisons of changes between the treatment groups

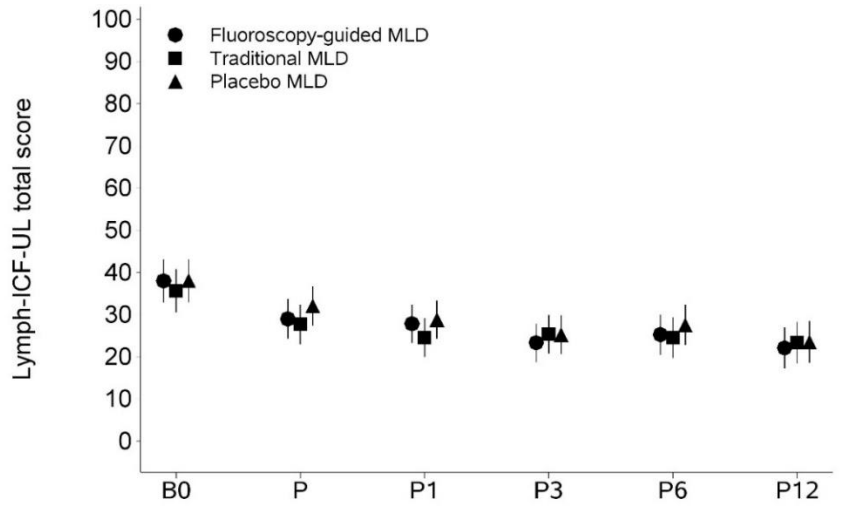
McGill QoL Total score								
	Fluoroscopy-guided MLD		***Traditional MLD***		***Placebo MLD***	*P-values for the comparison of the changes between groups*		
	Estimate (CI)		*Estimate (CI)*		*Estimate (CI)*	***Fluoroscopy-guided MLD vs Traditional MLD***	***Fluoroscopy-guided MLD vs Placebo MLD***	*Traditional MLD vs Placebo MLD*
B0	5.96 (5.58;6.35)	B0	6.15 (5.75;6.54)	B0	5.87 (5.48;6.26)			
P	6.06 (5.65;6.46)	P	6.18 (5.77;6.59)	P	5.82 (5.41;6.22)	0.8577	0.6453	0.7800
P1	6.14 (5.71;6.58)	P1	6.21 (5.77;6.65)	P1	5.98 (5.54;6.42)	0.7042	0.8238	0.8745
P3	5.85 (5.38;6.33)	P3	6.10 (5.62;6.58)	P3	5.82 (5.35;6.30)	0.8556	0.8557	0.7473
P6	5.92 (5.43;6.41)	P6	6.02 (5.53;6.52)	P6	6.09 (5.60;6.58)	0.8381	0.4692	0.3542
P12	5.56 (4.95;6.18)	P12	5.39* (4.78;6.00)	P12	5.26 (4.65;5.87)	0.4455	0.6580	0.7473
McGill QoL Physical symptoms score								
	Fluoroscopy-guided MLD		***Traditional MLD***		***Placebo MLD***	*P-values for the comparison of the changes between groups*		
	Estimate (CI)		*Estimate (CI)*		*Estimate (CI)*	***Fluoroscopy-guided MLD vs Traditional MLD***	***Fluoroscopy-guided MLD vs Placebo MLD***	*Traditional MLD vs Placebo MLD*
B0	1.67 (1.42;1.93)	B0	1.35 (1.09;1.60)	B0	1.45 (1.19;1.70)			
P	1.83 (1.43;2.24)	P	2.03* (1.62;2.44)	P	1.81* (1.40;2.22)	0.0894	0.2845	0.5241
P1	1.68 (1.32;2.04)	P1	1.33* (0.97;1.69)	P1	1.31 (0.95;1.67)	0.0610	0.5984	0.1758
P3	1.88 (1.45;2.31)	P3	1.40* (0.97;1.83)	P3	1.67 (1.24;2.09)	0.0763	0.6099	0.2716
P6	1.54 (1.18;1.91)	P6	1.10* (0.73;1.47)	P6	1.34 (0.97;1.71)	0.2542	0.8475	0.3424
P12	1.51 (1.13;1.89)	P12	1.29* (0.90;1.67)	P12	1.41* (1.03;1.79)	0.0337	0.2970	0.2716
McGill QoL Psychological symptoms score								
	Fluoroscopy-guided MLD		***Traditional MLD***		***Placebo MLD***	*P-values for the comparison of the changes between groups*		

	Estimate (CI)		*Estimate (CI)*		*Estimate (CI)*	***Fluoroscopy-guided MLD vs Traditional MLD***	***Fluoroscopy-guided MLD vs Placebo MLD***	*Traditional MLD vs Placebo MLD*
B0	6.77 (6.16;7.39)	B0	7.37 (6.75;7.99)	B0	6.88 (6.27;7.50)			
P	6.82 (6.15;7.49)	P	7.42 (6.75;8.09)	P	6.86 (6.19;7.53)	0.9915	0.8699	0.8620
P1	7.08 (6.47;7.70)	P1	7.53 (6.92;8.15)	P1	7.17 (6.55;7.78)	0.6773	0.9311	0.7414
P3	6.88 (6.22;7.53)	P3	7.57 (6.91;8.23)	P3	6.92 (6.27;7.58)	0.8245	0.8842	0.5643
P6	7.00 (6.30;7.69)	P6	7.10 (6.39;7.80)	P6	6.83 (6.13;7.52)	0.3262	0.5770	0.6694
P12	6.82 (5.99;7.65)	P12	6.50* (5.68;7.32)	P12	6.35 (5.54;7.16)	0.1202	0.3224	0.5643
McGill QoL Physical wellbeing score								
	Fluoroscopy-guided MLD		***Traditional MLD***		***Placebo MLD***	*P-values for the comparison of the changes between groups*		
	Estimate (CI)		*Estimate (CI)*		*Estimate (CI)*	***Fluoroscopy-guided MLD vs Traditional MLD***	***Fluoroscopy-guided MLD vs Placebo MLD***	*Traditional MLD vs Placebo MLD*
B0	6.69 (6.10;7.28)	B0	6.83 (6.23;7.42)	B0	6.67 (6.14;7.20)			
P	7.48* (6.91;8.06)	P	7.00 (6.42;7.57)	P	6.99 (6.48;7.50)	0.2088	0.1730	0.9196
P1	6.93 (6.31;7.54)	P1	7.16 (6.54;7.79)	P1	6.91 (6.40;7.41)	0.8564	0.5881	0.4734
P3	7.23 (6.60;7.85)	P3	6.88 (6.27;7.50)	P3	6.88 (6.29;7.46)	0.3383	0.3558	0.3536
P6	7.09 (6.50;7.68)	P6	7.12 (6.55;7.70)	P6	7.11 (6.52;7.69)	0.8342	0.6068	0.4681
P12	7.44* (6.82;8.06)	P12	6.92 (6.30;7.53)	P12	6.15 (5.42;6.89)	0.2190	0.7628	0.3536
McGill QoL Existential wellbeing score								
	Fluoroscopy-guided MLD		***Traditional MLD***		***Placebo MLD***	*P-values for the comparison of the changes between groups*		
	Estimate (CI)		*Estimate (CI)*		*Estimate (CI)*	***Fluoroscopy-guided MLD vs Traditional MLD***	***Fluoroscopy-guided MLD vs Placebo MLD***	*Traditional MLD vs Placebo MLD*
B0	6.88 (6.36;7.41)	B0	6.85 (6.32;7.38)	B0	6.67 (6.14;7.20)			
P	7.02 (6.50;7.53)	P	7.24 (6.73;7.76)	P	6.99 (6.48;7.50)	0.5274	0.6423	0.8654
P1	7.04 (6.53;7.55)	P1	7.13 (6.62;7.64)	P1	6.91 (6.40;7.41)	0.7552	0.8371	0.9149
P3	6.77 (6.18;7.35)	P3	7.04 (6.45;7.63)	P3	6.88 (6.29;7.46)	0.5113	0.4813	0.7149

P6	6.90 (6.32;7.49)	P6	6.83 (6.25;7.42)	P6	7.11 (6.52;7.69)	0.9276	0.3375	0.2948
P12	6.54 (5.80;7.28)	P12	6.55 (5.81;7.29)	P12	6.15 (5.42;6.89)	0.9463	0.7655	0.7149
McGill QoL Support score								
	Fluoroscopy-guided MLD		***Traditional MLD***		***Placebo MLD***	*P-values for the comparison of the changes between groups*		
	Estimate (CI)		*Estimate (CI)*		*Estimate (CI)*	***Fluoroscopy-guided MLD vs Traditional MLD***	***Fluoroscopy-guided MLD vs Placebo MLD***	*Traditional MLD vs Placebo MLD*
B0	7.15 (6.59;7.70)	B0	6.85 (6.32;7.38)	B0	7.35 (6.79;7.90)			
P	7.35 (6.81;7.89)	P	7.24 (6.73;7.76)	P	7.21 (6.67;7.75)	0.8581	0.4308	0.5443
P1	7.17 (6.60;7.74)	P1	7.13 (6.62;7.64)	P1	7.25 (6.69;7.82)	0.8225	0.7808	0.9579
P3	6.94 (6.35;7.53)	P3	7.04 (6.45;7.63)	P3	6.92 (6.33;7.52)	0.7010	0.6523	0.1679
P6	6.76 (6.16;7.36)	P6	6.83 (6.25;7.42)	P6	7.27 (6.67;7.87)	0.6336	0.5331	0.8852
P12	6.40 (5.66;7.15)	P12	6.55 (5.81;7.29)	P12	6.12* (5.38;6.85)	0.5917	0.4001	0.1679

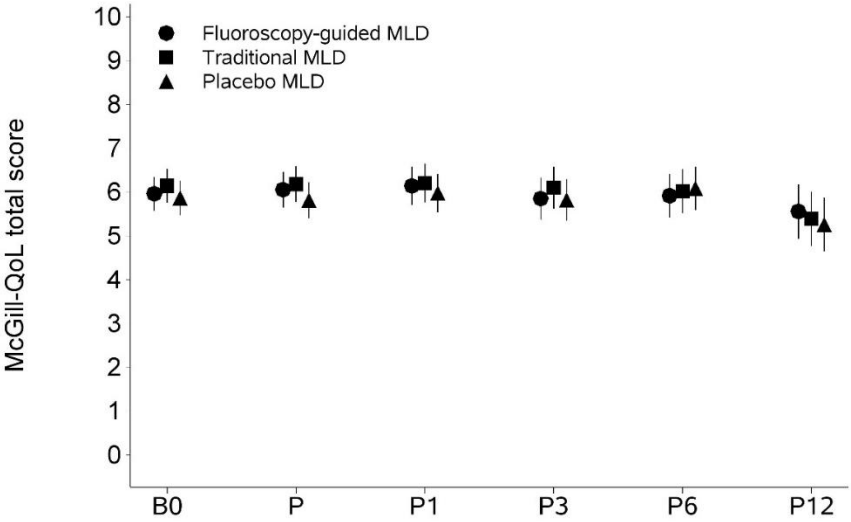
Estimated mean(95% confidence interval). Changes of the estimated mean versus baseline that are statistically significant are annotated with ** (p<.0001) or * (p<.05). These changes are compared between the groups.

Abbreviations: MLD = manual lymph drainage, QoL = quality of life



A)

	B0	P	P1	P3	P6	P12
Fluoroscopy-guided MLD (N)	65	65	65	65	65	65
Traditional MLD (N)	64	64	64	64	64	64
Placebo MLD (N)	65	65	65	65	65	64



B)

	B0	P	P1	P3	P6	P12
Fluoroscopy-guided MLD (N)	65	65	65	65	64	63
Traditional MLD (N)	64	64	64	64	64	64
Placebo MLD (N)	65	65	65	65	65	64

Figure 3.

A) *The mean Lymph-ICF-UL total score (first secondary outcome) over different time points*

B) *The mean McGill-QoL total score (second secondary outcome) over different time points*

Adverse effects

In the fluoroscopy-guided MLD group, four patients developed erysipelas during the maintenance treatment phase and one patient during follow-up (5/63 patients in total or 8%). In the traditional MLD group, two patients developed erysipelas during the maintenance treatment phase and four patients during follow-up (6/63 patients in total or 10%). In the placebo MLD group, three patients developed erysipelas during the maintenance treatment phase and six patients during follow-up (9/64 patients in total or 14%). All episodes occurred after bacterial infection due to wounds, insect bites or scratches. No adverse effects caused by the DLT or by the fluoroscopic examinations were reported by the patients.

Treatment and outcome satisfaction

Of all patients that already have attended the final clinical evaluation at the end of the follow-up phase (P12), 80% (n=134/168) of the patients indicated that at the end of the follow-up phase, their complaints have been slightly (n=46), much (n=61), or very much (n=27) improved in comparison with the period before the start of the study. Twenty percent (34/168) indicated their complaints were the same or worse after the 6-monthly follow-up phase, when patients no longer had to adhere to the study protocol. During this period, these patients showed a remarkable increase in excessive arm volume. The mean rating of the perceived effect of the MLD that patients received during the study, was 7 out of 10 (indicated on a numeric rating scale where 0 = totally no effect and 10 = a lot of effect) (n=169). The mean score in the fluoroscopy-guided MLD group was 8/10, the mean score in the two other groups was 7/10.

Discussion

This is the first sufficiently powered RCT demonstrating the absence of an additional effect of MLD for the treatment of BCRL in terms of volume reduction, reduction in amount of problems in functioning and improvement of quality of life.

Generally, it is assumed that the visualization of the superficial transport of lymph from the hand up to and over the axilla and thereby unravelling patient-specific alternative pathways towards other lymph nodes (through near infrared fluorescence imaging or lymphofluoroscopy), can contribute to a more efficient MLD.[16, 18] Also higher pressure gliding techniques on areas with dermal backflow patterns have already demonstrated to enhance the lymph flow in healthy volunteers and patients

with BCRL.[17, 19] However, whether the application of different sessions of fluoroscopy-guided MLD has a **clinical** and **long-lasting effect** on the lymphedema, superior to the traditional MLD and/or a placebo MLD, was unknown.

The findings of the present trial indicate that, according to our predefined hypotheses, patients receiving fluoroscopy-guided MLD during the intensive treatment phase, did not show 1) a significantly greater decrease in lymphedema volume at the level of the arm/hand, or 2) significantly less accumulation of lymph at the level of the shoulder/trunk, than patients receiving the traditional MLD or placebo MLD (primary outcomes). Neither did patients receiving fluoroscopy-guided MLD during the intensive treatment phase, show 1) a significantly greater reduction in amount of problems in functioning, or 2) a significantly greater improvement in quality of life (secondary outcomes). Results of this RCT not only failed to prove an additional effect of fluoroscopy-guided MLD compared to the placebo MLD, but also compared to the applied traditional MLD. The reduction of lymphedema volume (arm/hand) and the increase in fluid accumulation (shoulder/trunk) in the fluoroscopy-guided MLD group and traditional MLD group were not statistically significant different than in patients receiving a placebo MLD (which was a relaxing massage across the skin and muscles of the arm, neck and back) as an adjunct to DLT.

The **first primary outcome parameter** was the change in lymphedema volume at the level of the arm/hand. During the last decade, several reviews of the literature investigating the effect of MLD on volume reduction in patients with BCRL, have been published.[4, 5, 40-43] The most recent and methodologically well-founded systematic review only including RCT's or quasi RCT's of women with BCRL, is the Cochrane systematic review of Ezzo and colleagues.[5] In this review, six RCT's about three categories were included: MLD whether or not in combination with standard physiotherapy[44], compression bandaging[45, 46], and in combination with compression therapy versus nonMLD treatment with compression therapy[47-49] In general, findings were inconclusive: it was stated that MLD is safe and might offer an additional benefit of 7% to compression bandaging for swelling reduction, however, this should be confirmed by randomized data.[5] In the meta-analysis of Huang et al., results of the same studies were combined, concluding that no statistical significant differences between the MLD and standard treatment groups regarding arm volume reduction were detected.[4]

Also more recent RTC's aiming to measure the additional effect of MLD on arm volume, have shown insignificant effects on arm volume reduction after intensive DLT[6, 7] or intensive and maintenance DLT[8]. In contrast with the previous trials, this is the first trial comparing the effects of fluoroscopy-guided MLD with traditional MLD and with placebo MLD. First of all, in and between each group, the baseline excessive lymphedema volume in terms of an inter-limb ratio was compared with the

excessive lymphedema volume ratio at end of the intensive treatment phase (primary endpoint) and the ratios at the other time points during (P1, P3) and after (P6) the maintenance phase, as well as after the follow-up phase (P12). The relative percentage of volume reduction (i.e. the change in excessive arm volume before and after treatment relative to the baseline excessive arm volume) is a frequently reported outcome measure.[5] In the present study, there was a decrease in lymphedema volume over time in all treatment groups. There was a mean relative excessive volume reduction of 23.3% in the fluoroscopy-guided MLD group, of 20.9% in the traditional MLD group, and 24.8% in the placebo MLD group. All groups showed a slight increase again during the second part of the maintenance treatment. Other RCT's comparing DLT with and without MLD showed mean relative excessive volume reductions between 34.2%[6] and 47.4%[7] between baseline and post-intensive treatment (24 days and 2 weeks, respectively). The differences in mean excessive arm volumes at baseline between our study sample (501.5 ml) and the two other RCT's (776.2 ml[6] and 1017.7 ml[7] respectively) may be a reason why relative volume reduction in the present study is lower than in previous trials.[50] Also, although patients included in the present study showed at least at one location along the edematous limb signs of pitting (= inclusion criterion), generally the overall severity of pitting was mild.

For evaluating swelling, the water displacement method and circumference measurements are the most frequently used methods[1] and are recommended as best practice for measuring lymphedema in extremities.[29] As a study revealed better reliability and smaller standard errors of measurement, we used perimetry (after which the volume was calculated) to evaluate the excessive arm volume in patients with BCRL.[51] However, volume of the hand is not included in this calculation since the conical assumption has shown not to be valid for hand shape.[52] Therefore, hand volume was separately determined using water displacement[25], which has shown to be a reliable and time-efficient method.[51]

The **second primary outcome measure** was the change in fluid accumulation at the level of the shoulder/trunk. In the Cochrane systematic review of Ezzo and colleagues, it was recommended that future trials should include volumetric outcomes beyond solely arm volume. This because edema accumulation at the trunk[53] (or posterior axillary fold) has been recognized in patients with BCRL, and it has been suggested that MLD might play an important role in such areas that are not conducive to compression therapy. Nevertheless, there was only one of the Cochrane review's included trials that incorporated skin thickness (objectified with modified Harpenden skinfold calipers) at the trunk as an outcome measure. The trial showed that MLD according to Vodder did not statistically reduce caliper creep on the affected side after 3 weeks of intensive treatment (MLD + compression sleeve) ($p=0.06$).[48] Also in the present study, there was no significant difference in fluid accumulation at the

shoulder/trunk between the different treatment groups. Alternatively to caliper measurements representing the thickness of the skin, in the present study water content at the level of the shoulder and trunk was selected as second primary outcome measure using a MMDC device. This device can be used to determine the tissue dielectric constant in terms of the percentage of water content (PWC%), at any particular site of the body including the breast, trunk or other central body parts in which midline edema can manifest.[32, 54] However, only up to a depth of 2 mm this portable device allows measuring free and bounded water in the tissue through which the electromagnetic wave passes.[55] Therefore, questions arise whether the total accumulation of fluid can be taken into account using the MMDC device. Results in this trial indicated that in all three treatment groups, there was an increase in fluid accumulation after the intensive treatment phase due to the displacement of lymphedema volumes from the hand and arm towards the shoulder. As in the fluoroscopy-guided MLD a lot of emphasis is placed on drainage of the regions proximal to the bandage, it is surprising that only in this treatment group there was a statistically significant increase in fluid accumulation. Potentially, this increase in fluid accumulation in the skin might be caused by the extended drainage of these areas resulting in skin irritation. Additionally, although hydration of the skin at the level of the arm (without trunk) was performed daily in all patients during the intensive treatment phase, the fluoroscopy-guided MLD group was the only treatment group in which moisturizing lotion was also used during the MLD at the level of the arm and trunk, which can have influenced the water content of the skin of this group even more. Further secondary analyses in which changes in thickness of the cutis and subcutis (measured with ultrasonography) are being evaluated, will shed more light on this aspect. Nevertheless, significant changes in fluid accumulation between the groups were absent, and in all three groups the fluid accumulation in the skin of the shoulder/trunk restored during the first part of the maintenance phase when wearing a compression sleeve instead of a compression bandage.

Given the large role on subjective complaints associated with lymphedema, paying attention to only physical edema characteristics such as swelling is not enough to outline a holistic, patient-centered follow-up with tailored treatment and support.[9] Therefore, our **secondary outcome parameters** were 1) the change in amount of problems in functioning related to the lymphedema, and 2) the change in quality of life. Recently, a systematic review investigated the effect of MLD on health-related quality of life (HRQoL) in patient with edema of the upper and/or lower limbs.[56] Five RCT's were included that involved patients with BCRL.[7, 57-60] Nevertheless, of all five studies, only one study demonstrated a statistical significantly improved quality of life in the group that received MLD compared to no MLD (MLD and physical exercise vs. physical exercise).[59] However, the sample size of this study was very small (n=27). In the present study, overall quality of life was evaluated with the McGill-QoL questionnaire, which is a reliable questionnaire and validated in patients with BCRL.[28] During the trial,

the McGill-QoL total score remained stable in all groups (±6/10), representing moderate quality of life. As a change in total sore of at least 1.22 (12%) is needed to detect a factual change within a patient's quality of life[28], results of this RCT showed that the quality of life did not improve in none of the three treatment groups after treatment. This suggests that, significant improvement of lymphedema-related functions (such as physical, mental, social functions) alone, were not sufficient for these patients to indirectly impact the general quality of life.

In the study of Gradalski et al., the overall HRQoL did not differ between the two groups either, but the group receiving MLD reported significant improvements in social functioning.[7] Within each group, the overall HRQoL (measured with the Lymphedema Questionnaire) generally improved from pre- to post-intervention. In our study, comparable results were found, however, a different lymphedema-specific questionnaire was used to investigate the amount of problems in functioning (and not the overall quality of life): the Lymph-ICF-UL questionnaire; a valid, reliable and responsive instrument for patients with BCRL.[27, 36] The total score represents the mean score of five different subdomains: physical functioning, mental functioning, household activities, mobility activities, and social functioning. As reported, all three treatment groups showed a significant improvement in total score after treatment, however, there was no statistical significant difference between the groups. Mean baseline total score for the whole study sample was 37/100, representing a moderate amount of problems in daily functioning. After intensive treatment, this mean total score was decreased to 30/100, and after 6 months of maintenance treatments to 25/100. When looking at the different subdomains individually, results indicated a statistically significant improvement between baseline measures and the end of the intensive treatment phase in all three groups regarding physical functioning and mental functioning, without significant differences between the three groups (which was in none of the five subdomains). The amount of problems in household activities did not significantly improve after the intensive treatment phase in none of the three groups. Mobility activities significantly improved in patients receiving the fluoroscopy-guided MLD and traditional MLD, but not in the patients receiving placebo MLD ($p>0.05$). Lastly, social functioning only improved statistically significant in the patients receiving the fluoroscopy-guided MLD, but not in the other two treatment groups.

The present study has several strengths. First of all, a strength can be devoted to the design of this trial. As five study centers participated in this trial, patients could be recruited in almost all regions of Flanders. A sample size calculation was performed before the start of the study, to empower the trial. This was performed taking into account two primary outcome parameters. Also, a placebo MLD was added to the other components of DLT in the second control group instead of only providing DLT

without MLD, to ensure blinding of the patients. Randomization was concealed and both patients and assessors were blinded for patients' treatment allocation. The risk of performance bias (e.g. in patients receiving placebo MLD) was negligible, as more than 75% of the patients did not know their treatment allocation or indicated a wrong treatment group. Furthermore, drop-out rate was low. Only five patients dropped-out during the intensive treatment phase, of which four were lost to follow-up (out of nine that were estimated). Also long-term follow-up was good, as only three additional patients were lost to follow-up during the 6-monthly maintenance phase (7/194 patients in total during the entire study period or 3.6%). Next, in each study center patients of all three treatment groups were treated by the same team of therapists who moved between the different centers. This ensures that the treatment program was standardized. Another strength is that the patient characteristics at baseline were comparable between the three groups. Lastly, in the present study we have tried to get the most out of the MLD treatment effect by educating patients a self-MLD that they needed to perform during the maintenance treatment phase on the days no treatment was provided by the therapist. As a result, throughout the entire study period (except for the two weekends during the intensive treatment phase) MLD was applied on a daily basis.

A limitation of this study was that the inclusion of patients was ended before the project's predefined number of patients (n=201) was reached. Due to the relatively strict inclusion and exclusion criteria, together with the fact that participation in this trial required a relatively great effort of patients (e.g. more than 30 trips to the hospital), the accrual rate was slower than anticipated. Sixty-four subjects were needed in each group to detect an absolute difference of 15% excessive volume reduction.[22] Nevertheless, although the planned sample size was increased to 67 subjects per group to anticipate potential drop-out and the study was terminated earlier as there were fewer drop-outs than initially estimated (4 patients were lost to follow-up instead of 9 that were estimated), this did not jeopardize the final power of the primary analysis, since this analysis was still based on information from 194 subjects at baseline (65, 64, 65 in the 3 groups, respectively) and 190 subjects (63, 63, 64 in the 3 groups, respectively) after 3 weeks of intensive treatment.

Clinical implications

Literature emphasized the need for randomized trials investigating the relative contribution of MLD to DLT.[5] This multi-center, well-designed RCT showed that, regarding volume reduction and change in fluid accumulation (primary outcomes), as well as reduction in amount of problems in functioning and improvement in quality of life (secondary outcomes), no additional effect of MLD (as an adjunct to DLT) could be demonstrated. Fluoroscopy-guided MLD is not superior to placebo MLD or to the

traditional MLD. This means that, for these clinical outcomes, there is no indication for including (time-consuming) MLD in the limited treatment time per session. Alternatively, more time should be spent on other, well-investigated and evidence-based treatment options such as compression therapy[61-63] and exercise therapy[63, 64], together with a great emphasis on education and self-management.[9] Future studies in which the effect of (fluoroscopy-guided) MLD on other secondary outcome measures such as lymphatic transport in the long term, hardness and fibrosis of the skin, water content and skin thickness is investigated should and will be conducted as well, in order to elucidate whether MLD might have an added effect on these aspects. In addition, sub-group analyses should be performed to investigate whether or not sub-groups of patients with specific characteristics (for instance based on the severity of volume differences, amount of pitting or dermal rerouting/backflow patterns) may show different outcomes regarding the clinical effect of (fluoroscopic-guided) MLD in addition to DLT. However, as these outcomes are secondary outcome parameters (without corrections being made for multiple testing), and therefore were not taken into account in the initial power calculations, single significant values should be interpreted with caution.

Furthermore, for ethical reasons, the effect of the different types of MLD was examined in addition to the other components of DLT, instead of the different types of MLD alone. Although, there is evidence from practitioner surveys that MLD is often given alone.[3] Therefore another important question, whether fluoroscopy-guided or traditional MLD alone (without addition of any other component) would be of any benefit, remains unproven.

Conclusions

This trial supports previous findings that intensive DLT significantly reduces the lymphedema volume, and improves daily functioning in patients with BCRL. The results of this study however do not support the hypotheses that, after 3 weeks of intensive DLT treatment, additional fluoroscopy-guided MLD will provide a greater volume reduction at the level of the arm/hand, or less accumulation of lymph at the level of the shoulder/trunk, than traditional or placebo MLD. Also the amount of problems in functioning due to lymphedema improved significantly after DLT in all treatment groups, regardless of the type of MLD provided, and thus without statistical differences between treatment groups. General quality of life remained stable in all groups over time. Consequently, these findings support the conclusions of other RCT's that MLD as an adjunct to DLT, offers no additional benefit in lymphedema volume reduction or improvement in daily functioning and quality of life in patients with BCRL. This can diminish time consumption during therapy remarkably.

Acknowledgements

The authors are very grateful to the different hospitals and research teams collaborating in this study (Roxane Van Hemelrijck, Lien Billiet, An-Kathleen Heroes and Lore Vos in UH Leuven, Kevin Dusart and Sophie Vankerckhove in UH Saint-Pierre, Rita Hietbrink and Shanah Van den Bosch in UH Ghent and Ellen Callens and Shanah Van den Bosch in GH Groeninge). The authors also extend very grateful thanks to all the study participants. Finally, we are grateful to the nurses and medical staff of the multidisciplinary breast centers of the different participating hospitals to motivate the patients to participate in our study.

References

1. The Diagnosis and Treatment of Peripheral Lymphedema: 2020 Consensus Document of the International Society of Lymphology. Lymphology. 2020;53(1):3-19.
2. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet. 2015;385(9972):977-1010.
3. Karki A, Anttila H, Tasmuth T, Rautakorpi U. Lymphedema therapy in breast cancer patients -- a systematic review on effectiveness and a survey of current practices and costs in Finland. Acta Oncologica 2009 Aug;48(6):850-859. 2009.
4. Huang TW, Tseng SH, Lin CC, Bai CH, Chen CS, Hung CS, et al. Effects of manual lymphatic drainage on breast cancer-related lymphedema: a systematic review and meta-analysis of randomized controlled trials. World J Surg Oncol. 2013;11:15.
5. Ezzo J, Manheimer E, McNeely ML, Howell DM, Weiss R, Johansson KI, et al. Manual lymphatic drainage for lymphedema following breast cancer treatment. Cochrane Database Syst Rev. 2015(5):Cd003475.
6. Bergmann A, da Costa Leite Ferreira MG, de Aguiar SS, de Almeida Dias R, de Souza Abrahao K, Paltrinieri EM, et al. Physiotherapy in upper limb lymphedema after breast cancer treatment: a randomized study. Lymphology. 2014;47(2):82-91.
7. Gradalski T, Ochalek K, Kurpiewska J. Complex Decongestive Lymphatic Therapy With or Without Vodder II Manual Lymph Drainage in More Severe Chronic Postmastectomy Upper Limb Lymphedema: A Randomized Noninferiority Prospective Study. J Pain Symptom Manage. 2015;50(6):750-7.
8. Tambour M, Holt M, Speyer A, Christensen R, Gram B. Manual lymphatic drainage adds no further volume reduction to Complete Decongestive Therapy on breast cancer-related lymphedema: a multicentre, randomised, single-blind trial. Br J Cancer. 2018;119(10):1215-22.
9. Damstra RJ, Halk AB. The Dutch lymphedema guidelines based on the International Classification of Functioning, Disability, and Health and the chronic care model. Journal of vascular surgery Venous and lymphatic disorders. 2017;5(5):756-65.
10. Venereologie; NVvDe. Richtlijn lymfoedeem NL. 2015.
11. Kwon S, Price RE. Characterization of internodal collecting lymphatic vessel function after surgical removal of an axillary lymph node in mice. Biomed Opt Express. 2016;7(4):1100-15.
12. Ahmed RL, Schmitz KH, Prizment AE, Folsom AR. Risk factors for lymphedema in breast cancer survivors, the Iowa Women's Health Study. Breast cancer research and treatment. 2011;130(3):981-91.
13. Weissleder H, Weissleder R. Lymphedema: evaluation of qualitative and quantitative lymphoscintigraphy in 238 patients. Radiology. 1988;167(3):729-35.
14. Moshiri M, Katz DS, Boris M, Yung E. Using lymphoscintigraphy to evaluate suspected lymphedema of the extremities. AJR Am J Roentgenol. 2002;178(2):405-12.
15. Rasmussen JC, Tan IC, Marshall MV, Adams KE, Kwon S, Fife CE, et al. Human Lymphatic Architecture and Dynamic Transport Imaged Using Near-infrared Fluorescence. Transl Oncol. 2010;3(6):362-72.
16. Tomson D, Lessert C, Luthi I, Mazzolai L, Depairon M. [Lymphatic vascular pathologies: contribution of lympho-fluoroscopy]. Rev Med Suisse. 2015;11(460):362-5.
17. Belgrado JP, Vandermeeren L, Vankerckhove S, Valsamis JB, Malloizel-Delaunay J, Moraine JJ, et al. Near-Infrared Fluorescence Lymphatic Imaging to Reconsider Occlusion Pressure of Superficial Lymphatic Collectors in Upper Extremities of Healthy Volunteers. Lymphatic research and biology. 2016;14(2):70-7.
18. Suami H, Heydon-White A, Mackie H, Czerniec S, Koelmeyer L, Boyages J. A new indocyanine green fluorescence lymphography protocol for identification of the lymphatic drainage pathway for patients with breast cancer-related lymphedema. BMC cancer. 2019;19(1):985.

19. Tan IC, Maus EA, Rasmussen JC, Marshall MV, Adams KE, Fife CE, et al. Assessment of lymphatic contractile function after manual lymphatic drainage using near-infrared fluorescence imaging. Archives of physical medicine and rehabilitation. 2011;92(5):756-64.e1.
20. Lopera C, Worsley PR, Bader DL, Fenlon D. Investigating the Short-Term Effects of Manual Lymphatic Drainage and Compression Garment Therapies on Lymphatic Function Using Near-Infrared Imaging. Lymphatic research and biology. 2017;15(3):235-40.
21. Medina-Rodríguez ME, de-la-Casa-Almeida M, Martel-Almeida E, Ojeda-Cárdenes A, Medrano-Sánchez EM. Visualization of Accessory Lymphatic Pathways, before and after Manual Drainage, in Secondary Upper Limb Lymphedema Using Indocyanine Green Lymphography. Journal of clinical medicine. 2019;8(11).
22. De Vrieze T, Vos L, Gebruers N, Tjalma WAA, Thomis S, Neven P, et al. Protocol of a randomised controlled trial regarding the effectiveness of fluoroscopy-guided manual lymph drainage for the treatment of breast cancer-related lymphedema (EFforT-BCRL trial). European journal of obstetrics, gynecology, and reproductive biology. 2017.
23. Moher D, Schulz KF, Altman D. The CONSORT Statement: revised recommendations for improving the quality of reports of parallel-group randomized trials 2001. Explore (NY). 2005;1(1):40-5.
24. Devoogdt N, Lemkens H, Geraerts I, Van Nuland I, Flour M, Coremans T, et al. A new device to measure upper limb circumferences: validity and reliability. International angiology : a journal of the International Union of Angiology. 2010;29(5):401-7.
25. Martignon M VS, Fung LH, Vandermeeren L, Belgrado JP, editor Evaluation of the reliability of four measuring methods of hand's perimeter and volume: Buoyancy Forces Valgrado System, circumference measurement, figure-of-eight method and Manu3Metrix scanner. 8th International Lymphedema Framework Conference; 2018; Rotterdam, The Netherlands.
26. De Vrieze T, Gebruers N, Nevelsteen I, De Groef A, Tjalma WAA, Thomis S, et al. Reliability of the MoistureMeterD Compact Device and the Pitting Test to Evaluate Local Tissue Water in Subjects with Breast Cancer-Related Lymphedema. Lymphatic research and biology. 2019.
27. De Vrieze T, Vos L, Gebruers N, De Groef A, Dams L, Van der Gucht E, et al. Revision of the Lymphedema Functioning, Disability and Health Questionnaire for Upper Limb Lymphedema (Lymph-ICF-UL): Reliability and Validity. Lymphatic research and biology. 2019.
28. De Vrieze T, Coeck D, Verbelen H, Devoogdt N, Tjalma W, Gebruers N. Cross-cultural Psychometric Evaluation of the Dutch McGill-QoL Questionnaire for Breast Cancer Patients. Facts Views Vis Obgyn. 2016;8(4):205-9.
29. Hidding JT, Viehoff PB, Beurskens CH, van Laarhoven HW, Nijhuis-van der Sanden MW, van der Wees PJ. Measurement Properties of Instruments for Measuring of Lymphedema: Systematic Review. Physical therapy. 2016;96(12):1965-81.
30. Gebruers N, Truijen S, Engelborghs S, De Deyn PP. Volumetric evaluation of upper extremities in 250 healthy persons. Clinical physiology and functional imaging. 2007;27(1):17-22.
31. Gebruers N, Verbelen H, De Vrieze T, Vos L, Devoogdt N, Fias L, et al. Current and future perspectives on the evaluation, prevention and conservative management of breast cancer related lymphedema: A best practice guideline. European journal of obstetrics, gynecology, and reproductive biology. 2017;216:245-53.
32. Nuutinen J, Ikaheimo R, Lahtinen T. Validation of a new dielectric device to assess changes of tissue water in skin and subcutaneous fat. Physiological measurement. 2004;25(2):447-54.
33. Czerniec SA, Ward LC, Kilbreath SL. Assessment of breast cancer-related lymphedema: a comparison of moisture meter and spot bioimpedance measurement. Lymphatic research and biology. 2015;13(1):10-9.
34. Mayrovitz HN, Weingrad DN, Davey S. Local tissue water in at-risk and contralateral forearms of women with and without breast cancer treatment-related lymphedema. Lymphatic research and biology. 2009;7(3):153-8.

35. Devoogdt N, Van Kampen M, Geraerts I, Coremans T, Christiaens MR. Lymphedema Functioning, Disability and Health questionnaire (Lymph-ICF): reliability and validity. Physical therapy. 91. United States2011. p. 944-57.
36. De Vrieze T, Gebruers N, Nevelsteen I, Tjalma WAA, Thomis S, De Groef A, et al. Responsiveness of the Lymphedema Functioning, Disability, and Health Questionnaire for Upper Limb Lymphedema in Patients with Breast Cancer-Related Lymphedema. Lymphatic research and biology. 2020:10.1089/lrb.2019.0073.
37. De Vrieze T, Frippiat J, Deltombe T, Gebruers N, Tjalma WAA, Nevelsteen I, et al. Cross-cultural validation of the French version of the Lymphedema Functioning, Disability and Health Questionnaire for Upper Limb Lymphedema (Lymph-ICF-UL). Disabil Rehabil. 2020:1-8.
38. Devoogdt N, Christiaens MR, Geraerts I, Truijen S, Smeets A, Leunen K, et al. Effect of manual lymph drainage in addition to guidelines and exercise therapy on arm lymphedema related to breast cancer: randomised controlled trial. Bmj. 2011;343:d5326.
39. Cuschieri S. The CONSORT statement. Saudi journal of anaesthesia. 2019;13(Suppl 1):S27-s30.
40. Devoogdt N, Van Kampen M, Geraerts I, Coremans T, Christiaens MR. Different physical treatment modalities for lymphedema developing after axillary lymph node dissection for breast cancer: a review. European journal of obstetrics, gynecology, and reproductive biology. 2010;149(1):3-9.
41. McNeely ML, Peddle CJ, Yurick JL, Dayes IS, Mackey JR. Conservative and dietary interventions for cancer-related lymphedema: a systematic review and meta-analysis. Cancer. 2011;117(6):1136-48.
42. Li L, Yuan L, Chen X, Wang Q, Tian J, Yang K, et al. Current Treatments for Breast Cancer-Related Lymphedema: A Systematic Review. Asian Pacific journal of cancer prevention : APJCP. 2016;17(11):4875-83.
43. Shao Y, Zhong DS. Manual lymphatic drainage for breast cancer-related lymphedema. European journal of cancer care. 2016.
44. Andersen L, Hojris I, Erlandsen M, Andersen J. Treatment of breast-cancer-related lymphedema with or without manual lymphatic drainage--a randomized study. Acta oncologica (Stockholm, Sweden). 2000;39(3):399-405.
45. Johansson K, Albertsson M, Ingvar C, Ekdahl C. Effects of compression bandaging with or without manual lymph drainage treatment in patients with postoperative arm lymphedema. Lymphology. 1999;32(3):103-10.
46. McNeely ML, Magee DJ, Lees AW, Bagnall KM, Haykowsky M, Hanson J. The addition of manual lymph drainage to compression therapy for breast cancer related lymphedema: a randomized controlled trial. Breast cancer research and treatment. 2004;86(2):95-106.
47. Johansson K, Lie E, Ekdahl C, Lindfeldt J. A randomized study comparing manual lymph drainage with sequential pneumatic compression for treatment of postoperative arm lymphedema. Lymphology. 1998;31(2):56-64.
48. Williams AF, Vadgama A, Franks PJ, Mortimer PS. A randomized controlled crossover study of manual lymphatic drainage therapy in women with breast cancer-related lymphedema. European journal of cancer care. 2002;11(4):254-61.
49. Sitzia J, Harlow W. Lymphedema 4: research priorities in lymphedema care. Br J Nurs. 2002;11(8):531-41.
50. Liao SF, Li SH, Huang HY, Chen ST, Kuo SJ, Chen DR, et al. The efficacy of complex decongestive physiotherapy (CDP) and predictive factors of lymphedema severity and response to CDP in breast cancer-related lymphedema (BCRL). Breast (Edinburgh, Scotland). 2013;22(5):703-6.
51. De Vrieze T GN, De Groef A, Dams L, Van der Gucht E, Nevelsteen I, Devoodt N. Reliability and time efficiency of five different methods to determine arm volume in patients with breast cancer-related lymphedema. 2019.
52. Taylor R, Jayasinghe UW, Koelmeyer L, Ung O, Boyages J. Reliability and validity of arm volume measurements for assessment of lymphedema. Physical therapy. 2006;86(2):205-14.
53. Roberts CC, Levick JR, Stanton AW, Mortimer PS. Assessment of truncal edema following breast cancer treatment using modified Harpenden skinfold calipers. Lymphology. 1995;28(2):78-88.

54. Mazor M, Smoot BJ, Mastick J, Mausisa G, Paul SM, Kober KM, et al. Assessment of local tissue water in the arms and trunk of breast cancer survivors with and without upper extremity lymphedema. Clinical physiology and functional imaging. 2019;39(1):57-64.
55. Mayrovitz HN, Mikulka A, Woody D. Minimum Detectable Changes Associated with Tissue Dielectric Constant Measurements as Applicable to Assessing Lymphedema Status. Lymphatic research and biology. 2018.
56. Müller M, Klingberg K, Wertli MM, Carreira H. Manual lymphatic drainage and quality of life in patients with lymphedema and mixed edema: a systematic review of randomised controlled trials. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2018;27(6):1403-14.
57. Dayes IS, Whelan TJ, Julian JA, Parpia S, Pritchard KI, D'Souza DP, et al. Randomized trial of decongestive lymphatic therapy for the treatment of lymphedema in women with breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(30):3758-63.
58. Ridner SH, Poage-Hooper E, Kanar C, Doersam JK, Bond SM, Dietrich MS. A pilot randomized trial evaluating low-level laser therapy as an alternative treatment to manual lymphatic drainage for breast cancer-related lymphedema. Oncol Nurs Forum. 2013;40(4):383-93.
59. Odebiyi DO, Aborowa AT, Sokunbi OG, Aweto HA, Ajekigbe AT. Effects of exercise and edema massage on fatigue level and quality of life of female breast cancer patients. European Journal of Physiotherapy. 2014;16(4):238-45.
60. Belmonte R, Tejero M, Ferrer M, Muniesa JM, Duarte E, Cunillera O, et al. Efficacy of low-frequency low-intensity electrotherapy in the treatment of breast cancer-related lymphedema: a cross-over randomized trial. Clin Rehabil. 2012;26(7):607-18.
61. Damstra RJ, Partsch H. Compression therapy in breast cancer-related lymphedema: A randomized, controlled comparative study of relation between volume and interface pressure changes. Journal of vascular surgery. 2009;49(5):1256-63.
62. King M, Deveaux A, White H, Rayson D. Compression garments versus compression bandaging in decongestive lymphatic therapy for breast cancer-related lymphedema: a randomized controlled trial. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2012;20(5):1031-6.
63. Rogan S, Taeymans J, Luginbuehl H, Aebi M, Mahnig S, Gebruers N. Therapy modalities to reduce lymphedema in female breast cancer patients: a systematic review and meta-analysis. Breast cancer research and treatment. 2016;159(1):1-14.
64. Kwan ML, Cohn JC, Armer JM, Stewart BR, Cormier JN. Exercise in patients with lymphedema: a systematic review of the contemporary literature. Journal of cancer survivorship : research and practice. 2011;5(4):320-36.

ADDENDUM: Case example with different MLD drainage methods

Patient X.X. presents with BCRL of the right lower arm and hand (without fingers)

1. Drainage according to the fluoroscopy-guided MLD method

1) BASIC PRINCIPLES: interpretation of fluoroscopic images

An important advantage of lymphofluoroscopy is the real-time imaging of the superficial lymphatic transport. Disturbance of lymph flow and dermal rerouting or backflow is visualized in different patterns, according to the severity of the dermal rerouting/backflow:

- Linear: visualization of lymph fluid in the collectors
- Splash: visualization of lymph fluid in lymph capillaries
- Stardust: Leakage of lymph fluid from the capillaries into the interstitium
- Diffuse: Visualization of lymph fluid in the interstitium

- Dermal backflow / dermal rerouting: Due to a blockage in a lymph collector, the lymph cannot move proximally in the lymph collector but drains through the precollectors and the lymph capillaries towards the interstitium. This is seen in lymphedema patients. Because of the gravity, the lymph fluid in the interstitium often moves distally.

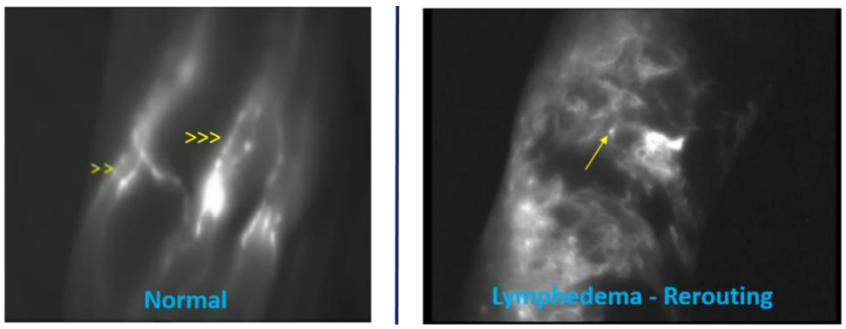


Figure 1. *Fluoroscopic image of the superficial lymphatic network and its schematic architecture. (A) represents a normal condition, in which the lymph fluid is being transported by the superficial lymph collectors. (B) represents an edematous condition, in which the lymph is rerouted through the lymph capillary network.*
(Illustrations adapted from: Near Infrared Fluorescence Lymphatic Imaging to Reconsider Occlusion Pressure of Superficial Lymphatic Collectors in Upper Extremities of Healthy Volunteers[1])

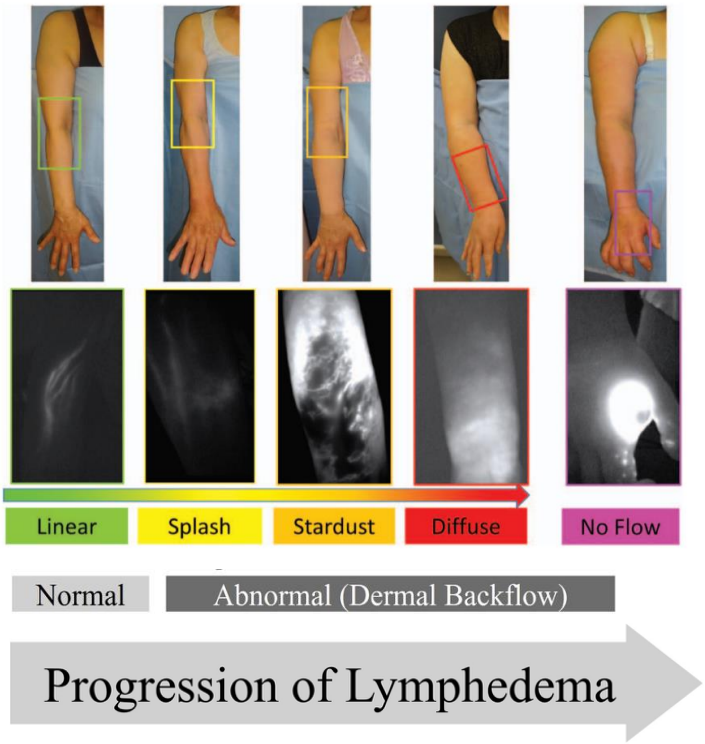
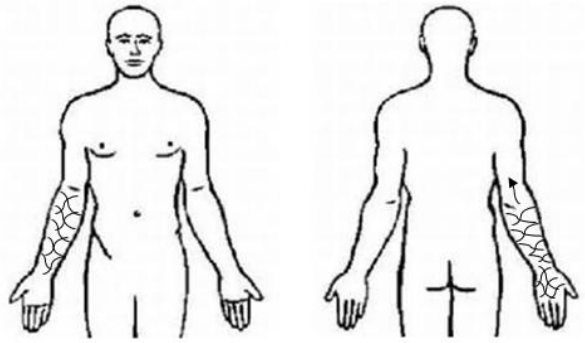


Figure 2. *Fluoroscopic images of a normal pattern, linear pattern, three dermal backflow patters (i.e. splash, stardust, diffuse) and no flow. (Illustration adapted from: Early Detection of Lymphatic Disorder and Treatment for Lymphedema following Breast Cancer[2])*

According to the fluoroscopic findings, mapping of 1) regions with dermal rerouting/backflow, and 2) functional draining pathways, can occur.

In this case example, mapping was presented as follows:



Lymphatic uptake is compromised at the level of the hand and forearm. A functional lymph collector has been visualized at the dorsal side of the upper arm, proximally to the elbow.

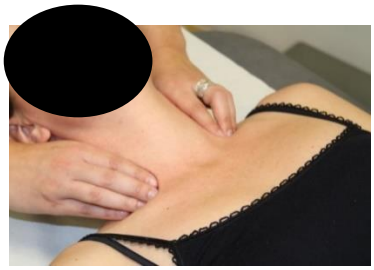
2) <u>OVERVIEW OF HAND MOVEMENTS DURING MLD</u>

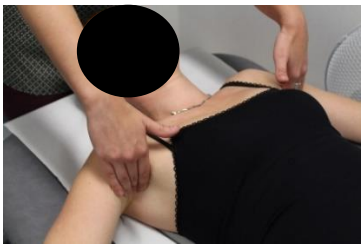
- <u>Fill in</u>: "Pushing" the lymph from the interstitium into the functional lymphatic system
- <u>Flush</u>: Transporting lymph fluid proximally in the collectors, capillaries or interstitium
  - ➔ <u>Collector flush</u>: low pressure, soft strokes *(functional lymph collectors)*
  - ➔ <u>Interstitial flush</u>: high pressure, squeezing strokes *(splash, stardust or diffuse pattern)*

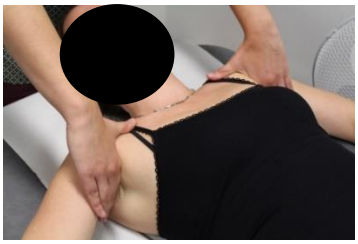
More enlightening videos regarding the different hand maneuvers and lymphatic draining patterns can be found at the web page of the Lymphology Research Unit, ULB.

3) PATIENT-SPECIFIC PROCEDURE MLD:

1. **Empty lymph nodes retroclavicular, axillar and humeral**

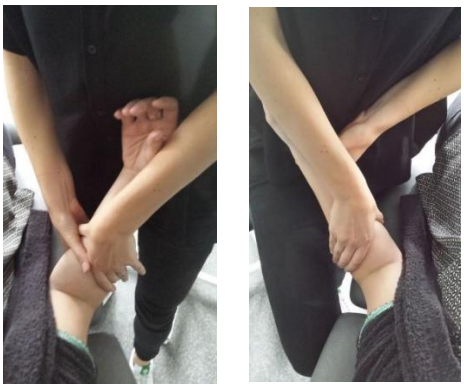

Retroclavicular


Axillar


Humeral

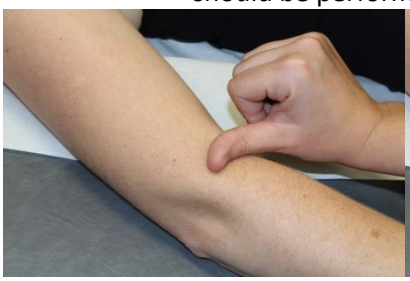
2. **Interstitial flush at the level of the lymphedema of the forearm**

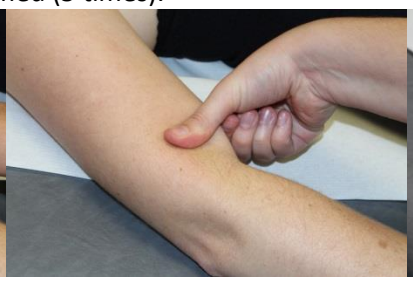
   → Don't begin distally on the forearm, but rather divide the lower arm into 2 to 3 zones in which you perform the interstitial flush separately. After each zone, a fill in to the functional lymph collector should be performed to stimulate the lymphatic reuptake before flushing a more distal zone of the forearm.

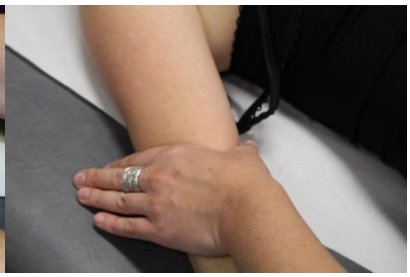

Interstitial flush forearm

3. **Fill in proximal of the lymphedema, above the elbow, into the functional lymph collector and collector flush**

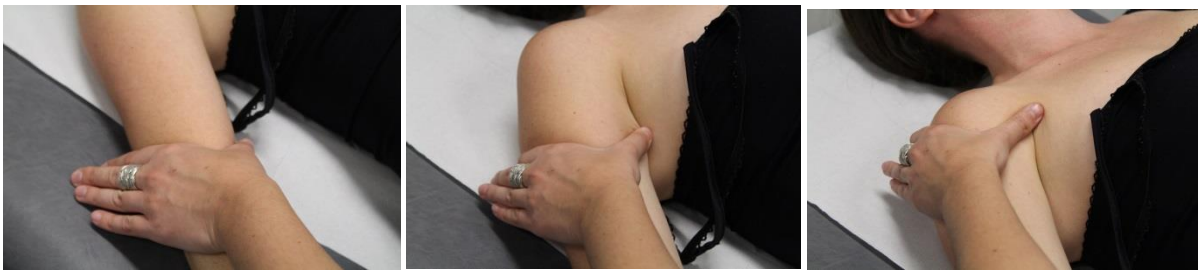
   → The fill in maneuver should be performed 5 times. Thereafter, a collector flush should be performed (5 times).


Fill in

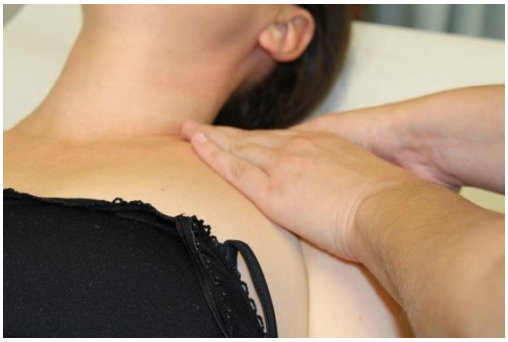



Collector flush

4. **Empty cubital lymph nodes**
5. **Collector flush upper arm + collector flush Mascagni pathway**



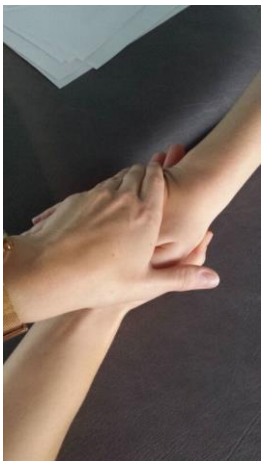
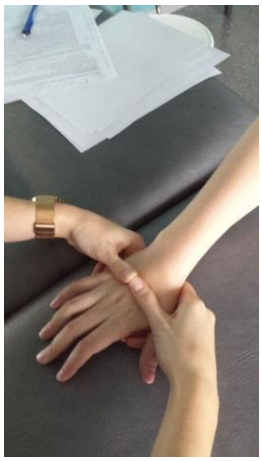
Collector flush upper arm



Collector flush Mascagni pathway

6. **Empty lymph nodes retroclavicular, axillar and humeral**
7. **Interstitial flush forearm (the other, more distally located zones)**

8. **Fill in proximal of the lymphedema into the functional lymph collector and collector flush**
9. **Empty cubital lymph nodes**
10. **Collector flush upper arm + collector flush Mascagni pathway**
11. **Empty lymph nodes retroclavicular, axillar and humeral**
12. **Interstitial flush of the lymphedema of the hand**



Interstitial flush hand

13. **Interstitial flush forearm**
14. **Fill in proximal of the lymphedema into the functional lymph collector and collector flush**
15. **Empty cubital lymph nodes**
16. **Collector flush upper arm + Mascagni pathway**
17. **Empty lymph nodes retroclavicular, axillar and humeral**

References

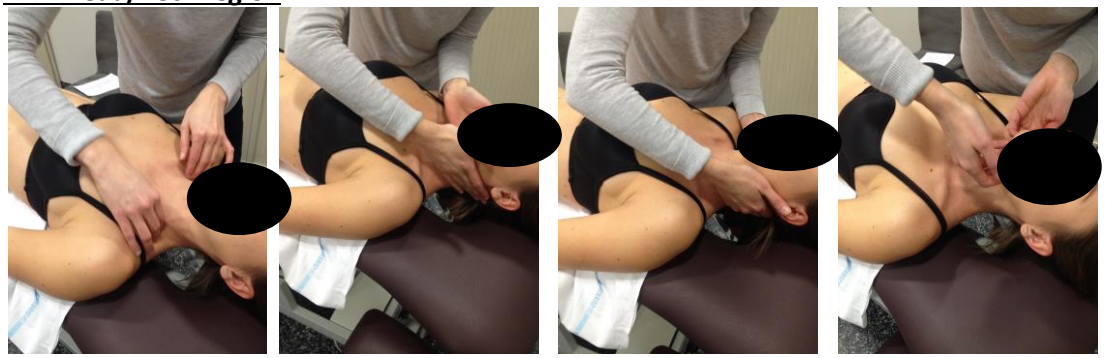
1. Belgrado JP, Vandermeeren L, Vankerckhove S, et al. Near-Infrared Fluorescence Lymphatic Imaging to Reconsider Occlusion Pressure of Superficial Lymphatic Collectors in Upper Extremities of Healthy Volunteers. Lymphatic research and biology 2016;**14**(2):70-7 doi: 10.1089/lrb.2015.0040[published Online First: Epub Date]|.
2. Akita S, Nakamura R, Yamamoto N, et al. Early Detection of Lymphatic Disorder and Treatment for Lymphedema following Breast Cancer. Plast Reconstr Surg 2016;**138**(2):192e-202e doi: 10.1097/prs.0000000000002337[published Online First: Epub Date]|.

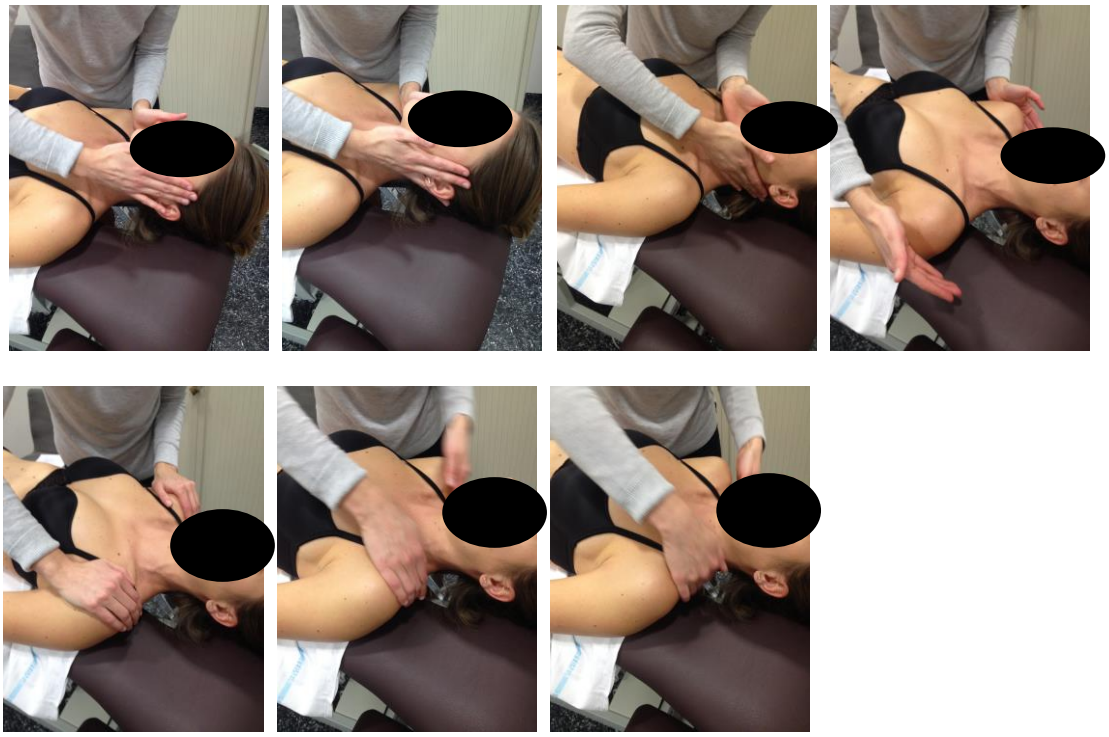
2. Drainage according to the traditional MLD method

A general, standardized MLD method was performed including:

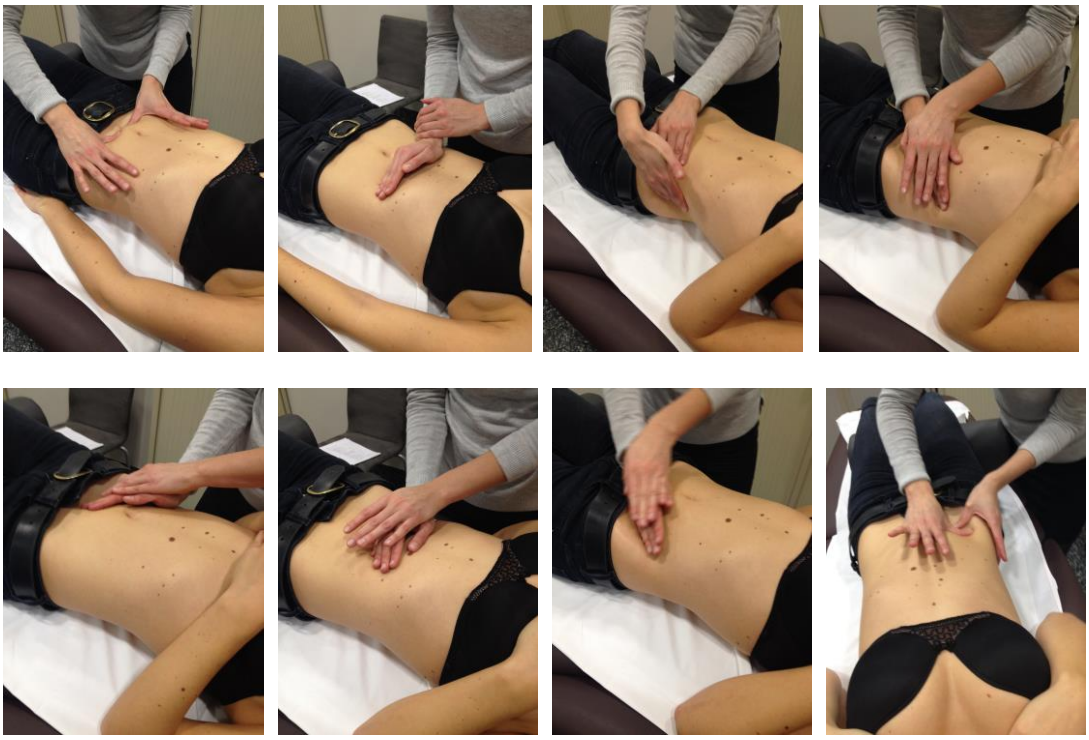
- MLD of the head/neck region
- MLD of the abdominal region
- MLD of the trunk, arm and hand

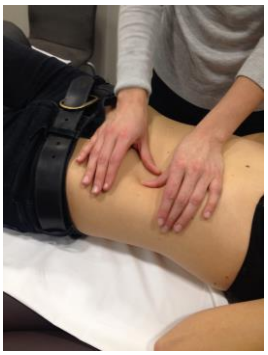
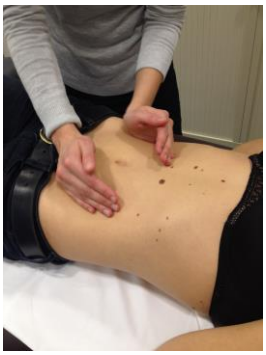
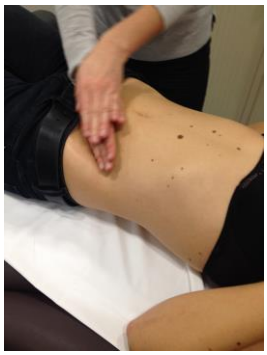
1. MLD head/neck region





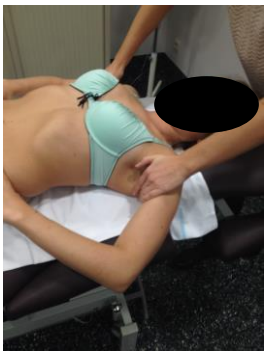
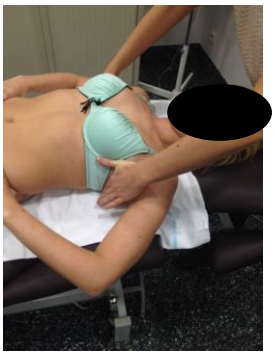
2. MLD abdomen



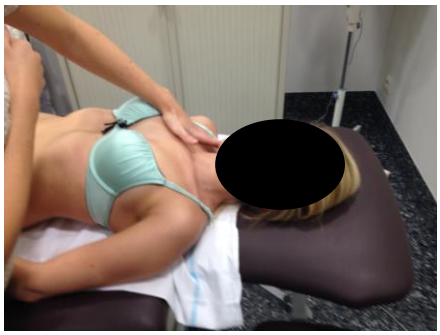
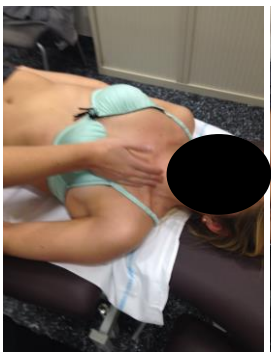
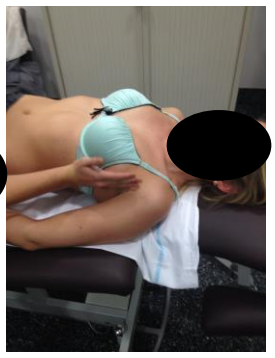




3. **<u>MLD trunk, arm and hand*</u>**
   **In the pictures below, MLD of the left arm is shown instead of the right arm*

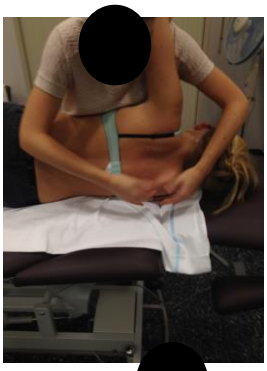
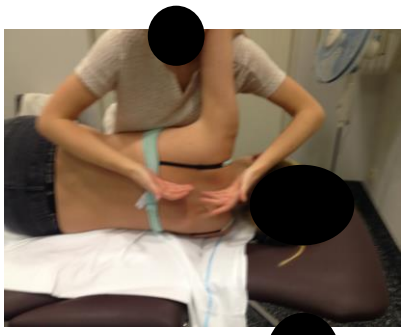
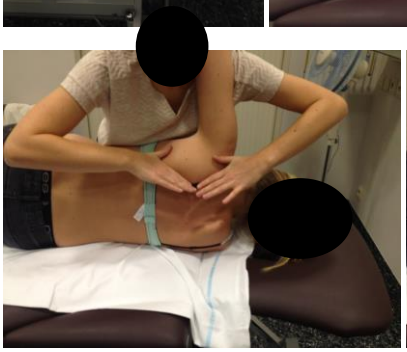
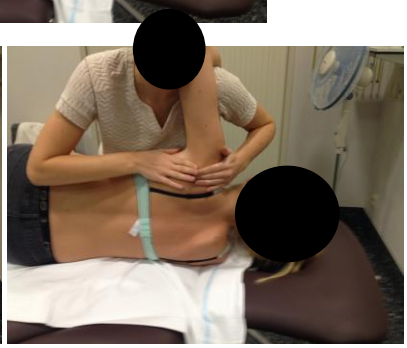
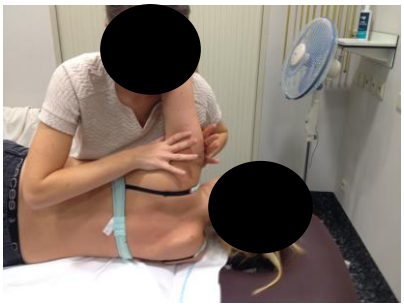
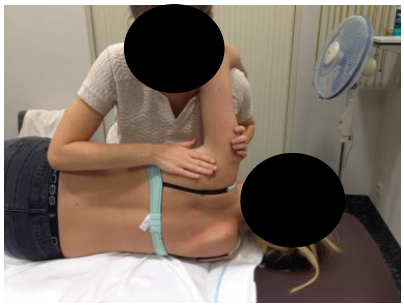
   - **Empty lymph nodes retroclavicular, axillar and humeral**

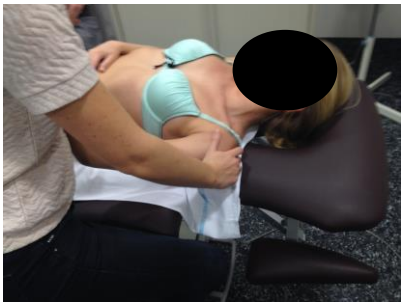
- **Evacuate ('call up') and reabsorb ventral anastomosis**

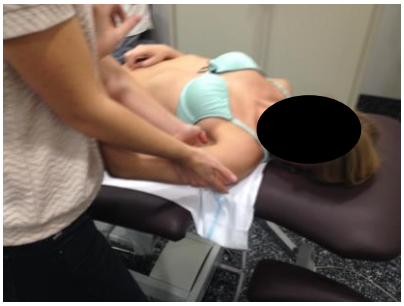
   - **Empty lymph nodes retroclavicular, axillar and humeral**
   - **Evacuate and reabsorb dorsal anastomosis**

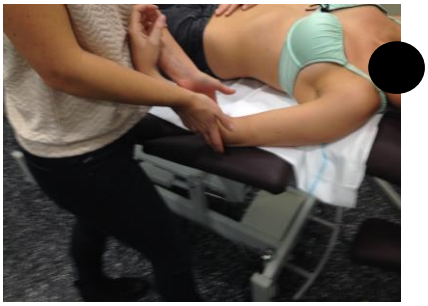
- **Empty lymph nodes retroclavicular, axillar and humeral**
- **Evacuate Mascagni pathway**



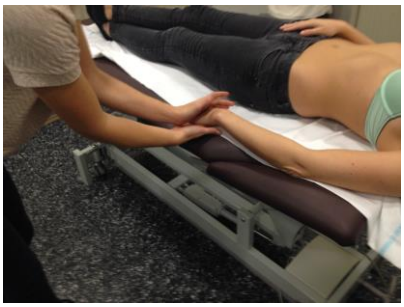
- **Evacuate upper arm**



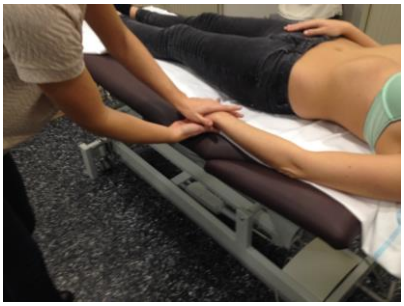
- **Empty cubital lymph node(s)**
- **Reabsorb lower arm**



- **Evacuate lower arm**
- **Empty cubital lymph node(s)**
- **Evacuate upper arm**
- **Evacuate Mascagni pathway**
- **Empty lymph nodes retroclavicular, axillar and humeral**
- **Evacuate Mascagni pathway**
- **Evacuate upper arm**
- **Empty cubital lymph node(s)**
- **Evacuate lower arm**
- **Reabsorb hand**



- **Evacuate hand**



- **Evacuate lower arm**
- **Empty cubital lymph node(s)**
- **Evacuate upper arm**
- **Evacuate Mascagni pathway**
- **Empty lymph nodes retroclavicular, axillar and humeral**

3. Drainage according to the placebo MLD method

A general, standardized placebo massage was performed including:

- Massage neck region
- Massage back region
- Massage arm and hand

1. **Massage neck (transverse stretch movements 5 times per region, bilaterally - supine position)**

- **Paravertebral neck muscles**
- **Trapezius muscle (upper part)**
- **Deltoid muscle (ventral part)**
- **Pectoral muscle**
- **Sternocleidomastoid muscle**

2. **Massage back (transverse stretch movements 5 times per region, bilaterally - prone position)**

- **Levator scapulae muscle**
- **Trapezius muscle (middle and lower part)**
- **Deltoid muscle (dorsal part)**
- **Latissimus dorsi muscle**
- **Paravertebral muscles (thorax)**

3. **Massage arm (transverse stretch movements 5 times per region, unilaterally – supine position)**

- **Biceps muscle**
- **Triceps muscle**
- **Lower arm ulnar side**
- **Lower arm radial side**
- **Hand ulnar side**
- **Hand radial side**

⇨ **Afterwards all movements in reverse all over again, proximally, up to the Trapezius muscle (upper part)**

CHAPTER 3

Chapter 3

WHAT IS THE BEST METHOD TO DETERMINE EXCESSIVE ARM VOLUME IN PATIENTS WITH BREAST CANCER-RELATED LYMPHEDEMA IN CLINICAL PRACTICE? RELIABILITY, TIME-EFFICIENCY AND CLINICAL FEASIBILITY OF FIVE DIFFERENT METHODS

Clin Rehabil. 2019 Jul; 33(7): 1221-1232.

Tessa De Vrieze
Nick Gebruers
Ines Nevelsteen
Wiebren A.A. Tjalma
Sarah Thomis
An De Groef
Lore Dams
Elien Van der Gucht
Jean-Paul Belgrado
Liesbeth Vandermeeren
Nele Devoogdt

Abstract

Objective: To investigate the reliability, time-efficiency and clinical feasibility of five commonly used methods for assessing excessive arm volume in patients with breast cancer-related lymphedema (BCRL)

Design: Cross-sectional study

Setting: University Hospitals Leuven, Belgium

Subjects: 30 participants with unilateral BCRL

Methods: Excessive arm volume was determined by five different methods: traditional volumetry with overflow, volumetry without overflow, inverse volumetry, opto-electronic volumetry and calculated volume based on circumference measurements. To investigate intra- and inter-rater reliability, measurements were performed twice by the same assessor and once by a different assessor. Intraclass correlation coefficients (ICCs), standard errors of the measurement (SEMs) and systematic changes between the means were calculated. To determine time-efficiency, the mean set-up time, execution time and total time were examined for each method. Furthermore, 12 limitations regarding clinical feasibility were listed and scored for each method. Finally, an overall ranking score was determined between the methods.

Results: Mean age was 65 (±8) years, mean body mass index was 28 (±4) kg/m^2. Intra- and inter-rater reliability ranged between strong and very strong. Calculated arm volume based on circumferences (mean excessive arm volume: assessor A: 477 (±367) ml; assessor B: 470 (±367) ml; assessor A (second time): 493 (±362) ml) showed the highest intra- and inter-rater ICCs of .987 and .984, respectively. Opto-electonic volumetry was the fastest method, representing a mean total time of 1 minute and 43 (±26) seconds for performing a bilateral measurement. The least limitations were reported on the calculated volume based on circumferences method (3 out of 12 limitations).

Conclusions: Calculated volume based on arm circumferences is the best measurement method for evaluating excessive arm volume over time in terms of reliability, low error rate, low cost, few limitations, and the time spent.

Introduction

More than 16% of the women treated for breast cancer develops lymphedema of the arm.[1]

The evaluation of the treatment effect in both research and clinical practice is not possible without an accurate, valid and reliable method to determine arm size. Especially in clinical practice, it is crucial that this measurement tool is easy-to-use and rapid as well.[2, 3]

To date, a plethora of different measurement methods capable of determining arm size is available, such as several methods for water displacement[4-6], opto-electronic volumetry[7] and circumference measurements.[8] The traditional way of performing the water displacement method is to measure the overflow of water.[6] An alternative method for determining arm volume is to measure the shortness of water, called inverse water volumetry.[4] Furthermore, recently a volumetry method that does not make use of an overflow, named ValGrado by the developers[10], has been introduced and will be further referred to as volumetry without overflow. Opto-electronic volumetry, or perometry, is another valid measurement tool that showed to be accurate and reproducible in homogeneous geometric shapes.[11] Additionally, based on circumference measurements of the arm, the total arm volume can be calculated by using geometric formulas, such as the truncated cone formula.[12] Table 1 provides an overview of evidence found in literature with regard to reliability, time-efficiency and reported limitations of five commonly used measurement methods. All methods show good to very good intra-rater and inter-rater reliability for measuring arm volume. However, almost none of the studies report on reliability of the assessment of excessive arm volume. Additionally, only a few studies also investigated the measurement error of each method. Regarding time-efficiency, standardized studies investigating the time needed to perform a certain measurement, are lacking.

A recent systematic review providing best evidence regarding which measurement method is most appropriate in measuring lymphedema, concluded that information on feasibility is scarce.[9] A literature search regarding reported limitations of each of the methods, resulted in nine possible limitations (see Table 1).

In conclusion, although plenty of research is already published concerning reliability of different measurement methods separately, a clear overview and comparison of their utility (in terms of reliability, time-efficiency and clinical feasibility), between different variants of water displacement methods, opto-electronic volumetry and calculated volume by using a perimeter, is still missing.

Therefore, the aim of the present study was to investigate and compare the reliability, time-efficiency and clinical feasibility of five different and commonly used methods for determining excessive arm volume in patients with BCRL in clinical practice.

Table 1. Overview of studies investigating reliability and measurement variability (when indicated) of measurement methods quantifying arm volume of the edematous limb

Traditional volumetry with overflow													
Reliability	**First author**	Chen et al 2008[13]	Deltombe et al 2007[14]	Galland et al 2002[15]	Gebruers et al 2007 (no lymphedema)[6]	Gjorup et al 2010[16]	Karges et al 2003[17]	Megens et al 2001[2]	Meijer et al 2004[18]	Mori et al 2015[19]	Sander et al 2002[20]	Taylor et al 2006[12]	**RANGE**
	ICC intra	0.999	0.991	0.996	0.999	0.984	0.990	0.990	0.970-0.980	0.950	0.990	≥0.950	0.950-0.999
	ICC inter	0.990	0.987		0.999			0.990	0.910		0.990		0.910-0.999
	SEM (ml)	Intra 27.20 ml Inter 27.30 ml					11.46 ml (TEM*)				117.00 ml	66.50-81.70 ml	27.20 ml – 117.00 ml
Time-efficiency	**First author**	Galland et al 2002[15]											
	Time (min)	20 min											

Limitations	1) No visual information regarding the shape of the limb[20] 2) Once filled with water, material is not portable[2, 17, 26] 3) Problems with hygiene[26] 4) Not appropriate in subjects with wounds[16, 17, 22] 5) No evaluation of the proximal part of the upper arm[7]												
Volumetry without overflow													
Reliability	**First author**	*No publications yet*											
Time-efficiency	**First author**	*No publications yet*											
Limitations	1) No visual information regarding the shape of the limb[20] 2) Once filled with water, material is not portable[2, 17, 26] 3) Problems with hygiene[26] 4) Not appropriate in subjects with wounds[16, 17, 22] 5) No evaluation of the proximal part of upper arm[7]												
Inverse volumetry													
Reliability	**First author**	Beek et al 2015 *(no lymphedema)*[21]	Damstra et al 2006[4]	Erends et al 2014 *(no lymphedema)*[22]									**RANGE**
	ICC intra	0.990	0.997	0.990									0.990-0.997

	ICC inter		0.995										0.995
	SEM (ml)												
Time-efficiency	**First author**	Beek et al 2015[21]	Damstra et al 2006[4]										
	Time (min)	15 min	5 min										
Limitations	1) No visual information regarding the shape of the limb[20] 2) Material is not portable[2, 17, 26] 3) Problems with hygiene[26] 4) Not appropriate in subjects with wounds[16, 17, 22] 5) No evaluation of the proximal part of upper arm[7]												
Opto-electronic volumetry													
Reliability	**First author**	Adriaenssens et al 2013[23]	Deltombe et al 2007[14]										
	ICC intra	0.999	0.997										0.997-0.999
	ICC inter		0.997										0.997
	SEM (ml)												

Time-efficiency	**First author**	Deltombe et al 2007[14]	Sharkey et al 2018[24]	Stanton et al 1997[11]									
	Time (min)	Few seconds	2 min	Few seconds									
Limitations	1) Device takes a lot of space[27] 2) Expensive equipment[27] 3) The formula used to calculate the volume is unknown and can differ[28] 4) No evaluation of hand volume[4]												
Calculated volume based on circumference measurements													
Reliability	**First author**	Deltombe et al 2007[14]	Devoogdt et al 2010[25]	Galland et al 2002[15]	Gjorup et al 2010[16]	Karges et al 2003[17]	Taylor et al 2006[12]						**RANGE**
	ICC intra	0.958	0.997	0.995	0.998	0.990							0.958-0.998
	ICC inter	0.937	0.994		0.997		0.970-0.990						0.937-0.997
	SEM (ml)		Intra 22.30 ml Inter 25.50 ml			Intra 9.35 ml TEM*)	Inter 64.5-71 ml						Intra 9.35-22.30 ml Inter 22.5-71.00 ml

Time-efficiency	**First author**	Devoogdt et al 2010[25]	Galland et al 2002 *(tapeline girth measures)*[15]	Sharkey et al 2018[24]									
	Time (min)	5 min	10 min	10 min									
Limitations	1) No evaluation of hand volume[4]												

Note: * outcome is mentioned as TEM (absolute technical error of measurement); no formula was presented.

Methods

This cross-sectional study is part of the EFforT-BCRL trial[30] for which approval was obtained by the Ethical Committee of the University Hospitals of Leuven (CME reference S58689, EudraCT 2015-004822-33, Clinicaltrials.gov NCT02609724). The study was conducted in accordance with the Declaration of Helsinki and is reported following the recommended STROBE guidelines for observational studies.

Participants

Between July and November 2017, participants of the EFforT-BCRL trial ware asked to contribute in this subtrial. Eligibility criteria were: 1) female/male patients with unilateral BCRL of the arm, 2) currently in the maintenance phase of the decongestive lymphatic therapy, 3) no known recurrence of cancer. Participants were excluded when they: 1) had solely hand edema, and 2) had open skin lesions on one of their arms at the time of the testing. All participants received written and oral information by mail as well as by phone. All participants signed the informed consent document in the prior EFforT-BCRL trial.

Data collection and assessments

All assessments were performed at the department of Physical Medicine and Rehabilitation of the University Hospitals of Leuven. Excessive arm volume of all participants was determined by five different methods:

- traditional volumetry with overflow, in which the overflow of water is weighted[6];
- volumetry without overflow, in which the volume of the upward displaced water is weighted when submerging the limb in the recipient[10];
- inverse water volumetry, an alternative method for determining arm volume whereby the shortness of water is measured[4];
- opto-electronic volumetry (or perometry), a method that makes use of an optical-electronic infrared device to detect volume differences (without considering hand volume)[11]; and
- calculated volume based on circumference measurements, whereby total arm volume (without considering hand volume) can be calculated by using geometric formulas, such as the truncated cone formula.[12] This formula postulates that every section of the limb represents a perfect circle, and that the walls of the cone are rectilinear.

For each participant, the volume of both arms was measured. To determine the excessive arm volume, the volume of the non-edematous arm was subtracted by the volume of the edematous arm. Table 2

comprises a detailed overview of the five different measurement methods for assessing arm volume and excessive volume and their standardized procedures.

Descriptive data was collected by interviewing the participants and by consulting their medical record. For each participant, only one visit to the hospital was necessary to collect all data. Participants arrived 15 minutes prior to the start of the measurements at the hospital in order to stabilize skin temperature with room temperature.[30] In our study room, a constant temperature of 21°C was maintained. During this time, compression sleeves and jewelry on both arms were removed.
The estimated duration for a single execution of the five different measurements was 30 minutes (i.e. one assessment block). Since the execution of an assessment block was performed three times consecutively, the total duration of the investigation was approximately 1.5 hours per participant. The sequence of the five measurement methods in one assessment block varied between the different participants, however, within each participant the same sequence was maintained among the three executions. The order of measured sides during the measurements was chosen randomly. Prior to the assessments, three different 2-hour training moments were scheduled to guarantee standardization between assessors (TDV, LV), as well as three consecutive 1-hour training moments focused on time measurements between the persons registering the scores (SVDS, AVH, MB, TP).

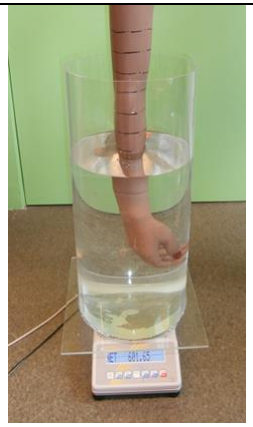
To investigate intra-rater reliability, the first and the last assessment block were performed by the same assessor (TDV). To investigate inter-rater reliability, the second one was performed by a different assessor (LV). In order to obtain blinding of the assessors for previous test results, a different person registered the score. To preserve blinding for the reference point(s), after completing each assessment block consisting of the five methods, reference points were removed using alcohol wipes.

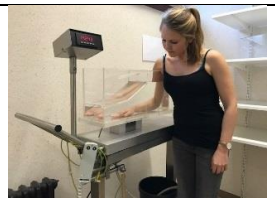
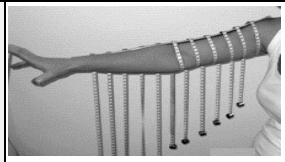
To provide an overview concerning time-efficiency of the five methods, a subdivision was made between: 1) the time needed to prepare the measurement and is reported as setup time, 2) the time needed for a bilaterally execution of the measurement and is reported as execution time, and 3) the total time required for the setup and execution of the measurement.
The setup of the measurement equipment was consistently prepared according to a predetermined and standardized protocol. Volumeters were filled with tepid water since literature showed that water temperatures across this range do not affect the density of water (and consequently, the weight of water measured), and do not cause vasodilatation/ vasoconstriction of the blood capillary system.[6, 26, 32] Setup time was determined for traditional volumetry with overflow, volumetry without overflow and inverse volumetry. Other methods did not require any preparation in advance (Table 2). Subsequently, execution of the five different methods was timed in a consistent and standardized

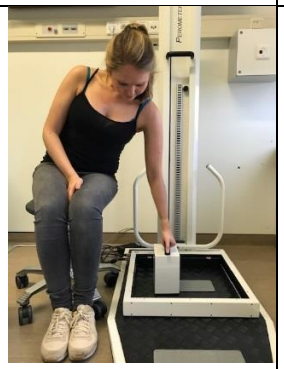
manner as well. In Table 2, the timing protocol for each method in particular is described in more detail.

Table 2. Protocol: overview of the five measurement methods and procedures

Assessment	Picture	Material	Reference points	Method *Setup*	*Procedure*	Outcome
Traditional volumetry with overflow[6]	 *(with permission illustration from Gebruers et al 2007[6])*	Cubically shaped tank with overflow (18x18x76 cm) filled with tepid tap water of 20-30°C, chair, recipient placed on electronic weighing balance with 0.1g accuracy (KERN 572) on top of a platform of 25 cm height, skin pencil, chair or stool.	Half the distance between acromion and proximal edge of epicondylus lateralis (elbow flexed in 90° whilst marking reference point).	Place a recipient on a scale underneath the overflow. Fill the tank with water until the level of the overflow has reached and flows out. When the water stops dripping (frequency $\leq$ 1 drop per second), calibrate the scale (= 0g). Subject is sitting down next to the tank. Setup time= from setup till the water level in the tank reached the overflow.	Extra water is added to the tank until the water level enters the overflow. During the time water is dripping, reference points are marked. Once the water stops to drip, the scale is tared. Subject lowers the arm into the tank until the water level reaches the marked reference point. The limb needs to be kept straight and perpendicular to the surface, with the palm of the hand placed against the edge of the volumeter. When the limb reaches the reference point, the position has to be maintained until the water stops dripping with frequency $\leq$ 1 drop per second. Read the weight of the water in the recipient. Execution time= started with adding some extra water to the tank before finally taring the scale and ended when water of the overflow dripped	Weight of the displaced water (g). Comparison left/right. Measurement of excessive volume of the whole arm = (volume edematous limb – non-edematous limb). Setup time, execution time and total time (= setup time + execution time) (seconds).

					with frequency ≤ 1 drop per second, after lowering the limb.	
Volumetry without overflow[10]		Cylinder filled with tepid tap water of 20-30°C, placed on weighing balance with 0.1g accuracy (KERN 572); both are placed on top of a platform of 25 cm height. Weighing balance is connected with 'Matlab' software program on laptop, skin pencil.	10 cm proximal to the middle skinfold of the elbow crease.	Place the cylinder on a scale. Tare the scale. Subject is positioned in standing beside the cylinder. Setup time= from setup till the water level in the tank reached a level of 15cm below the upper edge (= arbitrary chosen to preserve standardization).	Perpendicular to the water surface, subject lowers the arm into the cylinder until the water level reaches the marked reference point. Subject is given attention not to touch the border of the cylinder. Once the water level equals the level of the reference point on the upper arm, the assessor clicks on the assessment button; software program performs 10 volume measurements and calculates mean volume (Volume of upward displaced water = Mass of water/ density of water, density of water with T° between 20-30°C is 1); a signal is given if mean volume or its standard deviation is outside of preset range. Execution time= timed in two phases: 1) application of reference points 2) started from lowering the arm in the tank until predefined reference point was reached and the weight was shown on the computer screen.	Weight of the upward displaced water (g). Comparison left/right. Measurement of excessive lymphedema volume whole arm = cfr. Supra. Setup time, execution time and total time (= setup time + execution time) (seconds).

Inverse volumetry[4]		Tank filled with tap water of 28°C standing on a weighting device, based on the metal bending principal.	No reference point.	Calibration procedure: Fill the tank with water until the water reaches the overflow. When the water stops dripping at a frequency ≤ 1 drop per second, calibrate to zero and drain the water. This procedure needs to be performed only once daily. Measurement procedure: Subject is positioned in standing beside the tank. Adjust the height of the tank until subject is standing comfortable. Setup time= from filling the water tank till end of calibration.	Subject places the olecranon in the corner at the opposite side of the tank, elbow flexed in 90°, pronation of the forearm, extension of the fingers. Assessor fills the tank until the water reaches the overflow. When the water stops dripping at a frequency ≤ 1 drop per second, the arm is removed from the tank. The display of the weighting device shows the shortness of water compared with the initial situation. Execution time= started with placing the arm in the tank and ended when water of the overflow dripped with frequency ≤ 1 drop per second.	Weight of the added water (g). Comparison left/right. Measurement of excessive lymphedema volume whole arm = cfr. Supra. Setup time, execution time and total time (= setup time + execution time) (seconds).
Calculated volume based on circumferences[25]	 *(with permission illustration from*	Perimeter; which is a flexible stainless steel bar with a tapeline fixed every 4cm and a weight of 20g at the end, skin pencil, chair, table	Proximal border of the olecranon.	Subject is in sitting position with 90° anteflexion of the arm, straight elbow and hand supported on table.	Arm circumferences measured at olecranon and at 4, 8, 12, 16 and 20 cm proximal and distal of olecranon. First, the reference point at the upper border of the olecranon. The bar was placed on the dorsal side of the arm: the middle tapeline was	Volume of an arm segment of 4cm = $4 \times (C_1^2+C_1C_2+C_2^2)/12\pi$, where C_1 is the upper circumference and C_2 is the lower circumference of each segment[32]

	Devoogdt et al 2010[25]*)*	with adjustable height.			placed distal of the reference point perpendicular to the axis of the arm. The other tapelines were placed around the lower arm, also perpendicular to the axis of the arm. Then the circumference at each point was recorded. Afterwards, all tapes except the middle one were removed, and this procedure was repeated for the upper arm[25] Execution time= started with application of the reference point and ended after recording all circumferences of both arms.	Calculated volume of whole arm = sum of the volume of all segments of the arm Comparison left/right. Measurement of excessive lymphedema volume whole arm = cfr. Supra. Execution time (= total time) (seconds).
Opto-electronic volumetry[11]		Opto-electronic volumetry device (Perometer®) with a vertical arm, a portable block with handle on top of it, computer provided with 'PeroPlus' software (Pero-System Messgeräte GmbH, Wuppertal, Germany), chair or stool	No reference point.	Subject is in sitting position next to the device. Hand of the subject is placed on a handle block which position remained unchanged during the entire measurement. The wrist stays in neutral position with closed and connected fingers and the thumb facing forward. The elbow is straight and the armpit is located just	Subject keeps a fixed position with the arm straight. Assessor moves the handle of the Perometer slowly up until the frame reaches the armpit, then moves slowly back down; a signal is given when the axilla (moving up) and the floor (moving down), are reached.	Volume of the limb in ml. Comparison left/right. Measurement of excessive lymphedema volume whole arm = cfr. Supra. Measurement starts for every subject at a height of 58 cm (level of the wrist) end is ended at the corresponding height when the frame reaches the armpit. Subsequently, arm

		The Perometer consists of a vertically movable frame equipped with infrared light emitters and receptors. The infrared light beams are interrupted by the introduction of the arm into the frame[23]. By moving the frame along the long axis of the arm, a measure is automatically performed every 4.7 mm[24] for a distance which is varying per subject, according to the individual arm length.		above and perpendicular to the ipsilateral border of the frame. No setup time.	Execution time= started with providing the instructions how to sit down in a correct and predefined starting position, and ended when the software program finished processing the data. Time to open the program (PeroPlus) is included in the execution time.	volume is calculated for these measures. Execution time (= total time) (seconds).

Limitations regarding clinical feasibility of the different methods reported in literature (Table 1) were discussed by a team of experts in the field. Additionally, limitations reported by the experts retrieved from clinical experience were added to the list, after which all limitations were scored for each of the five measurement methods (yes/no). Two experts have many years of clinical and scientific experience in using the measurement methods (ND, NG), and the other expert has performed the assessments during the current study (TDV).

Finally, an overall comparison between the five methods regarding their reliability, time-efficiency and clinical feasibility is performed in order to provide an overview about the most appropriate method to use in clinical practice for measuring the excessive arm volume over time.

Data analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows version 24.0. The 0.05 level of significance was applied. Descriptive statistics for continuous values are presented as mean ±SD for normal distributed data and median and interquartile range for not normal distributed data. Categorical variables are presented as number and proportion (%).

Reliability of the volume measurements of the edematous limb, the non-edematous limb and of the excessive arm volume were analyzed. Intraclass correlation coefficients (ICCs) were used to examine intra-rater and inter-rater reliability between the different measurement occasions.[33] ICC estimates and their 95% confident intervals (CIs) were calculated based on a single rating (k=1), absolute agreement, two-way random-effects model.[34, 35] The ICCs were interpreted as follows: <.40 weak, .40 to .74 moderate, .75 to .90 strong and >.90 very strong.[36, 37]

To interpret the magnitude of the within-subjects variation of the two scores, the standard error of measurement (SEM) was calculated using following formula: SEM = SD(difference)/$(2)^{0.5}$, where SD was the standard deviation of the volume differences between the two assessments.

To calculate systematic changes in the mean between two measurement occasions, paired samples t-tests were applied since the Shapiro-Wilk test revealed a mainly normal distribution of data.

A one-way ANOVA analysis was executed to demonstrate statistical significant differences among group-means, assisted with post hoc analyses for further evaluation.

Descriptive statistics on the reported limitations were performed to describe the clinical feasibility of each method.

Finally, data was used to compile a ranking table. Therefore, reliability of each method was based on the intra- and inter-rater ICC values of the excessive volume and was ranked between 1 (most reliable method) and 5 (least reliable method). The rating of time-efficiency was based on the total time, and consequently resulted in a ranking between 1 (most time-efficient method) and 5 (least time-efficient method). The rating of clinical feasibility was determined as the sum of scores on the reported limitations for each method. Based on this score, all methods were ranked between 1 (most feasible method) and 5 (least feasible method). Finally, based on the sum of the different scores on each item, the methods were ranked between 1 (most appropriate method) and 5 (least appropriate method).

Results

Thirty women were enrolled in this study. All measurements were completed in all 30 participants. Mean age was 65 (±8) years and mean body mass index (BMI) was 28 (±4) kg/m^2. An overview of the characteristics of the included subjects is provided in Table 3.

Table 3. Characteristics of the included subjects (n=30)

Descriptives	
Variable	**Outcome** **Mean (SD)**
Age (y)	65 (8)
Body Mass Index (kg/m^2)	28 (4)
Duration lymphedema (mo)	74 (44)
Frequencies	
Variable	**Outcome** **N (%)**
Lymphedema stages	
stage I	3 (10%)
stage IIa	18 (60%)
stage IIb	9 (30%)
Location of lymphedema	
Lower arm	14 (53%)
Upper arm	0 (0%)
Total arm (lower arm + upper arm)	16 (47%)
Breast surgery	
Mastectomy	21 (70%)
Breast-conserving surgery	9 (30%)
Axillary lymph node clearance	
SLNB	1 (3%)
ALND	29 (97%)
Surgery on the dominant side	17 (57%)
Radiotherapy	30 (100%)
Chemotherapy	24 (80%)
Hormonal therapy	27 (90%)
Targeted therapy (Herceptin)	6 (20%)

Abbreviations: y= years, kg= kilogram, m^2= square meters, mL= milliliter, mo= months, lymphedema stages as described by the International Society of Lymphology (i.e. Stage I = Accumulation of interstitial fluid, with reduction by elevation. At this stage the edema can be pitting. / Stage IIa = Swelling disappears barely by elevation, the edema is clearly pitting. / Stage IIb = Pitting is clearly present by fibrotic formations in the edema), SLNB = sentinel lymph node biopsy, ALND = axillary lymph node dissection

Tables 4 and 5 list the intra-rater and inter-rater ICC values (with 95% CI), the SEMs (with 95% CI), and the mean volumes on each test occasion, supported with the outcomes of the paired samples t-tests.

- *Intra-rater reliability:*

  Taken into account the results considering the excessive arm volume, all methods showed satisfying ICCs, ranging from .777 to .987. Calculated arm volume based on circumferences showed the highest ICC of .987. Similar to the ICC results, calculated arm volume based on circumferences showed the lowest SEM, resulting in a variation of one test occasion to the other of 41.58ml.

- *Inter-rater reliability:*

  Likewise, considering the results regarding the excessive volume between the two arms, ICCs ranged between .791 and .984. Calculated arm volume based on circumferences showed the highest ICC of .984. Additionally, this method presented the lowest SEM, resulting in a test variation between two test occasions by different assessors, of 45.3ml.

Table 4. Intra-rater reliability (n= 30)

	Method	First assessment (assessor A) Mean volume (SD; Min-Max)	Second assessment (assessor A) Mean volume (SD; Min-Max)	ICC (95% CI)	SEM (95% CI)	Paired samples T-Test P-value
Edematous limb	Traditional volumetry with overflow	2662.64 (384.63; 1692.4-4401.3)	2681.16 (400.72; 1646.5-4389.8)	.950 (.899 - .976)	87.80 (-153.58 – 190.62)	0.643
	Volumetry without overflow	2253.21 (515.69; 1463.1-4401.3)	2246.16 (501.41; 1401.5-3287.7)	.950 (.898-.976)	113.72 (-216.3 – 229.46)	0.827
	Inversed volumetry	3160.4 (653.85; 2033-4760)	3166.23 (705.58; 1945-4672)	.979 (.957-.990)	98.5 (-187.23 – 198.89)	0.823
	Opto-electronic volumetry	5245.47 (747.32; 4140-7048)	5197.37 (729.05; 4084-6921)	.972 (0.941-.986)	123.52 (-194 – 290.2)	0.137
	Calculated arm volume based on circumferences	3000.88 (764.12; 1911.9-4727.6)	3016.16 (769.97; 1895.9-4776.2)	.999 (.997-.999)	24.26 (-40.26 - 54.82)	0.309
Non-edematous limb	Traditional volumetry with overflow	2180.99 (534.31; 1337.5-3720.6)	2139.78 (537.86; 1359.9-3689.8)	.983 (.960-.992)	69.90 (-95.79 – 178.21)	0.019*
	Volumetry without overflow	1816.66 (332.32; 1193.0-2623.0)	1817.93 (351.28; 1173.5-2654.2)	.985 (.968-.993)	41.86 (-80.78 – 83.32)	0.910
	Inversed volumetry	2635.97 (552.95; 1655-4150)	2614.07 (587.52; 1624-4231)	.991 (.980-.996)	54.10 (-84.13 – 127.93)	0.128
	Opto-electronic volumetry	4694.6 (551.47; 3832-6128)	4658.9 (575.43; 3685-6333)	.961 (.921-.981)	111.27 (-182.39 – 253.79)	0.219
	Calculated arm volume based on circumferences	2531.95 (564.85; 1547.3-4069.8)	2523.11 (584.37; 8.8)	.995 (.990-.998)	40.63 (-70.80 – 88.48)	0.404

	Method	First assessment (assessor A) Mean volume (SD; Min-Max)	Second assessment (assessor A) Mean volume (SD; Min-Max)	ICC (95% CI)	SEM (95% CI)	Paired samples T-Test P-value
Excessive volume	Traditional volumetry with overflow	481.65 (384.63; -56.9-1498.2)	541.38 (400.72; -307.5-1195.3)	.813 (.646-.906)	169.81 (-273.09 – 392.55)	0.179
	Volumetry without overflow	419.07 (330.83; -128.6-1285.7)	428.7 (289.04; -33.8-1227.0)	.777 (.582-.888)	146.36 (-277.24 – 296.5)	0.803
	Inversed volumetry	524.43 (355.2; -140-1159)	552.17 (378.95; -195-1593)	.922 (.843-.962)	102.52 (-173.2 – 228.68)	0.315
	Opto-electronic volumetry	550.87 (415.75; -201-1420)	538.47 (366.25; -207-1308)	.921 (.842-.962)	109.90 (-203.00 – 227.80)	0.670
	Calculated arm volume based on circumferences	476.93 (367.31; -126.8-1345.3)	493.05 (361.99; -28.1-1454.7)	.987 (.973-.994)	41.58 (-65.37 – 97.61)	0.130

Abbreviations: SD= standard deviation, ICC= intraclass correlation coefficient, CI= confidence interval, SEM= standard error of measurement;

* corresponds with p-value <.05, ** corresponds with p-value <.01

Table 5. Inter-rater reliability (n= 30)

	Method	**First assessment (assessor A)** **Mean volume (SD; Min-Max)**	**Second assessment (assessor B)** **Mean volume (SD; Min-Max)**	**ICC (95% CI)**	**SEM (95% CI)**	**Paired samples T-Test** **P-value**
Edematous limb	Traditional volumetry with overflow	2662.64 (384.63; 1692.4-4401.3)	2647.33 (708.74; 1596.4-4436.1)	.954 (.907-.978)	117.25 (-245.50 – 214.12)	0.694
	Volumetry without overflow	2253.21 (515.69; 1463.1-4401.3)	2228.16 (488.66; 1149.6-2901.4)	.980 (.957-.990)	71.02 (-114.15 – 164.25)	0.452
	Inversed volumetry	3160.4 (653.85; 2033-4760)	3195.97 (692.24; 1934-4632)	.974 (.947-.988)	108.53 (-177.14 – 248.28)	0.206
	Opto-electronic volumetry	5245.47 (747.32; 4140-7048)	5062.07 (720.13; 4081-6676)	.949 (.504-.986)	165.70 (-141.37 – 508.17)	<0.001**
	Calculated arm volume based on circumferences	3000.88 (764.12; 1911.9-4727.6)	2942.47 (732.58; 1861.4-4608.4)	.993 (.921-.998)	62.61 (-56.31 – 189.13)	<0.001**
Non-edematous limb	Traditional volumetry with overflow	2180.99 (534.31; 1337.5-3720.6)	2148.99 (525.8; 1370.7-3686.9)	.984 (.964 - .992)	67.05 (-99.41 – 163.41)	0.068
	Volumetry without overflow	1816.66 (332.32; 1193.0-2623.0)	1852.64 (394.29; 1149.6-2901.4)	.930 (.859-.966)	96.12 (-152.42 – 224.38)	0.354
	Inversed volumetry	2635.97 (552.95; 1655-4150)	2614.8 (565.49; 1521-4161)	.994 (.987-.997)	43.32 (-6373 – 106.07)	0.054
	Opto-electronic volumetry	4694.6 (551.47; 3832-6128)	4537.03 (534.1; 3743-6151)	.934 (.377-.982)	139.44 (-115.74 – 430.88)	<0.001**
	Calculated arm volume based on circumferences	2531.95 (564.85; 1547.3-4069.8)	2473.23 (545.88; 1516.7-3910.9)	.986 (.931 - .995)	65.71 (-70.07 – 187.51)	<0.001**

	Method	First assessment (assessor A) Mean volume (SD; Min-Max)	Second assessment (assessor B) Mean volume (SD; Min-Max)	ICC (95% CI)	SEM (95% CI)	Paired samples T-Test P-value
Excessive volume	Traditional volumetry with overflow	481.65 (384.63; -56.9-1498.2)	498.34 (354.15; -77.9-1293.3)	.861 (.729-.931)	137.72 (-253.24 – 286.62)	0.646
	Volumetry without overflow	419.07 (330.83; -128.6-1285.7)	375.53 (274; 1149.6-2901.4)	.791 (.606 – .895)	138.25 (-227.44 – 314.52)	0.520
	Inversed volumetry	524.43 (355.2; -140-1159)	581.17 (378.95; -20-1494)	.909 (.810-.957)	110.73 (-160.30 – 273.78)	0.046*
	Opto-electronic volumetry	550.87 (415.75; -201-1420)	525.03 (399.14; -229-1358)	.949 (.897-.975)	92.01 (-151.51 – 206.19)	0.285
	Calculated arm volume based on circumferences	476.93 (367.31; -126.8-1345.3)	469.24 (367.31; -88.7-1373.2)	.984 (.967-.992)	45.3 (-81.11 – 96.49)	0.523

Abbreviations: SD= standard deviation, ICC= intraclass correlation coefficient, CI= confidence interval, SEM= standard error of measurement;

* corresponds with p-value <.05, ** corresponds with p-value < 0.01

An overview of the results regarding mean setup time, mean execution time and mean total time (±SDs) of the different measurement methods is given in Table 6. Additionally, a visual comparison of the results, assisted with the ANOVA post hoc outcomes, is illustrated in Figure 1. Regarding the ANOVA post hoc analyses, Games-Howell post hoc analyses were performed since equal variances were not assumed.

- *Setup time:*

  Volumetry without overflow showed to require the least time, with a mean setup duration of 4 minutes and 40 (±12) seconds. Mean setup time differed statistically significant between traditional volumetry with overflow and volumetry without overflow ($p<0.01$).

- *Execution time:*

  Mean bilateral execution time was lowest for volumetry without overflow (56 (±12) seconds). Mean execution time was highest for inverse volumetry (5 minutes and 34 (±210) seconds) ($p<0.01$).

- *Total time:*

  With regard to the time needed for both setup (if required) as well as a bilaterally execution of the measurement, opto-electonic volumetry turned out to be the fastest method, representing a mean time of 1 minute and 43 (±26) seconds. Every pairwise comparison of methods showed statistical significant differences between their means ($p<0.05$).

Table 6. Setup time, mean execution time and mean total time of five different measurement methods (n= 30)

Measurement method	Mean setup time (SD) in seconds	ANOVA p-value	Mean execution time (SD) in seconds	ANOVA p-value	Mean total time (SD) in seconds	ANOVA p-value
Traditional volumetry with overflow	444.00 (11.51)[a]	P<.01	275.80 (89.56)[c]	P<.01	640.53 (89.11)[f]	P<.01
Volumetry without overflow	280.00 (16.80)[b]		55.67 (11.57)[d]		335.67 (11.57)[f]	
Inverse volumetry	362.00 (69.35)		333.70 (209.56)[c]		775.00 (212.57)[f]	
Opto-electronic volumetry*			102.67 (26.02)[e]		102.67 (26.02)[f]	
Calculated arm volume based on circumferences			264.13 (26.53)[c]		264.13 (26.53)[f]	

* Time to open the program (PeroPlus) is included in the execution time

[a] statistical significant difference with volumetry without overflow (p <.01)

[b] statistical significant difference with traditional volumetry with overflow (p <.01)

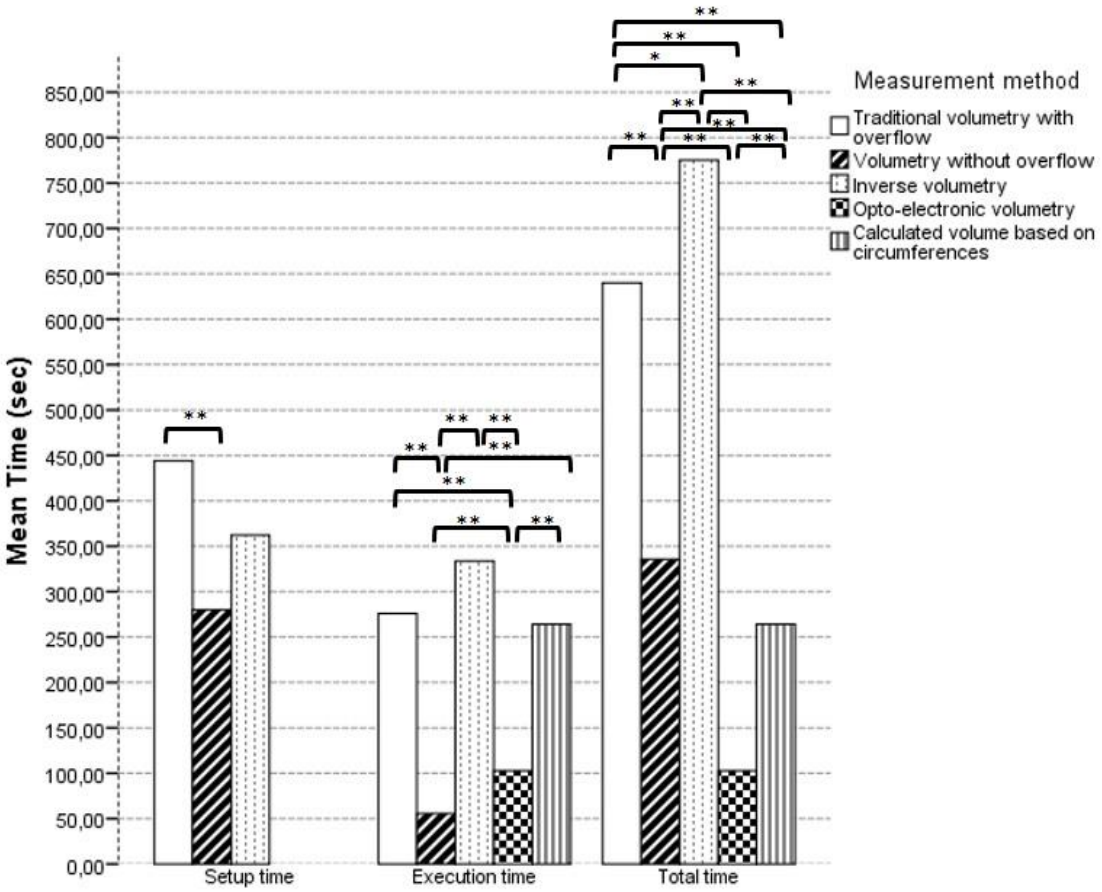
[c] statistical significant differences with opto-electronic volumetry and volumetry without overflow (p <.01)

[d] statistical significant differences with inverse volumetry, opto-electronic volumetry and calculated arm volume based on circumferences (p <.01)

[e] statistical significant differences with traditional volumetry with overflow, volumetry without overflow, inverse volumetry and calculated arm volume based on circumferences (p <.01)

[f] every pairwise comparison of methods showed statistical significant differences between their means (p <.05)

Figure 1. *Comparison of setup time, mean execution time and mean total time of five different measurement methods assisted with ANOVA post hoc analyses (n= 30)*



* statistical significant difference between the mean times of both methods (p<.05)
** statistical significant difference between the mean times of both methods (p<.01)

Nine limitations regarding clinical feasibility that were listed in Table 1 were supplemented with following three limitations, retrieved from clinical experience: 1) the device is difficult to apply in patients with limited postural balance, 2) segmental measurements for evaluation of local changes are not provided, and 3) indirect measurement of volume (calculations need to be performed after the measurement). Finally, these 12 limitations were scored in Table 7. Least limitations were seen in the calculated volume based on circumferences method.

Results regarding the ranking of the best method in clinical practice revealed that calculated volume based on circumference measurements received the highest overall rank. Therefore, this method is considered as the most appropriate method to use in clinical practice based on our scored items (see Table 7).

Table 7. Summary table with ranking of the five measurement methods regarding reliability (ICC), time-efficiency and clinical feasibility

		Traditional volumetry with overflow	**Volumetry without overflow**	**Inverse volumetry**	**Opto-electronic volumetry**	**Calculated volume based on circumferences**
Reliability	**ICC[a]** Outcome *(intra/inter)*	Intra: .813 Inter: .861	Intra: .777 Inter: .791	Intra: .922 Inter: .909	Intra: .921 Inter: .949	Intra: .987 Inter: .984
	Ranking	**4**	**5**	**3**	**2**	**1**
Time-efficiency	Outcome *(total time)*	640.53 seconds	335.67 seconds	775 seconds	102.67 seconds	264.13 seconds
	Ranking	**4**	**3**	**5**	**1**	**2**
Clinical feasibility	**Limitations** Outcome *(0= no limitation, 1= limitation)*					
	No visual info shape limb	1	1	1	0	1
	Not portable	1	1	1	1	0
	Problems with hygiene	1	1	1	0	0
	Not appropriate when having wounds	1	1	1	0	0
	No evaluation of proximal part upper arm	1	1	0	0	0
	Difficult to apply with limited postural balance	0	1	0	0	0

	Extensive device	0	0	1	1	0
	Expensive device/procedure (>3000 euros)	0	0	1	1	0
	No segmental evaluation of limb	1	1	1	0	0
	Formula for calculating volume is unknown	0	0	0	1	0
	No evaluation of hand volume	0	0	0	1	1
	Indirect volume measurement	0	0	0	0	1
	Total score	6	7	7	5	3
	Ranking clinical feasibility	**3**	**4**	**4**	**2**	**1**
Total score		*11*	*12*	*12*	*5*	*4*
TOTAL RANKING		**3**	**4**	**4**	**2**	**1**

[a]Note: presented inter- and intra- rater ICC values are based on excessive volume results

Discussion

In terms of reliability, low error rate, low cost, few limitations and time-efficiency, calculated volume based on arm circumferences is the best measurement method for evaluating excessive arm volume in patients with BCRL over time in clinical practice.

All five investigated methods showed good to very good **reliability**, which are comparable to previous results.[12, 14-17, 25] Nevertheless, it should be noted that previous results are mainly based on measurements executed on the edematous limb or on a healthy limb. However, we preferred to perform measurements on both arms in order to determine and analyze the excessive arm volume, since it has the advantage to be able to correct for changes in muscle size and subcutaneous fat when monitoring long-term treatment effects. Limited reliability studies did also investigate the measurement error, and of those who did, only a few have reported the formula that was used.[12, 13] Since the volumetry without overflow method has only recently been introduced[10], no previous publications regarding the clinimetric parameters of this method are available yet. When observing the results of this method in current study, one can notice a slight distinction with the other four methods due to a relatively lower intra- (.777) and inter-rater (.791) ICC of the excessive arm volumes, corresponding with a SEM of 146.36ml and 138.25ml, respectively. Nevertheless, these values still represent strong intra- and inter-rater reliability. A potential pitfall that can be causal for this variability, might be found in the accuracy of repeatedly indicating the same reference points before the measurement starts. The most important reference point is located in the elbow fold and is defined as the skin fold which is most centrally located in the elbow fold. Starting from this line, a proximal distance of 10 cm is measured to indicate the reference point required for measuring total arm volume. In our opinion, a difference in interpretation and perception between different assessors (and even within the same assessor) to define this most centrally located elbow fold, can contribute to this variability. As it was shown that volumes calculated from circumferences relative to anatomic (bony) landmarks are more accurate than those from segments using defined distances[12], an alternative approach in indicating reference points might be helpful to decrease this within-subjects as well as between-subjects variability.

This is the first study investigating **time-efficiency** of the different measurement procedures using a standardized protocol. Consequently, there is little information in literature available that allows us to compare our findings (Table 1). In the current study, opto-electronic volumetry showed the least total time required to complete a bilateral measurement (1min 42sec on average). Previous studies also mentioned opto-electronic volumetry being a quick device, taking only a few seconds[11, 14] to two minutes per measurement[24]. One study mentioned that the time required to complete volume measurements using a traditional volumetry device with overflow was 20 minutes[15], in contrast to

the mean total time of 10 minutes 40 seconds in the current study. Furthermore, studies reported an average duration of 10 minutes for performing separate girth measurements after which the arm volume was calculated using the formula for a truncated cone.[15, 24] In the current study, the measurement lasted about 4 minutes and 24 seconds on average by using a perimeter. In the study of Damstra et al, volume measurements of both arms by making use of inverse volumetry required 5 minutes[4], which is remarkably lower than the time required in the current study (12min 55sec on average). However, information whether this time also included calibration time, was not provided. In the current study, the execution time of the inverse volumetry without the calibration time was 5 minutes 33 seconds on average, which would be comparable with the results of Damstra et al.[4] Another study reported a mean total time of 15 minutes, with most time spent on the preparation.[21] Concerning **clinical feasibility**, there is no consistency found in literature. Moreover, a recent systematic review providing best evidence regarding which measurement method is most appropriate in measuring lymphedema, concluded that information on feasibility is scarce.[9] Results of our ranking revealed that water displacement methods yield more practical limitations than calculated volume based on circumference measurements and opto-electronic volumetry.

Some study limitations should be mentioned. Although good to very good reliability was demonstrated in all five methods, the relatively small number of participants might have lowered the variability between participants. However, as stated by Shrout and Fleiss, researchers should try to obtain at least 30 heterogeneous subjects for reliability studies which was established in this study.[35]

Next, an opto-electronic volumetry device primary designed for lower limbs was used. However, to encounter this hindrance, a strict and standardized protocol regarding sitting posture and measurement procedure was carried out in order to provide unambiguous measurements of the upper limb.

Besides the mentioned limitations, this investigation contains several strengths. First, since we analyzed the reliability of the different methods by measuring both the edematous and the non-edematous arm, our results can be extrapolated to a patient population as well as to a healthy population or to a patient population without clinical representation of lymphedema. Second, in order to investigate reliability and time-efficiency as accurate as possible, several training moments between assessors were organized ensuring standardization of the measurement procedure.

Third, to eliminate any risk for recall bias between the measurements, the assessor was supported by an independent assistant writing down the values and consequently, ensuring blinding of the data.

Calculated arm volume based on circumference measurements showed to be the most reliable and most feasible method to apply in clinical practice, in order to measure the excessive arm volume over time. Hereby, when measurements are performed by the same assessor, a test variation of more than

42ml should be considered as a change in excessive arm volume, exceeding the (potential) measurement error. In case the measurements are performed by different assessors, a test variation of more than 45ml exceeds the area of potential measurement errors. The device consists of materials with low costs, therefore it is easy to self-design a perimeter. Alternatively, it can be purchased as it is commercially available as well. For clinical centers having sufficient financial capacity, an opto-electronic volumeter can also be considered. However, a disadvantage of both methods is the fact that hand volume is not taken into account. Therefore, hand volume should be measured separately, for example by making use of a hand volumeter[38] or figure-of-eight method.[39, 40] In order to improve the hygienic conditions of the water volumetry method, an antiseptic (e.g. Chlorhexidine) or stabilized chlorine can be added to the water to disinfect the skin.

Since evidence is scarce regarding the recently introduced volumetry without overflow method, future research should focus on this technique. Results revealed that this is a very time-efficient water displacement method showing very strong intra- and inter-rater reliability for measuring the volume of an edematous and non-edematous limb, and strong intra- and inter-rater reliability for measuring the excessive arm volume. We believe that, with adjustment of the reference point's location, this method can be optimized which will result in smaller SEMs. Next, in current study we chose for a calculated volume based on circumference measurements method that made use of a perimeter instead of separate girth measurements (using a tapeline), since it comprises several advantages compared to separate girth measurements: 1) the device measures 11 circumferences at once by using only one reference point, resulting in quick measurements, 2) only one reference point needs to be marked and measured over time, which might result in smaller measurement errors, 3) since the tapelines are provided with weights (20g) at their end, the tension of the tapeline on the skin is standardized.[25] However, future studies should compare reliability and correlate these two measures, to investigate whether they could be used interchangeably. Furthermore, analysis of the data revealed that there is a remarkable difference in arm volume measured by the different methods at the edematous limb, with opto-electronic volumetry representing the largest deviation. Consequently, further research regarding the criterion validity of these methods is warranted to ascertain whether the measured arm volume fully corresponds the actual arm volume.

Acknowledgements

The authors are very grateful to the hospitals collaborating in this study. The authors also extend very grateful thanks to the study participants. All authors critically revised the manuscript for important intellectual content and approved the final manuscript.

References

1. DiSipio T, Rye S, Newman B, et al. Incidence of unilateral arm lymphedema after breast cancer: A systematic review and meta-analysis. *Lancet Oncol.* 2013;14(6):500-15.
2. Megens AM, Harris SR, Kim-Sing C, et al. Measurement of upper extremity volume in women after axillary dissection for breast cancer. *Arch Phys Med Rehabil*. 2001;82(12):1639-44.
3. Gerber LH. A review of measures of lymphedema. *Cancer*. 1998;83(12 Suppl American):2803-4.
4. Damstra RJ, Glazenburg EJ, Hop WC. Validation of the inverse water volumetry method: A new gold standard for arm volume measurements. *Breast Cancer Res Treat*. 2006;99(3):267-73.
5. Sagen A, Karesen R, Skaane P, et al. Validity for the simplified water displacement instrument to measure arm lymphedema as a result of breast cancer surgery. *Arch Phys Med Rehabil*. 2009;90(5):803-9.
6. Gebruers N, Truijen S, Engelborghs S, et al. Volumetric evaluation of upper extremities in 250 healthy persons. *Clin Physiol Funct Imaging.* 2007;27(1):17-22.
7. Tierney S, Aslam M, Rennie K, et al. Infrared optoelectronic volumetry, the ideal way to measure limb volume. *Eur J Vasc Endovasc Surg*. 1996;12(4):412-7.
8. Pani SP, Vanamail P, Yuvaraj J. Limb circumference measurement for recording edema volume in patients with filarial lymphedema. *Lymphology*. 1995;28(2):57-63.
9. Hidding JT, Viehoff PB, Beurskens CH, et al. Measurement properties of instruments for measuring of lymphedema: Systematic review. *Phys Ther*. 2016;96(12):1965-81.
10. Martignon M VS, Fung LH, Vandermeeren L, Belgrado JP, editor Evaluation of the reliability of four measuring methods of hand's perimeter and volume: Buoyancy forces valgrado system, circumference measurement, figure-of-eight method and manu3metrix scanner. 8th International Lymphedema Framework Conference; 2018; Rotterdam, The Netherlands.
11. Stanton AW, Northfield JW, Holroyd B, et al. Validation of an optoelectronic limb volumeter (perometer). *Lymphology*. 1997;30(2):77-97.
12. Taylor R, Jayasinghe UW, Koelmeyer L, et al. Reliability and validity of arm volume measurements for assessment of lymphedema. *Phys Ther*. 2006;86(2):205-14.
13. Chen YW, Tsai HJ, Hung HC, et al. Reliability study of measurements for lymphedema in breast cancer patients. *Am J Phys Med Rehabil.* 2008;87(1):33-8.
14. Deltombe T, Jamart J, Recloux S, et al. Reliability and limits of agreement of circumferential, water displacement, and optoelectronic volumetry in the measurement of upper limb lymphedema. *Lymphology*. 2007;40(1):26-34.
15. Galland C, Auvert JF, Flahault A, et al. Why and how post-mastectomy edema should be quantified in patients with breast cancer. *Breast Cancer Res Treat.* 2002;75(1):87-9.
16. Gjorup C, Zerahn B, Hendel HW. Assessment of volume measurement of breast cancer-related lymphedema by three methods: Circumference measurement, water displacement, and dual energy x-ray absorptiometry. *Lymphat Res Biol*. 2010;8(2):111-9.
17. Karges JR, Mark BE, Stikeleather SJ, et al. Concurrent validity of upper-extremity volume estimates: Comparison of calculated volume derived from girth measurements and water displacement volume. *Phys Ther*. 2003;83(2):134-45.
18. Meijer RS, Rietman JS, Geertzen JH, et al. Validity and intra- and interobserver reliability of an indirect volume measurements in patients with upper extremity lymphedema. *Lymphology*. 2004;37(3):127-33.
19. Mori T, Lustman A, Katz-Leurer M. Self-measurement of upper extremity volume in women post-breast cancer: Reliability and validity study. *Physiother Theory Pract.* 2015;31(4):283-7.
20. Sander AP, Hajer NM, Hemenway K, et al. Upper-extremity volume measurements in women with lymphedema: A comparison of measurements obtained via water displacement with geometrically determined volume. *Phys Ther*. 2002;82(12):1201-12.
21. Beek MA, te Slaa A, van der Laan L, et al. Reliability of the inverse water volumetry method to measure the volume of the upper limb. *Lymphat Res Biol*. 2015;13(2):126-30.

22. Erends M, van der Aa T, de Grzymala AP, et al. Validity and reliability of three-dimensional imaging for measuring the volume of the arm. *Lymphat Res Biol.* 2014;12(4):275-81.
23. Adriaenssens N, Buyl R, Lievens P, et al. Comparative study between mobile infrared optoelectronic volumetry with a perometer and two commonly used methods for the evaluation of arm volume in patients with breast cancer related lymphedema of the arm. *Lymphology*. 2013;46(3):132-43.
24. Sharkey AR, King SW, Kuo RY, et al. Measuring limb volume: Accuracy and reliability of tape measurement versus perometer measurement. *Lymphat Res Biol*. 2018;16(2):182-6.
25. Devoogdt N, Lemkens H, Geraerts I, et al. A new device to measure upper limb circumferences: Validity and reliability. *Int Angiol*. 2010;29(5):401-7.
26. Boland R, Adams R. Development and evaluation of a precision forearm and hand volumeter and measuring cylinder. *J Hand Ther*. 1996;9(4):349-58.
27. Levenhagen K, Davies C, Perdomo M, et al. Diagnosis of upper quadrant lymphedema secondary to cancer: Clinical practice guideline from the oncology section of the american physical therapy association. *Phys Ther*. 2017;97(7):729-45.
28. Veraart JCJM MI, Asselman AH, Neumann HAM. The volometer and the perometer; a clinical comparison. *Scripta Phlebologica*. 1995;5:9-11.
29. De Vrieze T, Vos L, Gebruers N, et al. Protocol of a randomised controlled trial regarding the effectiveness of fluoroscopy-guided manual lymph drainage for the treatment of breast cancer-related lymphedema (EFForT-BCRL trial). *Eur J Obstet Gynecol Reprod Biol.* 2017.
30. Rajapakse C, Grennan DM, Jones C, et al. Thermography in the assessment of peripheral joint inflammation--a re-evaluation. *Rheumatol Rehabil*. 1981;20(2):81-7.
31. King TI, 2nd. The effect of water temperature on hand volume during volumetric measurement using the water displacement method. *J Hand Ther*. 1993;6(3):202-4.40.
32. Casley-Smith JR, Casley-Smith JR. Modern treatment of lymphedema. I. Complex physical therapy: The first 200 australian limbs. *Australas J Dermatol*. 1992;33(2):61-8.
33. Lexell JE, Downham DY. How to assess the reliability of measurements in rehabilitation. *Am J Phys Med Rehabil*. 2005;84(9):719-23.
34. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med.* 2016;15(2):155-63.
35. Shrout PE, Fleiss JL. Intraclass correlations: Uses in assessing rater reliability. *Psychol Bull*. 1979;86(2):420-8.
36. Fleiss JL. Design and analysis of clinical experiments. New York, NY: John Wiley & Sons Inc; 1986.
37. Fleiss JL. Design and analysis of clinical experiments: John Wiley & Sons; 2011.
38. Farrell K, Johnson A, Duncan H, et al. The intertester and intratester reliability of hand volumetrics. *J Hand Ther*. 2003;16(4):292-9.
39. Maihafer GC, Llewellyn MA, Pillar WJ, Jr., et al. A comparison of the figure-of-eight method and water volumetry in measurement of hand and wrist size. *J Hand Ther*. 2003;16(4):305-10.
40. Borthwick Y, Paul L, Sneddon M, et al. Reliability and validity of the figure-of-eight method of measuring hand size in patients with breast cancer-related lymphedema. *Eur J Cancer Care (Engl)*. 2013;22(2):196-201.

CHAPTER 4

Chapter 4

RELIABILITY OF THE MOISTUREMETER D COMPACT DEVICE AND THE PITTING TEST TO EVALUATE LOCAL TISSUE WATER IN SUBJECTS WITH BREAST CANCER-RELATED LYMPHEDEMA

Lymphat Res Biol. 2019 Jul 19. [Epub ahead of print]

Tessa De Vrieze
Nick Gebruers
Ines Nevelsteen
An De Groef
Wiebren A.A. Tjalma
Sarah Thomis
Lore Dams
Elien Van der Gucht
Frauke Penen
Nele Devoogdt

Abstract

Background: Local tissue water (LTW) in patients with breast cancer-related lymphedema (BCRL) can be assessed by measurement of the tissue dielectric constant using the MoisturemeterD Compact® (MMDC) device, or by performing the pitting test. Although these assessment methods are commonly used in clinical practice, literature shows a lack of research on their clinimetric properties. Therefore, the aim of this study was to investigate reliability of both methods, in assessing the upper limb in BCRL.

Methods and results: Thirty women with BCRL were enrolled. LTW was evaluated at nine reference points on the upper limb and trunk, using both methods. To determine intra- and inter-rater reliability of the MMDC device (using the absolute percentages of water content (PWC%) and inter-arm PWC% ratios based on single and multiple measures), intraclass correlation coefficients (ICCs), and standard errors of the measurement (SEMs) were calculated. To determine intra- and inter-rater agreement of the pitting test, Cohen's Kappa coefficients were calculated as well as percentages of agreement. MMDC measurements yielded moderate to very strong intra- (ICC 0.648-0.947) and inter-rater (ICC 0.606-0.941) reliability, depending on the measurement location on the edematous limb. The pitting test showed a very strong intra-rater agreement at nearly all defined points, but a weak inter-rater agreement, especially at the medial elbow and the breast.

Conclusion: This study supports the MMDC device and pitting test as being useful tools in the clinical evaluation of BCRL. However, further research into the concurrent validity of both tools is warranted.

Introduction

For the clinical assessment of breast cancer-related lymphedema (BCRL), a variety of whole-arm volume measurement methods is available. The water displacement method and circumference measurements are the most frequently used methods[1] and are recommended as best practice for assessing lymphedema volume in extremities.[2] However, tissue dielectric constant (TDC) measurements are increasingly being applied as a tool to help characterizing edema[3-6], to detect its presence[7,8], and to evaluate treatment response[9-13].[14] This method relies on the measurement of the amount of local tissue water in the skin and has been validated experimentally on skin preparations.[15-18] Sensitivity and specificity for TDC measures have shown to be 65.8% and 83.9%, respectively.[19] The MoistureMeterD Compact® (MMDC) device can be used to determine the TDC in terms of the percentage of water content (PWC%), at any particular site of the body including the breast, trunk or other central body parts in which midline edema can manifest.[20,21] Up to a depth of 2mm, this portable device allows measuring free and bounded water in the tissue through which the electromagnetic wave passes.[14] More details about the physics and underlying principles of the device and the dielectric constant in general, have been extensively described elsewhere.[7,15,17,22-24] Despite the widespread use of the MMDC device for diagnosing and evaluating lymphedema, standardized research investigating its clinimetric properties in patients with BCRL is lacking. In a systematic review of Hidding et al[2], only one study[25] was listed that investigated inter-observer agreement of TDC measurements, showing good reliability for evaluating local tissue water at the ankle (ICC 0.94) and lower leg (ICC 0.94) in patients with lip- or lymphedema. Further, one study investigated intra-rater reliability of TDC measures at the self-reported most affected region in edematous upper limbs.[26] ICC calculations on inter-arm TDC ratio results were not performed. Recently, a paper was published in which test-retest reliability was investigated for evaluating local tissue water in the upper limb using the MMDC device.[14] However, since this investigation was performed on subjects free of lymphedema, the extent to which these results apply to patients with lymphedema is not known and still needs to be explored. Furthermore, to our knowledge, no study so far has examined reliability of the inter-arm TDC ratios in particular in patients with BCRL. This is surprisingly, as the ratio is the preferred TDC parameter to detect tissue water changes over time in unilateral conditions since studies have shown that absolute TDC values vary by site and depth but that inter-arm ratios are relatively independent of it.[6,27]

Next to the MMDC device, a second evaluation technique, the pitting test, can be applied to assess local tissue water in the skin. Pitting is usually tested by firmly pressing on the area of interest for at least 5 to 10 seconds.[28,29] If an indentation remains when the examiner releases pressure, then pitting is present. The depth of the indentation reflects on the amount of excess interstitial fluid, hence the

severity of the edema.[28] Soft tissues affected by lymphedema can change over time, from initially an extracellular fluid-rich edematous stage to a largely fibrotic condition.[26] Consequently, in advanced stages of lymphedema, the subcutaneous tissue can become fibrotic/fatty and will change into a non-pitting edema[30], which requires an altered approach in the treatment of lymphedema. To our knowledge, no previous studies have investigated reliability of the pitting test, which raises questions to its reproducibility in clinical practice.

Therefore, the aim of current study was to investigate the intra- and interrater reliability of both the MMDC device and the pitting test as easily applicable and non-invasive techniques for evaluating local tissue water in patients with BCRL in clinical practice. Furthermore, and with regard to the reliability of the MMDC device, a comparison was made between: 1) results regarding single PWC% measures and the recommended multiple PWC% measures, and 2) results regarding absolute PWC% measures and inter-arm PWC% ratios.

Materials and methods

Trial design

This cross-sectional study was conducted in accordance with the Declaration of Helsinki and was reported following the recommended STROBE guideline for observational studies. All assessments were performed at the department of Physical Medicine and Rehabilitation of the University Hospitals Leuven. This study is part of the EFforT-BCRL trial[31], for which approval was obtained by the Ethical Committee of the University Hospitals Leuven (CME reference S58689, EudraCT 2015-004822-33).

Participants

Between July and November 2017, patients of the EFforT-BCRL trial[31] were asked to participate in this subtrial. Eligibility criteria were: 1) female/male patients with BCRL of the arm/hand with at least 5% volume difference (corrected for limb dominance) at the time of inclusion in the EFforT-BCRL trial, 2) currently in the maintenance phase of the decongestive lymphatic therapy[1], 3) no known recurrence of cancer. Participants were excluded if they had no signs of pitting at any of the measurement points at the time of the testing. All participants received written and oral information by mail as well as by phone. All participants signed the informed consent document prior to their start in the EFforT-BCRL trial.

Assessment

Descriptive data (participant's age; body mass index; excessive arm volume; lymphedema stage as described by the International Society of Lymphology[1], location and duration of lymphedema; type of breast surgery and axillary lymph node dissection; side of surgery; hand dominance; type of adjuvant treatment (radiotherapy, chemotherapy, hormonal therapy or target therapy)) were collected by interviewing the participants and by consulting their medical record.

For each participant, only one visit to the hospital was necessary to collect all data. Participants arrived 15 minutes prior to the start of the measurements. During this time, compression sleeves and jewelry on both arms were removed.

The estimated duration for a single execution of the MMDC measurements (edematous and non-edematous limb) and the performance of the pitting test (edematous limb), was 30 minutes; i.e. one assessment block. Since the execution of an assessment block was performed three times consecutively without breaks in-between (i.e. the first and the last time by assessor 1 (LV), and the second time by assessor 2 (TDV)), the total duration of the investigation was approximately 1.5 hours per participant. The same sequence of the two measurement methods was maintained among the 3 assessment blocks for all participants, starting with the MMDC measurements and ending with the pitting test. This order was preferred, since in case pitting is present, the indentation of the skin takes a few minutes to restore. Prior to the assessments, two different 1-hour training moments were scheduled to guarantee standardization between assessors (TDV and LV; Masters in Rehabilitation Sciences and Physiotherapy), who were experts in the field of lymphology, as well as between the persons registering the scores (SVDS, AVH, MB and TP; Masters in Rehabilitation Sciences and Physiotherapy). During the training moment for the assessors, agreements were made regarding probe position, patient position and measurement procedure concerning the TDC measures, as well as regarding pressure time, patient position and measurement procedure concerning the pitting test. During the training moment for the persons registering the scores, the required fill-in documents were discussed in detail in order to get familiar with the measurement procedures.

TDC measurement procedure

To perform the measurements of local tissue water, this study used a commercially available compact version of an open ended coaxial probe with medium probe size[20] operating at 300 MHz, called the MoistureMeterD Compact® (MMDC) device (Delfin Technologies, Kuopio, Finland).[7] The absolute

results of the MMDC are based on a ratio scale between 0 and 100, representing the percentage (%) of local tissue water which is derived from following equation:

Percentage water content (PWC%) = 100 x (measured dielectric constant – 1)/77.5[20], and represents an approximate relationship between % local tissue water and TDC.[6] An outcome of 1 would illustrate a vacuum without water, while pure water yields a reading of 78.5.[20]

A total of 18 measurement points were marked with a soft pencil, including 9 reference points on the edematous and 9 on the non-edematous limb and trunk. The location of the measurement points and the positions of the participant were standardized, as shown in Table 1. Each reference point was measured in triplicate, as recommended in the user manual of this device. A single measurement was obtained by placing the probe in contact with the skin, where the pressure sensor inside the device helps to maintain good skin contact. After 3 to 5 seconds, an audible signal indicated completion of a single measurement. Simultaneously, the displayed percentages of water content were dictated to a blinded note taker who wrote down the outcomes on a preset form. The reporting of the local tissue water using the MMDC, was performed four-fold: 1) as a single measurement, 2) based on the average of three consecutive measurements (multiple measurements), 3) based on the calculated inter-arm PWC% ratios ($=\frac{PWC\%\ value\ edematous\ limb}{PWC\%\ value\ non-edematous\ limb}$) for each measurement point using single measurements, and 4) based on the calculated inter-arm PWC% ratios for each measurement point, using the average of the multiple measurements. Therefore, four datasets were compared: 1) the first out of three PWC% values obtained, 2) the mean of the triplicate PWC% values[4,32], 3) the calculated inter-arm ratios based on the first out of three PWC% values obtained, and 4) the calculated inter-arm ratios based on the mean of the triplicate PWC% values[4,8,26].

To preserve blinding of the next assessor for the reference points, after completing all the measurements, reference points were completely removed using alcohol wipes. By the time this was finished, all signs of pitting (in case these were present) had been disappeared. Measurements occurred in a room where the average temperature was 22°C.

Pitting measurement procedure

The pitting test involved application of sustained thumb pressure during 5 seconds on the skin and superficial tissue. Each of the nine points on the edematous limb and trunk was examined (see Table 1). On release of the applied pressure, an indentation of the tissue at the test site was defined as “pitting” and an absence of tissue changes was classified as “non-pitting”. After removing the thumb, the tissue was first evaluated visually and subsequently by palpation. Each point was scored on a 3-

point ordinal scale, where 0 = no clinical pitting edema, 1 = slight/doubtful pitting and 2 = noticeably pitting. The depth of the indentation and time of tissue rebound were taken into account to provide a score. Similar to the TDC measurement procedure, the test results were dictated to a blinded note taker.

Table 1. Overview of the nine different measurement points and participant's positions

Measurement point	Location	Posture
Hand	Central point between dorsal side of the thumb and index	Sitting - Forearm pronation
Ventral side forearm	15cm distal to the elbow fold	Sitting - Forearm supination
Dorsal side forearm	10 cm distal to caput radii with orientation towards the middle finger	Sitting - Forearm pronation
Medial elbow	3cm proximal to the medial epicondyle of the humerus	Sitting - Forearm supination
Ventral side upper arm	7cm proximal to the elbow fold.	Sitting - Forearm pronation
Dorsal side upper arm	7cm proximal to the upper edge of the olecranon	Sitting - Forearm pronation
Lateral shoulder (Deltoid muscle)	5cm distal to the acromion	Sitting - Forearm pronation
Breast/ventral trunk region	3 cm distal to the nipple or distal to the middle of the scar, if the patient had a mastectomy	Supine lying on table
Lateral trunk	5cm distal to the dorsal axillary fold	Standing – dropped arms
Participant position from hand to shoulder: Sitting position - arms in 45° anteflexion, resting on a table		

Data analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows version 24.0. The .05 level of significance was applied. Descriptive statistics for continuous values are presented as mean ±SD for normal distributed data and median and interquartile range for not normal distributed data. Categorical variables are presented as number and proportion (%).

Intra-rater reliability was assessed using Intraclass correlation coefficients ($ICC_{3,1}$), two-way mixed model[33], with 95% confidence intervals (CI) for continuous measures. Inter-rater reliability was assessed with intraclass correlation coefficients ($ICC_{2,1}$), two-way random model.[33] Calculations were based on two examiners assessing each participant and represent the expected reliability of a single examiner rating, as referred to Shrout and Fleiss 1979.[34] ICC values were classified into following categories: values <0.40 represent weak reliability, between 0.40 and 0.74 represent moderate reliability, between 0.75 and 0.90 represent strong reliability and ≥0.90 represent very strong reliability. For each measurement point, both intra- and inter-rater reliability analyses were conducted for a single measurement, for the average value of the multiple measures, as well as for the inter-arm PWC ratios based on single and multiple measures.

To interpret the magnitude of the within-subjects variation of the two scores, the standard error of measurement (SEM) was calculated using following formula: SEM =SD$\sqrt{(1 - ICC)}$, where SD was the standard deviation of the outcome differences between the two assessments.[33]

Cohen's Kappa and percentage of agreement statistics were calculated to evaluate the intra- and inter-rater reliability of the pitting test on the edematous arm. Kappa values were classified into: less than chance agreement (K<0.00), slight agreement (K=0.01-0.20), fair agreement (K=0.21-0.40), moderate agreement (K=0.41-0.60), substantial agreement (K=0.61-0.80) or almost perfect agreement (K=0.81-0.99).[35]

To calculate the percentage of agreement, differences between the two scores on the pitting test were calculated. In case the two scores were the same, this indicated agreement. The total percentage of agreement was calculated for each measurement point as follows: the total number of cases with agreement divided by 30 (number of participants), multiplied by 100.

Results

Thirty patients with BCRL were enrolled in this subtrial. The measurements of local tissue water with the MMDC and the pitting test were completed by both raters in all participants.

Participant characteristics

All participants were women (100%). An overview of the characteristics of the included subjects is provided in Table 2.

Table 2. Characteristics of the included subjects (n=30)

Descriptives	
Variable	**Outcome** **Mean (SD)**
Age (y)	65 (8)
Body Mass Index (kg/m^2)	28 (4)
Excessive arm volume (mL)	477 (367)
Duration lymphedema (mo)	74 (44)
Frequencies	
Variable	**Outcome** **N (%)**
Lymphedema stages	
stage I	3 (10%)
stage IIa	18 (60%)
stage IIb	9 (30%)
Location of lymphedema	
Lower arm	14 (53%)
Upper arm	0 (0%)
Total arm (lower arm + upper arm)	16 (47%)
Breast surgery	
Mastectomy	21 (70%)
Breast-conserving surgery	9 (30%)
Axillary lymph node clearance	
SLNB	0 (0%)
ALND	30 (100%)
Surgery on the dominant side	17 (57%)
Radiotherapy	30 (100%)
Chemotherapy	24 (80%)
Anti-hormonal therapy	27 (90%)
Targeted therapy (Herceptin)	6 (20%)

Abbreviations: y= years, kg= kilogram, m^2= square meters, mL= milliliter, mo= months, SLNB = sentinel lymph node biopsy, ALND = axillary lymph node dissection

Intra-rater reliability MMDC device

Results regarding intra-rater reliability (ICC, SEM) of the MMDC device after a single measurement of % local tissue water, as well as after multiple measures on each of the nine measurement points, are presented in Table 3. Results regarding intra-rater reliability (ICC, SEM) of the MMDC device after calculating the inter-arm PWC% ratio based on a single measurement, as well as based on multiple measures on each measurement point, are shown in Table 4.

Values of the edematous limb using **multiple measures** showed strong to very strong ICC values (ICCs≥0.75) for all measurement points, except for the lateral trunk (ICC 0.710), which showed moderate reliability.

The statistical analysis when using **single measurements** showed a strong to very strong intra-rater reliability (ICC ≥0.75) for all measurement points except for the ventral side of the forearm (ICC 0.664) and for the lateral trunk (ICC 0.648) (moderate reliability).

Values of the non-edematous limb using **multiple measures** showed, strong to very strong ICC values (ICCs≥0.75) for all measurement points, except for the lateral trunk (ICC 0.649) (moderate reliability).

The statistical analysis when using **single measurements** showed a strong to very strong intra-rater reliability (ICC ≥0.75) for all measurement points except for the lateral shoulder (ICC 0.699), for the breast (ICC 0.738) and for the lateral trunk (ICC 0.605) (moderate reliability).

Values of the inter-arm PWC ratios based on **multiple measures** showed strong intra-rater reliability for the measurement points at the hand (ICC 0.852), dorsal side of the forearm (ICC 0.847), ventral side of the upper arm (ICC 0.883) and breast (ICC 0.757).

Analysis of the inter-arm PWC ratios based on **single measurements** proved strong to very strong intra-rater reliability for the measurement points at the hand (ICC 0.839), ventral side of the upper arm (ICC 0.900), and dorsal side of the upper arm (ICC 0.774).

Table 3. Intra-rater reliability MMDC

	Multiple measurements				Single measurements			
	RATER 1 Mean PWC% (SD)	RATER 1 Mean PWC% (SD)	ICC (95% CI)	SEM (95% CI)	RATER 1 Mean PWC% (SD)	RATER 1 Mean PWC% (SD)	ICC (95% CI)	SEM (95% CI)
	EDEMATOUS LIMB							
Hand	49.33 (7.35)	48.59 (6.09)	0.917 (.834-.960)	1.90 (-2.99-4.47)	40.45 (9.73)	49.35 (8.53)	0.909 (.817-.956)	2.71 (-4.21-6.41)
Ventral side forearm	62.02 (9.04)	61.15 (9.21)	0.793 (.604-.897)	4.08 (-7.12-8.86)	61.34 (9.72)	60.79 (8.65)	0.664 (.403-.826)	5.23 (-9.7-10.8)
Dorsal side forearm	55.64 (6.92)	55.35 (6.29)	0.871 (.750-.937)	2.33 (-4.27-4.87)	55.46 (7.81)	55.32 (5.95)	0.795 (.612-.897)	3.06 (-3.86-8.14)
Elbow	52.51 (8.22)	52.84 (7.73)	0.889 (.780-.945)	2.61 (-4.79-5.45)	52.45 (8.27)	52.59 (7.57)	0.797 (.616-.898)	3.5 (-6.71-6.99)
Ventral side upper arm	44.99 (9.36)	45.86 (8.93)	0.947 (.891-.975)	2.07 (-3.16-4.96)	44.61 (9.46)	45.61 (8.99)	0.940 (.875-.971)	2.12 (-3.35-5.35)
Dorsal side upper arm	44.83 (6.60)	44.68 (6.59)	0.790 (.296-.922)	3.03 (-5.74-6.14)	44.16 (6.49)	44.28 (6.57)	0.888 (.778-.945)	2.15 (-4.09-4.33)
Lateral shoulder (Deltoid muscle)	46.50 (4.98)	46.45 (4.35)	0.908 (.816-.955)	1.39 (-2.68-2.78)	46.37 (5.22)	46.64 (4.56)	0.865 (.719-.929)	1.77 (-3.29-3.63)
Breast/ventral trunk region	51.22 (10.02)	51.77 (10.98)	0.939 (.876-.971)	1.76 (0.91-7.81)	51.08 (9.75)	50.90 (9.04)	0.937 (.871-.969)	2.32 (-4.36-4.72)
Lateral trunk	48.26 (5.28)	46.88 (4.49)	0.710 (.467-.852)	3.14 (-2.58-9.74)	48.02 (5.24)	46.82 (4.62)	0.648 (.386-.814)	2.87 (-4.43-6.83)

	RATER 1 Mean PWC% (SD)	RATER 1 Mean PWC% (SD)	ICC (95% CI)	SEM (95% CI)	RATER 1 Mean PWC% (SD)	RATER 1 Mean PWC% (SD)	ICC (95% CI)	SEM (95% CI)
	NON-EDEMATOUS LIMB							
Hand	43.76 (5.42)	42.60 (4.41)	0.814 (.631-.909)	2.08 (-2.92-5.24)	43.73 (5.38)	44.57 (4.36)	0.755 (.543-.876)	2.37 (-3.48-5.8)
Ventral side forearm	45.63 (7.12)	44.78 (5.94)	0.900 (.801-.951)	2.03 (-3.13-4.83)	45.13 (7.50)	44.9 (6.02)	0.799 (.619-.899)	2.98 (-5.61-6.07)
Dorsal side forearm	42.20 (6.86)	41.65 (6.16)	0.945 (.889-.974)	1.50 (-2.39-3.49)	42.10 (7.10)	41.57 (6.18)	0.943 (.885-.973)	1.56 (-2.53-3.59)
Elbow	36.76 (5.14)	37.44 (5.32)	0.885 (.773-.943)	1.74 (-2.74-4.1)	36.69 (4.69)	37.36 (5.40)	0.833 (.681-.917)	2.03 (-3.31-4.65)
Ventral side upper arm	37.52 (5.37)	36.78 (5.11)	0.882 (.766-.942)	1.77 (-2.73-4.21)	37.06 (5.49)	36.78 (5.08)	0.861 (.728-.931)	1.94 (-3.52-4.08)
Dorsal side upper arm	36.51 (4.90)	36.20 (4.76)	0.898 (.799-.950)	1.52 (-2.66-3.28)	36.63 (4.81)	36.14 (4.89)	0.883 (.770-.942)	1.63 (-2.70-3.68)
Lateral shoulder (Deltoid muscle)	46.54 (4.84)	45.23 (4.42)	0.859 (.639-.939)	1.71 (-2.04-4.66)	46.35 (5.06)	44.95 (4.43)	0.699 (.449-.846)	2.56 (-3.62-6.42)
Breast/ventral trunk region	43.16 (6.49)	45.05 (7.42)	0.777 (.562-.890)	3.23 (-4.45-8.21)	42.67 (6.53)	44.73 (7.31)	0.738 (.499-.870)	3.48 (-4.77-8.89)
Lateral trunk	45.60 (4.89)	44.75 (4.58)	0.649 (.388-.815)	1.05 (-1.21-2.91)	45.06 (4.87)	44.42 (4.76)	0.605 (.320-.790)	2.98 (-5.19-6.47)

*Abbreviations: PWC%= percentage water content, SD= standard deviation, ICC= intraclass correlation coefficient, CI= confidence interval, SEM= standard error of measurement, * corresponds with p-value <.05, ** corresponds with p-value <.01*

Table 4. Intra-rater reliability of the inter-arm PWC% ratio

	INTER-ARM PWC% RATIO							
	Multiple measurements				Single measurements			
	RATER 1 Inter-arm PWC% ratio (SD)	RATER 1 Inter-arm PWC% ratio (SD)	ICC (95% CI)	SEM (95% CI)	RATER 1 Inter-arm PWC% ratio (SD)	RATER 1 Inter-arm PWC% ratio (SD)	ICC (95% CI)	SEM (95% CI)
Hand	1.14 (0.20)	1.15 (0.14)	0.852 (.712-.927)	0.07 (1.03-1.29)	1.17 (0.25)	1.16 (0.19)	0.839 (.689-.920)	0.09 (0.98-1.34)
Ventral side forearm	1.35 (0.32)	1.37 (0.14)	0.340 (-.024-.622)	0.19 (0.48-1.22)	1.39 (0.22)	1.36 (0.15)	0.538 (.226-.751)	0.12 (0.61-1.09)
Dorsal side forearm	1.34 (0.19)	1.35 (0.18)	0.847 (.703-.924)	0.07 (0.41-0.69)	1.34 (0.21)	1.35 (0.20)	0.740 (.522-.867)	0.10 (0.35-0.75)
Medial elbow	1.44 (0.22)	1.42 (0.19)	0.718 (.488-.855)	0.11 (0.47-0.89)	1.44 (0.20)	1.42 (0.19)	0.528 (.210-.744)	0.17 (0.34-1.02)
Ventral side upper arm	1.20 (0.21)	1.26 (0.23)	0.883 (.717-.948)	0.08 (0.59-0.89)	1.21 (0.22)	1.25 (0.21)	0.900 (.789-.952)	0.07 (0.61-0.87)
Dorsal side upper arm	0.99 (0.13)	1.24 (0.16)	0.183 (-.092-.501)	3.01 (-5.58-6.2)	1.21 (0.16)	1.24 (0.16)	0.774 (.581-.885)	0.09 (0.14-0.48)
Lateral shoulder (Deltoid muscle)	1.00 (0.08)	1.03 (0.07)	0.723 (.452-.865)	0.04 (1.23-1.39)	1.00 (0.09)	1.04 (0.07)	0.446 (.122-.688)	0.07 (1.18-1.44)
Breast/ventral trunk region	1.20 (0.22)	1.15 (0.18)	0.757 (.547-877)	0.1 (1.69-2.07)	1.21 (0.22)	1.50 (0.18)	0.734 (.494-.866)	0.13 (1.63-2.13)
Lateral trunk	1.06 (0.11)	1.05 (0.09)	0.673 (.419-.830)	0.06 (0.74-0.96)	1.07 (0.11)	1.06 (0.1)	0.538 (.225-.750)	0.07 (0.7-1)

*Abbreviations: PWC%= percentage water content, SD= standard deviation, ICC= intraclass correlation coefficient, CI= confidence interval, SEM= standard error of measurement, * corresponds with p-value <.05, ** corresponds with p-value <.01*

Inter-rater reliability MMDC device

Results regarding the inter-rater reliability (ICC, SEM) of the MMDC device after a single measurement, as well as after multiple measures on each of the nine measurement points, are presented in Table 5. Results regarding inter-rater reliability (ICC, SEM) of the MMDC device after calculating the inter-arm PWC% ratio based on a single measurement, as well as based on multiple measures on each measurement point, are shown in Table 6.

Analysis of the **multiple measurements** at the edematous limb, showed strong to very strong reliability (ICCs≥0.75) of all measurement points, except at the ventral side of the forearm (ICC 0.606), and lateral trunk (ICC 0.726), which showed moderate reliability. The statistical analysis of the **single measurements** revealed strong to very strong reliability (ICCs≥0.75) of all measurement points, except at the elbow (ICC 0.636), dorsal side of the upper arm (ICC 0.711), and lateral trunk (ICC 0.643) (moderate reliability).

Analysis of the **multiple measures** at the non-edematous limb, yielded strong inter-rater reliability for all measurement points except for the hand (ICC 0.665) (moderate reliability). The statistical analysis of the **single measurements** revealed strong inter-rater reliability of all measurement points except for the hand (ICC 0.616), elbow (ICC 0.736), breast (ICC 0.736) and lateral trunk (ICC 0.744) (moderate reliability).

Values of the inter-arm PWC ratios based on **multiple measures** showed strong inter-rater reliability for the measurement points at the hand (ICC 0.752), ventral side of the upper arm (ICC 0.862), and lateral trunk (ICC 0.760). Similarly, analysis of the inter-arm PWC ratios based **on single measurements** revealed strong inter-rater reliability for the measurement points at the hand (ICC 0.775), ventral side of the upper arm (ICC 0.847), and lateral trunk (ICC 0.787).

Table 5. Inter-rater reliability MMDC

	Multiple measurements				Single measurements			
	RATER 1 Mean PWC% (SD)	RATER 2 Mean PWC% (SD)	ICC (95% CI)	SEM (95% CI)	RATER 1 Mean PWC% (SD)	RATER 2 Mean PWC% (SD)	ICC (95% CI)	SEM (95% CI)
	EDEMATOUS LIMB							
Hand	49.33 (7.35)	48.99 (6.97)	0.881 (.766-.941)	2.43 (-4.42-5.1)	40.45 (9.73)	50.20 (9.90)	0.858 (.914-.980)	3.63 (-7.87-7.37)
Ventral side forearm	62.02 (9.04)	60.93 (9.91)	0.606 (.319-.792)	5.84 (-10.36-12.54)	61.34 (9.72)	60.91 (10.94)	0.897 (.795-.950)	3.26 (-5.95-6.81)
Dorsal side forearm	55.64 (6.92)	55.19 (6.91)	0.911 (.823-.856)	2.03 (-3.52-4.44)	55.46 (7.81)	55.06 (7.42)	0.918 (.836-.960)	2.14 (-3.8-4.6)
Elbow	52.51 (8.22)	50.74 (9.82)	0.784 (.595-.891)	4.1 (-6.26-9.80)	52.45 (8.27)	50.22 (9.75)	0.636 (.367-.807)	5.34 (-8.24-12.7)
Ventral side upper arm	44.99 (9.36)	46.95 (9.17)	0.917 (.775-.965)	2.62 (-3.18-7.1)	44.61 (9.46)	46.72 (9.07)	0.941 (.973-.972)	2.21 (-2.23-6.45)
Dorsal side upper arm	44.83 (6.60)	48.00 (7.27)	0.790 (.296-.922)	3.13 (-2.96-9.3)	44.16 (6.49)	47.44 (7.77)	0.711 (.310-.873)	3.77 (-4.02-10.78)
Lateral shoulder (Deltoid muscle)	46.50 (4.98)	46.82 (5.15)	0.792 (.609-.896)	2.27 (-4.15-4.77)	46.37 (5.22)	46.68 (5.00)	0.790 (.603-894)	2.31 (-4.21-4.83)
Breast/ventral trunk region	51.22 (10.02)	51.78 (10.99)	0.877 (.759-.939)	3.62 (-6.54-7.66)	51.08 (9.75)	52.00 (11.22)	0.796 (.616-.897)	4.65 (-8.2-10.04)
Lateral trunk	48.26 (5.28)	48.11 (5.26)	0.726 (.498-.860)	2.71 (-5.16-5.46)	48.02 (5.24)	48.07 (5.40)	0.643 (.369-.813)	3.12 (-6.07-6.17)

	RATER 1 Mean PWC% (SD)	RATER 2 Mean PWC% (SD)	ICC (95% CI)	SEM (95% CI)	RATER 1 Mean PWC% (SD)	RATER 2 Mean PWC% (SD)	ICC (95% CI)	SEM (95% CI)
	NON-EDEMATOUS LIMB							
Hand	43.76 (5.42)	44.45 (6.16)	0.665 (.408-.825)	3.30 (-5.77-7.15)	43.73 (5.38)	44.25 (6.15)	0.616 (.334-.797)	3.51 (-6.37-7.41)
Ventral side forearm	45.63 (7.12)	46.78 (7.36)	0.895 (.785-.950)	2.31 (-3.37-5.67)	45.13 (7.50)	46.41 (7.19)	0.872 (.743-.938)	2.58 (-3.79-6.35)
Dorsal side forearm	42.20 (6.86)	42.16 (6.87)	0.867 (.739-.935)	2.46 (-4.78-4.86)	42.10 (7.10)	42.10 (6.97)	0.820 (.655-.910)	2.94 (-5.75-5.75)
Elbow	36.76 (5.14)	34.39 (4.96)	0.766 (.292-.909)	2.4 (-2.34-7.08)	36.69 (4.69)	34.05 (4.93)	0.736 (.152-.902)	2.43 (-2.12-7.4)
Ventral side upper arm	37.52 (5.37)	38.77 (5.05)	0.889 (.718-.952)	1.71 (-2.1-4.6)	37.06 (5.49)	38.54 (4.90)	0.828 (.612-.921)	2.12 (-2.67-5.63)
Dorsal side upper arm	36.51 (4.90)	38.13 (4.80)	0.867 (.739-.935)	1.74 (-1.79-5.03)	36.63 (4.81)	38.00 (5.06)	0.783 (.566-.894)	2.26 (-3.01-5.83)
Lateral shoulder (Deltoid muscle)	46.54 (4.84)	45.45 (5.53)	0.841 (.681-.923)	2.03 (-2.89-5.07)	46.35 (5.06)	45.46 (5.54)	0.834 (.681-.918)	2.12 (-3.27-5.05)
Breast/ventral trunk region	43.16 (6.49)	43.19 (8.05)	0.768 (.565-.882)	3.44 (-6.73-6.77)	42.67 (6.53)	42.84 (8.28)	0.736 (.514-.865)	3.74 (-7.16-7.50)
Lateral trunk	45.60 (4.89)	45.62 (4.36)	0.751 (.537-.873)	2.27 (-4.43-4.47)	45.06 (4.87)	45.81 (4.54)	0.744 (.533-.869)	2.34 (-3.84-5.34)

Abbreviations: PWC%= percentage water content, SD= standard deviation, ICC= intraclass correlation coefficient, CI= confidence interval, SEM= standard error of measurement, * corresponds with p-value <.05, ** corresponds with p-value <.01

Table 6. Inter-rater reliability of the inter-arm PWC% ratio

	INTER-ARM PWC% RATIO							
	Multiple measurements				Single measurements			
	RATER 1 Inter-arm PWC% ratio (SD)	RATER 1 Inter-arm PWC% ratio (SD)	ICC (95% CI)	SEM (95% CI)	RATER 1 Inter-arm PWC% ratio (SD)	RATER 1 Inter-arm PWC% ratio (SD)	ICC (95% CI)	SEM (95% CI)
Hand	1.14 (0.20)	1.11 (0.16)	0.752 (.546-.873)	0.09 (0.51-0.87)	1.17 (0.25)	1.14 (0.21)	0.775 (.580-.886)	0.11 (0.48-0.90)
Ventral side forearm	1.35 (0.32)	1.31 (0.15)	0.186 (-.188-.510)	0.21 (0.73-1.57)	1.39 (0.22)	1.32 (0.14)	0.406 (.072-.664)	0.14 (0.88-1.42)
Dorsal side forearm	1.34 (0.19)	1.33 (0.18)	0.719 (.487-.856)	0.1 (-0.15-0.23)	1.34 (0.21)	1.33 (0.20)	0.617 (.332-.798)	0.13 (-0.21-0.29)
Elbow	1.44 (0.22)	1.49 (0.29)	0.662 (.407-.823)	0.15 (2.08-2.66)	1.44 (0.20)	1.49 (0.3)	0.615 (.339-.795)	0.16 (2.07-2.67)
Ventral side upper arm	1.20 (0.21)	1.22 (0.22)	0.862 (.731-.931)	0.08 (1.09-1.41)	1.21 (0.22)	1.22 (0.21)	0.847 (.703-.924)	0.08 (1.09-1.41)
Dorsal side upper arm	0.99 (0.13)	1.27 (0.19)	0.167 (-.092-.472)	0.14 (1.34-1.9)	1.21 (0.16)	1.26 (0.20)	0.663 (.404-.823)	0.1 (1.42-1.82)
Lateral shoulder (Deltoid muscle)	1.00 (0.08)	1.04 (0.09)	0.470 (.152-704)	0.06 (0.97-1.21)	1.00 (0.09)	1.03 (0.09)	0.410 (.078-.664)	0.07 (0.95-1.23)
Breast/ventral trunk region	1.20 (0.22)	1.22 (0.25)	0.700 (.460-.845)	0.14 (-0.08-0.12)	1.21 (0.22)	1.24 (0.28)	0.644 (.377-813)	0.15 (-0.08-0.12)
Lateral trunk	1.06 (0.11)	1.06 (0.10)	0.760 (.553-.878)	0.05 (-0.08-0.12)	1.07 (0.11)	1.05 (0.11)	0.787 (.603-.892)	0.05 (-0.08-0.12)

Abbreviations: PWC%= percentage water content, SD= standard deviation, ICC= intraclass correlation coefficient, CI= confidence interval, SEM= standard error of measurement, * corresponds with p-value <.05, ** corresponds with p-value <.01

Intra-rater agreement pitting test

The statistical analysis of the pitting test values showed an almost perfect intra-rater agreement (K>0.81) for the majority of the measurement points (Table 7). The highest Kappa coefficients were found for the ventral side of the forearm (K=0.866) and the elbow (K=0.866). Hundred percent agreement was achieved at the lateral shoulder. The lowest Kappa coefficient was shown at the breast (K=0.694), suggesting substantial agreement (83.3%). With exception of this latter, all percentages of agreement were above 90%.

Table 7. Intra-rater agreement pitting test (n=30)

PITTING TEST Intra-rater	SCORE*	RATER 1 (#)	RATER 1 (#)	% AGREEMENT	COHEN'S KAPPA
EDEMATOUS LIMB					
Hand	Score 0 Score 1	25 5	22 8	90	0.710
Ventral side forearm	Score 0 Score 1 Score 2	2 19 9	1 19 10	96.7	0.866
Dorsal side forearm	Score 0 Score 1 Score 2	3 21 6	3 21 6	93.3	0.855
Elbow	Score 0 Score 1	16 14	16 14	93.3	0.866
Ventral side upper arm	Score 0 Score 1	28 2	27 3	96.7	0.783
Dorsal side upper arm	Score 0 Score 1	24 6	22 8	93.3	0.815
Lateral shoulder (Deltoid muscle)	Score 0	30	30	100	/
Breast/ventral trunk region	Score 0 Score 1 Score 2	10 18 2	10 17 3	83.3	0.693
Lateral trunk	Score 0 Score 1	29 1	30	96.7	/
*Score 0 = no clinical pitting edema ; score 1 = slight/doubtful pitting edema; score 2 = noticeably pitting edema					

Inter-rater agreement pitting test

Overall, the statistical analysis of the pitting test showed a slight to fair inter-rater agreement, with exception of the measurement points at the elbow and the breast which showed no agreement (K<0.00) (Table 8). The highest Kappa coefficient was found for the hand (K=0.304), and was classified as a fair agreement. Similar to the results of the intra-rater agreement, the highest percentage of inter-rater agreement was shown at the lateral shoulder (96.7%), this time together with the lateral trunk (96.7%). Lowest percentage of agreement was for the measurement point at the elbow (26.7%).

Table 8. Inter-rater agreement pitting test (n=30)

PITTING TEST Inter-rater	SCORE*	RATER 1 (#)	RATER 2 (#)	% AGREEMENT	COHEN'S KAPPA
EDEMATOUS LIMB					
Hand	Score 0 Score 1 Score 2	25 5	21 6 3	73.3	0.304
Ventral side forearm	Score 0 Score 1 Score 2	2 19 9	1 8 21	56.7	0.300
Dorsal side forearm	Score 0 Score 1 Score 2	3 21 6	2 6 22	40	0.151
Elbow	Score 0 Score 1 Score 2	16 14	11 5 14	26.7	-0.009
Ventral side upper arm	Score 0 Score 1 Score 2	28 2	22 5 3	76.7	0.234
Dorsal side upper arm	Score 0 Score 1 Score 2	24 6	16 8 6	50	0.038
Lateral shoulder (Deltoid muscle)	Score 0 Score 1	30	29 1	96.7	/
Breast/ventral trunk region	Score 0 Score 1 Score 2	10 18 2	13 12 5	36.7	-0.048
Lateral trunk	Score 0 Score 1	29 1	30	96.7	/
*Score 0 = no clinical pitting edema; score 1 = slight/doubtful pitting edema; score 2 = noticeably pitting					

Discussion

The widespread use of the pitting test and the more recently upcoming application of the MMDC device in clinical practice and research, together with the existing gaps in evidence regarding their clinimetric properties, underline the importance of this study. Both tools are easy applicable, non-invasive and useful for assessing changes in % local tissue water.

Due to the scarce amount of evidence on reliability of the MMDC device, it is difficult to compare the results of this study with previous findings. Only one study was found in which reliability of TDC measures was investigated on edematous upper limbs. Czerniec et al. examined intra-rater reliability of the MMDC device with different probe sizes (extra small, small and medium) on the upper limbs of 24 participants, 20 of whom with BCRL and four without lymphedema. ICC values of two averaged TDC measures with medium probe size at the self-reported most affected region (upper or lower arm) of the edematous limb ranged between 0.82 and 0.96, which is comparable to our results.[26] ICC calculations on inter-arm TDC ratio results were not performed. Recently, Mayrovitz et al investigated test-retest reliability of absolute TDC measures and inter-limb TDC ratios at three locations on healthy upper limbs, using the compact probe and multiprobe of the MoisturemeterD device.[14] Although they did not include patients with BCRL, their results were similar to our findings at the non-edematous limb, with exception of the hand, which showed moderate reliability in our study (ICC=0.665 vs. 0.945).[14] Also, their results were comparable with their earlier findings on inter-rater reliability of the MoisturemeterD device on different sites at the upper non-edematous limb of patients newly diagnosed with breast cancer.[6] Despite the fact that some of these previous studies used a MoisturemeterD instead of a MoisuremeterD Compact device[24 ,26], and consequently, the outcomes were reported in absolute TDC values instead of PWC% values, their results were comparable with the findings of our study at the non-edematous limb.

Both absolute PWC% values and inter-arm PWC% ratios have shown to be meaningful tools to evaluate the effects of therapeutic interventions.[9] In general, results of our study yielded lower inter-arm ratio ICC values compared to absolute PWC% value ICC results. Although we cannot directly compare our findings due to a different study cohort, this aspect was also observed in the recent study of Mayrovitz et al. in non-edematous limbs.[14] Nevertheless, they suggested that when the inter-arm ratio is the parameter of interest, studies using different probes would yield analogous results that can be compared, as confirmed by their findings.[14]

Depending on the measurement point, results of our reliability study ranged from moderate to very strong. In general, this revealed that the edematous and non-edematous limb could be evaluated during follow-up in a reliable way both by the same assessor as well as by different assessors.

In our study, for seven out of nine locations, intra-rater ICCs and SEMs were comparable between single and multiple measures. At the ventral side of the forearm, intra-rater reliability evolved from moderate to strong when using multiple measures instead of single measures. At the lateral shoulder, intra-rater reliability evolved from strong to very strong when using multiple measurements instead of single measures. Likewise, when comparing intra-rater reliability of inter-arm PWC% ratios, one can notice that results (ICC, SEM) based on single and multiple measures were similar. Remarkably, intra-rater reliability deteriorated from very strong to strong at the ventral side of the upper arm, from strong to weak at the dorsal side of the upper arm, and from moderate to weak at the ventral side of the forearm when using multiple measurements instead of single measures. Concerning the results for intra-rater reliability as well as inter-rater reliability, the ICC value at the dorsal side of the upper arm was noticeably higher when it was based on a single measurement instead of multiple measures.

Since our results showed that it seems sufficient to measure each reference point only once instead of in triplicate, evaluating BCRL with this tool can be even more time-efficient. These findings are confirmed by recent results of Mayrovitz[14], who conducted a study to investigate whether single measurements of reference points are sufficient for evaluating BCRL. Thirty women were recruited and TDC was measured in triplicate bilaterally at the ventral side of the forearm and at the hand palm. The agreement in absolute TDC values and inter-arm ratios was evaluated for assessments made using only the first TDC measurement, the average of duplicates and the standard triplicate. Results suggested that in upper limbs, useful TDC data may be obtained using single measurements.[14]

Results concerning the pitting test, presented a good to very good intra-rater agreement, with most measurement points showing almost perfect agreement (K between 0.82 and 0.87). At the lateral shoulder and lateral trunk, a high percentage of agreement together with the absence of Kappa values could be noticed. The lack of variation in measurement results, due to the absence of pitting edema presented in these areas within our study sample, impeded the calculation of Kappa values for these points.

In contrast to the very good intra-rater agreement, overall rather low Kappa values question the inter-rater agreement of this test. The inconsistencies such as the area, amount and duration of applied pressure between raters, could explain these results as described by Sanderson et al.[29] Although guidelines are advocating for the use of this test in the evaluation of lymphedema[28], even the most fundamental components of the pitting test, such as the required amount and area of pressure, have

not been consistently described in literature.[36] Consequently, this leads to a different interpretation of the test results among different assessors: what is the difference between 'noticeable pitting' and slight/doubtful' pitting?

The complex and sometimes varying skin tissue composition at the breast between patients due to surgery or radiotherapy could be a reason for the lowest Kappa value at this location (-0.048). The measurement point at the hand, revealing a fair Kappa (0.304) and 73% of agreement, indicated the highest inter-rater agreement. Given the paucity of research literature on this topic, we were unable to compare our findings.

Despite the fact that it is outside the scope of this study, it should be mentioned that (especially regarding the pitting test) it is uncertain which part of the skin is being measured. For the MMDC device, the effective penetration depth is about 2mm.[14] This effective penetration depth has been defined as the depth at which the incident energy falls to 37% of its surface value.[14,18] Although, the arm has a mean skin thickness of 2.23 mm (95% CI 2.18 – 2.28).[37]

When applying the pitting test, the indentation depths may vary but are likely to include both the epidermis and subcutis. Knowledge about what exactly is being measured, is lacking.

Strengths and limitations

The current study has several strengths. First, since we analyzed reliability of the MMDC device by measuring both the edematous and the non-edematous limb, our results can be extrapolated to a population with lymphedema as well as to a healthy population or to a patient population without clinical representation of lymphedema. Second, this study used nine different measurement points spread over the entire upper limb including the breast and lateral trunk, which are important locations as well that should not be neglected in this population.[38] This in contrast to most of the (few available) previous studies, which only focused on a small number of measurement points such as the hand and ventral side of the forearm. Third, to eliminate any risk for recall bias between the measurements, the assessor was supported by an assistant writing down the values and consequently, ensuring blinding of the data. A possible limitation of the study may be the relatively small number of participants which might have lowered the variability between participants. However, as stated by Shrout and Fleiss, researchers should try to obtain at least 30 heterogeneous subjects for reliability studies which was established in this study.[34] Furthermore, the applied procedure of the pitting test did not include an indication for the amount of pressure that was given, hindering the standardization of the test regarding this aspect. However, a 1-hour training moment between experienced assessors was

organized improving standardization of the measurement procedure considering patient position, pressure area and pressure time for this test.

Clinical implications and future research

This study showed that the MMDC device can reliably be used to evaluate patients with BCRL during follow-up, both by the same assessor as by different assessors. When single measurements are performed by the same assessor, a test variation of more than 5.23 PWC% (or 0.17 in case inter-limb ratios are calculated) should be considered as a change in local tissue water, exceeding the measurement error at the edematous limb. In case the measurement is performed by different assessors, a test variation of more than 5.34 PWC% (or 0.16 in case inter-limb ratios are calculated) exceeds the area of measurement error. Consequently, if 2 MMDC measurements differ more than 5.23 PWC% or 5.34 PWC%, respectively, the difference can be interpreted as an identifiable difference in local tissue water which is not related to a standard error of the measurement.

Additionally, this study showed that the pitting test has a very strong intra-rater agreement at well-nigh all measurement points, but a rather questionable inter-rater agreement, especially at the medial elbow and the breast. Therefore, follow-up evaluations over time should be performed by the same assessor per patient.

When interpreting these results, one should keep in mind that in both methods different parts of the skin are being assessed. MMDC measurements are mainly focused on the evaluation of epidermal edema (up to 2 mm) with only partly giving information regarding the subcutaneous area, whereas the pitting test does provide information concerning both skin layers. Further research should focus on the amount of pressure necessary to evaluate the skin tissue correctly and to improve the standardization of the pitting test. More evidence regarding what exactly is being measured up to which depth, is needed. In addition, after standardization of this test is completed, future studies that examine concurrent validity of the pitting test and the MMDC device, for instance by comparing obtained results with ultrasound images representing skin thickness, are warranted to increase the clinical relevance of both tools.

Conclusion

In summary, the overall positive findings support the use of MMDC device as a reliable tool for evaluating local tissue water in patients with BCRL, both by the same assessor as well as by different assessors. Absolute PWC% measures usually showed stronger reliability than inter-arm PWC% ratios. Additionally, reliability of single and multiple PWC% measures yielded comparable results at most measurement points. Furthermore, positive results regarding the pitting test applied by the same assessor empowers the use of this easy and quick test. However, rather low Kappa values regarding the inter-rater reliability question the reproducibility of the pitting test between different assessors.

The MMDC device and the pitting test as well are useful tools in the clinical evaluation of BCRL over time. Further research into the concurrent validity of both tools is warranted.

Acknowledgements

The authors are very grateful to the Universal Hospitals Leuven for collaborating in this study. The authors also extend very grateful thanks to the study participants. All authors critically revised the manuscript for important intellectual content and approved the final manuscript.

References

1. The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology. Lymphology 2013;**46**(1):1-11

2. Hidding JT, Viehoff PB, Beurskens CH, van Laarhoven HW, Nijhuis-van der Sanden MW, van der Wees PJ. Measurement Properties of Instruments for Measuring of Lymphedema: Systematic Review. Phys Ther 2016;**96**(12):1965-81 doi: 10.2522/ptj.20150412[published Online First: Epub Date]|.

3. Mayrovitz HN. Assessing local tissue edema in postmastectomy lymphedema. Lymphology 2007;**40**(2):87-94

4. Mayrovitz HN, Weingrad DN, Davey S. Local tissue water in at-risk and contralateral forearms of women with and without breast cancer treatment-related lymphedema. Lymphatic research and biology 2009;**7**(3):153-8 doi: 10.1089/lrb.2009.0008[published Online First: Epub Date]|.

5. Mayrovitz HN, Weingrad DN, Davey S. Tissue dielectric constant (TDC) measurements as a means of characterizing localized tissue water in arms of women with and without breast cancer treatment related lymphedema. Lymphology 2014;**47**(3):142-50

6. Mayrovitz HN, Weingrad DN, Lopez L. Patterns of temporal changes in tissue dielectric constant as indices of localized skin water changes in women treated for breast cancer: a pilot study. Lymphatic research and biology 2015;**13**(1):20-32 doi: 10.1089/lrb.2014.0024[published Online First: Epub Date]|.

7. Mayrovitz HN, Fasen M, Spagna P, Wong J. Role of handedness on forearm skin tissue dielectric constant (TDC) in relation to detection of early-stage breast cancer-related lymphedema. Clinical physiology and functional imaging 2018;**38**(4):670-75 doi: 10.1111/cpf.12466[published Online First: Epub Date]|.

8. Mayrovitz HN, Arzanova E, Somarriba S, Eisa S. Reference Values for Assessing Localized Hand Lymphedema Using Interhand Tissue Dielectric Constant Ratios. Lymphatic research and biology 2018;**16**(5):442-45 doi: 10.1089/lrb.2017.0065[published Online First: Epub Date]|.

9. Tugral A, Viren T, Bakar Y. Tissue dielectric constant and circumference measurement in the follow-up of treatment-related changes in lower-limb lymphedema. International angiology : a journal of the International Union of Angiology 2018;**37**(1):26-31 doi: 10.23736/s0392-9590.17.03843-3[published Online First: Epub Date]|.

10. Pigott A, Nixon J, Fleming J, Porceddu S. Head and neck lymphedema management: Evaluation of a therapy program. Head & neck 2018;**40**(6):1131-37 doi: 10.1002/hed.25086[published Online First: Epub Date]|.

11. Mayrovitz HN, Davey S. Changes in tissue water and indentation resistance of lymphedematous limbs accompanying low level laser therapy (LLLT) of fibrotic skin. Lymphology 2011;**44**(4):168-77

12. Mayrovitz HN, Davey S, Shapiro E. Localized tissue water changes accompanying one manual lymphatic drainage (MLD) therapy session assessed by changes in tissue dielectric constant inpatients with lower extremity lymphedema. Lymphology 2008;**41**(2):87-92

13. Fife CE, Davey S, Maus EA, Guilliod R, Mayrovitz HN. A randomized controlled trial comparing two types of pneumatic compression for breast cancer-related lymphedema treatment in the home. Supportive care in cancer : official journal of the Multinational Association of Supportive

Care in Cancer 2012;**20**(12):3279-86 doi: 10.1007/s00520-012-1455-2[published Online First: Epub Date]|.

14. Mayrovitz HN, Mikulka A, Woody D. Minimum Detectable Changes Associated with Tissue Dielectric Constant Measurements as Applicable to Assessing Lymphedema Status. Lymphatic research and biology 2018 doi: 10.1089/lrb.2018.0052[published Online First: Epub Date]|.

15. Aimoto A, Matsumoto T. Noninvasive method for measuring the electrical properties of deep tissues using an open-ended coaxial probe. Med Eng Phys 1996;**18**(8):641-6

16. Alanen E, Lahtinen T, Nuutinen J. Variational formulation of open-ended coaxial line in contact with layered biological medium. IEEE transactions on bio-medical engineering 1998;**45**(10):1241-8 doi: 10.1109/10.720202[published Online First: Epub Date]|.

17. Alanen E, Lahtinen T, Nuutinen J. Measurement of dielectric properties of subcutaneous fat with open-ended coaxial sensors. Physics in medicine and biology 1998;**43**(3):475-85

18. Alanen E, Lahtinen T, Nuutinen J. Penetration of electromagnetic fields of an open-ended coaxial probe between 1 MHz and 1 GHz in dielectric skin measurements. Physics in medicine and biology 1999;**44**(7):N169-76

19. Lahtinen T, Seppala J, Viren T, Johansson K. Experimental and Analytical Comparisons of Tissue Dielectric Constant (TDC) and Bioimpedance Spectroscopy (BIS) in Assessment of Early Arm Lymphedema in Breast Cancer Patients after Axillary Surgery and Radiotherapy. Lymphatic research and biology 2015;**13**(3):176-85 doi: 10.1089/lrb.2015.0019[published Online First: Epub Date]|.

20. Nuutinen J, Ikaheimo R, Lahtinen T. Validation of a new dielectric device to assess changes of tissue water in skin and subcutaneous fat. Physiol Meas 2004;**25**(2):447-54

21. Mazor M, Smoot BJ, Mastick J, et al. Assessment of local tissue water in the arms and trunk of breast cancer survivors with and without upper extremity lymphedema. Clinical physiology and functional imaging 2019;**39**(1):57-64 doi: 10.1111/cpf.12541[published Online First: Epub Date]|.

22. Stuchly MA, Athey TW, Stuchly SS, Samaras GM, Taylor G. Dielectric properties of animal tissues in vivo at frequencies 10 MHz--1 GHz. Bioelectromagnetics 1981;**2**(2):93-103

23. Lahtinen T, Nuutinen J, Alanen E. Dielectric properties of the skin. Physics in medicine and biology 1997;**42**(7):1471-2

24. Mayrovitz HN, Weingrad DN, Brlit F, Lopez LB, Desfor R. Tissue dielectric constant (TDC) as an index of localized arm skin water: differences between measuring probes and genders. Lymphology 2015;**48**(1):15-23

25. Birkballe S, Jensen MR, Noerregaard S, Gottrup F, Karlsmark T. Can tissue dielectric constant measurement aid in differentiating lymphoedema from lipoedema in women with swollen legs? Br J Dermatol 2014;**170**(1):96-102 doi: 10.1111/bjd.12589[published Online First: Epub Date]|.

26. Czerniec SA, Ward LC, Kilbreath SL. Assessment of breast cancer-related lymphedema: a comparison of moisture meter and spot bioimpedance measurement. Lymphatic research and biology 2015;**13**(1):10-9 doi: 10.1089/lrb.2014.0032[published Online First: Epub Date]|.

27. Koehler LA, Mayrovitz HN. Spatial and Temporal Variability of Upper Extremity Edema Measures After Breast Cancer Surgery. Lymphatic research and biology 2018 doi: 10.1089/lrb.2018.0022[published Online First: Epub Date]|.

28. International Lymphoedema Framework I. *Best Practice for the Management of Lymphoedema: International Consensus*, 2006.

29. Sanderson J, Tuttle N, Box R, Reul-Hirche HM, Laakso EL. THE PITTING TEST; AN INVESTIGATION OF AN UNSTANDARDIZED ASSESSMENT OF LYMPHEDEMA. Lymphology 2015;**48**(4):175-83

30. Warren AG, Brorson H, Borud LJ, Slavin SA. Lymphedema: a comprehensive review. Annals of plastic surgery 2007;**59**(4):464-72 doi: 10.1097/01.sap.0000257149.42922.7e[published Online First: Epub Date]|.

31. De Vrieze T, Vos L, Gebruers N, et al. Protocol of a randomised controlled trial regarding the effectiveness of fluoroscopy-guided manual lymph drainage for the treatment of breast cancer-related lymphoedema (EFforT-BCRL trial). Eur J Obstet Gynecol Reprod Biol 2017 doi: 10.1016/j.ejogrb.2017.12.023[published Online First: Epub Date]|.

32. Mayrovitz HN, Davey S, Shapiro E. Local tissue water changes assessed by tissue dielectric constant: single measurements versus averaging of multiple measurements. Lymphology 2008;**41**(4):186-8

33. Lexell JE, Downham DY. How to assess the reliability of measurements in rehabilitation. American journal of physical medicine & rehabilitation 2005;**84**(9):719-23

34. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979;**86**(2):420-8

35. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Fam Med 2005;**37**(5):360-3

36. Brorson H, Hoijer P. Standardised measurements used to order compression garments can be used to calculate arm volumes to evaluate lymphoedema treatment. J Plast Surg Hand Surg 2012;**46**(6):410-5 doi: 10.3109/2000656x.2012.714785[published Online First: Epub Date]|.

37. Gibney MA, Arce CH, Byron KJ, Hirsch LJ. Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations. Current medical research and opinion 2010;**26**(6):1519-30 doi: 10.1185/03007995.2010.481203[published Online First: Epub Date]|.

38. Lawenda BD, Mondry TE, Johnstone PA. Lymphedema: a primer on the identification and management of a chronic condition in oncologic treatment. CA: a cancer journal for clinicians 2009;**59**(1):8-24 doi: 10.3322/caac.20001[published Online First: Epub Date]|.

CHAPTER 5

Chapter 5

REVISION OF THE LYMPHEDEMA FUNCTIONING, DISABILITY AND HEALTH QUESTIONNAIRE FOR UPPER LIMB LYMPHEDEMA (LYMPH-ICF-UL) : RELIABILITY AND VALIDITY

Lymphat Res Biol. 2019 Jun; 17(3): 347-355.

Tessa De Vrieze
Lore Vos
Nick Gebruers
Ines Nevelsteen
An De Groef
Lore Dams
Elien Van der Gucht
Nele Devoogdt

Abstract

Background. Lymphedema is associated with significant physical and psychosocial problems. The Lymphedema Functioning, Disability and Health questionnaire (Lymph-ICF) for upper limb lymphedema is a valid and reliable tool quantifying the amount of problems in functioning in patients with breast cancer-related lymphedema. Although, patients suggested a revision of the scoring system to facilitate completion of the questionnaire. Therefore, adjustment of the questionnaire was carried out by implementing a numeric rating scale instead of the existing visual analogue scale. Purpose of this study was to investigate reliability and validity of the revised Lymph-ICF, called the Lymph-ICF-UL.

Methods and results. Reliability and validity of the Lymph-ICF-UL was examined in 56 participants with upper limb lymphedema. Intraclass correlation coefficients for test-retest reliability ranged from .79 to .95. Cronbach's alpha coefficients for internal consistency were higher than .80. Face and content validity were very good because the scoring system was clear for all participants (100%), questions were understandable for all participants (100%), and all complaints due to arm lymphedema were mentioned by 98% of the participants. Construct validity was good. Convergent validity was established since 4 out of 5 expected domains of the Lymph-ICF-UL showed a moderate correlation with expected domains of the 36-Item Short-Form Health Survey questionnaire. There was good divergent validity because 7 out of 9 hypotheses assessing divergent validity were accepted.

Conclusion. The Lymph-ICF-UL is a reliable and valid questionnaire using a simplified and clearer scoring procedure to assess impairments in function, activity limitations, and participation restrictions of patients with breast cancer-related arm lymphedema.

Introduction

Upper limb lymphedema is a debilitating morbidity affecting more than 16% of the women treated for breast cancer[1]. The swelling can be caused by destruction of the lymphatic vessels due to surgery or radiotherapy, resulting in a reduced lymphatic transport[2].

Lymphedema can be assessed objectively with different assessment methods that all are valid and reliable[3]. Examples of assessment methods are different kind of water displacement methods[4-7], and circumference measurements using a tapeline[7-9] or perimeter[10]. Subsequently, the calculated volume can be determined[8], which is described as the most widely used calculation for lymphedema in common clinical practice[11]. However, objective assessment of the amount of lymphedema volume lacks the power to encounter the real burden of lymphedema. Besides swelling, patients can suffer from problems in physical, social and mental functioning[12]. Additionally, breast cancer-related lymphedema (BCRL) can cause a lower quality of life[13-15]. Therefore, the Lymphedema Functioning, Disability and Health questionnaire for the upper limb (Lymph-ICF) was developed[10]. This questionnaire aims to quantify impairments in function, activity limitations and participation restrictions which are related to lymphedema of the upper limb. In contrast to other lymphedema-related questionnaires it is based on terminology of the International Classification of Functioning, Disability and Health (ICF) as introduced by the World Health Organization[16]. According to a recently published systematic review, the Lymph-ICF is one of the most complete and accurate questionnaires available to asses quality of life in patients with BCRL[17].

The quality and usefulness of a questionnaire is determined by its clinical properties, such as validity, reliability and responsiveness. Reliability and validity of the Lymph-ICF have already been examined and it has shown to be a valid and reliable Dutch questionnaire in patients with BCRL[10]. However, patients mentioned that the use of a scoring system with gradation like a numeric rating scale (NRS), would be an easier scoring method instead of the current scoring system which is a visual analog scale (VAS). Therefore, in 2014 when the Lymph-ICF-LL questionnaire for lower limbs was developed, the scoring mechanism was revised by implementing a NRS instead of a VAS[18]. This revision had not yet been extended to the Lymph-ICF questionnaire regarding upper limb lymphedema. As a result, revision of the Lymph-ICF questionnaire was established by implementing a NRS instead of the existing VAS. Although scores are not interchangeable, both VAS and NRS have proven to be valid, reliable and sensitive[19 ,20]. Moreover, NRS showed to be the recommended scale based on a higher compliance, better responsiveness with lower error rate, and better applicability compared to VAS[19]. Clinimetric properties of this revised questionnaire have not been investigated yet. Therefore, the aim of this study was to examine different aspects of reliability and validity of the Lymph-ICF-UL with NRS in patients with BCRL.

Materials and Methods

Study design

Included subjects were participants of the EFforT-BCRL trial (n=42)[21] and were recruited in the University Hospitals of Leuven and the Antwerp University Hospital in Belgium. To shorten the inclusion period, also a small group of participants (n=14) was recruited in the Lymphovenous Center of the University Hospitals of Leuven. Approval for this trial was obtained by the Ethical Committee of the University Hospitals of Leuven (main Ethical Committee) and received positive advice from the Ethical Committees of all other participating centers (CME reference S58689, EudraCT 2015-004822-33).

This cross-sectional study is reported following the COSMIN (COnsenus-based Standards for the selection of health Measurement INstruments) guidelines[22].

Participants

Fifty-six participants with BCRL were included between December 2016 and August 2017. Eligibility criteria were: 1)subjects diagnosed with unilateral lymphedema of the arm and/or hand, developed after treatment for breast cancer, 2)chronic lymphedema stage I to IIb (duration of >3 months), 3)at least 5% difference between both arms and/or between both hands at start of the treatment (in case of participation in EFforT-BCRL trial) or at the day of the consultation at the Lymphovenous Center, adjusted for limb dominance. Participants were excluded when 1)they had edema of the upper limb from other cause than breast cancer treatment, or 2)when they were not native Dutch speaking or able to read and fully understand the Dutch language.

Procedure

To analyze the clinimetric properties of the revised version of the Lymph-ICF questionnaire, called the Lymph-ICF-UL, the same methodology was applied as for the investigation of the clinimetric properties of the original questionnaires[10,18].

Lymph-ICF-UL questionnaire

In the introduction of the Lymph-ICF-UL questionnaire, the scoring system is explained. Then the patient is asked to score his/her average impairments in function, activity limitations, and participation restrictions during the past 2 weeks. Furthermore, the patient is asked not to discuss the questions with anyone to maintain the self-assessment characteristics of the questionnaire. The Lymph-ICF-UL questionnaire takes about 5 to 10 minutes to complete.

Different scores are obtained from the questionnaire. Each of the 29 questions has to be scored on an 11-point Likert scale between 0-10 (instead of a VAS between 0-100). The total score of the Lymph-

ICF-UL is equal to the sum of the scores on the questions divided by the total number of answered questions, and multiplied by 10. In addition, a score is determined for each of the 5 domains of the Lymph-ICF-UL: (1) physical function, (2) mental function, (3) household activities, (4) mobility activities, and (5) life and social activities. Thus, the total score on the Lymph-ICF-UL and the score on the 5 domains range between 0 and 100. Table 1 describes how to interpret the Lymph-ICF-UL scores in clinical practice[16]. The Lymph-ICF-UL has already been translated into the English and French language according to established international guidelines described by the World Health Organization[23,24]. For more details about the establishment of the original version of the Lymph-ICF questionnaire, we refer to Devoogdt et al[10].

Table 1. Interpretation of scores of the Lymph-ICF-UL questionnaire

According to the World Health Organization taxonomy[14], impairments in function, activity limitations, and participation restrictions can be quantified with the following scale:	
0% to 4%	No problems
5% to 24%	Small problems
25% to 49%	Moderate problems
50% to 95%	Severe problems
96% to 100%	Very severe problems

Reliability

To analyze test-retest reliability, patients completed the adapted questionnaire twice; once at the hospital and once at home with an interval of 24-48h after the first test. This time interval was chosen given the fact that problems related to arm lymphedema may change from one day to another. Since the questionnaire consists of 29 questions, the risk for recall bias is negligible. This second questionnaire needed to be returned by mail.

Validity

To analyze construct validity, patients also completed the Medical Outcomes Study 36-Item Short-Form Health Survey(SF-36) once at the hospital. The SF-36 is a valid, reliable and commonly used questionnaire to measure a person's health related quality of life[25,26]. It is a generic health status instrument, consisting of 36 questions, divided into eight domains. Scores range between 0-100; the higher the score on the SF-36, the better one's quality of life[26].

Furthermore, to analyze face and content validity of the Lymph-ICF-UL questionnaire, an additional questionnaire developed by one of the authors (ND) in the original investigation[10], was completed. This questionnaire consisted of following questions: (1) Was the scoring system clear? (yes/no), (2) Was each question of the Lymph-ICF-UL understandable? (yes/no), and (3) Were all complaints related to your lymphedema mentioned in the questionnaire? (yes/no). If a participant answered "no" to any of these questions, an explanation was asked.

Descriptive were collected by interviewing the participants and by consulting their medical records. Circumference measurements of both affected and non-affected arms were performed using a perimeter, after which the volume of the arm was calculated using following truncated cone formula: $4\times(C_1^2+C_1C_2+C_2^2)/12\pi$, where C_1 is the upper circumference and C_2 is the lower circumference of each segment[8]. Measurements were performed by one of three physical therapists specialized in edema therapy (ND,LV,TDV).

Data analysis

Statistical analyses were performed using the software SPSS for Windows version 24.0. The .05 level of significance was applied. Descriptive analyses were applied to describe the participants.

Reliability

Intraclass correlation coefficients(ICCs) were used to determine test-retest reliability of the total score of the Lymph-ICF-UL, of the scores on the 5 domains, and of the score on each question separately[27]. ICC estimates and their 95% confident intervals were calculated based on a single rating, absolute agreement, 2-way-mixed-effects model[28 ,29]. Cronbach's alpha coefficients were used to determine internal consistency of the entire questionnaire as well as of each domain[30]. The ICCs and Cronbach's alpha coefficients were interpreted as follows:<.40 was weak, .40 to .74 was moderate, .75 to .90 was strong and >.90 was very strong[31 ,32].

To calculate significant changes in the mean between the two test occasions, Wilcoxon-signed-rank tests were performed since the One-Sample-Kolmogorov-Smirnov test revealed non-normal distribution of data.

To interpret the magnitude of the within-subjects variation of the 2 scores, the standard error of measurement(SEM) was calculated using following formula: $SEM=SD\sqrt{(1-ICC)}$, where SD was the

average standard deviation of the 2 ratings[27]. To evaluate clinically important changes, we calculated the smallest real difference(SRD) using the formula: SRD=1.96 x SEM x$\sqrt{2}$[27]. To obtain a reference range for the mean difference of the scores of the 2 test occasions, we calculated 95% SRD as the mean difference between the 2 test occasions ±SRD.

Validity

Face, content and construct validity were examined. Face validity was examined by asking participants whether the scoring system was obvious and whether the questions in the Lymph-ICF-UL were understandable. Content validity was examined by analyzing the answers given by participants to the question about the comprehensiveness of the questionnaire. First, the number of positive answers on each of the 3 questions was counted. Next, the participants' explanations on the negative answers were discussed.

To investigate construct (convergent, divergent) validity of the Lymph-ICF-UL, the relationship between scores on domains of the Lymph-ICF-UL and scores on domains of the SF-36 was examined. Spearman rank correlation coefficients were used since data was non-normal distributed. To determine convergent and divergent validity and based on the content of the questions of each domain of Lymph-ICF-UL and SF-36, we used the same hypotheses as formulated in the validation study of the original Lymph-ICF[10]. In case of agreement between the questions in a specific domain of the Lymph-ICF-UL and SF-36, these domains were included in a hypothesis for assessing convergent validity. In case of disagreement, they were included in a hypothesis for assessing divergent validity. Table 2 shows an overview of the hypotheses for determining convergent and divergent validity and the rationale for the hypotheses. Correlation coefficients were interpreted as follows:<.4 was weak, .4 to .74 was moderate, .75 to .9 was strong and >.9 was very strong[31]. If a moderate to very good correlation was found between two corresponding domains, the hypothesis for convergent validity was accepted. In case of a weak correlation between two disagreeing domains, the particular hypothesis for divergent validity was accepted. Construct validity was defined as very good if more than 90% of all 14 hypotheses were confirmed, as good if between 75% and 90% of the hypotheses were confirmed, and as moderate if between 40% and 74% of the hypotheses were confirmed.

Table 2. Fourteen hypotheses and rationale for hypotheses for assessing construct validity

Hypothesis	Rationale
Convergent validity	Considering all correlation coefficients for various domains of the Lymph-ICF-UL and the SF-36, at least moderate correlation coefficients would occur between:
1: Lymph-ICF-UL physical function and SF-36 bodily pain	Lymph-ICF-UL physical function: Does your arm: feel heavy, feel stiff, feel swollen, feel like it has lost strength, tingle, hurt or have a tensed skin? SF-36 bodily pain: How much bodily pain have you had during the past 4 wk? During the past 4 wk, how much did pain interfere with your normal work?
2: Lymph-ICF-UL mental function and SF-36 mental health	Lymph-ICF-UL mental function: Due to your arm problems, do you feel sad, do you feel discouraged, do you have a lack of self-confidence, do you feel stressed? SF-36 mental health: How much time during the last 2 wk have you been a very nervous person, have you felt so down in the dumps that nothing would cheer you up, have you felt calm and peaceful, have you felt downhearted and low, and have you been a happy person?
3: Lymph-ICF-UL household activities and SF-36 physical functioning	Lymph-ICF-UL general tasks/household activities: How well are you able to: clean (scrub, vacuum, mop), cook, iron, work in the garden? SF-36 physical functioning: Does your health limit you in the following activities: vigorous activities, such as lifting heavy objects; moderate activities, such as moving a table, pushing a vacuum, lifting or carrying groceries, climbing several flights of stairs, climbing 1 flight of stairs, bending, kneeling, stooping, walking more than a mile, walking half a mile, walking 100 yd (91.44 m), and bathing or dressing yourself?
4: Lymph-ICF-UL mobility activities and SF-36 physical functioning	Lymph-ICF-UL mobility activities: How well are you able to: perform tasks with the arm elevated (e.g. hang out the laundry), lift or carry heavy objects (e.g. a filled bucket or shopping bags), sleep on the affected side, perform computer work (>30 min), sunbathe, drive a car, walk (>2 km), ride a bike? SF-36 physical functioning: Does your health limit you in the following activities: vigorous activities, such as lifting heavy objects; moderate activities, such as moving a table, pushing a vacuum, lifting or carrying groceries, climbing several flights of stairs, climbing 1 flight of stairs, bending, kneeling, stooping, walking more than a mile, walking half a mile, walking 100 yd, and bathing or dressing yourself?
5: Lymph-ICF-UL life and social activities and SF-36 social functioning	Lymph-ICF-UL life domains/social life: How well are you able to: go on vacation, perform your hobbies, practice sports, wear your clothes of choice, do your job, do social activities (e.g. going to parties, concerts,

	restaurant)? SF-36 social functioning: During the past 2 wk, to what extent have your physical health or emotional problems interfered with your normal social activities with family, neighbors, or groups? During the past 2 wk, how much of the time have your physical health or emotional problems interfered with your social activities?
Hypothesis	**Rationale**
Divergent validity	Considering all correlation coefficients for various domains of the Lymph-ICF-UL and the SF-36, weak correlation coefficients would occur between:
6-7: Lymph-ICF-UL physical function and SF-36 role– emotional and mental health	Lymph-ICF-UL physical function: Does your arm: feel heavy, feel stiff, feel swollen, feel like it has lost strength, tingle, hurt or have a tensed skin? SF-36 role–emotional: During the past 4 wk, how much time have you had problems with your work or other regular daily activities as a result of emotional problems? SF-36 mental health: How much time during the last 2 wk have you been a very nervous person, have you felt so down in the dumps that nothing would cheer you up, have you felt calm and peaceful, have you felt downhearted and low, and have you been a happy person?
8-9: Lymph-ICF-UL mental function and SF-36 physical functioning and role-physical	Lymph-ICF-UL mental function: Due to your arm problems, do you feel sad, do you feel discouraged, do you have a lack of self-confidence, do you feel stressed? SF-36 physical functioning: Does your health limit you in the following activities: vigorous activities, such as lifting heavy objects; moderate activities, such as moving a table, pushing a vacuum, lifting or carrying groceries, climbing several flights of stairs, climbing 1 flight of stairs, bending, kneeling, stooping, walking more than a mile, walking half a mile, walking 100 yd, and bathing or dressing yourself? SF-36 role-physical: During the past 4 wk, have you had any of the following problems with your work or other regular daily activities as a result of your physical health; cut down the amount of time you spent on work or other activities, accomplished less than you would like, were limited in the kind of work or other activities, had difficulty performing the work or other activities (for example, it took extra effort)?
10-11: Lymph-ICF-UL household activities and SF-36 role-emotional and mental health	Lymph-ICF-UL general tasks/household activities: How well are you able to: clean (scrub, vacuum, mop), cook, iron, work in the garden?

	SF-36 role–emotional: During the past 4 wk, how much time have you had problems with your work or other regular daily activities as a result of emotional problems? SF-36 mental health: How much time during the last 2 wk have you been a very nervous person, have you felt so down in the dumps that nothing would cheer you up, have you felt calm and peaceful, have you felt downhearted and low, and have you been a happy person?
12-13: Lymph-ICF-UL mobility activities and SF-36 role-emotional and mental health	Lymph-ICF-UL mobility activities: How well are you able to: perform tasks with the arm elevated (e.g. hang out the laundry), lift or carry heavy objects (e.g. a filled bucket or shopping bags), sleep on the affected side, perform computer work (>30 min), sunbathe, drive a car, walk (>2 km), ride a bike? SF-36 role–emotional: During the past 4 wk, how much time have you had problems with your work or other regular daily activities as a result of emotional problems? SF-36 mental health: How much time during the last 2 wk have you been a very nervous person, have you felt so down in the dumps that nothing would cheer you up, have you felt calm and peaceful, have you felt downhearted and low, and have you been a happy person?
14: Lymph-ICF-UL life and social activities and SF-36 physical functioning	Lymph-ICF-UL life domains/social life: How well are you able to: go on vacation, perform your hobbies, practice sports, wear your clothes of choice, do your job, do social activities (e.g. going to parties, concerts, restaurant)? SF-36 physical functioning: Does your health limit you in the following activities: vigorous activities, such as lifting heavy objects; moderate activities, such as moving a table, pushing a vacuum, lifting or carrying groceries, climbing several flights of stairs, climbing 1 flight of stairs, bending, kneeling, stooping, walking more than a mile, walking half a mile, walking 100 yd, and bathing or dressing yourself?

Results

Fifty-six volunteers with objective BCRL participated in this study. All participants had undergone breast surgery with axillary dissection (SLNB and/or ALND). For more details about the participant characteristics, see Table 3.

Table 3. Characteristics of the included subjects (n=56)

Variable	Outcome
Age (y)	62 (10)
Body Mass Index (kg/m^2)	27 (4)
Lymphedema volume arm (mL)	410 (351)
Duration lymphedema (mo)*	34.5 (13.5, 79.5 [66])
BCRL stages	
I n(%)	10 (17.9%)
IIa n(%)	33 (58.9%)
IIb n(%)	13 (23.2%)
Breast surgery	
Mastectomy n(%)	36 (58.1%)
Breast-conserving surgery n(%)	20 (32.3%)
Axillary lymph node clearance[a]	
SLNB alone(%)	4 (7.1%)
SLNB + ALND(%)	49 (87.5%)
Surgery on the dominant side n(%)	29 (46.8%)
Radiotherapy[b] n(%)	54 (87.1%)
Chemotherapy[b] n(%)	50 (80.6%)
Hormonal therapy[b] n(%)	45 (72.6%)
Targeted therapy (Herceptin)[b] n(%)	13 (21%)

*[a] n=52 since medical data of 3 patients is unknown due to surgery in different hospitals in the past (n=2) or due to previous treatment abroad (n=1); [b]n=55 since medical data of 1 patient is unknown due to previous treatment abroad; y= years, kg= kilogram, m^2= square meters, mL= milliliter, mo= months, BCRL stages as described by the International Society of Lymphology; descriptives are presented as "mean (standard deviation)" except when indicated with * where "median (25th, 75th percentile [interquartile range])" is shown.*

Reliability

Table 4 gives an overview of the ICCs, Cronbach's alpha coefficients, SEMs and SRDs for the total score on the Lymph-ICF-UL and for the scores on each domain separately. Test-retest reliability of the total score and of the mental function and mobility activities scores were very strong (ICC>.90). The other scores were found strong (ICC>.75). Test-retest reliability of the scores on 26 questions (90%) were strong to very strong (data not shown). Reliability of scores on the other 3 questions (about the abilities to cook, to iron and to wear clothes) were moderate (ICC=.60-.74).

Internal consistency of the Lymph-ICF-UL also ranged between strong and very strong. The Cronbach's alpha coefficient for all questions was .98 and ranged for the different domains between .89 and .98.

There were no statistical differences between the means of the total score, as well as of the separate domain scores, between the two test occasions which were calculated with Wilcoxon-signed-rank analyses (Table 4).

The total score on the Lymph-ICF-UL had a variation from one test occasion to the other of 4.9. A decrease or an increase in score of 10 or more is considered (with 95% certainty) as a statistically significant change. Furthermore, a decrease or increase in score of 14 or more is considered as a clinically relevant change (Table 4).

Validity

The questionnaire regarding face and content validity of the Lymph-ICF-UL was completed by all participants. All participants (100%) found the scoring system clear and all participants (100%) mentioned that the questions were understandable. Forty-three participants (77%) mentioned that all complaints were addressed in the questionnaire. Complaints not covered in the questionnaire are shown in Table 5. After discussion with a team of experts (ND,LV,TDV), only 1 missing complaint mentioned by 1 participant was considered to be relevant (2%).

Table 4. Reliability on the total score of the Lymph-ICF-UL and the scores on the 5 domains

Score		*Mean*			*Test-retest*		*Internal consistency*	*Variability*		*Clinically important changes*	
	N	*X1*	*X2*	*P -value*	*ICC*	*95% CI*	*$_{\alpha}$*	*SEM*	*95% CI*	*SRD*	*95% CI*
Lymph-ICF-UL total score	56	27.50	27.45	0.98	0.95	0.91 to 0.97	0.98	4.89	-9.57 to 9.61	13.56	-13.54 to 13.58
Physical function score	56	24.30	22.76	0.26	0.90	0.83 to 0.94	0.92	6.76	-11.70 to 14.78	18.73	-17.19 to 20.27
Mental function score	56	18.97	19.69	0.67	0.93	0.88 to 0.96	0.98	6.31	-13.09 to 11.65	17.49	-18.21 to 16.77
Household activities score	56	33.02	34.60	0.71	0.79	0.66 to 0.87	0.89	12.31	-25.71 to 22.55	34.13	-35.71 to 32.55
Mobility activities score	56	30.68	31.03	0.84	0.91	0.85 to 0.95	0.89	7.63	-15.31 to 14.61	21.16	-21.51 to 20.81
Life and social activities score	55	28.30	30.65	0.22	0.88	0.80 to 0.93	0.92	8.28	-18.58 to 13.88	22.96	-25.31 to 20.61

Abbreviations: X1= mean at time point 1, X2= mean at time point 2, p-value is resulting out of Wilcoxon signed rank analyses, CI= confidence interval, $_{\alpha}$ = Cronbach's alpha coefficient

Table 5. Overview of mentioned missing complaints (n=12) and reason why no inclusion in Lymph-ICF-UL

Lymph-ICF-UL domain	Complaint	Argumentation (see Table appendix)
Physical function domain	Pain in the breast	A
	Hypersensitivity of the skin	B
	Presence of paresthesia	B
	Number of episodes of erysipelas*	
Mental function domain	Feeling annoyed/embarrassed about wearing compression garment (n=3)	C
Mobility activity domain	Ability to perform more powerful activities	C
	A delayed onset of complaints after performing a task (i.e. not at the moment itself)	C
Life and social activities domain	The possibility of wearing any kind of bra	A
	The ability to meet the former (pre-surgery) sports/activity level	C
One participant found that the distinction between limb dominance within the questions was not covered		D
One participant found that the 2 questions about the ability to sport and to work were too vague		

Appendix

A: May indicate myofascial pain or pain due to breast edema[28]. The Lymph-ICF-UL is aimed to quantify the amount of problems in functioning in patients with BCRL of the arm, however, this questionnaire has not yet been validated in patients with breast edema. This needs to be further investigated.

B: Complications related to the treatment of breast cancer (i.e. due to lesions of sensory nerves after axillary lymph node dissection and/or radiotherapy) and not due to the arm lymphedema[29,30].

C: Can be scored with corresponding questions of the questionnaire. The patient has to give the mean score on his/her problems in functioning during the past two weeks, as reported in the introduction of the questionnaire.

D: Limb dominance is an item that is collected separately from the lymph-ICF-UL

*After discussion, only 1 complaint (2%) was considered relevant, nevertheless, it was not included in the questionnaire.

Table 6 provides an overview of the Spearman rank correlation coefficients between the different domains of the Lymph-ICF-UL and the SF-36. All participants completed both questionnaires. Concerning convergent validity, 4 out of 5 domains of the Lymph-ICF-UL correlated at least moderate with the expected corresponding domains of the SF-36, and were accepted. Correlation coefficients of these 4 ranged from -.42 to -.66 (moderate correlations). Concerning divergent validity, 7 out of 9 domains of the Lymph- ICF-UL showed a weak correlation with the expected corresponding domains of the SF-36. The correlation coefficients of these 7 ranged from -.19 to -.37 (no to weak correlation). Consequently, 7 out of 9 hypotheses for assessing divergent validity were accepted, resulting in an overall good construct validity of the Lymph-ICF-UL (79%).

Table 6. Correlation between the SF-36 and the Lymph-ICF-UL to determine convergent and divergent validity (Spearman rank correlation coefficient; n= 56)

	Spearman Rank Correlation Coefficient ($r_{s\ (p\text{-}value)}$) for:				
SF-36 domain	**Lymph-ICF-UL domains**				
	Impairments in function		**Activity limitations and participation restrictions**		
	Physical function Correlation Coefficient (Sign.)	Mental function Correlation Coefficient (Sign.)	Household activities Correlation Coefficient (Sign.)	Mobility activities Correlation Coefficient (Sign.)	Life and social activities *(n=55)* Correlation Coefficient (Sign.)
Physical functioning	-.249 (.640)	**-.311 (.020)**	-.244 (.070)	**-.415 (.001)**	-.426 (.001)
Role-physical	-.266 (.470)	-.526 (≤.001)	-.400 (.002)	-.428 (.001)	-.495 (≤.001)
Bodily pain	**-.440 (.001)**	-.292 (.029)	-.454 (≤.001)	-.437 (.001)	-.586 (≤.001)
General health	-.390 (.003)	-.388 (.003)	-.511 (≤.001)	-.471 (≤.001)	-.541 (≤.001)
Vitality	-.265 (.045)	-.542 (≤.001)	-.375 (.004)	-.384 (.003)	-.558 (≤.001)
Social functioning	-.399 (.002)	-.599 (≤.001)	-.522 (≤.001)	-.534 (≤.001)	**-.607 (≤.001)**
Role-emotional	**-.191 (.158)**	-.488 (≤.001)	**-.306 (.022)**	**-.369 (.005)**	-.419 (.001)
Mental health	**-.195 (.150)**	**-.661 (≤.001)**	**-.234 (.083)**	**-.341 (.010)**	-.431 (.001)

Values with bold frame= hypotheses for expected moderate correlations assessing convergent validity; Values with double frame= hypotheses for expected moderate correlations assessing divergent validity; Bold values= accepted hypotheses regarding convergent validity (Correlation Coefficient ≥0.4) or regarding divergent validity (Correlation Coefficient ≤0.4).

Discussion

In 2011, the original version of the first Dutch questionnaire based on terminology of the ICF to assess the impairments in function, activity limitations, and participation restrictions of patients with BCRL, was shown to be valid and reliable. The revised version, the Lymph-ICF-UL questionnaire, is also found appropriate and useful in clinical practice by showing very good (reliability) to good (validity) clinimetric properties.

Reliability of the Lymph-ICF-UL was very good. The ICCs of the total score on the Lymph-ICF-UL and the different domain scores varied between strong and very strong, showing over all higher ICC values than those shown in the original study, except for the household activities score[10]. However, this ICC value is still high enough to speak of good test-retest reliability. Moreover, the ICC value of life and social activities improved remarkably. Consequently, the test-retest reliability of this domain improved from moderate to strong. Compared to the original version of the Lymph-ICF-UL, also Cronbach's alpha coefficients are increased for both the total score as for the scores on the different domains, with exception of the household activities score where Cronbach's alpha remained stable. If we look at the differences in SEMs and SRDs between this revised version and the original version, we found similar SEMs and SRDs for the total score as for the different domains. Except for the household activities domain we found a higher SEM and SRD, and for the mental function domain as well as the life and social activities domain we found remarkably lower SEMs and SRDs in the present study.

Face and content validity of the Lymph-ICF-UL was very good for participants with BCRL. All participants (100%) found the revised scoring system (NRS) clear, in contrast to the original version in which the scoring system (VAS) was clear for only 88% of the participants and whereby participants mentioned preferring a scoring system with gradation. Thus, revision of the scoring system resulted in an improved face validity of the questionnaire. Similar to the original version, all questions were understandable for all participants. Only 1 participant (2%) reported missing a complaint in the Lymph-ICF-UL which we considered relevant. This was the complaint 'number of episodes of erysipelas'. However, it is not part of the questionnaire because during the development phase of the Lymph-ICF questionnaire, none of the patients reported erysipelas as complaint. Eleven other participants also mentioned missing a complaint in the Lymph-ICF-UL. However, after discussion we concluded that these complaints were irrelevant, and consequently, did not have to be included in the Lymph-ICF-UL (Table 5).

Construct validity of the Lymph-ICF-UL was tested in terms of convergent and divergent validity and gave good results. Concerning convergent validity, 4 out 5 domains (80%) of the Lymph-ICF-UL correlated at least moderately with the expected corresponding domains of the SF-36 (r between -.42 to -.66). In the original study, all 5 hypotheses concerning convergent validity could be accepted. In current study, the household activities (r=-.24) domain of the Lymph-ICF-UL did not show a moderate or strong correlation with the expected physical function domain of the SF-36. Noteworthy, this moderate correlation was also present between the life and social activities domain of the Lymph-ICF-UL and the social functioning domain of the SF-36, although this correlation was weak in previous version (r=-.61 versus r=-.33, respectively).

Concerning divergent validity, 7 out of 9 hypotheses (78%) were accepted in current study, whereas 3 out of 5 hypotheses (60%) were accepted in the original study. Unexpected, the mental function domain of the Lymph-ICF-UL showed a moderate correlation with the role-physical (r=-.53) domain of the SF-36, in contrast with the previous version where this correlation was weak (r=-.25).

Strengths and study limitations

Our study consisted of several strengths. First, different aspects of reliability and validity of the Lymph-ICF-UL were investigated. However, our study did not investigate responsiveness of the Lymph-ICF-UL. Research to determine this clinimetric property is ongoing. Second, the sample size of this study consisted of 56 participants. As stated by Shrout and Fleiss, researchers should try to obtain at least 30 heterogeneous subjects for reliability studies[29]. The sample of our study is heterogeneous since participants with BCRL stages I, IIa or IIb, with a broad range of duration in months and lymphedema volume were enrolled to accommodate this.

A limitation of our study is that testing of face and content validity occurred with an author-developed questionnaire. However, we are unaware of an available valid questionnaire to investigate these clinimetric properties.

Conclusion

In conclusion, the Lymph-ICF-UL is a reliable and valid Dutch questionnaire using a simplified and clearer scoring procedure to assess problems in functioning of patients with arm lymphedema developed after breast cancer treatment. This tool enables a better understanding of the quality of life of a patient. Based on the outcome of the Lymph-ICF-UL, treatment goals for patients with upper limb lymphedema can be set. Thereafter, the questionnaire may be used to monitor long-term results of this treatment and self-care. For the interpretation of follow-up assessments with the Lymph-ICF-UL, a decrease or increase of 14 or more of the total score should be considered as clinically relevant.

Acknowledgements

The authors are very grateful to the hospitals collaborating in this study. The authors also extend very grateful thanks to the study participants. All authors critically revised the manuscript for important intellectual content and approved the final manuscript.

References

1. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 2013;**14**(6):500-15 doi: 10.1016/S1470-2045(13)70076-7[published Online First: Epub Date]|.
2. Michael F. *Földi's Textbook of Lymphology*. Munich: Elsevier, 2012.
3. Hidding JT, Viehoff PB, Beurskens CH, van Laarhoven HW, Nijhuis-van der Sanden MW, van der Wees PJ. Measurement Properties of Instruments for Measuring of Lymphedema: Systematic Review. Phys Ther 2016;**96**(12):1965-81 doi: 10.2522/ptj.20150412[published Online First: Epub Date]|.
4. Gebruers N, Truijen S, Engelborghs S, De Deyn PP. Volumetric evaluation of upper extremities in 250 healthy persons. Clin Physiol Funct Imaging 2007;**27**(1):17-22 doi: 10.1111/j.1475-097X.2007.00708.x[published Online First: Epub Date]|.
5. Damstra RJ, Glazenburg EJ, Hop WC. Validation of the inverse water volumetry method: A new gold standard for arm volume measurements. Breast Cancer Res Treat 2006;**99**(3):267-73 doi: 10.1007/s10549-006-9213-0[published Online First: Epub Date]|.
6. Sagen A, Karesen R, Skaane P, Risberg MA. Validity for the simplified water displacement instrument to measure arm lymphedema as a result of breast cancer surgery. Arch Phys Med Rehabil 2009;**90**(5):803-9 doi: 10.1016/j.apmr.2008.11.016[published Online First: Epub Date]|.
7. Gjorup C, Zerahn B, Hendel HW. Assessment of volume measurement of breast cancer-related lymphedema by three methods: circumference measurement, water displacement, and dual energy X-ray absorptiometry. Lymphat Res Biol 2010;**8**(2):111-9 doi: 10.1089/lrb.2009.0016[published Online First: Epub Date]|.
8. Taylor R, Jayasinghe UW, Koelmeyer L, Ung O, Boyages J. Reliability and validity of arm volume measurements for assessment of lymphedema. Phys Ther 2006;**86**(2):205-14
9. Megens AM, Harris SR, Kim-Sing C, McKenzie DC. Measurement of upper extremity volume in women after axillary dissection for breast cancer. Arch Phys Med Rehabil 2001;**82**(12):1639-44 doi: 10.1053/apmr.2001.26822[published Online First: Epub Date]|.
10. Devoogdt N, Van Kampen M, Geraerts I, Coremans T, Christiaens MR. Lymphedema Functioning, Disability and Health questionnaire (Lymph-ICF): reliability and validity. Phys Ther. United States, 2011:944-57.
11. Johnson KC, Kennedy AG, Henry SM. Clinical measurements of lymphedema. Lymphat Res Biol 2014;**12**(4):216-21 doi: 10.1089/lrb.2014.0019[published Online First: Epub Date]|.
12. Woods M. Patients' perceptions of breast-cancer-related lymphedema. Eur J Cancer Care (Engl) 1993;**2**(3):125-8
13. Ridner SH. Quality of life and a symptom cluster associated with breast cancer treatment-related lymphedema. Support Care Cancer 2005;**13**(11):904-11 doi: 10.1007/s00520-005-0810-y[published Online First: Epub Date]|.
14. Lopez Penha TR, van Bodegraven J, Winkens B, Heuts EM, Voogd AC, von Meyenfeldt MF. The quality of life in long-term breast cancer survivors with breast cancer related lymphedema. Acta chirurgica Belgica 2014;**114**(4):239-44
15. Goker M, Devoogdt N, Van de Putte G, et al. Systematic review of breast cancer related lymphedema: making a balanced decision to perform an axillary clearance. Facts, views & vision in ObGyn 2013;**5**(2):106-15
16. World Health Organization; 2011; Geneva, Switzerland.

17. Cornelissen AJM, Kool M, Keuter XHA, et al. Quality of Life Questionnaires in Breast Cancer-Related Lymphedema Patients: Review of the Literature. Lymphat Res Biol 2018 doi: 10.1089/lrb.2017.0046[published Online First: Epub Date]|.
18. Devoogdt N, De Groef A, Hendrickx A, et al. Lymphedema Functioning, Disability and Health Questionnaire for Lower Limb Lymphedema (Lymph-ICF-LL): reliability and validity. Phys Ther 2014;**94**(5):705-21 doi: 10.2522/ptj.20130285[published Online First: Epub Date]|.
19. Hjermstad MJ, Fayers PM, Haugen DF, et al. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. Journal of pain and symptom management 2011;**41**(6):1073-93 doi: 10.1016/j.jpainsymman.2010.08.016[published Online First: Epub Date]|.
20. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. Journal of clinical nursing 2005;**14**(7):798-804 doi: 10.1111/j.1365-2702.2005.01121.x[published Online First: Epub Date]|.
21. De Vrieze T, Vos L, Gebruers N, et al. Protocol of a randomised controlled trial regarding the effectiveness of fluoroscopy-guided manual lymph drainage for the treatment of breast cancer-related lymphedema (EFforT-BCRL trial). European journal of obstetrics, gynecology, and reproductive biology 2017 doi: 10.1016/j.ejogrb.2017.12.023[published Online First: Epub Date]|.
22. Mokkink LB, Terwee CB, Knol DL, et al. The COSMIN checklist for evaluating the methodological quality of studies on measurement properties: a clarification of its content. BMC medical research methodology 2010;**10**:22 doi: 10.1186/1471-2288-10-22[published Online First: Epub Date]|.
23. Gandek B, Alacoque J, Uzun V, Andrew-Hobbs M, Davis K. Translating the Short-Form Headache Impact Test (HIT-6) in 27 countries: methodological and conceptual issues. Qual Life Res 2003;**12**(8):975-9
24. Gandek B, Ware JE, Jr. Methods for validating and norming translations of health status questionnaires: the IQOLA Project approach. International Quality of Life Assessment. J Clin Epidemiol. England, 1998:953-9.
25. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;**51**(11):1055-68
26. Ware JE, Jr., Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. J Clin Epidemiol 1998;**51**(11):903-12
27. Lexell JE, Downham DY. How to assess the reliability of measurements in rehabilitation. American journal of physical medicine & rehabilitation 2005;**84**(9):719-23
28. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. Journal of chiropractic medicine 2016;**15**(2):155-63 doi: 10.1016/j.jcm.2016.02.012[published Online First: Epub Date]|.
29. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychological bulletin 1979;**86**(2):420-8
30. Bland JM, Altman DG. Statistics notes: Cronbach's alpha. Bmj 1997;**314**(7080):572
31. Fleiss JL. *Design and Analysis of Clinical Experiments*. New York, NY: John Wiley & Sons Inc, 1986.
32. Fleiss JL. *Design and analysis of clinical experiments*: John Wiley & Sons, 2011.

LYMFOEDEEM STOORNIS, BEPERKING EN PARTICIPATIEPROBLEEM VRAGENLIJST

VOOR LYMFOEEDEEM VAN DE BOVENSTE LEDEMATEN (LYMPH-ICF-UL)

Naam en voornaam: Datum:

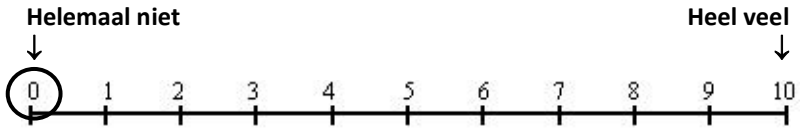
Een zwelling ter hoogte van de arm en/ of hand kan naast fysieke en mentale gevolgen, eveneens een aantal beperkingen in het uitvoeren van activiteiten met zich meebrengen. Hierdoor kunnen problemen ontstaan om deel te nemen aan het maatschappelijk leven.

Deze vragenlijst bevat **29 vragen** die opgesteld werd op basis van informatie van personen met dezelfde aandoening als u.

Naast elke vraag ziet u een 11-punten schaal, met aan de uiteinden van de schaal de woorden 'helemaal niet', 'heel veel' of 'heel goed'. Bij elke vraag dient u het **cijfer** te **omcirkelen dat het best overeenstemt met uw situatie**. Als u geen problemen ondervindt met de omschreven klacht omcirkelt u het cijfer '0'. Indien u heel veel problemen ondervindt met de omschreven klacht, omcirkelt u het cijfer '10'. Indien de activiteit niet voor u van toepassing is, maakt u het bolletje 'niet van toepassing' zwart.

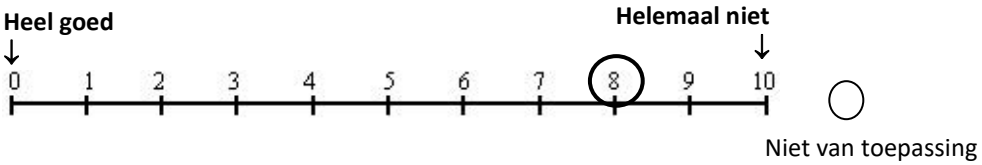
Bijvoorbeeld:

1. Hebt u pijn in uw arm?



U omcirkelt het cijfer '0', indien u helemaal geen pijn voelt.

2. Kan u strijken?



U omcirkelt het cijfer rechts indien u zo goed als niet meer kan strijken ten gevolge van uw arm lymfoedeem. Indien u nooit gestreken hebt, maar uw huishoudhulp dit steeds doet, maakt u het bolletje 'niet van toepassing' zwart.

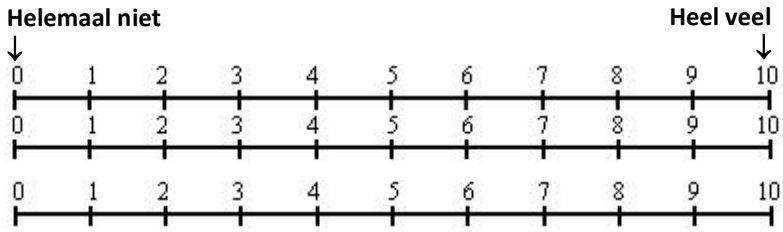
Kies het antwoord dat het best overeenstemt met uw eigen situatie gedurende **de laatste 2 weken**.

Probeer niet te lang na te denken over elke vraag en probeer op **elke vraag een antwoord** te geven.

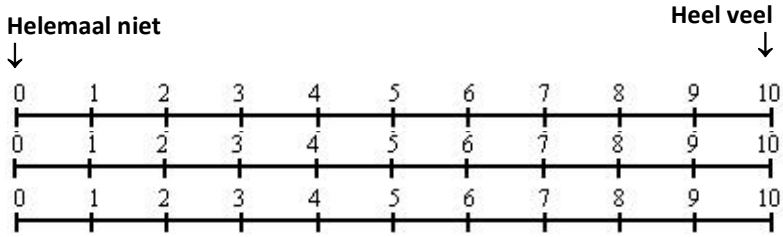
Dit is een persoonlijke vragenlijst, die door u moet worden ingevuld. Tracht tijdens het invullen van de vragenlijst de vragen niet te bespreken met een derde. Probeer tevens geen vragen te stellen over de inhoud van de vragen. Indien u niet zeker bent, antwoord dan op de vraag zoals u denkt wat ermee bedoeld wordt.

Fysieke functies

Voelt uw arm:

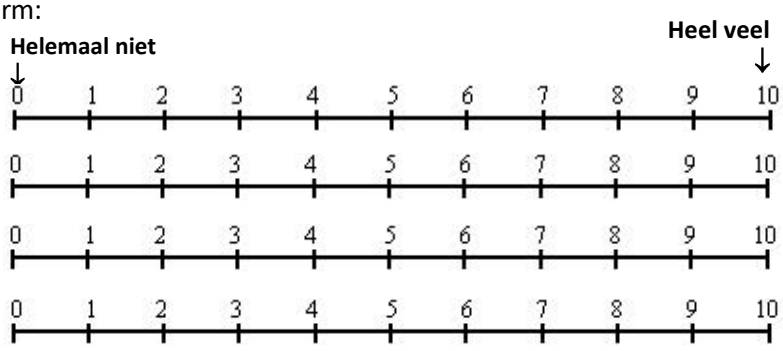


Hebt u ter hoogte van uw arm:



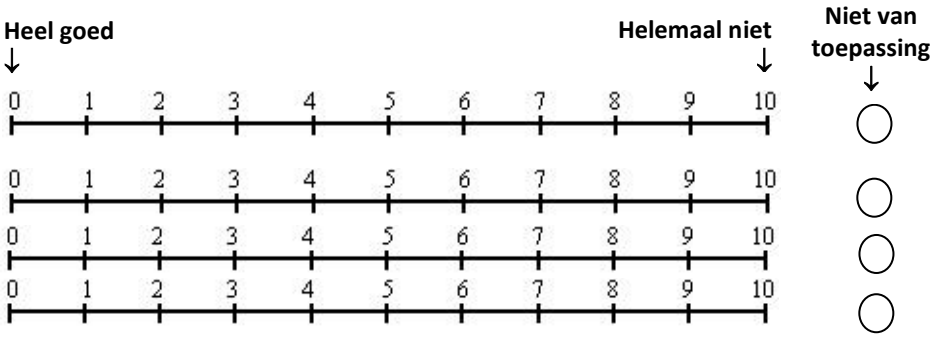
Mentale functies

Omwille van de problemen aan uw arm:



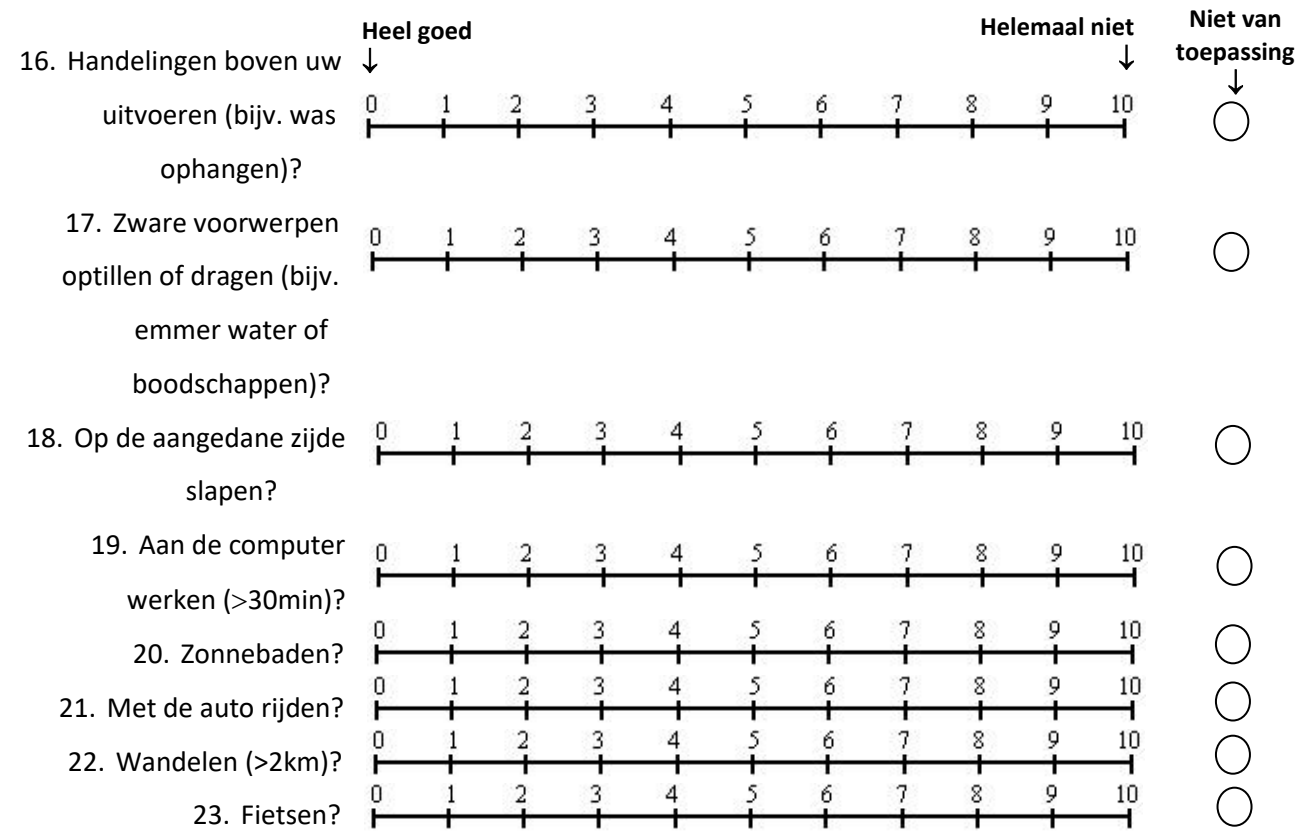
Huishouden

Kan u:



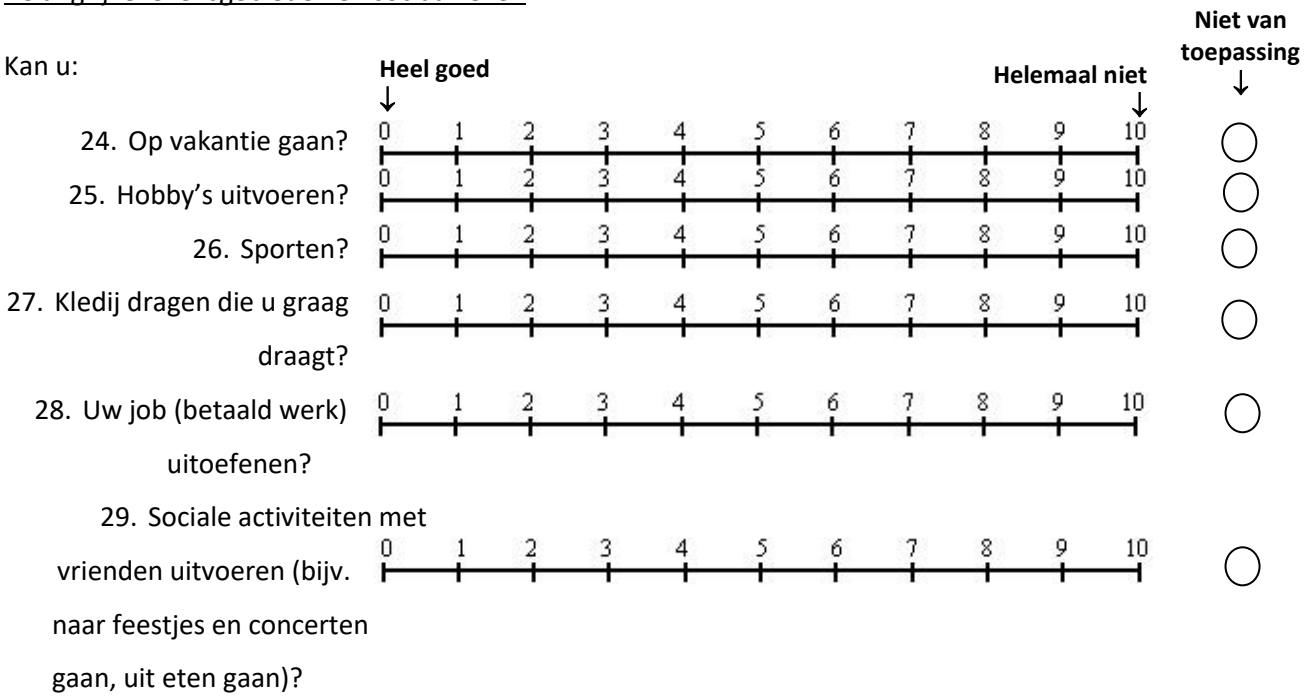
Mobiliteit

Kan u:



Belangrijke levensgebieden en sociaal leven

Kan u:



CHAPTER 6

Chapter 6

RESPONSIVENESS OF THE LYMPHEDEMA FUNCTIONING, DISABILITY AND HEALTH QUESTIONNAIRE FOR UPPER LIMB LYMPHEDEMA (LYMPH-ICF-UL) IN PATIENTS WITH BREAST CANCER-RELATED LYMPHEDEMA

Lymphat Res Biol. 2020 Jan 22. [Epub ahead of print]

Tessa De Vrieze
Nick Gebruers
Ines Nevelsteen
Wiebren A.A. Tjalma
Sarah Thomis
An De Groef
Lore Dams
Nele Devoogdt

Abstract

Background: The Lymph-ICF-UL is a health-related quality of life questionnaire for patients with breast cancer-related lymphedema (BCRL). Previous testing of this questionnaire showed very good clinimetric properties, however, responsiveness has not yet been established. The aim of this study was to determine its internal and external responsiveness.

Methods and Results: Ninety-five patients treated with decongestive lymphatic therapy in a longitudinal trial were recruited. Patients completed the Lymph-ICF-UL twice within a time interval of 7 weeks ('intensive group' receiving intensive treatment; n= 73) or 3 months ('stable group' receiving maintenance treatment; n= 22), and once the Global Perceived Effect questionnaire (GPE) at the second time point. The significance of change in scores and standardized response mean (SRM) were determined for the total and domain scores. Correlations between Lymph-ICF-UL and GPE were ascertained. Additionally, the Minimal Clinical Important Difference (MCID) was determined.

The Lymph-ICF-UL total score changed significantly in the intensive group ($p<0.001$) and non-significantly for the ones in the stable group ($p= 0.25$). The SRM represented moderate responsiveness (0.65). Patients who reported a clinical improvement (= responders) after intensive treatment showed a significant decrease in total score ($p<0.001$), this was also the case for non-responders ($p<0.001$). Lymph-ICF-UL total and domain scores showed non-significant weak correlations with the GPE ($p>0.05$). There was a significant difference in mean total score changes between responders and non-responders ($p<0.001$). MCID for the total score was 9%.

Conclusion: The Lymph-ICF-UL is responsive to change after decongestive lymphatic therapy. No correlations were found between Lymph-ICF-UL change scores and GPE. Future studies should be conducted in a clinical setting, with more variability between participants and their treatment responses.

Introduction

Lymphedema is a troublesome morbidity affecting about 17% of the women treated for breast cancer.[1] The edema can be measured objectively with different valid and reliable assessment methods (e.g. water displacement, circumference measurements, etc.).[2] However, an objective assessment of the volume lacks the power to encounter the real burden of lymphedema. Besides swelling, patients can suffer from problems in physical, social and mental functioning.[3,4] Additionally, breast cancer-related lymphedema (BCRL) lowers the quality of life.[5,6] Therefore, the Lymphedema Functioning, Disability and Health questionnaire for the upper limb (Lymph-ICF-UL) was developed to assess these impairments.[7] This questionnaire aims to quantify impairments in function, activity limitations and participation restrictions which are related to upper limb lymphedema. In contrast to other lymphedema-related questionnaires, it is based on the terminology of the International Classification of Functioning, Disability and Health (ICF) of the World Health Organization (WHO).[8]

The quality and usefulness of a questionnaire is determined by its psychometric properties, including validity, reliability and responsiveness. The reliability and validity of the Lymph-ICF-UL has already been examined in patients with BCRL and showed very good (reliability) to good (validity) psychometric parameters.[7,9] However, responsiveness of the Lymph-ICF-UL has yet to be ascertained.

Therefore, the aim of this study was to examine the internal and external responsiveness of the Lymph-ICF-UL in patients with BCRL.

Materials and Methods

Study design

Participants of the EFforT-BCRL trial[10] were recruited in the University Hospitals of Leuven, Antwerp University Hospital, Ghent University Hospital and General Hospital Groeninge in Kortrijk, Belgium. Approval for this study was obtained by the Ethical Committee of the University Hospitals of Leuven (main Ethical Committee), as well as of the Ethical Committees of all other participating centers (CME reference S58689, EudraCT Number 2015-004822-33). The present study was reported following the COSMIN guidelines.[11]

Participants

Female patients with BCRL of the arm and/or hand, who were about to start the intensive phase of decongestive lymphatic therapy through participation in the EFforT-BCRL trial *(= intensive group)*, or participants who were at least 3 months in the trial's maintenance phase of this study *(= stable group)*, were recruited. Criteria for in- and exclusion are presented in Table 1. Note that no formal power analysis has been performed, but that the sample size was completely determined by the response rate of the ongoing EFforT-BCRL trial[10].

Table 1. Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**
Female	Known local recurrence or metastasis
Diagnosis of breast cancer	Cognitive limitations
Surgery, chemotherapy, radiation therapy completed for at least 3 months	No breast cancer-related lymphedema/ other type of edema
Unilateral arm and/ or hand lymphedema (>5% difference at the time of inclusion in the EFforT-BCRL trial, adjusted for limb dominance)	
Starting an intensive decongestive treatment including multilayer bandaging, as part of the EFforT-BCRL trial *(intensive group)* OR being in the maintenance phase of the EFforT-BCRL trial for at least 3 months *(stable group)*	
Native Dutch speaking or being able to read, write and understand the Dutch language	

Study procedure

The current study was conducted between March 2016 and October 2018. All patients provided written informed consent prior to treatment. Descriptive data (participant's age, body mass index, type of breast surgery, side of surgery, hand dominance, type of adjuvant treatment (radiotherapy, chemotherapy, hormone therapy or targeted therapy), duration and stage of lymphedema) were collected by interviewing the participants and by consulting their medical record.

Figure 1 illustrates the study procedure. Patients were asked to complete the Lymph-ICF-UL questionnaire prior to the start of the intensive treatment phase *(intensive group)* or at the beginning of month 3 of their maintenance phase *(stable group)*. Additionally, the volume of each of the participants' arms was determined by circumference measurements using a perimeter after which the total arm volume was calculated using the truncated cone formula.[12 ,13]

The intensive treatment lasted for 3 weeks and consisted of all components of the decongestive lymphatic therapy, as recommended in the consensus document of the International Society of Lymphedema (ISL): manual lymph drainage, skin care, exercises and multilayer bandaging. When the volume of the arm was decreased optimally and pitting was absent, a compression stocking and glove

were measured. When patients received the compression garment, the 6-months lasting maintenance phase started, consisting of: manual lymph drainage, skin care, exercises and wearing the compression garment.[10 ,14]

The second time point for data collection was performed 4 weeks after wearing the stocking *(intensive group)* in order patients could get used to the feeling of wearing a stocking and/or gauntlet, or at the end of month 6 of their maintenance phase *(stable group).* Again, this second evaluation consisted of completing the Lymph-ICF-UL questionnaire, this time together with the Global Perceived Effect questionnaire (GPE) (Figure 1).

All treatments and assessments were provided at the department of Physical Medicine and Rehabilitation of the University Hospitals of Leuven, at the Multidisciplinary Breast Clinic of the Antwerp University Hospital, at the departments of Plastic Surgery and Radiotherapy of the Ghent University Hospital and at the Centre for Oncology at the General Hospital Groeninge in Kortrijk. Measurements were performed by one of three physical therapists, specialized in edema therapy (SVDB, LV, TDV) who were blinded for the treatment allocation of patients. Treatments were performed by one of four physical therapists, specialized in edema therapy (LB, RVH, LV, TDV).

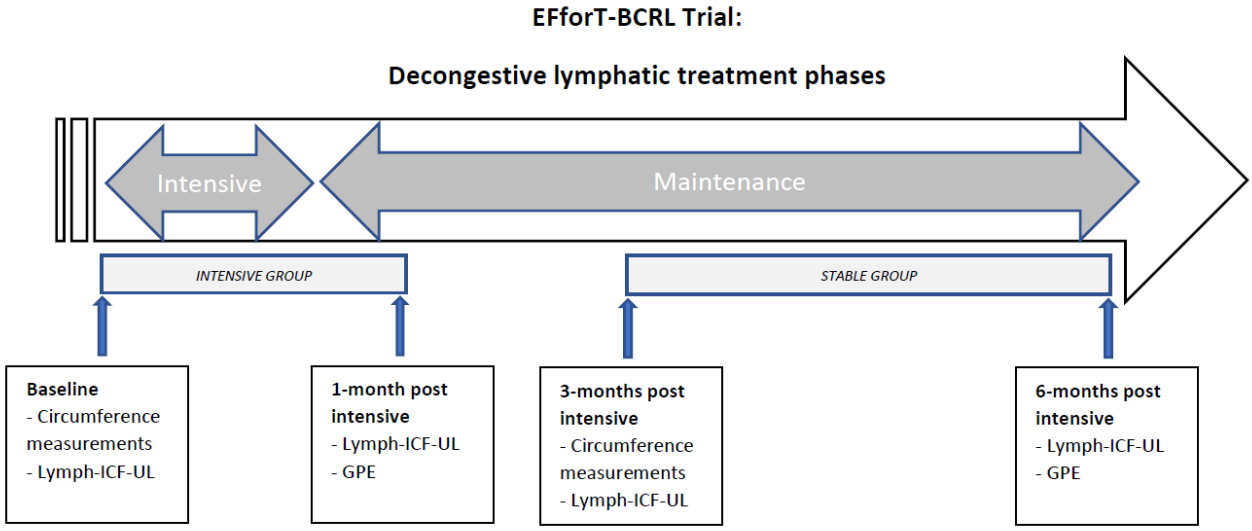


Figure 1. *Illustration of the study procedure*

Outcome variables

Following questionnaires and measurements were used.

Lymphedema Functioning, Disability and Health Questionnaire for Upper Limb Lymphedema (Lymph-ICF-UL)[7,9]

The Lymph-ICF-UL is a self-reported, comprehensive evaluation tool assessing impairments in functioning, activity limitations and participation restrictions in patients with BCRL during a two-week recall period. It consists of 29 questions, covering 5 domains: physical function, mental function, household activities, mobility activities and life and social activities. Each of the questions has to be scored on an 11-point Likert scale with a score between 0 and 10. The total score on the Lymph-ICF-UL and the scores on the 5 domains range between 0 and 100. The higher the score, the more problems patients experience. Reliability and content validity have shown to be very good; construct validity is good.[7,9]

Global Perceived Effect questionnaire (GPE)[15]

The reference criterion used in this study to investigate external responsiveness was the GPE scale. The GPE is a patient reported outcome measure stating the amount of improvement as perceived by the patient. The following question was asked to the patients of the intensive group: "To what extent did you recover from your lymphedema-related symptoms and complaints since the beginning of the treatment?". Alternatively, to the patients of the stable group following question was asked: "To what extent have your lymphedema-related symptoms and complaints (what you feel, can perform,..etc) changed compared to the previous evaluation moment within the EFforT-BCRL study? This means: we want to know the degree of change in your complaints, only between ……*(date previous assessment)* and ……*(today)* (<u>not</u> in comparison with the period before your participation in the study).".

It measures the perception of the patient with use of an ordinal scale. A 7-point Likert scale ranging from (1) very much better, (2) much better, (3) a little better, (4) unchanged, (5) a little worse, (6) much worse to (7) very much worse was used, as recommended by Ostelo.[16] Literature shows that scores 1 and 2 can be considered as a clinically relevant improvement[17], whereas a score of 3 (a little better) should be considered as unchanged as this reflects a minimum degree of improvement which could be experienced in patients just by being treated with attention for the current health related problems.[16,18] Consequently, patients scoring the GPE with 1 or 2 (very much better to much better) are further referred to as 'responders' whereas patients scoring the GPE with scores 3, 4, 5, 6 or 7 (a little better to very much worse) are further referred to as 'non-responders'[16,19-22] The GPE proved to have an excellent reproducibility.[23]

Investigation of responsiveness

There is no consensus on how responsiveness of measures should be quantified and it is further complicated by the multiple definitions that are used.[24] In general, literature suggests that there are two major facets of responsiveness: internal and external responsiveness. Internal responsiveness characterizes the ability of a measure to show changes within a particular period of time.[24] The observed changes in the measures are attributed to clinically relevant changes in health.[24] Consequently, the internal responsiveness of a measure will depend upon the particular treatment that is provided to patients as well as the specific outcomes that are described to determine treatment efficacy.[24]

Additionally, external responsiveness reflects the extent to which changes in a measure over a particular period of time relate to corresponding changes in an external reference measure of a person's health status.[24] In this type of responsiveness, the measure itself is not of primary interest, but the relationship between change in the measure and change in the external standard.[24] In contrast to internal responsiveness, the external responsiveness of a measure will solely depend on the choice of the external reference measure and not on the investigated treatment.[24]

To investigate the internal and external responsiveness of the Lymph-ICF-UL, we were interested in following topics for which we had formulated subsequent hypotheses:

Internal responsiveness

1. Whether or not the Lymph-ICF-UL could demonstrate a statistically significant change in scores before and after the intensive treatment phase;
   Hypothesis 1: In the intensive group, there would be a statistically significant change in mean total scores of the Lymph-ICF-UL between the two evaluation moments ($p<0.05$).
2. Whether or not the Lymph-ICF-UL could demonstrate a statistically significant change in scores before and after the 3 months of maintenance treatments;
   Hypothesis 2: In the stable group, there would be no statistically significant difference in mean total scores of the Lymph-ICF-UL between the two evaluation moments ($p>0.05$).
3. Whether or not the Lymph-ICF-UL is able to show a relatively small level of variability in change scores in relation to the average change in scores between the two evaluation moments, by means of the standardized response mean (SRM) as an effect size;
   Hypothesis 3: The calculated SRM values reflecting the variability of the change scores of the Lymph-ICF-UL would represent moderate (≥0.50) to large (≥0.80) responsiveness for the Lymph-ICF-UL total score.[24]

External responsiveness

4. Whether or not the Lymph-ICF-UL could demonstrate a statistically significant change in scores before and after intensive therapy in the responders on the one hand and the non-responders on the other hand. Additionally: Whether or not the Lymph-ICF-UL could demonstrate a statistically significant difference in mean change score between responders and non-responders after intensive treatments;

   Hypothesis 4: The change in mean Lymph-ICF-UL total score before and after intensive treatment would be statistically significant different between responders and non-responders ($p<0.05$).
5. Whether or not the Lymph-ICF-UL would show a correlation between the change in scores (before and after intensive/maintenance treatments) and the GPE;

   Hypothesis 5: There would be at least a moderate correlation (≥0.3) between the change in mean Lymph-ICF-UL scores (of both the intensive as well as the stable group together) and the score on the GPE.
6. The minimal clinical important difference (MCID) of the Lymph-ICF-UL;

   Hypothesis 6: the MCID for responders on the total score of the Lymph-ICF-UL would be less than 10 (10%).

Statistical analyses and interpretation

Data analyses were performed using the Statistical Package for Social Sciences 25 for Windows (SPSS Inc., Chicago, IL, USA). Normality of the variables was tested using the One-Sample Kolmogorov-Smirnov test and descriptive statistics were calculated. The 0.05 level of significance was applied.

Data are presented as number and percentage for categorical variables and mean with standard deviation (SD) (normal distribution) or median with interquartile range (IQR) (non-normal distribution) for continuous variables, unless otherwise stated.

Considering the investigation of internal responsiveness, the following statistical tests were performed:

1. Wilcoxon-signed-rank tests were used to determine whether the Lymph-ICF-UL total and domain scores were significantly different before and after the intensive treatment phase.
2. Also to determine whether the Lymph-ICF-UL total and domain scores were significantly different between the two evaluation moments during the maintenance phase, the Wilcoxon-signed-rank tests were performed.

3. The SRM as effect size was calculated for the intensive group using following formula[24]: $\frac{difference\ in\ Lymph-ICF-UL\ mean\ scores}{\text{standard deviation of the difference in mean scores}}$. SRM values of 0.20, 0.50 and 0.80 or higher have been proposed to represent small, moderate and large responsiveness, respectively.[24-27]

Considering the investigation of external responsiveness, the following statistical tests were performed:

4. Wilcoxon-signed-rank tests were used to determine whether the Lymph-ICF-UL total and domain scores were significantly different before and after the intensive phase of treatment in the responders and non-responders group separately. Comparability of the group responders and non-responders was tested with Mann-Whitney-U for numeric data and with Chi Square for categorical data. Additionally, to investigate significant differences in the mean change in scores between responders and non-responders before and after intensive therapy, a two-way ANOVA for repeated measures statistic was applied.
5. Spearman's rho correlation analysis was performed on the entire group (both the intensive and stable group) to determine the correlation between the change in Lymph-ICF-UL scores and the reported GPE. According to Cohen, the correlations required values of 0.3 or higher to be regarded as a good anchor.[28 ,29]
6. The MCID represents the smallest change in score that the participant perceives as a meaningful improvement.[30] If a participant's score is above the MCID, it is considered clinically relevant. To define the MCID, the mean change scores on the Lymph-ICF-UL of the participants that reported an important clinical important improvement (responders scoring the GPE with 2, i.e. 'much better') were used.[30] Consequently, to investigate the MCID, descriptive statistics were used to describe the mean (±SD) of the total and domain scores corresponding to the responders of the entire group (both the intensive and stable group).

Results

In this study, 95 participants were recruited. Of these, 73 participants were enrolled in the intensive group and 22 participants in the stable group. The mean age of the participants was 62 (10) years and mean body mass index was 29 (6). In the *intensive group* (n=73), the mean absolute difference in lymphedema volume of the arm was 541 (481) mL. In the *stable group* (n=22), the mean absolute difference in lymphedema volume of the arm was 384 (282) mL. The characteristics of the participants are presented in Table 2.

Table 2. Characteristics of the participants (n=95)

Variable	Outcome
Age (y)	62 (10)
Body mass index (kg/m^2)*	28.7 (5.6)
Lymphedema volume arm (absolute difference) (mL)	540 (388)
Hand circumference (absolute difference) (cm)*	3.0 (12.1)
Duration of lymphedema (mo)	53.0 (42.5)
BCRL stages	N (%)
I	*12 (12.6%)*
IIa	*56 (59.0%)*
IIb	*27 (28.4%)*
Breast surgery	
Mastectomy	*44 (46.3%)*
Breast-conserving surgery	*51 (53.7%)*
Axillary clearance	
Sentinel lymph node biopsy alone	*3 (3.2%)*
Axillary lymph node dissection	*92 (96.8%)*
Surgery at the dominant side	41 (43.2%)
Radiotherapy	92 (96.8%)
Chemotherapy	81 (85.3%)
Hormone therapy	77 (81.1%)
Targeted therapy (Herceptin)	21 (22.1%)

Abbreviations: y= years, kg= kilogram, m^2= square meters, mL= milliliter, mo= months, BCRL stages as described by the International Society of Lymphology; descriptives are depicted as mean (standard deviation).

Internal responsiveness

1. Change in Lymph-ICF-UL scores after treatment: intensive group

The mean pre- and post-intensive treatment scores of the Lymph-ICF-UL are shown in Table 3.

A statistically significant difference ($p<0.05$) was present in the intensive group between the pre- and post-intensive treatment total scores of the Lymph-ICF-UL as well as in all domain scores, except for the mobility activities domain ($p=0.06$).

2. Change in Lymph-ICF-UL scores after treatment: stable group

The mean pre- and post-maintenance treatment scores of the Lymph-ICF-UL are presented in Table 3. There was no statistically significant difference in total nor domain scores between the two assessments (p>0.05).

Table 3. Mean pre- and post-treatment scores of the Lymph-ICF-UL in both the intensive and stable group

Score	***Intensive group (n=73)***			***Stable group (n=22)***		
	Mean score PRE	Mean score POST	P-value	Mean score PRE	Mean score POST	P-value
Lymph-ICF-UL total score	38	28	<0.001**	27	31	0.25
Physical function score	44	25	<0.001**	26	30	0.32
Mental function score	31	20	<0.001**	19	24	0.33
Household activities score	41	33	<0.001**	30	30	1.00
Mobility activities score	37	32	0.06	32	39	0.08
Life and social activities score	35	29	0.03*	26	29	0.43

* corresponds with p-value <0.05, ** corresponds with p-value <0.01

3. Effect size: standardized response mean (SRM)

SRM values are presented in Table 4. The effect size of the total score represented moderate responsiveness (0.65). Highest SRM value was shown in the physical functions domain (0.99), representing good responsiveness. Lowest value was for the mobility activities domain, showing small responsiveness (0.21).

Table 4. Standardized response means (SRMs) calculated for the intensive group (n=73)

Lymph-ICF-UL	**Total**	**Physical functions**	**Mental functions**	**Household activities**	**Mobility activities**	**Life and social activities**
SRM	0.65	0.99	0.54	0.36	0.21	0.27

External responsiveness

4. Difference in pre- and post-intensive treatment scores for responders and non-responders

Table 5 presents an overview of the mean total and domain scores of the Lymph-ICF-UL before and after intensive treatment, as well as the mean change scores before and after intensive treatment for/between responders and non-responders. Responders (n=39) showed a statistically significant decrease in the Lymph-ICF-UL total score, physical function, mental function and mobility activities domain scores over time ($p<0.05$). Other domains were not significantly different before and after intensive treatment. Non-responders (n=34) showed a statistically significant decrease in the Lymph-ICF-UL total score, physical function, mental function and household activities domain scores ($p<0.05$). Pre-intensive treatment scores on the Lymph-ICF-UL were significantly different in both groups for the total score ($p=0.02$) as for the domains physical function ($p=0.01$), household activities ($p=0.08$) and life and social activities ($p=0.04$) domain scores of the Lymph-ICF-UL, in which the non-responders showed relatively more problems in functioning at baseline compared to the responders.

The mean change in scores before and after intensive treatment was significantly different between responders and non-responders for the total score ($p<0.001$), physical function ($p<0.001$), mental function ($p<0.001$), household activities ($p=0.01$), life and social activities ($p=0.03$) scores (Table 5).

Table 5. Separate mean pre- and post-treatment scores of Lymph-ICF-UL for responders and non-responders and the mean change in scores before and after intensive treatment between responders and non-responders

Intensive group									
Score	***Responders (n=39)***				***Non-responders (n=34)***				
	Mean score PRE (SD)	Mean score POST (SD)	*Difference (SD)*	P-value (within group)	Mean score PRE (SD)	Mean score POST (SD)	*Difference (SD)*	P-value (within group)	**P-value mean change between groups (ANOVA)**
Lymph-ICF-UL total score	32 (21)	21 (18)	*11 (16)*	<0.001**	44 (21)	36 (20)	*8 (14)*	<0.001**	**<0.001****
Physical function score	36 (20)	19 (17)	*17 (15)*	<0.001**	52 (25)	32 (22)	*20 (22)*	<0.001**	**<0.001****
Mental function score	26 (26)	15 (21)	*11 (19)*	0.001**	37 (32)	26 (25)	*11 (22)*	0.006**	**<0.001****
Household activities score	32 (27)	25 (23)	*7 (22)*	0.092	51 (28)	41 (28)	*10 (25)*	0.033*	**0.010****
Mobility activities score	32 (25)	24 (22)	*8 (26)*	0.028*	42 (24)	41 (24)	*1 (19)*	0.662	**0.093**
Life and social activities score	30 (27)	23 (21)	*7 (25)*	0.142	41 (26)	36 (26)	*5 (20)*	0.155	**0.030***

* corresponds with p-value <0.05, ** corresponds with p-value <0.01

5. Correlations between change scores and GPE

Correlations between changes in scores of the Lymph-ICF-UL (Δ-Lymph-ICF-UL) and the GPE scores are shown in Table 6. The scores of all the 95 participants were used. The Lymph-ICF-UL total score as well as the physical functions, mental functions, household activities and mobility activities domains showed non-significant weak positive correlations with the GPE.

Table 6. Spearman's rho correlations between change scores of Lymph-ICF and GPE scores (n=95)

	Domain	r_s	P-values
ΔLymph-ICF-UL	Total	.134	0.20
	Physical functions	.092	0.37
	Mental functions	.164	0.11
	Household activities	.112	0.28
	Mobility activities	.195	0.06
	Life and social activities	-.041	0.70
ΔLymph-ICF-UL = Mean change of scores of Lymph Functioning, Disability and Health questionnaire for Upper Limb Lymphedema, GPE= Global Perceived Effect			

6. Minimal Clinical Important Difference in Lymph-ICF-UL score

An overview of the MCIDs (SDs) associated with the Lymph-ICF-UL total and domain scores is provided in Table 7. The MCID estimate for the Lymph-ICF-UL total score was 9%, physical function 14%, mental function 7%, household activities 8%, mobility activities 6% and life and social activities 5%.

Table 7. Overview of the MCIDs (SDs) of the Lymph-ICF-UL scores according to the different scores on the GPE (n=95)

GPE	Lymph-ICF-UL domains					
	Total score	Physical functions	Mental function	Household activities	Mobility activities	Life and social activities
1=very much better	n=8 7 (6)	n=8 7 (13)	n=8 17 (18)	n=8 10 (16)	n=8 4 (11)	n=8 2 (9)
2=much better	n=37 **9** (18)	n=37 **14** (17)	n=37 **7** (21)	n=37 **8** (23)	n=37 **6** (28)	n=36 **5** (28)
3=a little better	n=31 9 (12)	n=31 20 (22)	n=31 14 (18)	n=31 6 (19)	n=31 2 (15)	n=31 3 (18)
4=the same	n=15 3 (17)	n=15 9 (24)	n=15 3 (18)	n=15 6 (32)	n=15 3 (23)	n=15 7 (20)
5= worse	n=4 17 (19)	n=4 20 (24)	n=4 18 (27)	n=4 8 (14)	n=4 19 (23)	n=4 12 (20)
Scores are depicted as mean (SD) *Abbreviations: Lymph-ICF-UL=Lymph Functioning, Disability and Health questionnaire for Upper Limb Lymphedema, GPE=Global Perceived Effect*						

Discussion

The aim of this study was to investigate the responsiveness of the Lymph-ICF-UL questionnaire.

As an answer to the methodological inconsistencies in literature regarding responsiveness, the COSMIN (COnsenus-based Standards for the selection of health Measurement INstruments) panel reached consensus on the definitions of measurement properties for health-related patient reported outcomes in an international Delphi study.[31] A checklist was developed to determine the methodological quality of studies on measurement properties.[32 ,33] The definition of responsiveness according to the COSMIN initiative is "the ability of a health-related patient reported outcome instrument to detect change over time in the construct to be measured".[31] In the current study, this was translated to the ability of the Lymph-ICF-UL to detect a clinically important change in amount of problems in functioning of patients with BCRL, as part of the external responsiveness of the questionnaire.

Results showed that, in the present study, only one out of the six hypotheses regarding the internal and external responsiveness was rejected. All three hypotheses regarding internal responsiveness (hypotheses 1-3), were accepted. There was a statistically significant difference in the intensive group between the pre- and post-intensive treatment total scores of the Lymph-ICF-UL as well as in all domain scores, except for the mobility activities domain (*hypothesis 1*). A reason for this might be that restrictions in mobility activities can be influenced by other factors as well, besides BCRL. Furthermore, there was no statistically significant difference in total nor domain scores between the two evaluation moments in the maintenance phase (*hypothesis 2*). Finally, the effect size of the total score represented moderate responsiveness (SRM 0.65), suggesting that the questionnaire is able to indicate a clinically meaningful change in total score[24] (*hypothesis 3*).

Regarding external responsiveness, 2 out of 3 hypotheses (hypotheses 4 and 6) were accepted. We expected that there would be a statistically significant difference between the change in total score of the responders and non-responders, which was confirmed by this study (*hypothesis 4*). Only for the mobility activities domain, this change score was non-significantly different.

Responders showed a statistically significant decrease in total score as well as in most of the domain scores of the Lymph-ICF-UL after the intensive treatments. However, surprisingly this was also the case for non-responders. Although, our analyses revealed that the non-responders showed a relatively higher level of problems in functioning at baseline compared to the responders. Consequently, in patients with a higher amount of problems in functioning at baseline, a relatively greater improvement in functioning after treatment can be expected.

Furthermore, when correlating the change scores of the Lymph-ICF-UL with the reported GPE, we expected at least moderate correlations (*hypothesis 5*). However, results revealed mainly non-significant weak positive correlations. Therefore, this hypothesis could not be accepted. A major

drawback for this correlation analysis was the relatively under-representation of patients who reported to be deteriorated after their treatment. Although, while designing this study, we decided to include also a subgroup of patients that were currently at the end of the maintenance phase (the *stable group*) as an attempt to encounter this and to include also patients that might have been deteriorated. Nevertheless, results indicated that, of the entire group, only 4% reported to be worse, 16% reported to be unchanged, 33% reported to have a little bit improved, and 47% reported to have improved (much or very much better). Consequently, the majority of participants reported to be improved or unchanged, resulting in a rather homogeneous study sample. Other authors have discussed the use GPE as an anchor as it might be very dependent on the current status of a patient and therefore it might be more a measure of the patient's present status than of the change in health status over time.[23 ,34]

Lastly, we hypothesized that the MCID for responders on the total score of the Lymph-ICF-UL would be less than 10 (10%) (*hypothesis 6*), which was an arbitrary chosen cut-off point based on empirical experience. As the total score of the Lymph-ICF-UL represented a MCID of 9%, our last hypothesis could be accepted as well. This result entails that if this total score decreases with at least 9 on 100, an overall clinical improvement will be experienced. This MCID exceeds the earlier reported Standard Error of Measurement (SEM) of 5, thereby eliminating the possibility that the change in score could be due to any measurement error.[9] Consequently, the reported limitation that the MCID does not take measurement precision into account[35], is partially compensated this way.

Limitations and strengths

A strength of the current study is that, in the investigation on responsiveness, the recommendations of the COSMIN panel were taken into account. An integrated system making use of multiple methods to define internal and external, anchor-based responsiveness was applied.

Some limitations should be considered. First, as this investigation was conducted on a cohort of participants of the EFforT-BCRL trial, patient characteristics, protocol and treatment outcomes were rather homogeneous as the majority of the participants indicated to have improved or not to have changed, which might have induced a selection bias. There was a lack of participants who reported a deterioration (only 4 out of 95 participants), which was a shortcoming for the purpose of this investigation.

Second, the moment of completion of the questionnaires was for each patient at the end of a 1-hour clinical assessment. This could have entailed an influence on patient's motivation and concentration level to spend some extra time and effort on reading every question with full attention. For this reason, we might suspect that some interpretation errors of the scoring system could have occurred (for instance when the anchors "very well" and "not at all" were converted in some questions but was not

noticed by the participant). However, this was explained in advance. Last, as completion of the questionnaires occurred at the end of fixed evaluation moments in accordance with the EFforT-trials' protocol, the time in-between the two evaluations were different for the intensive group (7 weeks) as for the stable group (3 months). However, we believe this has not affected our study results.

Implications for clinical practice

The Lymph-ICF-UL questionnaire already proved to be appropriate and useful in clinical practice by showing very good reliability (ICCs between 0.79 and 0.95 and Cronbach alpha coefficients higher than .80), very good face and content validity and good construct validity (79% of accepted hypotheses regarding convergent/divergent validity).[9] The current study reveals that the Lymph-ICF-UL is sensitive to detect changes over time. A change of 9% in total score indicates a clinically relevant change in the amount of problems in functioning, of a patient with BCRL. A change of 14% in the physical function domain score designates a clinically relevant change in the amount of problems regarding physical functions. Furthermore, a change of 7% in the mental function domain score indicates a clinically relevant change in the amount of problems regarding mental functions. In the household activities domain, a change of 8% describes a clinically relevant change in the amount of problems regarding household activities. Likewise, in the mobility activities domain, a change of 6% indicates a clinically relevant change in the amount of problems regarding mobility activities. Lastly, in the life and social activities domain, a change of 5% indicates a clinically relevant change in the amount of participation problems.

Recommendations for future research

When correlating the Lymph-ICF-UL scores with the GPE, the questionnaire showed a reduced ability to discriminate between the amount of changes in Lymph-ICF-UL scores and the actual clinical improvement as reported by participants. As in our opinion this is mainly due to the strict protocol in which this investigation occurred, a future investigation should be continued in a clinical setting, resulting in more variability between the study participants and consequently, in their treatment responses. Furthermore, attention should be paid on the moment of completion of the questionnaires in order patients to be fully concentrated.

Conclusion

The current study revealed that the lymph-ICF-UL questionnaire is responsive to change after decongestive lymphatic therapy, in patients with BCRL. Based on the GPE as anchor-based method, a MCID of 9% indicates a clinically relevant change. No correlation between Lymph-ICF-UL change scores and GPE was found. Future studies should be conducted in a clinical setting, enabling a greater amount of variability between the study participants and treatment responses.

Acknowledgements

The authors are very grateful to the hospitals collaborating in this study. The authors also extend grateful thanks to the study participants, to Lien Billiet, Roxane Van Hemelrijck and Lore Vos for performing the treatments and to Shanah Van den Bosch and Lore Vos for measuring and handing over the questionnaires to the study participants. All authors critically revised the manuscript for important intellectual content and approved the final manuscript.

References

1. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 2013;**14**(6):500-15 doi: 10.1016/S1470-2045(13)70076-7[published Online First: Epub Date]|.
2. Hidding JT, Viehoff PB, Beurskens CH, van Laarhoven HW, Nijhuis-van der Sanden MW, van der Wees PJ. Measurement Properties of Instruments for Measuring of Lymphedema: Systematic Review. Physical therapy 2016;**96**(12):1965-81 doi: 10.2522/ptj.20150412[published Online First: Epub Date]|.
3. Fu MR, Ridner SH, Hu SH, Stewart BR, Cormier JN, Armer JM. Psychosocial impact of lymphedema: a systematic review of literature from 2004 to 2011. Psycho-oncology 2013;**22**(7):1466-84 doi: 10.1002/pon.3201[published Online First: Epub Date]|.
4. Bojinovic-Rodic D, Popovic-Petrovic S, Tomic S, Markez S, Zivanic D. Upper extremity function and quality of life in patients with breast cancer related lymphedema. Vojnosanitetski pregled 2016;**73**(9):825-30 doi: 10.2298/vsp150208075b[published Online First: Epub Date]|.
5. Ridner SH, Dietrich MS. Development and validation of the Lymphedema Symptom and Intensity Survey-Arm. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 2015;**23**(10):3103-12 doi: 10.1007/s00520-015-2684-y[published Online First: Epub Date]|.
6. Lopez Penha TR, van Bodegraven J, Winkens B, Heuts EM, Voogd AC, von Meyenfeldt MF. The quality of life in long-term breast cancer survivors with breast cancer related lymphedema. Acta chirurgica Belgica 2014;**114**(4):239-44
7. Devoogdt N, Van Kampen M, Geraerts I, Coremans T, Christiaens MR. Lymphedema Functioning, Disability and Health questionnaire (Lymph-ICF): reliability and validity. Physical therapy. United States, 2011:944-57.
8. International Classification of Functioning, Disability and Health: ICF; 2001; Geneva, Switzerland.
9. De Vrieze T, Vos L, Gebruers N, et al. Revision of the Lymphedema Functioning, Disability and Health Questionnaire for Upper Limb Lymphedema (Lymph-ICF-UL): Reliability and Validity. Lymphatic research and biology 2019 doi: 10.1089/lrb.2018.0025[published Online First: Epub Date]|.
10. De Vrieze T, Vos L, Gebruers N, et al. Protocol of a randomised controlled trial regarding the effectiveness of fluoroscopy-guided manual lymph drainage for the treatment of breast cancer-related lymphedema (EFforT-BCRL trial). European journal of obstetrics, gynecology, and reproductive biology 2017 doi: 10.1016/j.ejogrb.2017.12.023[published Online First: Epub Date]|.
11. Mokkink LB, Terwee CB, Knol DL, et al. The COSMIN checklist for evaluating the methodological quality of studies on measurement properties: a clarification of its content. BMC Med Res Methodol 2010;**10**:22 doi: 10.1186/1471-2288-10-22[published Online First: Epub Date]|.
12. Taylor R, Jayasinghe UW, Koelmeyer L, Ung O, Boyages J. Reliability and validity of arm volume measurements for assessment of lymphedema. Physical therapy 2006;**86**(2):205-14
13. Devoogdt N, Lemkens H, Geraerts I, et al. A new device to measure upper limb circumferences: validity and reliability. International angiology : a journal of the International Union of Angiology 2010;**29**(5):401-7
14. The Diagnosis and Treatment of Peripheral Lymphedema: 2016 Consensus Document of the International Society of Lymphology. Lymphology 2016;**49**(4):170-84

15. Hudak PL, Wright JG. The characteristics of patient satisfaction measures. Spine 2000;**25**(24):3167-77
16. Ostelo RW, de Vet HC. Clinically important outcomes in low back pain. Best Pract Res Clin Rheumatol 2005;**19**(4):593-607 doi: 10.1016/j.berh.2005.03.003[published Online First: Epub Date]|.
17. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. Pain 2000;**88**(3):287-94
18. Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. European journal of pain (London, England) 2004;**8**(4):283-91 doi: 10.1016/j.ejpain.2003.09.004[published Online First: Epub Date]|.
19. Ostelo RW, de Vet HC, Knol DL, van den Brandt PA. 24-item Roland-Morris Disability Questionnaire was preferred out of six functional status questionnaires for post-lumbar disc surgery. Journal of clinical epidemiology 2004;**57**(3):268-76 doi: 10.1016/j.jclinepi.2003.09.005[published Online First: Epub Date]|.
20. Hagg O, Fritzell P, Nordwall A. The clinical importance of changes in outcome scores after treatment for chronic low back pain. Eur Spine J 2003;**12**(1):12-20 doi: 10.1007/s00586-002-0464-0[published Online First: Epub Date]|.
21. Davidson M, Keating JL. A comparison of five low back disability questionnaires: reliability and responsiveness. Physical therapy 2002;**82**(1):8-24
22. Stewart MJ, Maher CG, Refshauge KM, Herbert RD, Bogduk N, Nicholas M. Randomized controlled trial of exercise for chronic whiplash-associated disorders. Pain 2007;**128**(1-2):59-68 doi: 10.1016/j.pain.2006.08.030[published Online First: Epub Date]|.
23. Kamper SJ, Ostelo RW, Knol DL, Maher CG, de Vet HC, Hancock MJ. Global Perceived Effect scales provided reliable assessments of health transition in people with musculoskeletal disorders, but ratings are strongly influenced by current status. Journal of clinical epidemiology 2010;**63**(7):760-66.e1 doi: 10.1016/j.jclinepi.2009.09.009[published Online First: Epub Date]|.
24. Husted JA, Cook RJ, Farewell VT, Gladman DD. Methods for assessing responsiveness: a critical review and recommendations. Journal of clinical epidemiology 2000;**53**(5):459-68
25. Liang MH, Fossel AH, Larson MG. Comparisons of five health status instruments for orthopedic evaluation. Medical care 1990;**28**(7):632-42
26. Beaton DE, Hogg-Johnson S, Bombardier C. Evaluating changes in health status: reliability and responsiveness of five generic health status measures in workers with musculoskeletal disorders. Journal of clinical epidemiology 1997;**50**(1):79-93
27. Garratt AM, Ruta DA, Abdalla MI, Russell IT. SF 36 health survey questionnaire: II. Responsiveness to changes in health status in four common clinical conditions. Quality in health care : QHC 1994;**3**(4):186-92
28. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. Journal of clinical epidemiology 2008;**61**(2):102-9 doi: 10.1016/j.jclinepi.2007.03.012[published Online First: Epub Date]|.
29. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Second ed, 1988.
30. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials 1989;**10**(4):407-15

31. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. Journal of clinical epidemiology 2010;**63**(7):737-45 doi: 10.1016/j.jclinepi.2010.02.006[published Online First: Epub Date]|.
32. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2010;**19**(4):539-49 doi: 10.1007/s11136-010-9606-8[published Online First: Epub Date]|.
33. Terwee CB, Mokkink LB, Knol DL, Ostelo RW, Bouter LM, de Vet HC. Rating the methodological quality in systematic reviews of studies on measurement properties: a scoring system for the COSMIN checklist. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2012;**21**(4):651-7 doi: 10.1007/s11136-011-9960-1[published Online First: Epub Date]|.
34. Viehoff PB, van Genderen FR, Wittink H. Upper limb lymphedema 27 (ULL27): Dutch translation and validation of an illness-specific health-related quality of life questionnaire for patients with upper limb lymphedema. Lymphology 2008;**41**(3):131-8
35. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. Journal of clinical epidemiology 2003;**56**(5):395-407

CHAPTER 7

Chapter 7

CROSS-CULTURAL VALIDATION OF THE FRENCH VERSION OF THE LYMPHEDEMA FUNCTIONING, DISABILITY AND HEALTH QUESTIONNAIRE FOR UPPER LIMB LYMPHEDEMA (LYMPH-ICF-UL)

Disabil Rehabil. 2020 Jan 28; 1-8. [Epub ahead of print]

Tessa De Vrieze
Jacqueline Frippiat
Thierry Deltombe
Nick Gebruers
Ines Nevelsteen
Wiebren A.A. Tjalma
Sarah Thomis
Liesbeth Vandermeeren
Jean-Paul Belgrado
An De Groef
Nele Devoogdt

Abstract

Purpose. Upper limb lymphedema is a vexing morbidity that can occur after the treatment for breast cancer. The Lymphedema Functioning, Disability and Health questionnaire for Upper limb Lymphedema (Lymph-ICF-UL) is a valid and reliable tool assessing problems in functioning in patients with breast cancer-related lymphedema. Until now, a French language version was lacking. The aim of this study was to perform a cross-cultural validation of the French version of the Lymph-ICF-UL questionnaire.

Methods. A forward-backward translation process between the original language (Dutch) and the target language (French) was performed. Psychometric properties of this final French version were examined in 50 participants.

Results. Intraclass correlation coefficients for test-retest reliability ranged from .66 to .95. Cronbach's alpha coefficients for internal consistency were higher than .77. Face and content validity were very good because the scoring system was clear for all participants (100%), questions were understandable (100%), and all complaints due to BCRL were mentioned by 78% of the participants. Construct validity was moderate. Convergent validity was established since 3 out of 5 expected domains of the Lymph-ICF-UL showed a moderate correlation with expected domains of the 36-Item Short-Form Health Survey. There was satisfactory divergent validity as 6 out of 9 hypotheses assessing divergent validity were accepted.

Conclusion. The French version of the Lymph-ICF-UL is a reliable and valid questionnaire and ready for use in clinical as well as in scientific practice.

Introduction

The Lymphedema Functioning, Disability and Health Questionnaire for Upper Limb Lymphedema (Lymph-ICF-UL) is a lymphedema-specific questionnaire which aims to quantify impairments in function, activity limitations and participation restrictions that are related to upper limb lymphedema. In contrast to other lymphedema-related questionnaires it is based on terminology of the International Classification of Functioning, Disability and Health (ICF)[1] as introduced by the World Health Organization (WHO).[2] In this questionnaire, a total score is determined as well as a score for each of the five domains of the Lymph-ICF-UL: (1) physical function, (2) mental function, (3) household activities, (4) mobility activities, and (5) life and social activities. For more details about the establishment of the original version of the Dutch Lymph-ICF-UL questionnaire, we refer to Devoogdt et al.[3] According to a recently independent published systematic review, the Lymph-ICF and the Lymphedema Quality of Life Inventory (LyQLI) are the most complete and accurate questionnaires available to asses self-reported problems in functioning and quality of life in patients with breast cancer-related lymphedema (BCRL).[4] This original questionnaire[3] has been translated into Turkish[5], which revealed very good reliability and good construct validity. However, recently the questionnaire has been revised by altering the scoring procedure through implementation of a numeric rating scale instead of the existing visual analogue scale. This revised version showed to be a valid and highly reliable questionnaire in its original, Dutch language, using an easier and simplified scoring procedure.[6] Lately, this revised version has been translated into Danish and subsequently tested on reliability.[7] Although French is the fifth most spoken language in the world representing more than 300 million people[8], a French language version of this questionnaire is still lacking. Therefore, the aim of current study was to perform a cross-cultural validation of the Lymph-ICF-UL French version in patients with BCRL of the arm and/or hand.

Materials and Methods

This cross-sectional study is reported following the COSMIN guidelines.[9] Approval for this trial was obtained by the Ethical Committee of the University Hospitals of Leuven (main Ethical Committee) as well as by the Ethical Committees of all other participating centers (CME reference S58689, EudraCT 2015-004822-33). All participants provided written informed consent.

Study design

This study was conducted in two phases: 1) translation of the original Dutch version of the Lymph-ICF-UL questionnaire into French, and 2) investigation of the psychometric properties of this translated version.

Participants

Subjects were partly recruited from a cohort of participants of the EFforT-BCRL trial in three university hospitals in Belgium: at the Lymphology Clinic of Brussels in Saint-Pierre University Hospital (n=6), at the department of Physical Medicine and Rehabilitation of the University Hospitals of Leuven (n=3) and at the Multidisciplinary Breast Clinic of the Antwerp University Hospital (n=1).[10] Furthermore, additional eligible participants were recruited at the Lymphology Clinic of Brussels in Saint-Pierre University Hospital (n=9) and at the Centre de Référence du Lymphoedème at CHU UCL Namur site Godinne (n=31).

Participants were recruited between December 2016 and January 2019 during a consultation or treatment for their lymphedema at one of the hospitals. Eligibility criteria were: 1) patients with unilateral BCRL of the arm and/or hand, 2) chronic lymphedema stage I to IIb (duration of ≥3 months), 3) at least 5% difference between both arms and/or between both hands, adjusted for limb dominance, 4) native French-speaking. Patients were excluded when: 1) they had edema of the upper limb from another cause than breast cancer treatment, or 2) when they were not able to read and fully understand the French language.

Procedure

Translation process

A sequential approach was applied for the translation process from the Dutch version of the Lymph-ICF-UL questionnaire [3,6] into a French language version.[11,12] This was established in different stages following a standard forward–backward translation process according to international guidelines, which has become standard in health status assessments.[11,13-15]

First, two translators independently translated the original Dutch version of the Lymph-ICF-UL into the target language, French. These translators were bilingual speakers of the target language as well as of the original language. Each of the two translators performed a forward translation. After a consensus meeting, a reconciled translation was developed. To do so, the cultural and lifestyle context of the target language was taken into account, making use of appropriate idioms if required.[13] Subsequently, a native Dutch speaker who was fluent in the target language then translated the reconciled form back

into Dutch. Comparison of this backward translation with the original Dutch version of the Lymph-ICF-UL was performed, and modifications were provided to the translation as needed.
Before investigating the clinimetric properties of the French version of the Lymph-ICF-UL, the questionnaire was proofread by a small number of French-speaking patients (n=3) to check for any gross ambiguities or difficulties.

Reliability and validity of the Lymph-ICF-UL French version

In assessing the clinimetric properties of the French version of the questionnaire, the same methodology was applied as was done in the original questionnaires[3,6], as this facilitates comparison between the results.[16]

To analyze test-retest reliability, participants completed the final French version of the Lymph-ICF-UL twice individually; once at the hospital and once at home with an interval of 24 to 48h after the first test. This second questionnaire was returned by mail.
To analyze construct validity, participants also completed the 36-item Short-Form Health Survey (SF-36) once at the hospital. This generic questionnaire, originally developed and validated in English, has been translated into French.[17]
To analyze content and face validity of the French Lymph-ICF-U, each patient completed an additional questionnaire, developed by one of the authors (ND).[3] This questionnaire consisted of following questions: (1)Was the scoring system clear?(yes/no), (2)Was each question of the Lymph-ICF-UL understandable?(yes/no), and (3)Were all complaints related to your lymphedema mentioned in the questionnaire?(yes/no). If a participant answered “no” to any of these questions, an explanation was asked. This additional questionnaire was also translated into French following the forward-backward translation by three separate translators as recommended.

Collection of medical history of participants and excessive arm volume

Descriptive data was collected by interviewing the participants and by consulting their medical records. Circumference measurements of the edematous and non-edematous arm were performed using a perimeter, after which the volume of the both arms was calculated using a truncated cone formula.[18] Excessive arm volume was calculated by reducing the volume of the edematous limb with the volume of the non-edematous limb, corrected for limb dominance.[19] Measurements were performed by one of four physical therapists specialized in edema therapy (JF, KD, TDV, LV).

Data analysis

Statistical analyses were performed using SPSS for Windows version 24.0. The .05 level of significance was applied. Descriptive analyses were applied to describe the participants.

Reliability

Intraclass correlation coefficients (ICCs) were used to determine test-retest reliability of the total score of the French Lymph-ICF-UL, of the scores on the five domains, and of the score on each question separately.[20] Cronbach alpha coefficients were used to determine internal consistency of the entire questionnaire as well as of each domain[21]. To calculate significant changes in the mean between the two test occasions, Wilcoxon-signed-rank tests were performed. To interpret the magnitude of the within-subjects variation of the two scores, the standard error of measurement (SEM) and corresponding 95% Confidence Interval (CI) was calculated.[20] To evaluate clinically important changes, we calculated the smallest real difference (SRD) and corresponding 95% Confidence Interval (CI).[20] To obtain a reference range for the mean difference of the scores between the two test occasions, we calculated 95% SRD as the mean difference between the two test occasions ±SRD.

Validity

Face validity was examined by asking participants whether the scoring system was obvious and whether the questions in the French Lymph-ICF-UL were understandable. Content validity was examined by analyzing and discussing the answers given by participants to the question about the comprehensiveness of the questionnaire.

To investigate construct (convergent, divergent) validity of the French Lymph-ICF-UL, the relationship between scores on domains of the Lymph-ICF-UL and scores on domains of the SF-36 was examined. Spearman rank correlation coefficients were used since data was non-normally distributed. To determine convergent and divergent validity and based on the content of the questions of each domain of Lymph-ICF-UL and SF-36, we used the same hypotheses as formulated in the Dutch validation study.[6] In case of agreement between the questions in a specific domain of the Lymph-ICF-UL and SF-36, these domains were included in a hypothesis for assessing convergent validity. In case of disagreement, they were included in a hypothesis for assessing divergent validity. Table 1 shows an overview of the hypotheses for determining convergent and divergent validity and the rationale for the hypotheses. Correlation coefficients were interpreted as follows:<.4 was weak, .4 to .74 was moderate, .75 to .9 was strong and >.9 was very strong[22]. If a moderate to very good correlation was found between two corresponding domains, the hypothesis for convergent validity was accepted. In

case of a weak correlation between two disagreeing domains, the particular hypothesis for divergent validity was accepted. Construct validity was defined as very good if more than 90% of all 14 hypotheses were confirmed, as good if between 75% and 90% of the hypotheses were confirmed, and as moderate if between 40% and 74% of the hypotheses were confirmed.

For full details regarding psychometric methodology and statistical analyses, we refer to the validation study of the Dutch Lymph-ICF-UL.[6]

Table 1. Fourteen hypotheses and rationale for hypotheses for assessing construct validity

Hypothesis	Rationale
Convergent validity	Considering all correlation coefficients for various domains of the Lymph-ICF-UL and the SF-36, at least moderate correlation coefficients would occur between:
1: Lymph-ICF-UL physical function and SF-36 bodily pain	Lymph-ICF-UL physical function: Does your arm: feel heavy, feel stiff, feel swollen, feel like it has lost strength, tingle, hurt or have a tensed skin? SF-36 bodily pain: How much bodily pain have you had during the past 4 wk? During the past 4 wk, how much did pain interfere with your normal work?
2: Lymph-ICF-UL mental function and SF-36 mental health	Lymph-ICF-UL mental function: Due to your arm problems, do you feel sad, do you feel discouraged, do you have a lack of self-confidence, do you feel stressed? SF-36 mental health: How much time during the last 2 wk have you been a very nervous person, have you felt so down in the dumps that nothing would cheer you up, have you felt calm and peaceful, have you felt downhearted and low, and have you been a happy person?
3: Lymph-ICF-UL household activities and SF-36 physical functioning	Lymph-ICF-UL general tasks/household activities: How well are you able to: clean (scrub, vacuum, mop), cook, iron, work in the garden? SF-36 physical functioning: Does your health limit you in the following activities: vigorous activities, such as lifting heavy objects; moderate activities, such as moving a table, pushing a vacuum, lifting or carrying groceries, climbing several flights of stairs, climbing 1 flight of stairs, bending, kneeling, stooping, walking more than a mile, walking half a mile, walking 100 yd (91.44 m), and bathing or dressing yourself?
4: Lymph-ICF-UL mobility activities and SF-36 physical functioning	Lymph-ICF-UL mobility activities: How well are you able to: perform tasks with the arm elevated (e.g. hang out the laundry), lift or carry heavy objects (e.g. a filled bucket or shopping bags), sleep on the affected side, perform computer work (>30 min), sunbathe, drive a car, walk (>2 km), ride a bike?

	SF-36 physical functioning: Does your health limit you in the following activities: vigorous activities, such as lifting heavy objects; moderate activities, such as moving a table, pushing a vacuum, lifting or carrying groceries, climbing several flights of stairs, climbing 1 flight of stairs, bending, kneeling, stooping, walking more than a mile, walking half a mile, walking 100 yd, and bathing or dressing yourself?
5: Lymph-ICF-UL life and social activities and SF-36 social functioning	Lymph-ICF-UL life domains/social life: How well are you able to: go on vacation, perform your hobbies, practice sports, wear your clothes of choice, do your job, do social activities (e.g. going to parties, concerts, restaurant)? SF-36 social functioning: During the past 2 wk, to what extent have your physical health or emotional problems interfered with your normal social activities with family, neighbors, or groups? During the past 2 wk, how much of the time have your physical health or emotional problems interfered with your social activities?
Hypothesis	**Rationale**
Divergent validity	Considering all correlation coefficients for various domains of the Lymph-ICF-UL and the SF-36, weak correlation coefficients would occur between:
6-7: Lymph-ICF-UL physical function and SF-36 role–emotional and mental health	Lymph-ICF-UL physical function: Does your arm: feel heavy, feel stiff, feel swollen, feel like it has lost strength, tingle, hurt or have a tensed skin? SF-36 role–emotional: During the past 4 wk, how much time have you had problems with your work or other regular daily activities as a result of emotional problems? SF-36 mental health: How much time during the last 2 wk have you been a very nervous person, have you felt so down in the dumps that nothing would cheer you up, have you felt calm and peaceful, have you felt downhearted and low, and have you been a happy person?
8-9: Lymph-ICF-UL mental function and SF-36 physical functioning and role-physical	Lymph-ICF-UL mental function: Due to your arm problems, do you feel sad, do you feel discouraged, do you have a lack of self-confidence, do you feel stressed? SF-36 physical functioning: Does your health limit you in the following activities: vigorous activities, such as lifting heavy objects; moderate activities, such as moving a table, pushing a vacuum, lifting or carrying groceries, climbing several flights of stairs, climbing 1 flight of stairs, bending, kneeling, stooping, walking more than a mile, walking half a mile, walking 100 yd, and bathing or dressing yourself?

	SF-36 role-physical: During the past 4 wk, have you had any of the following problems with your work or other regular daily activities as a result of your physical health; cut down the amount of time you spent on work or other activities, accomplished less than you would like, were limited in the kind of work or other activities, had difficulty performing the work or other activities (for example, it took extra effort)?
10-11: Lymph-ICF-UL household activities and SF-36 role-emotional and mental health	Lymph-ICF-UL general tasks/household activities: How well are you able to: clean (scrub, vacuum, mop), cook, iron, work in the garden? SF-36 role–emotional: During the past 4 wk, how much time have you had problems with your work or other regular daily activities as a result of emotional problems? SF-36 mental health: How much time during the last 2 wk have you been a very nervous person, have you felt so down in the dumps that nothing would cheer you up, have you felt calm and peaceful, have you felt downhearted and low, and have you been a happy person?
12-13: Lymph-ICF-UL mobility activities and SF-36 role-emotional and mental health	Lymph-ICF-UL mobility activities: How well are you able to: perform tasks with the arm elevated (e.g. hang out the laundry), lift or carry heavy objects (e.g. a filled bucket or shopping bags), sleep on the affected side, perform computer work (>30 min), sunbathe, drive a car, walk (>2 km), ride a bike? SF-36 role–emotional: During the past 4 wk, how much time have you had problems with your work or other regular daily activities as a result of emotional problems? SF-36 mental health: How much time during the last 2 wk have you been a very nervous person, have you felt so down in the dumps that nothing would cheer you up, have you felt calm and peaceful, have you felt downhearted and low, and have you been a happy person?
14: Lymph-ICF-UL life and social activities and SF-36 physical functioning	Lymph-ICF-UL life domains/social life: How well are you able to: go on vacation, perform your hobbies, practice sports, wear your clothes of choice, do your job, do social activities (e.g. going to parties, concerts, restaurant)? SF-36 physical functioning: Does your health limit you in the following activities: vigorous activities, such as lifting heavy objects; moderate activities, such as moving a table, pushing a vacuum, lifting or carrying groceries, climbing several flights of stairs, climbing 1 flight of stairs, bending, kneeling, stooping, walking more than a mile, walking half a mile, walking 100 yd, and bathing or dressing yourself?

Results

Translation

Before examining the psychometric properties, the questionnaire was tested on three bilingual patients to clarify any ambiguities or difficulties. One patient proposed a few grammatical reconsiderations, which resulted in the final version after unanimous agreement of all translators.

Validation French version Lymph-ICF-UL

Fifty native French-speaking subjects participated in this study. Mean age was 64 (±11) years and mean body mass index was 27 (±5) kg/m^2. All participants had undergone breast surgery with axillary dissection. For more details about the participant characteristics, see Table 2.

Table 2. Characteristics of the included subjects (n=50)

Variable	Outcome
Age (y)	64 (11)
Body Mass Index (kg/m^2)	27 (5)
Lymphedema volume arm (absolute difference) (mL)	734 (374)
Duration lymphedema (mo)*	78 (30, 177 [147])
BCRL stages	
I n(%)	0 (0%)
IIa n(%)	19 (38%)
IIb n(%)	31 (62%)
Breast surgery	
Mastectomy n(%)	28 (56%)
Breast-conserving surgery n(%)	22 (44%)
Surgery on the dominant side n(%)	23 (46%)
Radiotherapy[b] n(%)	48 (96%)
Chemotherapy[b] n(%)	39 (78%)
Endocrine therapy[b] n(%)	30 (60%)
Targeted therapy (Herceptin)[b] n(%)	9 (18%)

*Abbreviations: y= years, kg= kilogram, m^2= square meters, mL= milliliter, mo= months, BCRL stages as described by the International Society of Lymphology; descriptives are presented as "mean (standard deviation)" except when indicated with * where "median (25th, 75th percentile [interquartile range])" is shown.*

Reliability

Table 3 provides an overview of the ICCs, Cronbach's alpha coefficients, SEMs and SRDs for the total score on the French version Lymph-ICF-UL and for the scores on each domain separately. The table also includes data from previous research conducted on the Dutch[6], Turkish[5] and Danish[7] versions of the questionnaire in order to facilitate comparison of results. Test-retest reliability of the total score of the French Lymph-ICF-UL, physical function and mental function scores were very strong (ICC>.90). The household and mobility activities score were found strong (ICC>.75), while the life and social activities score was moderate (ICC=.66). Test-retest reliability of the scores on 22 questions (90%) were strong to very strong (data not shown). Reliability of scores on the remaining 7 questions (about feelings of heaviness and swelling, the abilities to lift or carry heavy objects, to go on vacation, to perform hobbies, to practice sports and to do social activities) were moderate (ICC=.62-.73).

Internal consistency of the French Lymph-ICF-UL also ranged between strong and very strong. The Cronbach's alpha coefficient for all questions was .95 and ranged for the different domains between .77 and .89.

There were no statistical differences between the means of the total score, as well as of the separate domain scores, between the two test occasions which were calculated with Wilcoxon-signed-rank analyses.

The total score on the French Lymph-ICF-UL had a variation from one test occasion to the other of 5.5. A decrease or an increase in the total score of 11 or more is considered (with 95% certainty) as a statistically significant change. Furthermore, a decrease or increase in the total score of 15.4 or more is considered as a clinically relevant change.

Table 3. Reliability on the total score of the Lymph-ICF-UL and the scores on the 5 domains in relation to the results of the original Dutch questionnaire[6], the Turkish version[5] and the Danish version[7]

Score		*Mean*			*Test-retest*			*Internal consistency*	*Variability*		*Clinically important changes*	
		N	*X1*	*X2*	*P - value*	*ICC*	*95% CI*	$_{\alpha}$	*SEM*	*95% CI*	*SRD*	*95% CI*
Lymph-ICF-UL total score	French version	50	36.26	36.36	0.57	0.91	0.85 to 0.95	0.95	5.54	-10.95 to 10.75	15.35	-15.45 to 15.25
	Dutch version	56	27.50	27.45	0.98	0.95	0.91 to 0.97	0.98	4.89	-9.57 to 9.61	13.56	-13.54 to 13.58
	Turkish version	30	46.53	46.90		0.90		0.99				
	Danish version	50	33.00	34.00	0.26	0.95	0.92 to 0.97	0.98	4.51		12.50	
Physical function score	French version	50	37.31	36.14	0.43	0.90	0.83 to 0.94	0.78	6.28	-11.14 to 13.48	17.40	-16.23 to 18.57
	Dutch version	56	24.30	22.76	0.26	0.90	0.83 to 0.94	0.92	6.76	-11.70 to 14.78	18.73	-17.19 to 20.27
	Turkish version	30	43.33	43.53		0.99		0.99				
	Danish version	50	44.00	42.00	0.20	0.93	0.88 to 0.96	0.97	6.40		17.60	
Mental function score	French version	50	34.60	34.15	0.90	0.95	0.91 to 0.97	0.89	6.34	-11.97 to 12.87	17.56	-17.11 to 18.01
	Dutch version	56	18.97	19.69	0.67	0.93	0.88 to 0.96	0.98	6.31	-13.09 to 11.65	17.49	-18.21 to 16.77
	Turkish version	30	41.90	42.73		0.99		0.99				

	Danish version	50	23.00	22.00	0.59	0.88	0.79 to 0.93	0.93	9.12		25.30	
Household activities score	French version	50	38.91	40.94	0.35	0.88	0.80 to 0.93	0.79	9.19	-20.04 to 15.98	25.47	-27.50 to 23.44
	Dutch version	56	33.02	34.60	0.71	0.79	0.66 to 0.87	0.89	12.31	-25.71 to 22.55	34.13	-35.71 to 32.55
	Turkish version	30	54.13	52.00		0.80		0.89				
	Danish version	50	30.00	34.00	0.04	0.84	0.73 to 0.90	0.92	10.21		28.30	
Mobility activities score	French version	50	38.12	39.19	0.13	0.88	0.80 to 0.93	0.88	8.49	-17.70 to 15.56	23.52	-24.59 to 22.45
	Dutch version	56	30.68	31.03	0.84	0.91	0.85 to 0.95	0.89	7.63	-15.31 to 14.61	21.16	-21.51 to 20.81
	Turkish version	30	57.16	53.46		0.85		0.92				
	Danish version	50	31.00	33.00	0.09	0.94	0.89 to 0.96	0.97	5.69		15.80	
Life and social activities score	French version	50	33.30	32.18	0.50	0.66	0.46 to 0.79	0.77	12.60	-23.57 to 25.81	34.91	-33.79 to 36.03
	Dutch version	56	28.30	30.65	0.22	0.88	0.80 to 0.93	0.92	8.28	-18.58 to 13.88	22.96	-25.31 to 20.61
	Turkish version	30	47.13	48.53		0.98	0.99					
	Danish version	50	30.00	33.00	0.11	0.92	0.87 to 0.96	0.96	7.09		19.60	

Abbreviations: X1= mean at time point 1, X2= mean at time point 2, CI= confidence interval, $_{\alpha}$ = Cronbach's alpha coefficient, p-value is resulting out of Wilcoxon signed rank analyses

Validity

The questionnaire regarding face and content validity of the French Lymph-ICF-UL was completed by all participants. Each one of them (100%) found the scoring system clear and all participants (100%) mentioned that the questions were understandable. Thirty-nine participants (78%) mentioned that all complaints were addressed in the questionnaire. Complaints not covered in the questionnaire are shown in Table 4. After discussion with a team of experts (ND, TDV), only three missing complaints mentioned by two participants were considered to be relevant of which two were incorporated in the questionnaire afterwards.

Table 4. Overview of mentioned missing complaints (n=12) and reasons why they are not included in the French version Lymph-ICF-UL

Lymph-ICF-UL domain	Complaint	Argumentation (see Table appendix)
Physical function domain	Tingling fingers	A (Question 5)
	Feeling of imbalance in body posture	A (Question 1)
	Number of episodes of erysipelas	*
Mental function domain	Feeling annoyed/embarrassed about wearing compression garment	A (Questions 9, 10 or 11)
	Feeling of incomprehension of others	A (Question 9)
Mobility activities domain	Ability to carry the groceries	A (Question 17)
	Ability to carry a purse	A (Question 17)
	Ability to write readable (n=2), to sew, to fold	A (Question 19)
	Ability to ride a bike	A (Question 23)
Life and social activities domain	Ability to function in the heat	A (Question 24, or Question 20 'Mobility activities domain')
	Ability to play with grandchildren	A (Question 25)

One participant found that a question about the age of the patient should be included in the questionnaire	B
One participant found that the question regarding the ability to go on vacation should make a distinction between different kind of holidays* (e.g. city trip versus long distance destinations) , and that the question regarding the ability to sport should include a distinction between different kind of sports*	
Appendix A: Can be scored with corresponding questions of the questionnaire. The patient has to give the mean score on his/her problems in functioning during the past two weeks, as reported in the introduction of the questionnaire. B: Patient's age is an item that is collected separately from the lymph-ICF-UL in during the clinical evaluation.	

**After discussion, only three complaints mentioned by two participants were considered relevant. For two mentioned complaints, adjustments were made in the questionnaire (i.e. questions 24 and 26).*

Table 5 provides an overview of the Spearman rank correlation coefficients between the different domains of the Lymph-ICF-UL and the SF-36. The table also includes data from previous research conducted on the Dutch[6] and Turkish[5] versions of the questionnaire in order to facilitate comparison of the results. All participants completed both questionnaires. Concerning convergent validity, 3 out of 5 domains of the French Lymph-ICF-UL correlated at least moderate with the expected corresponding domains of the SF-36, and were accepted. Correlation coefficients of these 3 ranged from -.40 to -.70 (moderate correlations). Concerning divergent validity, 6 out of 9 domains of the French Lymph- ICF-UL showed a weak correlation with the expected corresponding domains of the SF-36. The correlation coefficients of these 6 ranged from -.14 to -.39 (no to weak correlation). Consequently, 9 out of 14 hypotheses for assessing construct validity were accepted, resulting in an overall moderate construct validity of the French Lymph-ICF-UL (64%).

Table 5. Correlation between the SF-36 and the French version Lymph-ICF-UL to determine convergent and divergent validity (Spearman rank correlation coefficient; n= 50) in relation to the results of the original Dutch questionnaire[6] and the Turkish version[5]

		Spearman Rank Correlation Coefficient ($r_{s\ (p\text{-}value)}$) for:				
SF-36 domain		**Lymph-ICF-UL domains**				
		Impairments in function		**Activity limitations and participation restrictions**		
		Physical function Correlation Coefficient (Sign.)	Mental function Correlation Coefficient (Sign.)	Household activities Correlation Coefficient (Sign.)	Mobility activities Correlation Coefficient (Sign.)	Life and social activities Correlation Coefficient (Sign.)
Physical functioning	French version	-0.275 (.053)	-0.476 (≤.001)	**-0.399 (.005)**	**-0.472 (.001)**	**-0.144 (.317)**
	Dutch version	-0.249	-0.311	-0.244	-0.415	-0.426
	Turkish version	-0.498	-0.075	0.026	-0.136	-0.088
Role-physical	French version	-0.190 (.186)	**-0.229 (0.109)**	-0.376 (.008)	-0.189 (.188)	-0.260 (.068)
	Dutch version	-0.266	-0.526**	-0.400	-0.428	-0.495
	Turkish version	-0.139	0.071	0.056	0.182	0.337
Bodily pain	French version	-0.321 (.023)	-0.399 (.004)	-0.308 (.033)	-0.335 (.017)	-0.232 (.104)

	Dutch version	-0.440**	-0.292	-0.454	-0.437	-0.586
	Turkish version	-0.266	-0.076	0.066	-0.223	-0.393
General health	French version	-0.240 (.093)	-0.387 (.006)	-0.413 (.004)	-0.270 (.058)	-0.263 (.065)
	Dutch version	-0.390**	-0.388**	-0.511**	-0.471**	-0.541**
	Turkish version	-0.185	-0.349	-0.357	-0.416*	-0.323
Vitality	French version	-0.249 (.082)	-0.432 (.002)	-0.322 (.026)	-0.246 (.086)	-0.230 (.108)
	Dutch version	-0.265*	-0.542**	-0.375**	-0.384**	-0.558**
	Turkish version	-0.150	-0.355	-0.184	-0.287	-0.203
Social functioning	French version	-0.175 (.223)	-0.368 (.008)	-0.158 (.285)	-0.145 (.315)	-0.156 (.278)
	Dutch version	-0.399**	-0.599**	-0.522**	-0.534**	-0.607**
	Turkish version	-0.463	-0.087	-0.030	-0.208	-0.262
Role-emotional	French version	-0.451 (.001)	-0.629 (≤.001)	-0.499 (≤.001)	**-0.350 (.013)**	-0.319 (.024)
	Dutch version	-0.191	-0.488**	-0.306*	-0.369**	-0.419**

	Turkish version	-0.274	0.056	0.077	0.071	-0.156
Mental health	French version	**-0.392 (.005)**	**-0.704 (≤.001)**	**-0.340 (.018)**	**-0.227 (.113)**	-0.153 (.289)
	Dutch version	-0.195	-0.661**	-0.234	**-0.341***	-0.431**
	Turkish version	-0.030	-0.215	-0.133	-0.171	-0.371

Values with bold frame= hypotheses for expected moderate correlations assessing convergent validity; Values with double frame= hypotheses for expected weak correlations assessing divergent validity; Bold values= accepted hypotheses regarding convergent validity (Correlation Coefficient ≥0.4) or regarding divergent validity (Correlation Coefficient <0.4).

Discussion

This study showed that the French version of the questionnaire is appropriate for use in clinical practice and research, showing very good (reliability) to satisfactory (validity) psychometric properties.

Reliability of the French Lymph-ICF-UL was very good. The ICCs of the total score on the Lymph-ICF-UL and the different domain scores varied between strong and very strong, showing over all comparable ICC values than those obtained in the Dutch, Turkish and Danish versions of the Lymph-ICF [5 ,7]. Only the life and social activities score was lower in the present study, representing moderate test-retest reliability (Table 3).

As compared to the Dutch, Turkish and Danish versions, internal consistency determined with Cronbach's alpha coefficients were very strong and similar for the total score but were slightly less for the physical function, the household activities and the life and social activities domains.[5-7]

Face and content validity of the French Lymph-ICF-UL were very good. All participants (100%) found the scoring system clear, which was similar to the results regarding the Dutch version with revised scoring system[6], as well as the Danish version[7]. Likewise, all questions were understandable for all participants. Only two participants (4%) reported missing one or two complaints in the French Lymph-ICF-UL which were considered relevant (three in total). The first one was the complaint 'number of episodes of erysipelas'. However, it is not part of the questionnaire as this item should be additionally queried by the therapist during the clinical assessment. Next, a participant suggested that the question regarding the ability to go on vacation *(question 24)* should make a distinction between different kind of holidays (e.g. city trip versus long distance destinations), and secondly, that the question regarding the ability to practice sports *(question 26)* should include a distinction between different kinds of sports. Therefore, our team of experts advised to add an extra line below questions 24 and 26 in the questionnaire on which the type(s) of vacation(s) and the type(s) of sport(s) being practiced, respectively, can be specified (see Supplementary File S1). Patients should complete the questionnaire by themselves and average their problems in functioning or participation over the past two weeks, and therapists or assessors should instruct patients who repeatedly fill in the Lymph-ICF-UL to score the same type(s) of vacation(s) and sport(s) each time.

Construct validity was tested in terms of convergent and divergent validity and gave acceptable results. Concerning convergent validity, 3 out 5 domains (60%) of the French Lymph-ICF-UL correlated at least moderately with the expected corresponding domains of the SF-36 (r between -.40 to -.70). In the Dutch validation study, 4 out of 5 hypotheses concerning convergent validity were accepted.[6] In current study, the physical function domain of the French Lymph-ICF-UL did not show a moderate or

strong correlation with the expected domain bodily pain of the SF-36 (r=-.32). In the Turkish study, this correlation between both domains was weak as well (r=.27)[5] (Table 5). A possible explanation might be retrieved in the fact that the physical function domain of the Lymph-ICF-UL comprises six questions regarding six different symptoms, in which pain is one out of six. On the other hand, the bodily pain domain of the SF-36 is a domain comprising only two questions exclusively based on pain.

Surprisingly, there was also a weak correlation between the life and social activities domain of the Lymph-ICF-UL and the social functioning domain of the SF-36 (r=.16) in the present study, despite its moderate correlation in the Dutch validation study (r=-.61).[6] In these domains, patients tended to score more negatively on the SF-36 (comprises two questions) compared to the Lymph-ICF-UL (comprises six questions). However, also in the Turkish study this correlation appeared to be weak (r=-.26).[5] (Table 5) Nevertheless, in the current study the hypothesis regarding convergent validity between the household activities domain of the Lymph-ICF-UL and the physical functioning domain of the SF-36 (r=-.40) could be accepted, although this was not the case in the Dutch validation study (r=-.24)[6], nor in the Turkish study (r=-.03).[5]

Concerning divergent validity, 6 out of 9 hypotheses (67%) were accepted in current study, whereas 7 out of 9 hypotheses (78%) were accepted in the Dutch validation study.[6]. Unexpectedly, the mental function domain of the Lymph-ICF-UL showed a moderate correlation with the physical functioning domain of the SF-36 (r=-.48), in contrast with the Dutch version where this correlation was weak (r=-.31). Similarly, a moderate correlation was present between the household activities domain of the French Lymph-ICF-UL and the role-emotional domain of the SF-36 (r=-.50), whereas this correlation was weak in the Dutch version (r=-.31), as we would expect. Nevertheless, in current study the hypotheses between the mental function domain of the Lymph-ICF-UL and the role-physical domain of the SF-36 (r=.-23) as well as between the life and social activities domain of the Lymph-ICF-UL and the physical functioning domain of the SF-36 (r=-.14) could be accepted, albeit this was not the case in the Dutch version (r=-.53 and -.43 respectively).[6] (Table 5).

Strengths and study limitations

Current study consisted of several strengths. First, the translation of the questionnaire comprised sequential stages in which a forward-backward translation process was incorporated, as recommended.[14] Secondly, different aspects of reliability and validity of the French Lymph-ICF-UL were investigated. Thirdly, the sample size of this study consisted of 50 participants. As stated by Shrout and Fleiss, researchers should try to obtain at least 30 heterogeneous subjects for reliability studies.[22] The sample of our study is heterogeneous since participants with BCRL stages IIa or IIb, with a broad range of duration in months and lymphedema volume were enrolled to accommodate this.

A first limitation of our study is that testing of face and content validity occurred with an author-developed questionnaire. However, we are unaware of an available valid questionnaire to investigate these psychometric properties. Second, the forward-backward translation was not performed by professional translators as recommended by the ISPOR Task Force[23], however, a meticulous translation was carried out by bilingual speakers with an extensive knowledge of both languages.
This questionnaire can be used for research but also in clinical practice. It provides patient information in the different domains of the ICF, which facilitates evaluating the impact of BCRL. This is an important step in promoting a patient goal-centered approach in BCRL management. Further research establishing its responsiveness is warranted.

Conclusion

In conclusion, the French version of the Lymph-ICF-UL is a reliable and valid questionnaire for assessing problems in functioning of patients with BCRL of the arm and/or hand, enabling a better understanding of the functional status and related experiences of a patient. Based on the outcomes of the Lymph-ICF-UL, treatment goals can be set. Thereafter, the questionnaire may be used to monitor long-term results of this treatment and self-care.

Acknowledgements

The authors are very grateful to the hospitals collaborating in this study. The authors also extend very grateful thanks to the study participants, and to Kevin Dusart and Lore Vos for measuring and handing over the questionnaires to the study participants. All authors critically revised the manuscript for important intellectual content and approved the final manuscript.

References

1. Kostanjsek N. Use of The International Classification of Functioning, Disability and Health (ICF) as a conceptual framework and common language for disability statistics and health information systems. BMC public health 2011;**11 Suppl 4**:S3 doi: 10.1186/1471-2458-11-s4-s3[published Online First: Epub Date]|.
2. International Classification of Functioning, Disability and Health: ICF; 2001; Geneva, Switzerland.
3. Devoogdt N, Van Kampen M, Geraerts I, Coremans T, Christiaens MR. Lymphedema Functioning, Disability and Health questionnaire (Lymph-ICF): reliability and validity. Physical therapy. United States, 2011:944-57.
4. Cornelissen AJM, Kool M, Keuter XHA, et al. Quality of Life Questionnaires in Breast Cancer-Related Lymphedema Patients: Review of the Literature. Lymphatic research and biology 2018 doi: 10.1089/lrb.2017.0046[published Online First: Epub Date]|.
5. Kostanoglu A, Hosbay Z, Tarakci E. Lymphedema functioning, disability and health questionnaire Turkish version: translation, cross-cultural adaptation and validation. Journal of physical therapy science 2016;**28**(6):1728-32 doi: 10.1589/jpts.28.1728[published Online First: Epub Date]|.
6. De Vrieze T, Vos L, Gebruers N, et al. Revision of the Lymphedema Functioning, Disability and Health Questionnaire for Upper Limb Lymphedema (Lymph-ICF-UL): Reliability and Validity. Lymphatic research and biology 2019 doi: 10.1089/lrb.2018.0025[published Online First: Epub Date]|.
7. Grarup KR, Devoogdt N, Strand LI. The Danish version of Lymphedema Functioning, Disability and Health Questionnaire (Lymph-ICF) for breast cancer survivors: Translation and cultural adaptation followed by validity and reliability testing. Physiotherapy theory and practice 2019;**35**(4):327-40 doi: 10.1080/09593985.2018.1443186[published Online First: Epub Date]|.
8. francophonie OIdl. Rapport de la Secrétaire générale de la Francophonie, 2016-2018.
9. Mokkink LB, Terwee CB, Knol DL, et al. The COSMIN checklist for evaluating the methodological quality of studies on measurement properties: a clarification of its content. BMC Med Res Methodol 2010;**10**:22 doi: 10.1186/1471-2288-10-22[published Online First: Epub Date]|.
10. De Vrieze T, Vos L, Gebruers N, et al. Protocol of a randomised controlled trial regarding the effectiveness of fluoroscopy-guided manual lymph drainage for the treatment of breast cancer-related lymphedema (EFforT-BCRL trial). European journal of obstetrics, gynecology, and reproductive biology 2017 doi: 10.1016/j.ejogrb.2017.12.023[published Online First: Epub Date]|.
11. Gandek B, Alacoque J, Uzun V, Andrew-Hobbs M, Davis K. Translating the Short-Form Headache Impact Test (HIT-6) in 27 countries: methodological and conceptual issues. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2003;**12**(8):975-9
12. Gandek B, Ware JE, Jr. Methods for validating and norming translations of health status questionnaires: the IQOLA Project approach. International Quality of Life Assessment. Journal of clinical epidemiology. England, 1998:953-9.
13. Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. Journal of clinical epidemiology 1993;**46**(12):1417-32

14. Bullinger M, Alonso J, Apolone G, et al. Translating health status questionnaires and evaluating their quality: the IQOLA Project approach. International Quality of Life Assessment. Journal of clinical epidemiology 1998;**51**(11):913-23
15. Aaronson N, Alonso J, Burnam A, et al. Assessing health status and quality-of-life instruments: attributes and review criteria. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2002;**11**(3):193-205
16. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine 2000;**25**(24):3186-91
17. Leplege A, Ecosse E, Verdier A, Perneger TV. The French SF-36 Health Survey: translation, cultural adaptation and preliminary psychometric evaluation. Journal of clinical epidemiology 1998;**51**(11):1013-23
18. Taylor R, Jayasinghe UW, Koelmeyer L, Ung O, Boyages J. Reliability and validity of arm volume measurements for assessment of lymphedema. Physical therapy 2006;**86**(2):205-14
19. Gebruers N, Truijen S, Engelborghs S, De Deyn PP. Volumetric evaluation of upper extremities in 250 healthy persons. Clinical physiology and functional imaging 2007;**27**(1):17-22 doi: 10.1111/j.1475-097X.2007.00708.x[published Online First: Epub Date]|.
20. Lexell JE, Downham DY. How to assess the reliability of measurements in rehabilitation. American journal of physical medicine & rehabilitation 2005;**84**(9):719-23
21. Bland JM, Altman DG. Statistics notes: Cronbach's alpha. Bmj 1997;**314**(7080):572
22. Fleiss JL. *Design and analysis of clinical experiments*: John Wiley & Sons, 2011.
23. Wild D, Grove A, Martin M, et al. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2005;**8**(2):94-104 doi: 10.1111/j.1524-4733.2005.04054.x[published Online First: Epub Date]|.

Supplementary File S1. The French version of the Lymphedema Functioning, Disability and Health Questionnaire for Upper Limb Lymphedema (Lymph-ICF-UL)[a]

OEDÈME LYMPHATIQUE DU MEMBRE SUPÉRIEUR, HANDICAP ET PROBLÈME DE PARTICIPATION:

QUESTIONNAIRE LYMPH-ICF-MS

Nom et prénom: Date:

Un œdème lymphatique du bras et/ou de la main peut avoir des effets sur le physique et le mental, ainsi que limiter vos activités quotidiennes et poser des problèmes dans la vie sociale.

Ce questionnaire comprend **29 questions** établies sur base d'informations fournies par des personnes souffrant de la même affection que vous.

À côté de chaque question, vous voyez les numéros de 0 à 10. S'il vous plaît indiquez le nombre de plaintes que vous avez à la suite de votre œdème et dans quelle mesure vous pouvez effectuer vos activités ou participer à la vie sociale. 0 correspond à "aucune plainte / douleur» ou «aucun effort» pour réaliser l'activité et 10 correspond à «incapable d'exécuter" ou "insupportable symptômes / douleur» ou. Cochez le cercle vide si ce n'est pas d'application.

Par exemple:

3. Avez-vous mal au bras? **Pas du tout** 0 1 2 3 4 5 6 7 8 9 10 **Énormément**

Si vous ne ressentez aucune douleur à votre bras, vous encerclez le chiffre 0.

4. Etes-vous capable de repasser? **Très bien** 0 1 2 3 4 5 6 7 8 9 10 **Pas du tout** ○ Pas d'application

Si vous repassez difficilement, vous encerclez le chiffre 9.

Si vous n'avez jamais repassé parce que vous avez une aide-ménagère ou que vous repassez avec l'autre bras, mettez une croix dans le cercle ⊗ "pas applicable" à côté de la ligne.

Choisissez la réponse qui correspond le mieux à votre situation **au cours des deux dernières semaines**. Essayez de ne pas passer trop de temps par réponse et tentez de répondre à toutes les questions.

Ceci est un questionnaire personnel et ne peut être rempli que par vous personnellement. Lorsque vous remplissez le questionnaire, ne discutez pas de vos réponses avec votre entourage immédiat.

Fonctions physiques

Dans votre bras, sentez-vous:

Pas du tout ↓ **Énormément** ↓

1. Une sensation de lourdeur (fatigue) ? 0 1 2 3 4 5 6 7 8 9 10
2. Une sensation de raideur? 0 1 2 3 4 5 6 7 8 9 10
3. Un gonflement? 0 1 2 3 4 5 6 7 8 9 10

Au niveau de votre bras, avez-vous:

Pas du tout ↓ **Énormément** ↓

4. Une perte de force? 0 1 2 3 4 5 6 7 8 9 10
5. Des picotements? 0 1 2 3 4 5 6 7 8 9 10
6. Des douleurs? 0 1 2 3 4 5 6 7 8 9 10
7. Une tension au niveau de la peau? 0 1 2 3 4 5 6 7 8 9 10

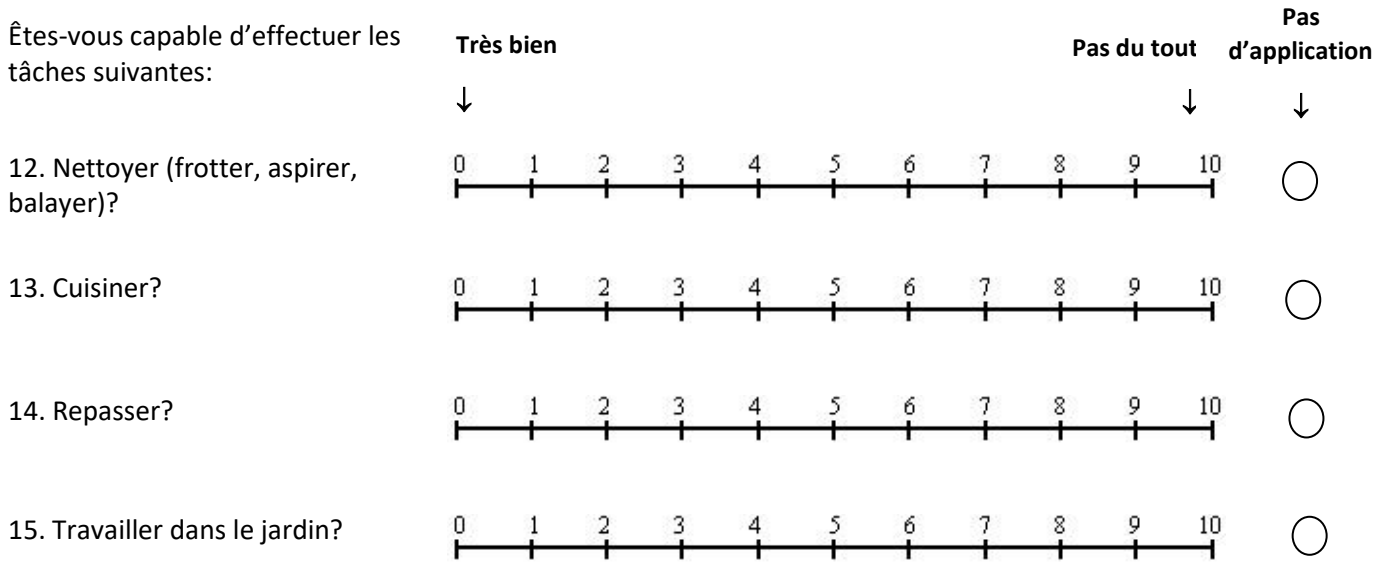
Fonctions mentales

Suite à vos problèmes au niveau du bras:

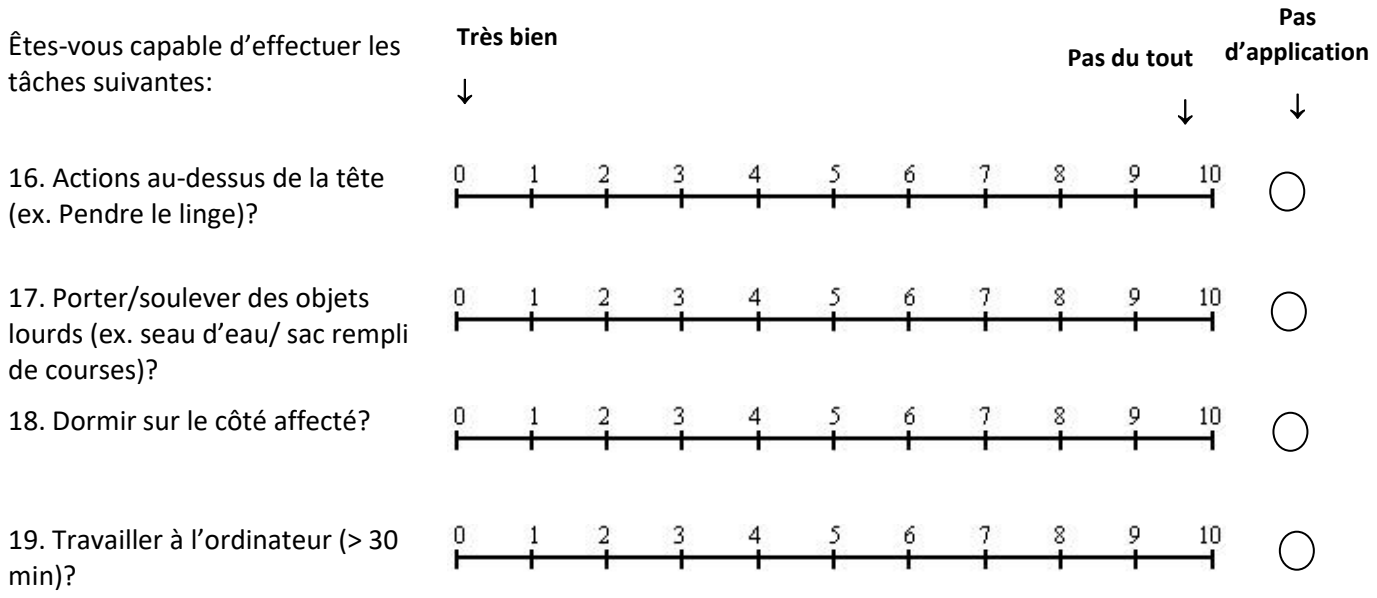
Pas du tout ↓ **Énormément** ↓

8. Êtes-vous triste? 0 1 2 3 4 5 6 7 8 9 10
9. Vous sentez-vous découragé(e)? 0 1 2 3 4 5 6 7 8 9 10
10. Manquez-vous de confiance en vous? 0 1 2 3 4 5 6 7 8 9 10
11. Êtes-vous tendu(e)? 0 1 2 3 4 5 6 7 8 9 10

Vie domestique



Mobilité



	Très bien	Pas du tout	Pas d'application
20. Bronzer?	0 1 2 3 4 5 6 7 8 9 10		○
21. Conduire?	0 1 2 3 4 5 6 7 8 9 10		○
22. Marcher à pied (>2 km)?	0 1 2 3 4 5 6 7 8 9 10		○
23. Rouler à vélo?	0 1 2 3 4 5 6 7 8 9 10		○

Grands domaines de la vie et vie sociale

Êtes-vous capable d'effectuer les tâches suivantes:	Très bien	Pas du tout	Pas d'application
24. Partir en vacances? *Quel(s) type(s) de vacances:*_____	0 1 2 3 4 5 6 7 8 9 10		○
25. Pratiquer vos hobbys?	0 1 2 3 4 5 6 7 8 9 10		○
26. Faire du sport? *Quel(s) sport(s):*_____	0 1 2 3 4 5 6 7 8 9 10		○
27. Portez les vêtements de votre choix?	0 1 2 3 4 5 6 7 8 9 10		○
28. Exercer votre métier?	0 1 2 3 4 5 6 7 8 9 10		○
29. Vie sociale avec vos proches (ex. sorties restaurant, concerts, soirées)?	0 1 2 3 4 5 6 7 8 9 10		○

CHAPTER 8

Chapter 8

WHAT ARE THE ECONOMIC BURDEN AND COSTS ASSOCIATED WITH THE TREATMENT OF BREAST CANCER-RELATED LYMPHEDEMA? A SYSTEMATIC REVIEW

Support Care Cancer. 2020 Feb; 28(2): 439-449.

Tessa De Vrieze
Ines Nevelsteen
Sarah Thomis
An De Groef
Wiebren A.A. Tjalma
Nick Gebruers
Nele Devoogdt

Abstract

Objectives: To provide an overview of costs associated with the treatment of breast cancer-related lymphedema (BCRL) and its possible sequelae, borne by patients or by society.

Data sources: According to the PRISMA guideline, a systematic literature search was carried out in four electronic databases: PubMed, Web of Science, Cochrane Clinical Trials and EMBASE. Searches were performed on October, 1st 2018.

Study selection: Eligibility criteria: 1) expenses of adults (age >18y), 2) concerning patients with BCRL, 3) overview of (in)direct costs associated with BCRL, 4) expenses in which at least one type of conservative treatment modality for lymphedema is included and/or costs for hospital admissions due to infections. Reviews and meta-analyses were excluded.

Data extraction: After assessing the risk of bias and level of evidence, quantitative data on (in)direct costs for BCRL treatment during a well-mentioned timeframe were extracted.

Data synthesis: Eight studies were included. Three studies reported on patient-borne costs related to BCRL. Mean directs costs per year borne by patients ranged between US $2 306 and US $2 574. Indirect costs borne by patients ranged between US $3 325 and US $5 545 per year. Five studies estimated society-borne costs related to BCRL from claims data, billing prices and providers' services during 12 to 24 months of follow-up. Mean direct treatment costs after 1 year of decongestive lymphatic therapy ranged between €799 (= US $1 126.60) and US $3 165.

Conclusion: This systematic review revealed that BCRL imposes a substantial economic burden on patients and society. However, more standardized high-quality health economic analyses among this field are required. Recent economic analyses related to BCRL treatment in Europe, Asia, Africa and South America are lacking. Worldwide, further scrutiny of the economic impact of DLT for BCRL in clinical settings is needed.

Introduction

Worldwide, breast cancer is the most common cancer in women.[2] Although breast cancer-related lymphedema (BCRL) is not the most prevalent complication after treatment for breast cancer[3], it is internationally recognized as one of the most dreaded morbidities. Since the introduction of more effective treatment modalities[4-7] increasing the number of breast cancer survivors, the amount of patients dealing with long-term side effects, such as lymphedema, rises likewise.[8] BCRL is caused by a decreased lymphatic transport capacity and/or increased lymphatic load after which fluid accumulates in the extracellular spaces of soft tissues, resulting in swelling.[9] Today, pooled data reveals a BCRL incidence rate of 16.6%.[10]

Besides an impact on functional and psychosocial well-being[1], there can be an additional deleterious effect of lymphedema on patients in terms of financial costs.[11, 12] Daily living can be affected by copayments for the increase in medical and therapeutic consultations, as well as by other direct costs for compression garments and other (in)direct therapy-related expenses.[11] Moreover, financial burdensome can be emphasized through the impact of (advanced) lymphedema on career and employment.[12] This happens for instance when a transition from fulltime to part-time employment is required in order to spend more time on complex care.[12] Besides the lymphedema which requires appropriate treatment, complications secondary to BCRL, such as repeated infections, may arise as well.[13] These episodes need early antibiotic therapy and may require hospitalization, increasing the costs of care even more.[14]

According to the recommendations of the International Society of Lymphology (ISL), BCRL needs to be treated with decongestive lymphatic therapy (DLT).[15] This is a two-stage treatment program, consisting of different conservative treatment modalities. During the first or intensive phase, lymphedema is maximally reduced. This phase consists of skin care, manual lymph drainage (MLD), multi-layer bandaging and exercise therapy. The second or maintenance phase aims to conserve and optimize the results obtained in the first phase. It consists of skin care, compression by a low-stretch compression sleeve, exercises and MLD.[16] Although DLT is recognized as the gold standard for conservative treatment of lymphedema[15, 17], reimbursement for DLT has been hampered by a lack of rigorous research evidence.[9] Additionally, current literature on the financial burden of BCRL treatment is extremely limited. An overview between patient-borne and society-borne costs within this financial burden is missing. However, this is essential to estimate the actual economic impact of BCRL for patients as for society.

Therefore, the aim of this review was to make an overview of the currently available literature on direct and indirect patient-borne as well as society-borne costs associated with the treatment of BCRL and its sequelae.

Methods

Literature search and inclusion criteria

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline[18] (www.prisma-statement.org), a systematic review of the literature was performed. This review has been registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO) with registration number CRD42018114649. In order to identify eligible studies, four electronic databases were screened on October 1st, 2018: PubMed, Web of Science, EMBASE and Cochrane Clinical Trials. A PICOS search strategy was built up, resulting in a Boolean search where following indexing terms (i.e. MeSH for PubMed and Cochrane, Emtree for EMBASE) and keywords were combined: 'breast cancer(P)', 'lymphedema(P)', 'decongestive lymphatic therapy(I)', 'treatment(I)', 'economic analysis(O)', 'economic evaluation(O)', and 'costs(O)'. A comparison was not defined (not applicable). Equivalent searches were executed in all four databases, although modifications in keywords were included due to differences in usage of indexing terms. When using Web of Science, an additional restriction was added to the search with the filter "document type: Article", and in EMBASE the search was limited to "Articles" or "Articles in press" and studies based on "Humans". In Appendix 1, an overview of the applied search strategies for the different databases is presented.

The screening for eligible articles was two-fold and performed by two raters (T.D.V. and N.G.). A first screening upon title and abstract was achieved for all references in each database, in order to assess which articles were relevant for further scrutiny. Thereafter, a second screening on the full-texts of the selected articles was performed. Both screenings were based upon predetermined inclusion and exclusion criteria, reported in Table 1. In case of disagreement between the reviewers regarding the in- or exclusion of studies, consensus was reached during a meeting.

Table 1. Eligibility criteria used in both screenings

PICOS	Inclusion	Exclusion
P	Adults (age > 18y)	
P	Patients with breast cancer-related lymphedema	Solely breast cancer patients without upper limb lymphedema
I	Decongestive lymphatic therapy or other conservative treatment modalities	No overview of costs regarding any type of treatment modality for BCRL and/or costs for hospital admissions due to infections
C	Not specified	/
O	Economic overview or analysis of costs related to the treatment of lymphedema and/or its sequelae	When only indirect costs are included (i.e. loss of productivity,..) without incorporation of direct costs related to any treatment modality for lymphedema or its sequelae
O	Outcome should be a quantitative overview of (patient-borne and/or community-based) costs during a certain timeframe	Solely qualitative results
S	Randomized controlled trial, cohort study, cross-sectional study	Review, meta-analysis
Other	Language: English, Dutch or French	Other languages
Other	Humans, Articles or Articles in press	Animal studies, unpublished material or abstracts

Methodological quality assessment and data extraction

To assess the methodological quality of the selected full-texts, the 19-item NICE checklist for (partial) economic evaluations provided by the National Institute for Health and Care Excellence (NICE)[19] (https://www.nice.org.uk/process/pmg20/chapter/incorporating-economic-evaluation) was used. Full-texts were evaluated by both reviewers (T.D.V. and N.G.). As the NICE checklist initially is designed for the UK, some minor adjustments in questions were necessary to generalize the feasibility of the questions to all countries.[19] An item was scored "1" if adequate information was provided and bias was unlikely. An item was scored "0" if the criterion was not met. An item was scored "?" if the required information was lacking. Afterwards, the total methodological quality was expressed as the sum of all items receiving score "1" (Table 2). In case disagreement occurred between reviewers regarding assigning a score to an item, consensus was sought during a meeting. Additionally, according to the Dutch Cochrane Centre guidelines, levels of evidence were determined for all selected studies (http://netherlands.cochrane.org).

Data on study design, research question, study region, number of participants, inclusion and exclusion criteria, timespan, applied treatment for BCRL, cost- (and other) related outcome measures, and cost-related main results were extracted and summarized from the included full-texts in Table 3. If studies reported both quantitative and qualitative data concerning the economic burden of BCRL, only quantitative data was extracted. If studies compared treatment costs for patients with and without BCRL, or compared (so-called) standard treatment costs and an experimental/model-based treatment cost, only the BCRL treatment costs and standard treatment costs were mentioned. To increase the interpretability of the amount of costs in the different currencies, we converted the costs that are reported in Euros, Australian Dollars or British Pounds in the result section and/or discussion, into the US $ currency and added them in parentheses next to the original currency. This currency exchange is based on the actual exchange rate at the time of the online publication of the article (month, year): €1 = US $1.41 (August 2009)[19] and US $1.18 (October 2017)[19]; 1A$=US $0.85 (December 2014)[19] and US $0.76 (August 2016)[19]; £1= US $1.43 (February 2018)[19].

Table 2. Overview of the methodological quality of the eight included studies (NICE checklist)

Risk of Bias													
Author, year	Section 2: Limitations												
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	**Methodological Quality (Total)**	**Level of Evidence**
Shih et al., 2009	1	1	1	1	1	?	1	1	0	0	1	**8/11**	**A2**
Kärki et al., 2009	1	1	?	1	1	?	1	1	0	0	1	**7/11**	**B**
Stout et al., 2012	1	1	0	1	1	?	1	1	1	0	1	**8/11**	**B**
Bilir et al., 2012	1	1	?	1	?	?	1	1	1	0	1	**7/11**	**B**
Schmitz et al., 2015	1	1	1	1	?	1	1	1	0	0	1	**8/11**	**A2**
Basta et al., 2016	1	1	0	?	1	0	1	1	0	0	1	**6/11**	**B**
Boyages et al., 2016	1	1	1	1	?	?	1	1	0	0	1	**7/11**	**B**
Dean et al., 2018	1	1	1	1	?	?	1	1	0	0	1	**7/11**	**A2**

Table 3. Table of evidence with characteristics of the eight included studies

Author, year	Study design	Research question	Study region	Participants			Time span	BCRL treatment	Measures and outcome		Main findings: costs
				Inclusion criteria	Exclusion criteria	Number of inclusions (n)			Cost measures and resource use	Other measures	
SOCIETY-BORNE COSTS											
Shih et al., 2009	Prospective cohort study	To estimate the economic burden of BCRL among working-age women	USA	Cohort of breast cancer patients identified using a validated algorithm	Males, less than 27 months of enrollment, missing enrollee identifiers	Total n= 1877 (mean age 48.8 years) - BCRL n= 180 - no BCRL n= 1697	24 months starting post-surgery (between 1997 and 2003)	Not enlightened	Productivity information, medical and pharmacy claims data of the Medstat MarketScan Health and Productivity Management (HPM) database	Age, comorbidities, demographic data, working status, breast cancer treatment modalities	Total not cancer-related medical cost in 24 months: -BCRL group: US $45 896 Total medical cost for PT and supplies, in 24 months: -**BCRL group: US $1 083** Total medical cost for infections, in 24 months: -BCRL group: US $2 151
Kärki et al., 2009	Cross-sectional quantitative study	To explore current treatment practices and costs for BCRL	Finland	/	Patients with BCRL with reimbursed costs for LE therapy	/	12 months during treatment (between January and March 2007 for prices obtained from	106 LE therapist reported treating BCRL patients. LE therapy consisted of a	- Prices of CB's, CS's, gloves and 60-min sessions were obtained from service providers and manufactures (2007) - Data on reimbursed costs for	Origins of referrals, use and duration of treatments, pre- and post-therapy assessments by questionnaires to lymphedema therapist's	<u>Total direct costs</u> for 1 patient treated with DLT = €**799:** - Ten 60-min therapy sessions: €450 EUR - One compression bandage: €37.5 - Two sleeves: €155.5

							manufacturers/ service providers, between January and December 2004 for costs for reimbursed LE therapy sessions)	combination of: - MLD (99%) - guidance (79%) - CS (74%) - CB (63%) - exercises (55%) Most therapist (80%) used 60-min sessions, 11 to 15 sessions	therapy sessions were obtained from the national Social Insurance Institution (SII)	- Usage volumes of lymph therapy and compression bandages was collected from three hospital district and three major cities in 2005	- Two handkerchiefs: €156
Stout et al., 2012	Quantitative cross-sectional cost analysis	To provide an estimation of the direct costs associated with a prospective surveillance model of care compared with the direct treatment costs of a traditional model for managing BCRL	USA	/	/	/	12 months starting post-surgery (estimated costs with a 1-year timeline)	DLT vs. Prospective Surveillance Model after breast cancer surgery	Costs for skilled therapy (direct treatment costs) and durable medical equipment (average retail costs) based on Medicare 2009 physician fee schedule	/	Direct costs after 1 year of DLT per patient: **US $3 124.92** (therapy sessions US $1 494.92, 2 sets of bandages US $230, 4 custom-made arm sleeves and hand gloves US $1 400)
Bilir et al., 2012	Payer-perspective decision model	To estimate and compare the economic outcomes associated with routine use of bio-impedance spectroscopy	USA	Women with breast cancer, at least 18y old	/	Cohort model begins with a hypothetical population of 1 million covered lives. Then	12 months starting post-surgery (estimated costs with a 1-year timeline)	LE treatment: current standard quarterly LE assessment and treatment if required	Healthcare costs were derived from publicly available fee schedules, and reflect Medicare national average reimbursement rates (costs	Parameter values were obtained from the medical literature, including population characteristics,	For the 627 newly treated post-surgery BC patients, based upon the CTCAE v3.0 definition of lymphedema and other

		(BIS) vs. current standard methods following breast cancer treatment				the cohort is stratified by disease risk characteristic ; n=627 newly treated post-surgery BC patients			regarding compression sleeves, pneumatic pump use, DLT, in- and outpatient physician fees, hospitalization, antibiotic therapy, depression treatment)	lymphedema incidence, resource utilization	base-case model input values, the total (direct + indirect) 1-year budget impact, from the payer perspective, is: **- US $1 984 529** for standard assessment and lymphedema treatment (= **US $3 165.12** per patient); - **US $1 819 896** for the standard lymphedema treatments alone (= **US $2 902.55** per patient)
Basta et al., 2016	Retrospective cohort study	To quantify the hospital recourse utilization for LE-related sequelae	USA (Arkansas, California, Florida, Nebraska, New York)	Women, at least 18y old, who underwent lumpectomy or mastectomy with ALND	Discharges with concurrent coding for both lumpectomy and mastectomy or lumpectomy with breast reconstruction, patients with metastatic diseases, unknown	Total n= 56 075 (mean age 60.5 years) - BCRL n= 1279 - no BCRL n= 54 796	24 months follow-up starting post-surgery (between 1/1/2007 and 31/12/2010) Note: for California: 12 months (between 1/1/2007 and 31/12/2009)	Not enlightened	Cost claims using the Healthcare Cost and Utilization Project (HCUP) inpatient databases (= census of hospital discharges from acute care, nonfederal, community hospitals). Primary outcomes: - all-cause hospital admissions -LE-specific hospital admissions - and corresponding healthcare charges	- Demographic data: age, primary payer (private insurance vs. other) - Initial treatment variables: primary diagnosis - Number of chronic medical conditions - History of tobacco use Using questionnaires	<u>Direct costs</u> due to hospitalization (all-cause admissions, LE-specific hospital admissions, and corresponding healthcare charges): - BCRL: ± **US $58 088 costs/patient/2 years**

					discharges or death						
PATIENT-BORNE COSTS											
Schmitz et al., 2015	Prospective cohort study	To evaluate the economic burden of adverse treatment effects from breast cancer treatment, comparing burden across women with and without these outcomes	Australia	Women who recently had undergone surgery for breast cancer, representative of the wider breast cancer population	/	Total n= 287 (mean age 55.3 years) - BCRL[a] patients with direct costs n= 75 - BCRL patients with indirect costs n= 52 - no BCRL patients with direct costs n= 111 - no BCRL patients with indirect costs n= 85	12 months follow-up between 6-18 months post-surgery	Not enlightened	Patient's out-of-pocket direct, indirect and total costs between breast cancer diagnosis and 18 months post-surgery (questionnaire)	- Demographic data (e.g. age, children, occupation, private health insurance,…) - Tumor Characteristics - Type of adjuvant treatment received - Adverse treatment effect Using questionnaires	BCRL group: - <u>Direct</u> out-of-pocket costs for LE between 6 and 18 months post-surgery**: A$5 545** per patient - Total costs for LE between 6 and 18 months post-surgery**: A$6 121** per patient
Dean et al., 2018	Prospective explanatory mixed methods design	To compare long-term out-of-pocket direct and indirect costs among women with BCRL to those without LE diagnosis	USA (New Jersey, Pensylvania)	Women with stages I-III invasive breast cancer, active breast cancer treatment completed, >1 lymph node removed, current residents of New Jersey or Pennsylvania	Active cancer, currently pregnant or planning to become pregnant in the next 6 months	Total n= 129 (mean age 63) - BCRL n= 60 - no BCRL n= 69	12 months during treatment (started: 2015)	Not enlightened	<u>Quantitatively:</u> 1) (in)direct costs and productivity losses using a cost diary (3 months retrospectively, 6 months prospectively and estimated costs last 3 months) 2) subjective rating of economic burden using the Breast	At baseline: Demographics (self-reported), cancer history and treatment (self-reported), health conditions (self-reported) and LE (inter-limb volume difference using Perometry)	Excluding productivity losses: - BCRL group: ± **US $2 306** out-of-pocket costs/patient/year Including productivity losses: - BCRL group: ± **US $3 325** out-of-

									Cancer Finances Survey <u>Qualitatively:</u> semi-structured interview (n= 40 with at least n= 10 of each group)		pocket costs/patient/year
Boyages et al., 2016	Mixed-method qualitative and cross-sectional quantitative study	To investigate the impact of lymphedema over and above breast cancer on the financial costs borne by women	Australia	Control group: female, older than 18y old, previously diagnosed with primary stage I, II or III breast cancer, completed treatment at least 1y prior to recruitment, fluent in English BCRL group: Idem + confirmed diagnosis of LE	/	Total n= 361 - BCRL n= 152 - no BCRL n=209	Cross-sectional survey (recruitment between November 2014 and March 2015)	Patients with BCRL: - 41% skin care - 53% exercises - 61% MLD - 32% CS's - 23% laser therapy - 13% Taping - 3% IPC - 1% liposuction	Electronic survey containing questions regarding impact of BCRL on employment, cost of seeing therapists, cost of CS's	LE stage, patients with breast cancer (whether or not having the diagnosis of BCRL) received questions regarding: 1) employment/career, 2) family life, 3) social/leisure, 4) self-image and 5) feeling about self	Subdivision of reposted costs was made regarding LE severity. In general: - Overall mean out-of-pocket costs for BCRL/patient/year = **A$977** - Average cost of garment/patient/year= **A$392**

Abbreviations: PT= physical therapy, MLD= manual lymphatic drainage, CB= compression bandages, CS= compression sleeves, IPC= intermittent pneumatic compression, LE= lymphedema, DLT= decongestive lymphatic therapy

Notes: [a] patients with an L-Dex score of at least 10 (BIS), or a difference in sum of arm circumferences between both arms of at least 5cm.

Results

Study selection

At first, the search yielded 387 references, including duplicates. After a first screening upon title and abstract for each selected database, 28 full-texts were retrieved for further scrutiny. After a second screening upon eligibility criteria (Table 1), duplicates (n=14) were removed. Finally, eight studies were included for the results section of this review: 4 cohort studies[14, 20-22] and 4 cross-sectional studies[12, 23-25] respectively. Figure 1 provides a detailed flowchart of the search strategy and selection procedure.

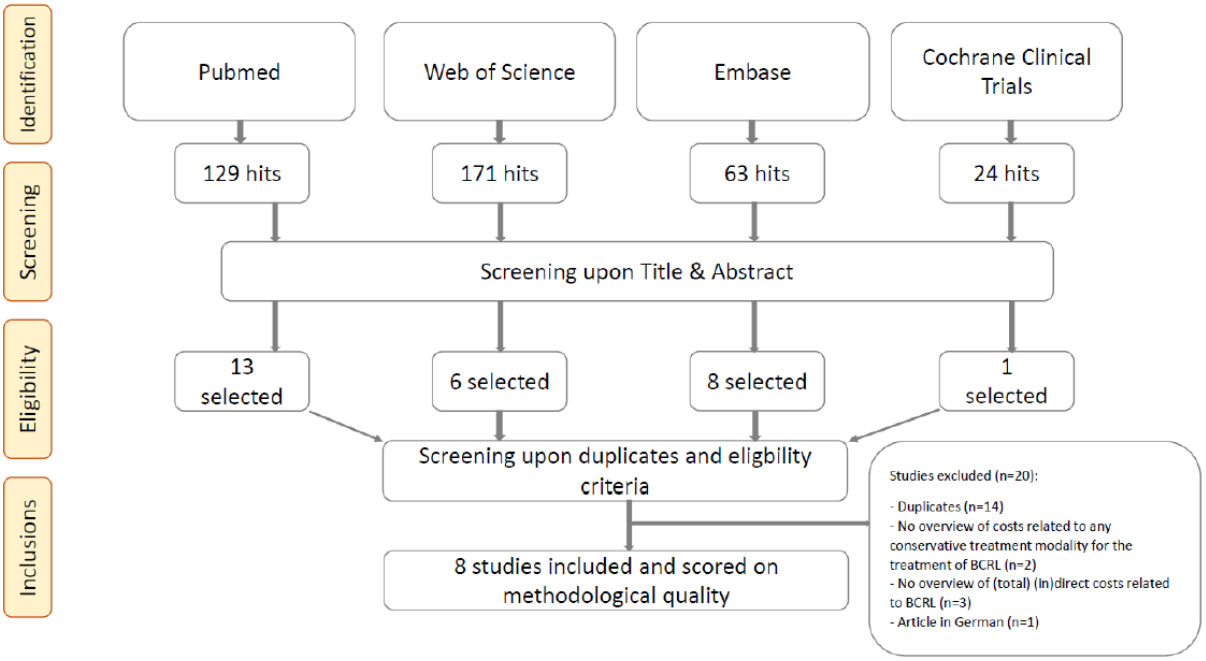


Figure 1. *Flowchart of the Boolean search and selection procedure (PRISMA)*

Methodological quality

An overview of the risk of bias and level of evidence of the included studies is presented in Table 2. Regarding study quality, scores for the (partly) economic evaluations in both cohort and cross-sectional studies ranged between 6/11 and 8/11. A question that frequently scored negative or of which information was lacking, was the following: "Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?", because in most cases the aim of the studies was to provide an overview of costs, rather than to make a cost-effectiveness evaluation. According to the Dutch Cochrane Centre guidelines, levels of evidence ranged between A2[14, 20, 22] and B[12, 21, 23-25].

Characteristics of the included studies

Altogether, costs were analyzed of 2421 patients with BCRL from 6 out of 8 included studies which were all women.[12, 14, 20-22, 25] Two studies did not report the amount of patients upon which their cost-related outcomes were based, nor did they specify the gender of the included patients.[23, 24] Mean age of the included patients ranged between 49[14] and 63 years[22]. One study did not define mean age[12], and in one study this was not mentioned since results were based on a hypothetical decision model[25]. Study regions comprised the USA[14, 21, 22, 24, 25], Australia[12, 20], and Finland[23].

Costs related to BCRL

The timespan in which costs were estimated in the different studies ranged between 12 months[20, 22, 23, 25] and 24 months[14, 21]. Either, these costs were retrieved from a convenience sample of patients with BCRL during an arbitrary follow-up of 12 months[22, 23], during the first 12 months after surgery for breast cancer[25], between 6 and 18 months after surgery[20] or during the first 24 months after surgery[14, 21].

Three studies[12, 20, 22] investigated patient-borne costs related to BCRL. Of these, two studies made a distinction between direct (i.e. costs directly related to the treatment for BCRL such as costs for therapeutic measures, physician fees, drugs, compression therapy/garment) and indirect (i.e. productivity losses; values of lost income, unpaid help and lost unpaid work) patient-borne costs.[20, 22] Mean direct costs per patient per year ranged between US $2 306[22] and US $2 574[20]. Indirect costs ranged between US $3 325[22] and USD $5 545[20] costs per year. In the article of Boyages et al., the overall mean patient-borne costs for BCRL per patient per year were provided, resulting in an average of A$977 (= US $742.52) per year.[12] Hereby, no distinction between direct and indirect costs was made.

The five remaining studies[14, 21, 23-25], discussed medical costs from a societal perspective. These included costs collected from claims data from (national) insurers[14, 23], physician Medicare fees[24, 25], hospitalization charges[21, 25] and/or manufacturer's and service providers' prices[23]. In these studies, no separate overview of out-of-pocket costs borne by patients was provided. One study showed that the average of non-cancer-related medical costs for BCRL was estimated on US $45 896 per patient during 2 years (US $22 948 per patient per year), of which US $1 083 per patient was charged for physical therapy and supplies.[14] In Bilir et al., the total 1-year economic impact with direct and indirect costs was US $1 984 529 for standard assessment and lymphedema treatment in 627 patients (US $3 165 per patient per year).[25] Three studies provided an overview of solely direct costs[21, 23, 24]. Direct

BCRL-related healthcare charges due to hospitalization (e.g. for systemic infections) were estimated on US $58 088 per patient during 2 years (US $29 044 per patient per year).[21] Direct treatment costs after 1 year of DLT per patient were estimated on US $3 125.[24] In Finland, total direct costs per patient treated with DLT was €799 (=US $1 126.60) per year.[23] An overview of the extracted data is shown in Table 3.

Discussion

The purpose of this systematic review was to provide an overview of the direct and indirect patient-borne as well as society-borne costs associated with the treatment of BCRL and its sequelae (Table 3 'main findings: costs').

Three out of eight of the included studies were prospective cohort studies with sufficient sample size and follow-up. These studies were graded with a level of evidence A2.[14, 20, 22] However, scores on methodological quality in terms of risk of bias of the included studies were relatively similar to each other.

This review reveals that BCRL imposes a substantial economic burden on patients and society. When solely direct costs are taken into account, in most cases a significant proportion of costs is spent on physical therapy sessions and materials (e.g. compression garment), medication and hospital admissions in case of infections. During a 2-year post-operative period, patients with BCRL required significantly more hospitalizations and nearly 7 times higher healthcare charge per patient compared with patients without BCRL (US $141 388 vs. US $21 141 per patient, respectively).[21] If productivity losses were taken into account as well, the financial burden increased even more.

In the article of Stout et al., direct treatment costs associated with a traditional model of DLT were compared with costs associated with a prospective surveillance model.[24] In the USA, the cost to manage early-stage BCRL per patient per year using a prospective surveillance model was US $636. In contrast, the costs associated with DLT using the traditional model was US $3 125[24], highlighting the importance of an early treatment onset in favor of less invasive treatment expenses due to fewer treatment sessions and less material required.

This review comprised only one study that investigated the treatment cost for DLT in a European country, whereby results showed an average cost of €799 (=US $1 126.60) per patient per year.[23] However, more information is available concerning treatment costs for lower limb lymphedema in European settings. Recently, Gutknecht et al. performed in Germany an observational cross-sectional study in patients with chronic lymphedema or lipolymphedema in order to analyze all the direct and

indirect costs for patients, health insurance and society.[26] The average total cost for each patient per year was €5 784 (=US $6 825.12), of which €4 445 (=US $5 245.1) (76%) were direct costs and €1 338 (=US $1 578.84) (24%) were indirect costs. Patient-borne costs were €648 (=US $764.64) on average per year, wherein the highest costs were for MLD and disability costs (e.g. prescription fees including private costs for remedies and aids, payments for physician visits, hospitalization and rehabilitation, skin care products).[26] Each year, a mean cost of €2 510 (=US $2 961.80) per patient is spent on MLD, which was considered the main cost factor for statutory health insurances.[26] However, as this study relies on costs regarding the treatment for lower limb edema, it was not included in our review. Likewise, in another recently published study of Moffatt et al., the aim was to develop and evaluate health service and patient outcomes using an appropriate model of care within a London-based primary care trust.[27] Patients with chronic swelling of the arm(s) or leg(s), were recruited and treated for a period of 6 months. Results of this study showed the benefits of a service model for chronic edema, with clinical improvements due to a reduction in limb volume and reduced complications. Recourses moved from the acute care setting to lower cost interventions in community: overall costs reduced from £50 171 (=US $71 744.53) before implementation, to £27 352 = US $39 113.96) within the first 6 months and subsequently £17 618 (=US $25 193.74) between 6 months and 1 year.[27]

Several limitations of the included studies of this review need to be discussed. First and foremost, studies investigating the financial costs related to BCRL by making use of claims data[14, 21, 25] are likely to underestimate the real cost rates.[28] Because claims data are designed for billing purposes, they only offer information of patients who are insured. Thus, they only provide an estimation of the costs related to BCRL as they do not yield information about patients with BCRL without health insurance.[29] Furthermore, one should notice that, in case only direct costs related to hospitalizations are taken into account[21], an important underestimation of the complete (direct) costs of BCRL occurs. Evaluation of resource utilization and charges associated with outpatient care would provide a more complete assessment of the impact related to BCRL.[21]

Difficulties are being experienced regarding the comparability, transferability and generalizability of the present study results. Transferability is defined as the extent to which the results of a study hold true for a different population or setting.[19, 30] Since different continents, even different states/countries within the same country/continent, are subjected to different healthcare insurance policies and reimbursement procedures, it is difficult to transfer the amount of healthcare costs derived in the USA[14, 21, 22, 24, 25] or Australia[12, 20] to European countries and vice-versa. Besides that, differences in money currencies between countries make the amount of costs derived in the different studies hard to compare. Generalizability is defined as the extent to which the results of a study can be generalized to the population from which the sample size was drawn.[19, 30] As stated by Dean et al.,

even findings derived from studies conducted solely in the USA are difficult to compare over time, since some of these investigations[14] conducted in the past are predate the 2010 Affordable Care Act that expanded coverage for cancer-related care.[22] Another example is following: in Shih et al., the study sample was limited to working-age women (mean age 49 years), therefore their findings regarding medical costs may not be generalizable to elderly with BCRL.[14]

Limitations and strengths

In this review, literature searches were limited to mainly (bio)medical databases. The NHS Economic Evaluation Database (NHS EED) focuses primarily on the economic evaluation of healthcare interventions.[31] As a result, combining databases such as PubMed and NHS EED should have been an optimal search strategy for economic evaluations.[31, 32] Therefore, a post-hoc search was performed on the NHS EED database on October, 19th 2018 (https://www.crd.york.ac.uk/CRDWeb). However, this search yielded no additional eligible records.

The present systematic review contains several strengths. Firstly, it has a compliance with the PRISMA guideline.[18] Furthermore, to our knowledge, this is the first overview of reported direct and indirect patient-borne as well as society-borne costs specifically associated with the treatment of BCRL, in literature. Lastly, the screening and data extraction process was performed by two blinded researchers.

Knowledge of costs related to BCRL not only improves the understanding of the economic burden of this morbidity, but also launches a baseline of comparison for future cost-analytic or cost-effectiveness studies.[14] Therefore, future studies on the effectiveness of treatment modalities for BCRL should consider defining health economic analyses a priori in order to be able to withdraw proper high quality conclusions based on cost-effectiveness outcomes such as the Incremental Cost-Effectiveness Ratio (ICER) and/or quality adjusted life-years (QALY). An appropriate time-horizon (≥12 months) should be defined and both incremental (direct and indirect) cost elements from a patient and societal perspective should be considered and collected prospectively. Additionally, it is recommended to include a generic health-related quality of life questionnaire such as the EQ-5D-5L and utility instrument to allow comparisons across interventions and populations.

Conclusion

This review reveals that BCRL imposes a substantial economic burden on patients and society. In the USA, patient-borne direct costs related to BCRL range between US $2 306 and US $2 574 per patient per year. Patient-borne indirect costs range between US $3 325 and US $5 545 per patient per year. Mean direct treatment costs after one year of DLT ranged between €799 (=US $1 126.60) and US $3 165. However, these conclusions are based on limited research data and due to the differences in (public) insurance protocols and currencies, it is difficult to compare costs between countries. Therefore, more standardized high-quality health economic analyses among this field are required. Additionally, recent economic analyses related to BCRL treatment in Europe, Asia, Africa and South America are lacking. Worldwide, further scrutiny of the economic impact of DLT for BCRL in clinical settings is needed.

Acknowledgements

All authors critically revised the manuscript for important intellectual content and approved the final manuscript.

References

1. Fu MR, Ridner SH, Hu SH, Stewart BR, Cormier JN, Armer JM. Psychosocial impact of lymphedema: a systematic review of literature from 2004 to 2011. Psycho-oncology. 2013;22(7):1466-84.
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer. 2015;136(5):E359-86.
3. Devoogdt N, Van Kampen M, Christiaens MR, Troosters T, Piot W, Beets N, et al. Short- and long-term recovery of upper limb function after axillary lymph node dissection. European journal of cancer care. 2011;20(1):77-86.
4. Kast K, Schoffer O, Link T, Forberger A, Petzold A, Niedostatek A, et al. Trastuzumab and survival of patients with metastatic breast cancer. Archives of gynecology and obstetrics. 2017;296(2):303-12.
5. Eggemann H, Altmann U, Costa SD, Ignatov A. Survival benefit of tamoxifen and aromatase inhibitor in male and female breast cancer. Journal of cancer research and clinical oncology. 2018;144(2):337-41.
6. Christiansen P, Carstensen SL, Ejlertsen B, Kroman N, Offersen B, Bodilsen A, et al. Breast conserving surgery versus mastectomy: overall and relative survival-a population based study by the Danish Breast Cancer Cooperative Group (DBCG). Acta oncologica (Stockholm, Sweden). 2018;57(1):19-25.
7. Yoon TI, Hwang UK, Kim ET, Lee S, Sohn G, Ko BS, et al. Survival improvement in hormone-responsive young breast cancer patients with endocrine therapy. Breast cancer research and treatment. 2017;165(2):311-20.
8. Beckjord EB, Reynolds KA, van Londen GJ, Burns R, Singh R, Arvey SR, et al. Population-level trends in posttreatment cancer survivors' concerns and associated receipt of care: results from the 2006 and 2010 LIVESTRONG surveys. Journal of psychosocial oncology. 2014;32(2):125-51.
9. Lasinski BB, McKillip Thrift K, Squire D, Austin MK, Smith KM, Wanchai A, et al. A systematic review of the evidence for complete decongestive therapy in the treatment of lymphedema from 2004 to 2011. PM & R : the journal of injury, function, and rehabilitation. 2012;4(8):580-601.
10. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol. 2013;14(6):500-15.
11. Morgan CL LB. Classification and Staging of Lymphedema. Lymphedema. USA: Springer; 2008. p. 21-30.
12. Boyages J, Xu Y, Kalfa S, Koelmeyer L, Parkinson B, Mackie H, et al. Financial cost of lymphedema borne by women with breast cancer. Psycho-oncology. 2017;26(6):849-55.
13. Armer JM, Radina ME, Porock D, Culbertson SD. Predicting breast cancer-related lymphedema using self-reported symptoms. Nursing research. 2003;52(6):370-9.
14. Shih YC, Xu Y, Cormier JN, Giordano S, Ridner SH, Buchholz TA, et al. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(12):2007-14.
15. The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology. Lymphology. 2013;46(1):1-11.
16. Gebruers N, Verbelen H, De Vrieze T, Vos L, Devoogdt N, Fias L, et al. Current and future perspectives on the evaluation, prevention and conservative management of breast cancer related lymphoedema: A best practice guideline. European journal of obstetrics, gynecology, and reproductive biology. 2017;216:245-53.
17. International Lymphoedema Framework I. Best Practice for the Management of Lymphoedema: International Consensus2006.

18. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of clinical epidemiology. 2009;62(10):e1-34.
19. Wijnen B, Van Mastrigt G, Redekop WK, Majoie H, De Kinderen R, Evers S. How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: data extraction, risk of bias, and transferability (part 3/3). Expert review of pharmacoeconomics & outcomes research. 2016;16(6):723-32.
20. Schmitz KH, DiSipio T, Gordon LG, Hayes SC. Adverse breast cancer treatment effects: the economic case for making rehabilitative programs standard of care. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2015;23(6):1807-17.
21. Basta MN, Fox JP, Kanchwala SK, Wu LC, Serletti JM, Kovach SJ, et al. Complicated breast cancer-related lymphedema: evaluating health care resource utilization and associated costs of management. American journal of surgery. 2016;211(1):133-41.
22. Dean LT, Moss SL, Ransome Y, Frasso-Jaramillo L, Zhang Y, Visvanathan K, et al. "It still affects our economic situation": long-term economic burden of breast cancer and lymphedema. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2018.
23. Karki A, Anttila H, Tasmuth T, Rautakorpi UM. Lymphoedema therapy in breast cancer patients: a systematic review on effectiveness and a survey of current practices and costs in Finland. Acta oncologica (Stockholm, Sweden). 2009;48(6):850-9.
24. Stout NL, Pfalzer LA, Springer B, Levy E, McGarvey CL, Danoff JV, et al. Breast cancer-related lymphedema: comparing direct costs of a prospective surveillance model and a traditional model of care. Physical therapy. 2012;92(1):152-63.
25. Bilir SP, DeKoven MP, Munakata J. Economic benefits of BIS-aided assessment of post-BC lymphedema in the United States. The American journal of managed care. 2012;18(5):234-41.
26. Gutknecht M, Herberger K, Klose K, Purwins S, Dietz D, Blome C, et al. Cost-of-illness of patients with lymphoedema. Journal of the European Academy of Dermatology and Venereology : JEADV. 2017;31(11):1930-5.
27. Moffatt CJ, Doherty DC, Franks PJ, Mortimer PS. Community-Based Treatment for Chronic Edema: An Effective Service Model. Lymphatic research and biology. 2018;16(1):92-9.
28. Stout NL, Weiss R, Feldman JL, Stewart BR, Armer JM, Cormier JN, et al. A systematic review of care delivery models and economic analyses in lymphedema: health policy impact (2004-2011). Lymphology. 2013;46(1):27-41.
29. Brayton KM, Hirsch AT, PJ OB, Cheville A, Karaca-Mandic P, Rockson SG. Lymphedema prevalence and treatment benefits in cancer: impact of a therapeutic intervention on health outcomes and costs. PloS one. 2014;9(12):e114597.
30. Knies S, Ament AJ, Evers SM, Severens JL. The transferability of economic evaluations:testing the model of Welte. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2009;12(5):730-8.
31. Evers SM, Hiligsmann M, Adarkwah CC. Risk of bias in trial-based economic evaluations: identification of sources and bias-reducing strategies. Psychology & health. 2015;30(1):52-71.
32. Alton V, Eckerlund I, Norlund A. Health economic evaluations: how to find them. International journal of technology assessment in health care. 2006;22(4):512-7.

APPENDIX 1. Overview of the Boolean search strategies used in the different databases

PubMed 1-10-2018 ("Health Care Costs"[Mesh] OR "Healthcare Costs"[All Fields] OR "Costs and Cost Analysis"[Mesh] OR "health care economics"[All Fields] OR "Costs and Cost Analysis"[All Fields] OR "Cost-Benefit Analysis"[Mesh] OR "Cost-Benefit Analysis"[All Fields] OR "Cost of Illness"[Mesh] OR "Cost of Illness"[All Fields] OR "Cost-of-illness"[All Fields] OR "Hospital Costs"[Mesh] OR "Hospital Costs"[All Fields] OR "Health Expenditures"[Mesh] OR "Health Expenditures"[All Fields] OR "Cost"[All Fields] OR "cost evaluation"[All Fields] OR "economic evaluation"[All Fields] OR "cost analysis"[All Fields] OR "economic analysis"[All Fields] OR "cost effectiveness"[All Fields]) AND ("lymphedema"[MeSH Terms] OR "lymphoedema"[All Fields] OR "lymphedema"[All Fields]) AND ("breast neoplasms"[All Fields] OR "breast neoplasms"[MeSH] OR "breast cancer"[All Fields] OR "costs"[All Fields] OR "breast cancer treatment"[All Fields] OR "direct costs"[All Fields] OR "health outcomes"[All Fields] OR "upper limb"[All Fields])
Web of Science 1-10-2018 (TS=(("Health Care Costs" OR ("Health" AND "Care" AND "Costs") OR "Cost Analysis" OR ("costs" AND "analysis") OR "health care economics" OR ("health" AND "care" AND "economics") OR "Cost-Benefit Analysis" OR ("cost-benefit" AND "analysis") OR "Cost of Illness" OR ("cost" AND "illness") OR "Hospital Costs" OR ("Hospital" AND "Costs") OR "Health Expenditures" OR ("Health" AND "Expenditures") OR "Cost" OR "cost evaluation" OR ("cost" AND "evaluation") OR "economic evaluation" OR ("economic" AND "evaluation") OR "direct costs" OR ("direct" AND "costs") OR "health outcomes" OR ("health" AND "outcomes") OR "economic analysis" OR ("economic" AND "analysis") OR "cost effectiveness" OR ("cost" AND "effectiveness")) AND ("lymphedema" OR "lymphoedema") AND ("breast neoplasms" OR ("breast" AND "neoplasms") OR "breast cancer" OR ("breast" AND "cancer") OR "lymphedema treatment" OR ("lymphedema" AND "treatment") OR "upper limb" OR ("upper" AND "limb")))) *AND* **DOCUMENT TYPES:** (Article)
Cochrane Clinical Trials 1-10-2018 (("Health Care Costs" OR "Costs and Cost Analysis" OR "health care economics" OR "Cost-Benefit Analysis" OR "Cost of Illness" OR "Cost-of-illness" OR "Hospital Costs" OR "Health Expenditures" OR "Cost" OR "cost evaluation" OR "economic evaluation" OR "cost analysis" OR "economic

analysis" OR "cost effectiveness" OR "direct costs" OR "health outcomes") AND ("lymphedema" OR "lymphoedema") AND ("breast neoplasms" OR "breast cancer" OR "lymphedema treatment" OR "upper limb")) in Title Abstract Keyword
EMBASE 1-10-2018 ('health care cost'/exp OR 'healthcare cost' OR 'cost analysis'/exp OR 'cost analysis' OR 'costs' OR 'health care economics'/exp OR 'health care economics' OR 'cost-benefit analysis'/exp OR 'cost-benefit analysis' OR 'cost of illness'/exp OR 'cost of illness' OR 'hospital costs'/exp OR 'hospital costs' OR 'health expenditures'/exp OR 'health expenditures' OR 'cost evaluation' OR 'economic evaluation'/exp OR 'economic evaluation' OR 'direct costs' OR 'health outcomes'/exp OR 'health outcomes' OR 'economic analysis' OR 'cost effectiveness'/exp OR 'cost effectiveness') AND ('lymphedema'/exp OR 'lymphedema' OR 'lymphoedema'/exp OR 'lymphoedema') AND ('breast neoplasms'/exp OR 'breast neoplasms' OR 'breast cancer'/exp OR 'breast cancer' OR 'lymphedema treatment' OR 'upper limb'/exp OR 'upper limb') AND ([article]/lim OR [article in press]/lim) AND [humans]/lim

CHAPTER 9

Chapter 9

BREAST CANCER-RELATED LYMPHEDEMA AND ITS TREATMENT: HOW BIG IS THE FINANCIAL BURDEN?

Draft – in preparation for submission

Tessa De Vrieze
Nick Gebruers
Ines Nevelsteen
Wiebren A.A. Tjalma
Jean-Paul Belgrado
Sarah Thomis
An De Groef
Lore Dams
Vincent Haenen
Elien Van der Gucht
Nele Devoogdt

Abstract

Background: Breast cancer related lymphedema (BCRL) is a progressive and chronic morbidity. It should be treated with the so called decongestive lymphatic therapy (DLT), which comprises multiple treatment modalities. Different healthcare providers are involved and various materials are being used. With 17% of the patients treated for breast cancer developing BCRL, this morbidity imposes a tremendous financial burden for patients and society. The burden aggravates when complications such as erysipelas are involved. Knowledge about this financial burden related to BCRL and its conservative treatment in a European setting, is lacking.

Objective: To estimate the direct healthcare costs related to BCRL and its treatment in a European setting.

Design: Prospective, longitudinal cohort study within the EFforT-BCRL trial.

Methods: Patients with BCRL were treated with DLT consisting of an intensive treatment phase of 3 weeks, followed by a maintenance treatment phase of 6 months. Additionally, the follow-up period comprised 6 months. During these 3 weeks and 12 months, all directs costs associated with the treatment of BCRL and its sequelae were collected through billing prices and a self-developed questionnaire which was administered after the intensive treatment phase, and subsequently three-monthly during the entire period.

Results: In total, 170 patients were enrolled in this study, whose direct treatment costs were documented. Of these, 14.7% (n= 25) showed lymphedema stage I, 55.9% (n= 95) had lymphedema stage IIa, and 29.4% (n= 50) had lymphedema stage IIb. Total direct healthcare costs per patient were € 2 279.10 on average during the entire period of 3 weeks of intensive treatments and 12 months of maintenance treatments. Within these mean direct costs, € 1 827.36 (80%) were accounted for statutory health insurances and € 451.74 (20%) were out-of-pocket expenses for patients.

Conclusion: This study is one of the first cost analyses giving insights into the financial burden of BCRL and its treatment in a European setting. Findings indicate that BCRL treatment is accompanied by a high amount of direct treatment costs.

Introduction

Since the introduction of more effective treatment modalities for breast cancer[1-4] with increasing survivors, the amount of patients dealing with long-term side effects, such as lymphedema, has risen correspondingly.[5] Breast cancer-related lymphedema (BCRL) is the most feared complication after treatment for breast cancer.[6] It is caused by a decreased lymphatic transport capacity and/or increased lymphatic load after which fluid accumulates in the extracellular spaces of soft tissues, resulting in swelling.[7] Today, pooled data reveals a BCRL incidence rate of 16.6%.[8]

Besides its impact on functional and psychosocial well-being[9], there can be an additional detrimental effect of lymphedema on women in terms of financial costs.[10, 11] Traditionally, cost-of-illness studies stratify costs into three categories: direct costs, indirect costs and intangible costs.[12] However, intangible costs, which are the costs related to pain or psychosocial suffering[13], are rarely being quantified due to their assessment difficulties. Direct costs can be borne by the healthcare system, family, and the individual patient and comprise healthcare (or medical) costs and non-healthcare (or non-medical) costs.[12] Healthcare costs are medical care expenditures for diagnosis, treatment and rehabilitation, while non-healthcare costs are related to the consumption of non-medical recourses such as transportation, household expenditures, and property losses.[12] Indirect costs encompass productivity losses (e.g. presenteeism, absenteeism, premature mortality) or leisure time losses, borne by the individual patient, family, healthcare system, or the employer.[12, 13] In general, there are two approaches used in cost-of-illness studies in order to estimate the economic burden of a condition: the prevalence-based and the incidence-based approach.[13] In prevalence-based research, the costs associated with past and present consequences of a disease or condition in a given time period (typically a year), are estimated.[12, 13] In incidence-based studies, the costs and consequences associated with new cases of the disease or condition in the present and future years, are estimated.[12, 13]

In patients with BCRL, daily living can be affected by copayments for the increase in medical and therapeutic consultations, as well as by direct costs for compression garments and therapy-related expenses.[10] Besides the lymphedema which requires appropriate treatment, complications secondary to BCRL, such as repeated infections, may arise as well.[14] These episodes need early antibiotic therapy and may require hospitalization, increasing the costs of care even more.[15]

According to the recommendations of the International Society of Lymphology (ISL), BCRL has to be treated with decongestive lymphatic therapy (DLT).[16] This is a two-stage treatment program, consisting of different conservative treatment modalities. During the first or intensive phase, lymphedema is maximally reduced. This phase consists of skin care, manual lymph drainage (MLD),

multi-layer bandaging and exercise therapy. The second or maintenance phase aims to conserve and optimize the results obtained in the first phase. It consists of skin care, compression by a low-stretch compression sleeve, exercises and MLD.[17] Although DLT is recognized as the gold standard for conservative treatment of lymphedema[16, 18], reimbursement for DLT has been hampered by a lack of rigorous research evidence.[7] Recently, a systematic review was conducted in order to provide a summary of the literature regarding direct and indirect costs associated with the treatment of BCRL and its sequelae.[19] It was stated that BCRL imposes a substantial economic burden on patients and society, with yearly directs costs borne by patients ranging between US $2 306 (= € 2 125 in April 2020) and US $2 574 (= € 2 372 in April 2020) on average.[19] However, what became apparent while reviewing the literature, was the need for economic analyses associated with BCRL in particularly European countries. Insights into the financial impact of BCRL are important to inform decision makers (e.g. policy makers and insurers) about the burden of this disease, which may assist them to inaugurate evidence-based public health policies and guidelines.

To address this gap in literature, the aim of the present study was to assess direct healthcare costs related to BCRL, in order to provide an overview of the mean annual costs covered by the healthcare system, as well as of the out-of-pocket expenses paid by Belgian patients.

Methods

Design

This prospective cohort study is part of the EFforT-BCRL trial, a multi-center randomized controlled trial (RCT) in which the effectiveness of fluoroscopy-guided MLD for the treatment of BCRL is being investigated.[20] Details are described elsewhere.[20] Approval for this trial was obtained by the Ethical Committee of the University Hospitals of Leuven (main Ethical Committee) as well as by the Ethical Committees of all other participating centers (CME reference S58689, EudraCT 2015-004822-33, Clinicaltrials.gov NCT02609724). The study was conducted in accordance with the Declaration of Helsinki and is reported following the recommended STROBE guidelines for observational studies.

Participants

Patient recruitment started in February 2016 at the University Hospitals of Leuven, CHU Saint-Pierre University Hospital in Brussels, Antwerp University Hospital, General Hospital Groeninge in Kortrijk, and Ghent University Hospital. Inclusion criteria were: 1) unilateral lymphedema of the arm/hand with signs of pitting, developed after treatment for breast cancer, 2) stage I to IIb lymphedema present for at least 3 months, 3) a difference ≥5% between hands and/or arms (adjusted for limb dominance), 4) no active metastases, 5) age ≥18 years. Exclusion criteria were: 1) non BCRL-related lymphedema, 2) inability to participate the whole study period, 3) inability of participation due to mental or physical causes, 4) bilateral axillary lymph node dissection. Recruitment of participants for this cost analysis continued until January 2019. All participants provided written informed consent.[20]

Intervention

During the EFforT-BCRL trial, treatment sessions were standardized.[20] First, participants were planned to receive 14 sessions (**60 min**/ session) during three weeks of intensive DLT (including education, skin care, bandaging, exercises, MLD). Treatment started with drainage of the shoulder and trunk, was followed by removal of the bandage and circumference measurements of the arm using a perimeter.[21] Afterwards, drainage of the arm (and hand), shoulder and trunk was continued. After MLD, skin care and bandaging was applied and the session ended with exercises. Thereafter, participants received during 6 months standardized maintenance treatments (including education, skin care, compression sleeve/glove, exercises, MLD) including 18 sessions (**30 min**/ session) in decreasing frequency (i.e. 2 weekly sessions during month 1; 1 weekly session during month 2; 2 two-weekly sessions during months 3-4; 1 monthly session during months 5-6). In this maintenance phase, therapeutic sessions lasted for 30 minutes as they only consisted of skin care and MLD. Participants performed exercises at home as they were wearing compression garment during daytime (custom-made Mediven 550 (Medi) compression sleeve and glove, compression class 2). Additionally, patients were followed up for another 6 months in which they were allowed to consult a physiotherapist of their own preference to continue the maintenance treatments. This implies that, for the present study, the total maintenance phase comprised a period of 12 months.

Treatments during the intensive treatment phase and first 6 months of the maintenance phase were provided by four physiotherapists in the University Hospitals of Leuven (RVH, LB, AH, LV), two in Saint-Pierre University Hospital in Brussels (LV, TDV), in Ghent University Hospital (LV, TDV) as well as in General Hospital Groeninge in Kortrijk (LV, TDV) and one in Antwerp University Hospital (TDV); all experts in the field of edema treatment.

Data collection

Collection of direct healthcare costs

In this study, a *prevalence-based approach* was applied to examine direct healthcare costs of patients with BCRL in Belgium. The collected direct healthcare costs comprised different categories: compression materials, medication, diagnostics and human resources. The procedure for collecting the costs is demonstrated in Table 1.

Costs were collected through billing prices of the compression sleeves/gloves and of the equipment used during the intensive and maintenance treatment phases of the EFforT-BCRL trial, and through a self-developed questionnaire:

1. *Billing prices*

   Treatment costs related to BCRL and its treatment are collected through the project's billing prices of orders for treatment equipment such as compression bandages and materials. For each patient, used materials and corresponding costs were noted down in a separate data sheet.

2. *Cost questionnaire*

   Similar to previously published cost studies[22, 23], participants reported their direct healthcare cost data over a period of at least 12 months (see Figure 1). This was captured through a 3-weekly retrospective self-developed cost questionnaire (filled out retrospectively after 3 weeks of intensive treatment) and 4 times a 3-monthly retrospective self-developed cost questionnaire (filled out retrospectively during and after the 6 months lasting maintenance treatment phase, as well as during and after the 6 months lasting follow-up phase in which maintenance treatments were continued externally). Patients were asked to complete the questionnaires at the hospital at the end of the trial's standardized clinical evaluations. Only the questionnaire after 3 months of follow-up was sent by postal mail, as there was no scheduled clinical assessment at the hospital at this time point.

   In particular, units consumed regarding the different cost categories, and their accompanying prices were asked. Patients were asked to report their resource use in a detailed way, to allow the multiplication with unit prices. Also he or she was asked to report the name or address of consulted healthcare provider(s), providing the opportunity to check certain information in case the written text was unclear or incomplete. In case patients were not able to recall certain costs by heart at the moment of completion, they were allowed to look up the prices at home and forward them by mail. The first included patients of the RCT did not complete the

questionnaires at the end of the intensive treatment phase, as these first patients were already participating the RCT before the cost questionnaire was finalized. Consequently, they filled in the questionnaire for the first time during their maintenance treatment phase. On that moment these patients needed to recall (or look up the prices at home) all previously made BCRL-related costs during the entire study period, which were added to the trials' materials billing prices.

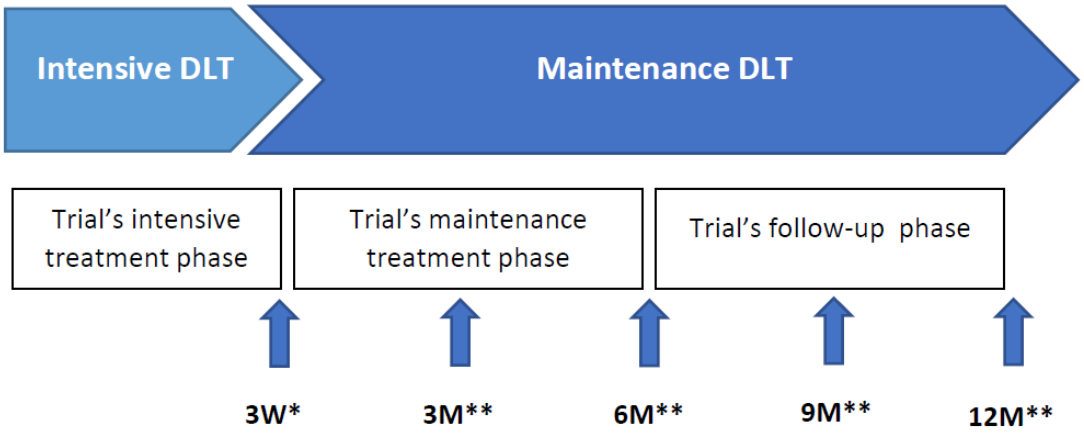


Figure 1. *Schematic overview of different time points on which the cost questionnaire was completed*

Data analysis

Valuation of costs

Billing prices per patient as well as the results from the questionnaires were manually imputed into a spreadsheet (Microsoft Excel 2016). Direct healthcare costs were reported in 2020 Euros (€). In case patients did not mention the unit prices of newly measured compression sleeves/gloves, or of consultations to certain healthcare providers (without specifying contact details), the fees determined on 01/01/2020 were consulted on the website of the National Institute for Health and Disability Insurance ('NIHDI' or 'RIZIV' in Dutch).[24-28] This is the Belgian federal institution organizing the mandatory health insurances.[13] In Table 1 a detailed overview regarding the valuation of costs per cost category is included.

To summarize, costs were derived for a total time span of nearly 13 months, of which 3 weeks of intensive DLT and 12 months of maintenance DLT. Costs were analyzed from a societal perspective, which is compiled by 1) costs covered by the health insurer, and 2) costs borne by the patient.

Statistical analyses

Descriptive data analyses were performed using SPSS Statistics version 26.0 for Windows. Descriptive statistics for baseline characteristics of the participants are presented as mean ± standard deviation (SD) for normally distributed continuous values, and as median ± inter quartile range (IQR) for non-normally distributed continuous values. Categorical variables are presented as number (n) and proportion (%). Descriptive statistics for the direct healthcare costs were applied: mean, SD as well as minimum and maximum were calculated.

Table 1. Procedure to determine the direct healthcare costs related to BCRL and its treatment

Type		Outcome	Content collected	Collected through	Valuation of costs		Additional price information
					Health insurance	***Patient***	
Compression material							
Bandaging material	1) Used during the trial's intensive treatment phase	Number of items and price	-Short stretch bandages -Finger bandages -Skin protection tubular bandages -Padding (synthetic undercast padding, foam rubber bandages, foam sheets, and lymph pads) -Tape	Billing prices	Bandaging materials are not covered by the Belgian health insurers	All costs regarding bandaging materials are out-of-pocket expenses	/
	2) Additional bandaging material during intensive and maintenance phase, bought by patients	Number of items and price	Bandaging materials to be specified by the patient	Cost questionnaire			
Compression sleeves and gloves	1) Individualized measurements during trial (after the intensive treatment phase and after	Number of items and price	Custom-made Mediven 550 (Medi) compression sleeve and glove, compression class 2	Billing prices	Belgian health insurers cover the costs of 2 (basic) custom-made Mediven 550 (Medi) compression	If a patient required individual adjustments to a compression sleeve (e.g. a comfort lining at the elbow region) or glove	In case patients did not mention the unit prices of newly measured compression stockings/gloves, the fees determined on 01/01/2020 were consulted on the website of the National Institute for Health and Disability

	6 months of maintenance treatments)				sleeves and 4 gloves (without fingers) per 12 months	(e.g. compression covering the fingers), or if a patient bought more than 2 compression sleeves/ 4 gloves during this period, these costs were assigned to out-of-pocket expenses	Insurance (NIHDI) [26], the Belgian federal institution organizing the mandatory health insurances.[13]
	2) Additional measurements undertaken by patients	Number of items and price	Individualized compression sleeves/ gloves, to be specified by the patient	Cost questionnaire			
Skin care products	1) Used during the trial's intensive and maintenance treatments	Number of items and price	Dermalex Moisturizing body milk	Billing prices	Generally, accessories and skin care products are not covered by health insurers	All costs regarding accessories and skin care products were considered as out-of-pocket expenses	/
	2) Additional skin care products bought by patients	Number of items and price	Skin care products to be specified by the patient	Cost questionnaire			
Accessories (e.g. pull aids,…)	Bought by patients	Number of items and price	Accessories to be specified by the patient	Cost questionnaire			
Medication							
Diuretics, antibiotics, pain	Bought by patients	Number of items and price	Medication related to the treatment of the acquired side effects of lymphedema (i.e.	Cost questionnaire	Depending of the (name of the) product, it is partially or	According to the (name of the) product, it is partially or entirely	Medication costs were calculated based on the product's name and the units consumed, using the

medication, etc.			diuretics, antibiotics, pain medication, etc.), to be specified by patients		entirely covered by health insurers	a patient-borne cost	Belgian commented online drug compendium.[29]
Diagnostics							
Imaging procedures related to the disease, blood examination, etc.	Undertaken by patients	Number of investigations/ imaging procedures and price	Type of investigation/ imaging procedure, to be specified by the patient	Cost questionnaire	According to the investigation, it is partially or entirely covered by health insurers	According to the investigation, it is partially or entirely a patient-borne cost	For the evaluation of costs for imaging procedures, the billing service tariff of the University Hospitals of Leuven was applied.
Human recourses							
Admissions to the hospital and/or consultation(s) with a healthcare provider, due to the disease	Undertaken by patients	Number of admissions/ consultations and price	Type of consultation (general practitioner, medical doctor or specialist/ physiotherapist/ psychologist/ dietitian/nurse/ other), to be specified by the patient	Cost questionnaire <u>Specific questions physiotherapist's consultations:</u> 1) how many treatment sessions were provided during the last 3 months, 2) price per treatment session, 3) whether the patient was entitled for an increased reimbursement (Fb-pathology or E-pathology), and 4) whether the physiotherapist was	According to the type of consultation/ medical specialist visited, it is partially or entirely covered by health insurers or partially/ entirely a patient-borne cost. For details regarding the fees for physical therapy sessions and the different reimbursement rates according to the patients' lymphedema severity, see Appendix 1.		For the evaluation of costs for a medical doctor's consultation, the billing service tariff of the University Hospitals of Leuven was applied. For other healthcare provider consultations (in case unit prices were not mentioned), the fees determined on 01/01/2020 were consulted on the website of the National Institute for Health and Disability Insurance (NIHDI)[24, 25, 27, 28] See Appendix 1 for more details about the applied fees for physical therapy sessions during the first 3 weeks of intensive treatments and 6 months of maintenance treatments.

				accredited or not (as this has an impact on the amount of out-of-pocket expenses for patients)		During the 6-monthly follow-up phase, patients were allowed to consult a physiotherapist of their own preference. In case patients indicated to have no idea of the price of each session and did not report the name or other contact details of the therapist, it was assumed that an accredited physiotherapist was consulted. Additionally, price was set based on the patients' percentage of excessive arm/hand volume at the end of the maintenance treatment phase of the trial, in order to select the appropriate reimbursement rate (Appendix 1).

Results

In total, data of the first 170 participants of the EForT-BCRL trial, who completed both the intensive treatment phase (3 weeks), maintenance treatment phase (6 months) and follow-up phase which is a continuation of the maintenance phase (6 months), were used for this cost analysis. Five participants dropped-out during the intensive treatment phase. Of them, one patient was still willing to attend the trial's clinical evaluations, enabling cost inventories throughout the entire period. Characteristics of the included patients are presented in Table 2. Mean age of the enrolled patients was 61 (±10) years. Mean body mass index (BMI; kg/m^2) was 28 (± 5). The vast majority were women (n= 169, 99.4%), and the median duration of lymphedema was 28 months (IQR 61).

All direct healthcare costs that were collected during the intensive and 12-monthly maintenance phase, are shown in Table 3. A subdivision was made between costs borne by the health insurer as well as by the patients, together representing the total societal costs. The average direct healthcare costs for 3 weeks of intensive DLT and 12 months of maintenance DLT, was € 2 279.10 per patient. Of this, € 1 827.36 (80%) on average is borne by the health insurer and € 451.74 (20%) on average is borne by the patient.

No patients reported to have received a (Doppler) ultrasound evaluation, or to have consulted a dietitian or occupational therapist during the entire study period. Hence, these costs were not valued. During the intensive treatment phase, no patients reported 1) to have required other medication than these for erysipelas, 2) to have received medical imaging or blood examinations, or 3) to have consulted a medical doctor, psychotherapist, or (another than mentioned) healthcare provider. During the maintenance phase, no patients reported to have consulted a nurse or (another than mentioned) healthcare provider.

During the intensive treatment phase, all 166 patients received treatments on a daily basis. The average number of treatment sessions was 14 (60 min). In Appendix 2, an overview is shown of the bandaging materials used per patient on average. During the first six months of the maintenance treatment phase (i.e. during the EFforT-trial), all 166 patients received treatment at a decreasing frequency. Patients received 17 maintenance treatment sessions on average (30 min). During the last six months of the maintenance treatment phase (i.e. during the EFforT-trial's follow-up phase), patients could choose whether they preferred to consult a physiotherapist to continue the maintenance treatments with MLD, or to continue their maintenance therapy on their own. Seventy-six patients (45.8%) consulted a physiotherapist during this second part of the maintenance phase. Of these, the average number of maintenance treatment sessions was 19, which is comparable to the amount of treatment sessions in the first 6 months of the maintenance phase. All 166 patients received

a custom-made Mediven 550 (Medi) compression sleeve and glove (compression class 2) at the end of the intensive treatment phase. All but one patients ordered new compression hosiery during 12 months of maintenance treatments, of which on average two custom-made compression sleeves and two gloves per patient.

Table 2. Baseline patient characteristics

Variable	N	Mean (SD)
Age (y)	170	61 (10)
Body mass index (kg/m^2)	170	28 (5)
Lymphedema volume arm (absolute difference) (mL)	170	504 (374)
Percentage excessive arm volume (%)	170	25 (19)
Duration of lymphedema (mo)*	170	28 (61)*
		N (%)
Lymphedema stages	170	
I		*25 (14.7%)*
IIa		*95 (55.9%)*
IIb		*50 (29.4%)*
Lymphedema at the dominant side	170	78 (45.9%)
Breast surgery	170	
Mastectomy		*97 (57.1%)*
Breast-conserving surgery		*73 (42.9%)*
pT	169	
1		*52 (30.8%)*
2		*92 (54.4%)*
3		*15 (8.9%)*
4		*10 (5.9%)*
pN	169	
0		*45 (26.6%)*
1		*85 (50.3%)*
2		*21 (12.4%)*
3		*18 (10.7%)*
cM	169	
0		*167 (98.8%)*
1		*2 (1.2%)*
Radiotherapy	170	165 (97.1%)
Chemotherapy	170	149 (87.6%)
Hormonal therapy	170	133 (78.2%)
Targeted therapy (Herceptin)	170	35 (20.6%)

Abbreviations: y= years, kg= kilogram, m^2= square meters, mL= milliliter, mo= months, lymphedema stages as described by the International Society of Lymphology. Descriptives are depicted as mean (standard deviation), except when indicated with * where median (interquartile range) is shown.

Table 3. Average direct healthcare costs (€) during intensive and maintenance DLT, from the perspective of the health insurer, patient and society

Cost category				**Cost health insurer (€)**				**Cost patient (€)**				**Cost society (€)**
			N consumer	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean
Intensive treatment phase – DLT (3 weeks)												
Bandaging material and skin care			*166*	/	/	/	/	60.44	31.87	17.31	158.33	60.44
Compression sleeves/ gloves			*166*	275.01	37.41	72.03	468.8	65.60	61.93	0.00	287.40	340.61
Medication	Erysipelas		*1*	9.52		9.52	9.52	10.77		10.77	10.77	20.29
Human resources	Physiotherapist/ edema therapist	Total	*166 (±14 sessions / consumer)*	468.49	38.80	242.55	623.70	58.72	9.15	28.00	77.00	527.21
		Reimbursement rate 'Fb pathology'	*31*	439.74	18.42	384.00	448.00	75.58	3.17	66.00	77.00	515.32
		Reimbursement rate 'E pathology'	*135*	475.09	38.77	242.55	623.70	54.84	4.48	28.00	72.00	529.93
	General practitioner		*1 (1 session)*	18.22		18.22	18.22	4.00		4.00	4.00	22.22

Cost category				Cost health insurer (€)				Cost patient (€)				Cost society (€)
			N consumer	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean
	Nurse		*2 (±4 sessions / consumer)*	17.16		17.16	17.16	5.72		5.72	5.72	22.88
Maintenance treatment phase – DLT (12 months)												
Bandaging material and skin care			*10*	/	/	/	/	39.39	24.89	3.00	100.00	39.39
Compression sleeves /gloves			*165*	531.92	95.08	142.82	835.38	122.71	109.25	0.00	415.60	654.63
Medication	Erysipelas		*8*	19.21	25.82	0.00	81.16	6.70	5.72	0.00	16.84	25.91
	Allergy		*1*	/	/	/	/	15.00		15.00	15.00	15.00
	Pain		*4*	0.51	0.59	0.00	1.02	9.40	6.62	4.09	17.77	9.91
	Diuretics		*1*	/	/	/	/	7.99		7.99	7.99	7.99
Medical imaging	Lymphoscintigraphy		*2*	214.76	0.00	214.76	214.76	/	/	/	/	214.76
	Other (CT-scan)		*1*	90.98		90.98	90.98	2.48		2.48	2.48	93.46
Blood test			*2*	1.28		1.28	1.28	/	/	/	/	1.28
Human resources	Physiotherapist/ edema therapist	Total	*166 during first 6mo (±17 sessions /consumer), 76 during last 6mo (±19*	545.68	295.17	210.00	1764.00	129.64	113.29	40.00	1012.00	675.32

			sessions /consumer)									
Cost category				**Cost health insurer (€)**				**Cost patient (€)**				**Cost society (€)**
			N consumer	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean
		Reimbursement rate 'Fb pathology'	*50 during first 6mo, 21 during last 6mo*	497.12	237.57	234.00	1080.00	152.98	137.53	66.00	1012.00	650.10
		Reimbursement rate 'E pathology'	*116 during first 6mo, 55 during last 6mo*	566.61	315.42	210.00	1764.00	119.59	100.08	40.00	771.00	686.2
	General practitioner		*12 (±2 sessions /consumer)*	41.00	35.71	18.22	109.32	9.00	7.84	4.00	24.00	50.00
	Medical specialist		*4 (±1 sessions /consumer)*	47.39	18.50	22.33	66.99	18.00	12.00	12.00	36.00	65.39
	Psychologist		*1 (3 sessions)*	149.91		149.91	149.91	33.60		33.60	33.60	183.51
	Other (acupuncturist)		*1 (18 sessions)*	/	/	/	/	1 800		1 800	1 800	1 800
Mean direct costs per patient after intensive (3 weeks) and maintenance (12 months) DLT			***166***	**1 827.36**	**340.23**	**956.59**	**3 211.79**	**451.74**	**257.81**	**125.91**	**2 347.61**	**2 279.1**

Abbreviations: DLT = decongestive lymphatic therapy, SD = standard deviation, Min = minimum, Max = maximum, mo = months

Note: The number of consumers (n) indicates the number of patients receiving the corresponding services

Discussion

This longitudinal study showed that BCRL imposes a significant economic burden to the society. Three weeks of intensive DLT and 12 months of maintenance DLT, requires € 2 279.10 per patient on average, without considering the direct non-medical (i.e. the consumption of non-healthcare resources like transportation[12]) and indirect costs (i.e. productivity losses due to morbidity and mortality[12]). Of this amount, € 1 827.36 (80%) on average is borne by the health insurer, and € 451.74 (20%) is borne by the patient. The main cost drivers for health insurers and patients were the costs for physical therapy sessions comprising MLD (on average € 1 014.17 (55.5% of the health insurance expenses) and € 188.36 (41.7% of the patient-borne expenses) respectively) and for compression stockings/gloves (on average € 806.93 (44.2% of the health insurance expenses) and € 188.31 (41.7% of the patient-borne expenses) respectively). During the intensive treatment phase, a crucial treatment modality that precedes wearing compression stockings, is bandaging. The mean cost for this equipment was € 60.44 per patient. Unfortunately, despite its necessity, these costs are entirely borne by patients.

A recent review reported that, in the USA, mean direct BCRL-treatment costs per year borne by patients range between US $2 306[23] (= € 2 125 in April 2020) and US $2 574[22] (= € 2 372 in April 2020), and mean direct BCRL-treatment costs per year borne by insurers are estimated on US $3 125[30] (= € 2 882 in April 2020). Additionally, it was stated that few data exist on costs related to treatment for BCRL in European settings[19] impeding comparison of our findings. Since different continents have differences in money currencies, but more important, are subjected to different healthcare insurance policies and reimbursement procedures, it is difficult to transfer the amount of healthcare costs derived in the USA to European countries.[19] One study showed that in Finland, the annual reimbursed cost per patient for DLT, including 10 therapy sessions (with bandaging, MLD sessions, exercises and guidance for self-treatment), two compression sleeves and gloves, is €799 on average.[31]

However, more information is available concerning treatment costs for lower limb lymphedema in European settings. Recently, Gutknecht et al. performed in Germany an observational cross-sectional study in patients with chronic lymphedema or lipolymphedema, in order to analyze all the direct and indirect costs for patients, health insurance and society in general.[32] The average total cost for each patient per year was €5 784, of which €4 445 (76%) were direct costs and €1 338 (24%) were indirect costs. Patient-borne costs were €648 on average per year, wherein the highest costs were for MLD sessions and disability costs (e.g. prescription fees including private costs for remedies and aids, payments for physician visits, hospitalization and rehabilitation, skin care products).[32] Each year, a mean cost of €2 510 per patient is spent on MLD, which was considered the main cost factor for statutory health insurances.[32] In another recently published study of Moffatt et al., the aim was to develop and evaluate health service and patient outcomes using an appropriate model of care within

a London-based primary care trust.[33] Patients with chronic swelling of the arm(s) or leg(s), were recruited and treated for a period of 6 months. Results of this study showed the benefits of a service model for chronic edema, with clinical improvements due to a reduction in limb volume and reduced complications. Resources moved from the acute care setting to lower cost interventions in community: overall costs reduced from £50 171 (= € 57 435 in April 2020) before implementation, to £27 352 (= € 31 312 in April 2020) within the first 6 months and subsequently £17 618 (= €20 169 in April 2020) between 6 months and 1 year.[33] Also concerning BCRL, previous research has already shown the benefits of an early treatment onset in favor of less invasive treatment expenses, due to fewer therapy sessions and less materials required.[30]

Strengths and limitations

This study contains several strengths. First of all, in this study with longitudinal design, 166 participants supplied 1 year of cost data. Knowledge of costs related to BCRL not only improves the understanding of the economic burden of this morbidity, but also launches a baseline of comparison for future cost-analytic or cost-effectiveness studies.[15] As the present study did not compare the costs and the consequences of two or more interventions (as with a cost-effectiveness or cost-utility analysis), we should speak of a cost-descriptive study, rather than a *full* economic evaluation.[34] Secondly, the sample size is large and by including patients with lymphedema stages I and II and a broad range of excessive arm volume percentages, it is reflective of a large population of patients with BCRL. Thirdly, the approach of both using billing prices of materials used during treatment, as well as collection of additional costs made by patients by using standardized questionnaires, allowed a detailed collection on consumption data associated with DLT in patients with BCRL.

There are some limitations as well that require consideration. First of all, indirect costs were omitted in the current study, possibly inducing a narrow perspective bias.[35] A reason for this is the fact that, primarily, these costs may not be caused by the lymphedema but by the (previous) treatment for malignant disease.[32] However, these costs are important to take into consideration, knowing that for diseases in general, 70% of the total costs are direct and 30% are indirect.[23] Secondly, costs were captured through a retrospective cost questionnaire. Expenses during the past three months were reported by the patients, which relies on momentary recall that may induce some recall error.[36] Thirdly, as we specifically emphasized that patients should only report “lymphedema-related” costs, a relative underreporting of patients consulting for example a psychologist or dietician could be induced due to this misperception. Furthermore, in case patients indicated to have no idea of the cost of their received physical therapy session and did not report the name or other contact details of the therapist,

it was assumed that the participants visited an accredited physiotherapist. However, as 16% of the Belgian physiotherapists have not joined the NIHDI convention, this might underestimate the actual (patient-borne) economic burden. Also, in the present study we preferred to work with traditional, short stretch bandages that were changed on a daily basis, instead of with cohesive bandages such as 3M™ Coban™ or CoFlex. Exceptionally, we used 3M™ Coban™ 2 Lite finger bandages in case patients presented edema at the fingers and non-cohesive finger wraps (Hartmann Peha®-Lastotel®) showed not to be sufficient enough. Cohesive bandages last longer, which can reduce the amount of treatment sessions per week, but are remarkably more expensive. Consequently, when cohesive bandages are being used in clinical practice, the patient-borne costs will be higher. Lastly, any additional, individual insurances (e.g. for hospitalizations), were not encountered. However, as no patients reported any hospitalizations or surgical procedures, this should not have affected the present study results significantly.

Recommendations for future research

Findings of this study have implications for clinical practice, future studies and policy-making. Future studies on the effectiveness of specific treatment modalities for BCRL should consider defining health economic analyses a priori in order to be able to withdraw proper high quality conclusions based on cost-effectiveness outcomes such as the Incremental Cost-Effectiveness Ratio (ICER) and/or quality adjusted life-years (QALY).[35] Full economic evaluations (taking into consideration the consequences of treatment) can provide well-founded answers on efficacy questions.[34] To do so, it is suggested to include a generic health-related quality of life questionnaire (e.g. the EQ-5D-5L) and utility instrument to allow comparisons across interventions and populations.[35] An appropriate time-horizon (≥12 months) should be defined and both incremental (direct and indirect) cost elements from a societal (health insurers and patients) perspective should be considered and collected prospectively. While questionnaires mostly rely on momentary recall, the use of a diary in a clinical trial might provide more complete information over a certain period of time.[36]

Conclusion

The economic burden of BCRL and its treatment is high, both for patients and for healthcare. The main cost drivers for health insurers and patients are the costs for physical therapy sessions comprising MLD and for compression hosiery. Of all direct healthcare costs, the costs for physical therapy sessions are on overage € 1 014.17 (55.5%) for health insurers and € 188.36 (41.7%) for patients. Concerning compression stockings/gloves, on average € 806.93 (44.2%) is covered by healthcare and € 188.31 (41.7%) are out-of-pocket expenses. Further scrutiny into prospective, full economic evaluations is needed to provide answers on efficacy questions regarding certain treatment modalities, such as MLD in particular, for the treatment of BCRL.

Acknowledgements

The authors are very grateful to all hospitals and research teams for collaborating in this study. The authors also extend very grateful thanks to the study participants.

References

1. Kast K, Schoffer O, Link T, Forberger A, Petzold A, Niedostatek A, et al. Trastuzumab and survival of patients with metastatic breast cancer. Archives of gynecology and obstetrics. 2017;296(2):303-12.
2. Eggemann H, Altmann U, Costa SD, Ignatov A. Survival benefit of tamoxifen and aromatase inhibitor in male and female breast cancer. Journal of cancer research and clinical oncology. 2018;144(2):337-41.
3. Christiansen P, Carstensen SL, Ejlertsen B, Kroman N, Offersen B, Bodilsen A, et al. Breast conserving surgery versus mastectomy: overall and relative survival-a population based study by the Danish Breast Cancer Cooperative Group (DBCG). Acta oncologica (Stockholm, Sweden). 2018;57(1):19-25.
4. Yoon TI, Hwang UK, Kim ET, Lee S, Sohn G, Ko BS, et al. Survival improvement in hormone-responsive young breast cancer patients with endocrine therapy. Breast cancer research and treatment. 2017;165(2):311-20.
5. Beckjord EB, Reynolds KA, van Londen GJ, Burns R, Singh R, Arvey SR, et al. Population-level trends in posttreatment cancer survivors' concerns and associated receipt of care: results from the 2006 and 2010 LIVESTRONG surveys. Journal of psychosocial oncology. 2014;32(2):125-51.
6. Norman SA, Localio AR, Potashnik SL, Simoes Torpey HA, Kallan MJ, Weber AL, et al. Lymphedema in breast cancer survivors: incidence, degree, time course, treatment, and symptoms. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(3):390-7.
7. Lasinski BB, McKillip Thrift K, Squire D, Austin MK, Smith KM, Wanchai A, et al. A systematic review of the evidence for complete decongestive therapy in the treatment of lymphedema from 2004 to 2011. PM & R : the journal of injury, function, and rehabilitation. 2012;4(8):580-601.
8. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol. 2013;14(6):500-15.
9. Fu MR, Ridner SH, Hu SH, Stewart BR, Cormier JN, Armer JM. Psychosocial impact of lymphedema: a systematic review of literature from 2004 to 2011. Psycho-oncology. 2013;22(7):1466-84.
10. Morgan CL LB. Classification and Staging of Lymphedema. Lymphedema. USA: Springer; 2008. p. 21-30.
11. Boyages J, Xu Y, Kalfa S, Koelmeyer L, Parkinson B, Mackie H, et al. Financial cost of lymphedema borne by women with breast cancer. Psycho-oncology. 2017;26(6):849-55.
12. Jo C. Cost-of-illness studies: concepts, scopes, and methods. Clin Mol Hepatol. 2014;20(4):327-37.
13. Hens W, Vissers D, Annemans L, Gielen J, Van Gaal L, Taeymans J, et al. Health-related costs in a sample of premenopausal non-diabetic overweight or obese females in Antwerp region: a cost-of-illness analysis. Archives of public health = Archives belges de sante publique. 2018;76:42.
14. Armer JM, Radina ME, Porock D, Culbertson SD. Predicting breast cancer-related lymphedema using self-reported symptoms. Nursing research. 2003;52(6):370-9.
15. Shih YC, Xu Y, Cormier JN, Giordano S, Ridner SH, Buchholz TA, et al. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(12):2007-14.
16. The Diagnosis and Treatment of Peripheral Lymphedema: 2020 Consensus Document of the International Society of Lymphology. Lymphology. 2020;53(1):3-19.
17. Gebruers N, Verbelen H, De Vrieze T, Vos L, Devoogdt N, Fias L, et al. Current and future perspectives on the evaluation, prevention and conservative management of breast cancer related lymphedema: A best practice guideline. European journal of obstetrics, gynecology, and reproductive biology. 2017;216:245-53.

18. International Lymphedema Framework I. Best Practice for the Management of Lymphedema: International Consensus2006.
19. De Vrieze T, Nevelsteen I, Thomis S, De Groef A, Tjalma WAA, Gebruers N, et al. What are the economic burden and costs associated with the treatment of breast cancer-related lymphedema? A systematic review. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2020;28(2):439-49.
20. De Vrieze T, Vos L, Gebruers N, Tjalma WAA, Thomis S, Neven P, et al. Protocol of a randomised controlled trial regarding the effectiveness of fluoroscopy-guided manual lymph drainage for the treatment of breast cancer-related lymphedema (EFforT-BCRL trial). European journal of obstetrics, gynecology, and reproductive biology. 2017.
21. Devoogdt N, Lemkens H, Geraerts I, Van Nuland I, Flour M, Coremans T, et al. A new device to measure upper limb circumferences: validity and reliability. International angiology : a journal of the International Union of Angiology. 2010;29(5):401-7.
22. Schmitz KH, DiSipio T, Gordon LG, Hayes SC. Adverse breast cancer treatment effects: the economic case for making rehabilitative programs standard of care. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2015;23(6):1807-17.
23. Dean LT, Moss SL, Ransome Y, Frasso-Jaramillo L, Zhang Y, Visvanathan K, et al. "It still affects our economic situation": long-term economic burden of breast cancer and lymphedema. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2018.
24. Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (R.I.Z.I.V.). Omzendbrief VI nr 2020/17 2020 [updated 23/01/2020. Available from: https://www.riziv.fgov.be/SiteCollectionDocuments/tarief_artsen_deel01_20200101corr.pdf.
25. Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (R.I.Z.I.V.). Omzendbrief VI nr 2019/368 2020 [updated 23/12/2019. Available from: https://www.riziv.fgov.be/SiteCollectionDocuments/tarief_kinesitherapeuten_20200101.pdf.
26. Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (R.I.Z.I.V.). Omzendbrief VI nr 2019/363 2020 [updated 23/12/2019. Available from: https://www.riziv.fgov.be/SiteCollectionDocuments/tarief_bandagisten_20200101.pdf.
27. Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (R.I.Z.I.V.). Omzendbrief VI nr 2019/332 2020 [updated 13/12/2019. Available from: https://www.riziv.fgov.be/SiteCollectionDocuments/tarief_verpleegkundigen_20200101.pdf.
28. Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (R.I.Z.I.V.). Omzenbrief VI nr 2019/337 2020 [updated 17/12/2019. Available from: https://www.riziv.fgov.be/SiteCollectionDocuments/tarief_revalidatie_verstrekkingen_20200101.pdf
.
29. Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI). Gecommentarieerd Geneesmiddelenrepertorium 2020 [Available from: https://www.bcfi.be/nl/chapters.
30. Stout NL, Pfalzer LA, Springer B, Levy E, McGarvey CL, Danoff JV, et al. Breast cancer-related lymphedema: comparing direct costs of a prospective surveillance model and a traditional model of care. Physical therapy. 2012;92(1):152-63.
31. Karki A, Anttila H, Tasmuth T, Rautakorpi UM. Lymphedema therapy in breast cancer patients: a systematic review on effectiveness and a survey of current practices and costs in Finland. Acta oncologica (Stockholm, Sweden). 2009;48(6):850-9.
32. Gutknecht M, Herberger K, Klose K, Purwins S, Dietz D, Blome C, et al. Cost-of-illness of patients with lymphedema. Journal of the European Academy of Dermatology and Venereology : JEADV. 2017;31(11):1930-5.
33. Moffatt CJ, Doherty DC, Franks PJ, Mortimer PS. Community-Based Treatment for Chronic Edema: An Effective Service Model. Lymphatic research and biology. 2018;16(1):92-9.
34. Goossens ME, Evers SM, Vlaeyen JW, Rutten-van Molken MP, van der Linden SM. Principles of economic evaluation for interventions of chronic musculoskeletal pain. European journal of pain (London, England). 1999;3(4):343-53.

35. Evers SM, Hiligsmann M, Adarkwah CC. Risk of bias in trial-based economic evaluations: identification of sources and bias-reducing strategies. Psychology & health. 2015;30(1):52-71.
36. Goossens ME, Rutten-van Molken MP, Vlaeyen JW, van der Linden SM. The cost diary: a method to measure direct and indirect costs in cost-effectiveness research. Journal of clinical epidemiology. 2000;53(7):688-95.

Appendices

APPENDIX 1. Information regarding fees and reimbursement rates for physical therapy sessions in Belgium

Regarding the costs for physical therapy sessions, a Belgium-specific reimbursement protocol was applied. According to the NIHDI, patients with unilateral BCRL may be entitled to an increased reimbursement by the health insurer in case a number of conditions, that are based on the severity of their lymphedema, are met:

- In case circumference measurements of the arm or volume measurements of the hand, indicate at least **5%** of excessive volume, OR a lymphoscintigraphic investigation confirms the presence of at least two of the predetermined 'minor criteria' indicative for a lymphatic problem, a patient can receive an increased reimbursement, as this condition is included in the 'NIHDI chronic pathology list (Fb-list)'. The price for a **30 min** treatment is € 25 of which € 19,5 is reimbursed by the insurer (in case the physiotherapist joined the NIHDI convention and the patient has right to the normal reimbursement rate), resulting in an out-of-pocket cost for the patient of € 5,5.[25] The price for a **45 min** treatment is € 37,50 of which € 32 is reimbursed by the insurer, resulting in an out-of-pocket cost for the patient of € 5,5.[25]
- In case circumference measurements of the arm or volume measurements of the hand, indicate at least **10%** of excessive volume, OR a lymphoscintigraphic investigation confirms the presence of at least one of the predetermined 'major criteria' indicative for a lymphatic problem, a patient can receive an increased reimbursement, as this condition is included in the 'NIHDI serious pathology list (E-list)'. The price for a **30 min** treatment is €25 of which € 21 is reimbursed by the insurer (also in case the physiotherapist joined the NIHDI convention and the patient has right to the normal reimbursement rate), resulting in an out-of-pocket cost for the patient of € 4.[25] The price for a **60 min** treatment is € 38,65 of which € 34,65 is reimbursed by the insurer, resulting in an out-of-pocket cost for the patient of € 4.[25]

<u>During the EFforT-BCRL trial, treatment sessions were standardized:</u>

- During the *3 weeks of intensive treatments*, patients were planned to receive 14 sessions lasting for **60 min**. The 6-monthly maintenance phase comprised 18 sessions of **30 min**.

  Based on patients' baseline percentage of excessive volume, corresponding prices were selected according to the NIHDI increased reimbursement rates:
  - In case the patient's arm or hand percentage of excessive volume was ≥ 5%, it was assumed the patient could receive an increased reimbursement in accordance with the 'NIHDI chronic pathology list (Fb-list)'. Consequently, corresponding prices were applied: € 37,5 (45 min) for each intensive treatment session (although the session lasted for 60 min) and € 25 (30 min) for each maintenance treatment session.
  - In case the patient's arm or hand percentage of excessive volume was ≥ 10% (corrected for hand dominance), it was assumed the patient could receive an increased reimbursement in accordance with the 'NIHDI serious pathology list (E-list)'. Consequently, corresponding prices were applied: € 38,65 (60 min) for each intensive treatment session and € 25 (30 min) for each maintenance treatment session.

- During the *6-monthly follow-up phase*, patients were allowed to consult a physiotherapist of their own preference. In the questionnaire was asked: 1) how many treatment sessions were provided during the last 3-months, 2) the price per treatment session, 3) whether the patient was entitled for an increased reimbursement (Fb- pathology or E-pathology), and 4) whether the physiotherapist was accredited or not (as this has an impact on the amount of out-of-pocket expenses for patients). In case patients indicated to have no idea of the price of each session and did not report the name or other contact details of the therapist, it was assumed that an accredited physiotherapist was consulted. Additionally, price was set based on the patients' percentage of excessive arm/hand volume at the end of the maintenance treatment phase of the trial, in order to select the appropriate reimbursement rate (Fb- pathology or E-pathology).

APPENDIX 2. Bandaging materials used per patient during the intensive treatment phase

Type	**N consumers**	**Amount (on average)**	**Price per unit (€)**	**Total price per consumer (€)**
Short stretch bandages (Lohmann & Rauscher Durelast® and Rosidal® K)	166			
6cm x 5m (Durelast®)	166	2	2.11	4.27
8cm x 5m (Rosidal® K)	166	4	1.83	7.42
10cm x 5m (Rosidal® K)	43	2	2.19	4.38
Finger bandages (Hartmann Peha®-Lastotel® 4cm x 4m)	116	9	0.40	3.60
Finger bandages (3M™ Coban™ 2 Lite 2,5cm x 2,7m)	71	7	4.00	21.00
Tape (3M Durapore™)	166	2	1.25	2.50
Medi Lymphpads 19,5cm x 28,5cm	152	0.5	6.00	3.00
Lohmann & Rauscher Cellona® synthetic undercast padding 10cm x 3m	166	1	1.60	1.60
Lohmann & Rauscher Komprex® foam rubber bandages 8cm x 2m	5	0.25	10.25	2.56
Komprex II® foam sheets 65cm x 65cm	57	0.5	61.80	30.90
Tricodur® Softgrip 10m – hand	166	2 x ±30cm	10.50	0.64
Tricodur® Softgrip 10m - arm	166	2 x ±60cm	12.92	1.62
Dermalex bodymilk 500ml	166	0.5	13.84	6.92
Pulling aids for compression sleeves bought by patients	41	1	29.95	29.95

GENERAL DISCUSSION

1. Main findings

In Western countries such as Belgium, one out of eight women is being diagnosed with BC at some point during their life.[1] Depending on the disease stage and the choice of treatment, up to 17% of the patients develop BCRL.[2] Thanks to early diagnosis and improved treatment modalities, survival rates after BC are increasing. Therefore health-related quality of life after BC, including for patients with BCRL, has received great emphasis.

The main objective of this doctoral project was to investigate the effectiveness of fluoroscopy-guided MLD for the treatment of BCRL, through a multi-center, double-blind, randomized, placebo-controlled trial. Additionally, seven other studies were carried out, most of them investigating assessment methods that can be attributed for evaluating the objective or subjective clinical impact of different lymphedema treatments on patients with BCRL.

1. The first chapters of this doctoral thesis depict the findings of the project investigating the effectiveness of fluoroscopy-guided MLD in the treatment of BCRL, as this acted as the main project for this PhD and was the thriving force for the elaboration of the different subtrials within this doctoral thesis. Consequently, in a first stage, the study protocol of this multi-center RCT was reported and published (**Chapter 1**).[3]
2. Secondly, the results of this RCT were reported (**Chapter 2**). In this three-arm trial, participants with unilateral BCRL were treated with 3 weeks of intensive DLT consisting of education, skin care, exercises, bandaging and one of the three types of MLD; either a fluoroscopy-guided MLD (intervention group), a traditional MLD (control group 1), or a placebo MLD (control group 2). Subsequently, a 6-month maintenance phase followed consisting of 18 sessions of the same type of MLD as in the intensive phase, in decreasing frequency. Compression stockings needed to be worn during daytime, and exercises had to be performed twice daily. Each day patients needed to perform skin care independently, as well as a self-drainage on the days when no professional drainage was carried out at the hospital. A follow-up period of 6 months ensued. One hundred ninety-four patients were included, of which 189 completed the intensive treatment phase. Results indicated that, patients in all three treatment groups showed a significant decrease in lymphedema volume at the level of the arm/hand, after three weeks of intensive treatment. However, between the groups there were no significant differences. Also did all patients show an increase in fluid accumulation at the level of the shoulder/trunk, which was statistically significant in the group receiving fluoroscopy-guided MLD. Nevertheless, no significant differences between the groups

were present either. All patients showed a statistically significant reduction in amount of problems in daily functioning due to the lymphedema, without any significant differences between the three groups. Lastly, general quality of life did not change after three weeks of intensive treatment, in none of the treatment groups. This means that, in all four investigated outcome measures (of which two primary and two secondary), the type of MLD that was provided showed to have **no additional value** to the other components of DLT.

3. The evaluation of the treatment response in research as well as in clinical practice is not possible without an accurate, valid and reliable method to determine arm size. Preferably, this method is easy-to-use and rapid as well. To date, a plethora of different measurement methods capable of determining arm size is available. Although plenty of research is already published concerning reliability of different measurement methods separately, a clear overview and comparison of their utility (in terms of reliability, time-efficiency and clinical feasibility), between different variants of water displacement methods, opto-electronic volumetry and calculated volume by using a perimeter, is still missing. Therefore, reliability, time-efficiency and clinical feasibility of five different and commonly used methods (traditional volumetry with overflow, volumetry without overflow, inverse volumetry, opto-electronic volumetry and calculated volume based on circumference measurements) for determining excessive arm volume in patients with BCRL, were investigated and compared (**Chapter 3**). Intraclass correlation coefficients (ICC's), standard errors of the measurement (SEMs) and systematic changes between the means were calculated to investigate reliability. The mean set-up time, execution time and total time were examined for each method to determine time-efficiency, and 12 limitations regarding clinical feasibility were listed and scored for each method. Calculated arm volume based on circumferences (mean excessive arm volume: assessor A: 477 (±367) ml; assessor B: 470 (±367) ml; assessor A (second time): 493 (±362) ml) showed the highest intra- and inter-rater ICC's of .987 and .984, respectively. Opto-electronic volumetry was the fastest method, representing a mean total time of 1 minute and 43 (±26) seconds for performing a bilateral measurement. The least limitations were reported on the calculated volume based on circumferences method (3 out of 12 limitations). Therefore, calculated volume based on arm circumferences turned out to be the best measurement method for evaluating excessive arm volume over time in terms of reliability, low error rate, low cost, few limitations, and time spent.[4]

4. We learned from the previous chapter that calculated volume based on arm circumferences is recommended as best practice for assessing lymphedema volume in extremities. However, additional techniques such as tissue dielectric constant (TDC) measurements and the pitting test are other tools that are being applied to help characterizing the edema, and to evaluate treatment response by particularly assessing the local tissue water of the skin. Despite the widespread use of these tools for diagnosing and evaluating lymphedema, standardized research investigating its clinimetric properties in patients with BCRL was lacking. Therefore, reliability of both methods for evaluating the upper limb in BCRL, was investigated (**Chapter 4**). TDC measurements using the MMDC device yielded moderate to very strong intra- (ICC 0.648-0.947) and inter-rater (ICC 0.606-0.941) reliability, depending on the measurement location on the edematous limb. The pitting test showed a very strong intra-rater agreement at nearly all defined points, but a weak inter-rater agreement, especially at the medial elbow and the breast.[5]
5. The former two chapters comprised investigation of clinimetric parameters of objective methods to quantify the amount or character of lymphedema. However, besides swelling, patients with BCRL can suffer from problems in physical, social and mental functioning as well. To encounter this burden of BCRL, questionnaires can be used. The Lymphedema Functioning, Disability and Health questionnaire for the upper limb (Lymph-ICF) was developed to quantify impairments in function, activity limitations and participation restrictions which are related to BCRL.[6] As patients mentioned that the scoring system of this questionnaire would be easier if a numeric rating scale was implemented instead of a visual analog scale, this questionnaire was revised. A study investigated the psychometric properties of this revised Lymph-ICF-UL questionnaire (**Chapter 5**), and findings showed that ICC's for test-retest reliability ranged from .79 to .95. Cronbach's alpha coefficients for internal consistency were higher than .80. Face and content validity were very good and construct validity was good. Hence, the Lymph-ICF-UL proved to be a reliable and valid questionnaire as well, using a simplified and clearer scoring procedure.[7]
6. As reported by the Cosmin Checklist, the quality and usefulness of a questionnaire is determined by its psychometric properties, including validity, reliability and responsiveness.[8] As shown in the previous chapter, the Lymph-ICF-UL is a reliable and valid tool. Although, whether or not the questionnaire is responsive as well, still had to be determined. Therefore, in an additional study, responsiveness and the minimal important change indicating a clinically relevant change, were investigated (**Chapter 6**).

Patients completed the Lymph-ICF-UL twice within a time interval of 7 weeks ('intensive group' receiving intensive treatment; n=73) or 3 months ('stable group' receiving maintenance treatment; n=22), and once the Global Perceived Effect of change questionnaire (GPE) at the second time point. Correlations between Lymph-ICF-UL and GPE were ascertained. The Lymph-ICF-UL total score changed significantly in the intensive group ($p<0.001$) and non-significantly for the ones in the stable group ($p=0.25$). There was a significant difference in mean total score changes between responders and non-responders ($p<0.001$). Therefore, the Lymph-ICF-UL is responsive to change after DLT. No correlations were found between Lymph-ICF-UL change scores and GPE.[9]

7. Clinimetric properties of this Dutch questionnaire were thoroughly investigated and reported, although, a French language version of this questionnaire was still lacking so far. To encounter this, a translation and cross-cultural validation of the Lymph-ICF-UL into French was performed (**Chapter 7**). ICC's for test-retest reliability ranged from .66 to .95. Cronbach's alpha coefficients for internal consistency were higher than .77. Face and content validity were very good and construct validity was moderate. Thus, the Lymph-ICF-UL French version is a reliable and valid questionnaire ready for use in French-speaking patients with BCRL.[10]
8. Besides an impact on functional and psychosocial well-being, there can be an additional deleterious effect of BCRL on women in terms of financial costs. Despite it is essential to estimate the actual economic impact of BCRL for patients as for health insurers, current literature on the financial burden of BCRL treatment is extremely limited. Therefore, a systematic literature search was carried out in order to make an overview of the currently available knowledge on direct and indirect patient-borne as well as Healthcare-borne costs associated with the treatment of BCRL and its sequelae (**Chapter 8**). Eight studies were included and revealed that BCRL imposes a substantial economic burden on patients and society. However, there remains a lack of economic analyses associated with BCRL in European countries. In future endeavor, analyses of the economic impact of DLT in European care settings are warranted.[11]
9. Consequently, the aim of this last chapter's study was to prospectively collect all direct costs related to BCRL and its sequelae, in order to provide an estimation of the financial burden for patients with BCRL as well as for Health Care, in a European setting (**Chapter 9**). To do so, all direct healthcare costs associated with the treatment of BCRL (and its sequelae) were collected through billing prices and a self-developed questionnaire that was administered after three weeks of intensive treatments, and subsequently three-

monthly up to 12 months after the end of the intensive treatment phase. In total, 170 patients were enrolled in this study. On average, total direct healthcare costs per patient were € 2279.10 during 12 months and 3 weeks. Within these direct costs, € 1827.36 were accounted for statutory health insurances and € 451.74 were out-of-pocket expenses for patients. Consequently, BCRL treatment is also in Belgium accompanied by a high amount of treatment costs.

2. Interpretation and critical findings

2.1 What is breast cancer-related lymphedema?

Despite the wide range of available measurement methods, efforts are being made to set standards on consistency for defining and quantifying BCRL.[12] There is a high need to standardize the **diagnosis** of upper limb lymphedema, as it can influence clinical research on the evaluation of treatment responses and the ability to compare published data in a reliable way as well.[13-15] It has been shown that the 1-year incidence of BCRL varies between 21% and 70% depending on the criteria used.[16] Mainly three factors are responsible for the little agreement on the diagnosis of lymphedema[17]: the wide variety in available measurement methods and tools[2], the extensive range of diagnostic thresholds for each measurement tool[18], and the current lack of a diagnostic gold standard measurement method and corresponding threshold.[19] A relative arm volume difference of at least 5% with the contralateral arm (corrected for arm/hand dominance), was selected as cut-off for lymphedema volume and consequently as one of the inclusion criteria in our RCT (**Chapters 1 and 2**).[3] There are several arguments for this choice. As said, nowadays, a plethora of tools is available to evaluate lymphedema. For evaluating swelling, the water displacement method and circumference measurements are the most frequently used methods[20] and are recommended as best practice for measuring lymphedema in extremities.[21] For each of these measurement methods, different detection thresholds have been reported to determine the presence of lymphedema.[17] Even within the same measurement method, many definitions are reported in literature to indicate a positive diagnosis of lymphedema. The most common are a girth difference of ≥ 2cm, a volume difference of ≥ 200 ml, 5% or 10% between the edematous and non-edematous limb.[2, 16, 22] Hereby it is important to take into account the arm dominance of the patient, since the volume of the non-dominant hand/arm is on average 3.3% smaller than the dominant hand/arm.[23] The superiority of relative arm size changes (5% or 10%) was demonstrated, as for quantifying lymphedema it is important to account for pre-operative arm asymmetry as well as for changes in the size of the contralateral arm over time.[12] An absolute change in arm volume over time has a greater impact in patients with low body weight (and consequently a relatively small arm volume) than in patients with high body weight (and consequently

a relative large arm volume).[24] The International Society of Lymphology defined mild lymphedema as an arm volume difference of 5% or more.[20] Furthermore, it has been shown that an increase in arm volume of ≥5% - <10% might represent an appropriate threshold for intervention in order to prevent progression of the edema to ≥10%.[25] These reasons pledge for the choice of (at least) 5% volume difference (corrected for arm dominance) as cut-off value (and inclusion criteria) in our RCT (**Chapters 1 and 2**).

One of the most recent and well-developed meta-analyses investigating the **incidence rates of BCRL**, is the systematic review and meta-analysis of DiSipio et al.[2] In this meta-analysis, a pooled estimate for arm lymphedema incidence of 16.6% (95% CI 13.6 - 20.2) was calculated, using abstracts from 72 studies of 29 612 women with BC.[2] Of this general pooled incidence rate, the estimate for BCRL after ALND was about four times higher (19.9%, 95% CI 13.5 – 28.2) than it was in those who received SNLB (5.6%, 95% CI 6.1 – 7.9).[2] Due to improved screening and treatment modalities for BC during the past years, the proportion of patients presenting with clinically negative axilla (cN0) has been increased.[26] In these patients, the role of ALND has been scrutinized as most of them (70%-80%) show pathologically free nodes (pN0).[26, 27] Therefore, during the last years, the request for avoiding unnecessary ALND (and its morbid sequelae) also grew, paving way for more SLNB's in BC.[26] Consequently, questions arise whether the reported pooled incidence rate of 16.6% in 2013, today anno 2020, might be obsolete and overestimated.

The fact that less patients develop BCRL nowadays as throughout the last years more and more SLNB's were being performed during surgery for BC instead of (accessory) ALND's, might explain why we experienced difficulties in recruiting patients for our RCT in nearly all of our study centers. To accommodate this, our inclusion period was extended by six months. Additionally, two other study centers (UH Ghent and GH Groeninge) were asked to participate in the trial as well. Consequently, patients with BCRL could be recruited among five different study centers in Flanders, instead of three.

2.2 Critical reflection on MLD as part of DLT

Given the fact that the more recently published RCT's investigating the added value of MLD failed to prove an additional effect[28-30], and that the Cochrane systematic review only showed an additional effect of 7.11% on volume reduction compared to compression therapy alone[31], there is a valid reason to question this true merit and to further investigate it. To do so, literature emphasized the need for randomized trials investigating the relative contribution of MLD to DLT.[31] For this reason, but especially out of ethical considerations as well, we opted for a design in which the effects of different types of MLD (including placebo MLD) were examined in addition to the other components of DLT, instead of the different types of MLD alone.

a. Critical reflection on the method of traditional MLD

Since many years, **several schools** train physiotherapists in MLD (e.g. Lerner, Casley-Smith, Leduc, Vodder, and colleagues), whereas each school has developed their own technique based on different insights. As a result, MLD has a worldwide application as a treatment modality for many years.[32] This makes it difficult to develop a method that includes all MLD methods, a so-called 'traditional MLD' that could act as a control group in our RCT. In order to define this traditional method of MLD, consensus was reached after discussion with a team of experts in the field of lymphology with manifold years of experience in MLD according to the Leduc and the Vodder method. We have opted for a combination of these two methods because 1) the effects of these methods were investigated in the various RTC's reported in the meta-analysis of Huang et al[32] and systematic review of Ezzo et al[31], and 2) these two methods are most frequently applied in Belgium. Furthermore, in clinical practice a combination of different methods of MLD is also often used, supporting the relevance of our compound traditional MLD method. The (limited) available literature about this traditional MLD methods shows that there is a lot of controversy about the required application force when performing this drainage. For a long time is being told that the procedure needs a light application of pressure to the areas with superficial lymphatic vessels just below the skin. If the pressure is too high (i.e. higher than 40 mm Hg), it can result in a spasm of the smooth muscle sheath of the superficial lymphatic vessels, or it can lead to damage of the thin anchoring filaments.[33, 34] With the introduction of fluoroscopy-guided MLD in which a higher pressure is applied, criticism was voiced by several traditional MLD schools as they claim to have implemented higher pressure techniques as well in their methods. Nevertheless, no information about these adaptations can be found in the literature, let alone evidence regarding its effectiveness. Therefore, the traditional MLD techniques in our RCT were applied according to the manner as they were taught to our clinical experts by the MLD schools themselves.

Recently, also other studies have demonstrated a positive (short-term) physiological effect by means of an enhanced lymphatic transport (whether or not assisted with compression) after a single session of MLD according to Vodder[35] and Leduc[36] MLD schools, assisted with fluoroscopy. However, as the clinical and long-term effects after several MLD sessions have not yet been investigated in randomized trials, the relevance of these studies is limited for clinical practice.

b. Critical reflection on the method of fluoroscopy-guided MLD

As a fluoroscopic investigation **visualizes the individual superficial transport** of lymph from the hand up to the axilla, it can demonstrate alternative pathways towards other lymph nodes as well as areas with dermal backflow. During fluoroscopy-guided MLD, **higher pressure** resorption techniques by

using the thumb instead of the hand are performed, as well as and higher pressure gliding techniques on regions with evidence of dermal backflow. In contrast with was believed before, during these higher-pressure hand maneuvers, the superficial lymphatic system is not being damaged. Research revealed that in 30 healthy volunteers the mean lymphatic occlusion pressure in the upper limb was 86 mmHg.[37] This is more than the double of the previous reported pressure applied during traditional MLD methods. In addition, **gliding** (compared to no gliding) is hypothesized to be more effective to enhance lymphatic transport through the lymph collectors as well as through the lymph capillary network and interstitium.[37]

Therefore, the aim of our RCT was to investigate the clinical effect of a completely optimized MLD technique (i.e. optimization of the MLD maneuvers of which physiological effects after one session of fluoroscopy-guided MLD have already been proven in healthy volunteers and in patients with BCRL[37, 38], as well as having knowledge of the patient-specific superficial lymphatic network). In case this technique showed to be more effective, a new study had to be set up to investigate why it is more effective: because of the maneuvers or because of the knowledge of the lymphatic network.

Other advantages of the ICG imaging technique are that it is not radioactive, it is minimally invasive, and has better resolution compared to other lymphatic imaging techniques such as a lymphoscintigram.[39, 40] Especially its real-time imaging is an advantage for clinical practice as the lymph vessels and areas of disturbances are immediately projected on the screen, where after these areas can be marked on the affected limb. As the patient can visualize the images and marks, he or she may understand the pathology better.

A limitation of this investigation might be the fact that only the progression of the ICG uptake and transport through the superficial lymphatic network can be observed, up to a depth of ± 2 cm underneath the skin surface. The fluorescence intensity of ICG is dependent on the albumin concentration in the tissues and the presence of subcutaneous fat[39, 40] and vessel depth, and fatty tissues can result in scattering of the fluorescence which may lead to misinterpretation of the observed lymphatic flow and patterns.[40, 41] Generally, one could state that a limitation of fluorosocopy might be that the interpretation of images is rather subjective.[42] Therefore, research on the reproducibility of this imaging technique and, more specifically, of the applied protocol in our RCT, has been performed by colleagues of our research team. Results indicated that, overall, there was a moderate to good degree of agreement between the two assessors when evaluating the lymphatic architecture and transport by lymphofluoroscopy according to the trial's protocol. These results will be published in due course.

c. Critical reflection on the method of placebo MLD

The RCT included in this doctoral project comprised a three-arm design, consisting of an intervention group and two control groups, of which one was a placebo control group. This placebo MLD was added in the second control group instead of only providing DLT without MLD to ensure blinding of the patients, as experience in clinical practice revealed that patients report a positive subjective feeling after MLD, due to the pleasant, soothing character of the treatment. In our RCT this placebo drainage was a gentle massage in which relaxing transverse movements on the muscles of the ipsilateral neck, back, shoulder, arm and hand were performed. This way, patients of all three groups received the same amount and type of attention during their treatments. Of course, a condition was that this placebo drainage in no case exerted a stimulating effect on the lymph flow, which was verified through fluoroscopic real-time imaging.

d. Critical reflection on the effect of MLD

It was hypothesized that patients receiving fluoroscopy-guided MLD during the intensive treatment phase, should show 1) a significantly greater decrease in lymphedema volume at the level of the arm/hand, or 2) significantly less accumulation of lymph at the level of the shoulder/trunk, than patients receiving the traditional MLD or placebo MLD (primary outcomes). Also, that patients receiving fluoroscopy-guided MLD during the intensive treatment phase, should show 1) a significantly greater reduction in amount of problems in lymphedema-related functioning, or 2) a significantly greater improvement in quality of life than patients receiving the traditional MLD or placebo MLD (secondary outcomes). Nevertheless, results of our RCT expressed that, in terms of these primary and secondary outcomes, infrared fluorescence imaging or lymphofluoroscopy **did not contribute to a more efficient MLD** (as an adjunct to DLT). Future studies in which the effect of (fluoroscopy-guided) MLD on other secondary outcome measures such as hardness and fibrosis of the skin, water content, skin thickness and lymph transport in the long term, should and will be investigated as well, in order to elucidate whether MLD might have a relevant beneficial effect on these aspects.

One can postulate that patients receiving placebo MLD might have been aware of their treatment allocation, and as a result, a performance bias could be induced. However, when patients at the end of the follow-up phase were asked to denote the treatment group they believed they were allocated to, only 23% (n=38/168) of the patients indicated (knew it or made a right guess) the correct treatment group (of them, only 5% were patients from the placebo MLD group). Alternatively, 77% (n=130/168) of the patients claimed not to have any idea to which group they were allocated to (n=69/168), or indicated a wrong treatment group (n=60/168). As a result, the risk for performance bias was negligible.

2.3 Critical reflection on evaluation methods of lymphedema

a. Primary outcome parameters

The first primary outcome parameter in our RCT was the *change in excessive lymphedema volume at the level of the arm/hand*. For evaluating swelling, the water displacement method and circumference measurements are the most frequently used methods[20] and are recommended as best practice for measuring lymphedema in extremities.[21] As the study in Chapter 3 revealed better reliability and less limitations for its use in clinical practice, we used circumference measurements with the perimeter to evaluate the excessive arm volume in patients with BCRL.[4] Based on circumference measures, the volume of the arm was calculated using the widely accepted truncated cone formula. This formula assumes that the arm resembles a conical shape, rather than a cylinder, which is assumed to be a truer representation of a lymphedematous limb.[43, 44] However, this formula postulates that every section of the limb represents a perfect circle, and that the walls of the cone are rectilinear. Consequently, using this method can also result in an overestimation or underestimation of the actual limb volume.[45] Furthermore, the volume of the hand is not included in this calculation since the conical assumption has shown not to be valid for hand shape.[46] Therefore, hand volume was separately determined using water displacement, which has shown to be a reliable and time-efficient method as well in Chapter 3.[4] Consequently, based on the results of this subtrial, the final procedure for analyzing the change in excessive lymphedema volume (i.e. first primary outcome measure of our RCT), was selected. With regard to the timing of the different subtrials, it might have been more logical if this reliability study would have been conducted earlier in time, prior to the start of the RCT's assessments. Yet, as my PhD period started when the recruitment of participants for the RCT was already ongoing, it was impossible to do so. Fortunately, however, the clinical evaluations of our EFforT-BCRL trial consisted of an extensive test battery, in which both arm circumferences and water displacement measures already were incorporated.

The second primary outcome measure was the *change in excessive fluid accumulation at the level of the shoulder/trunk*. Edema accumulation at the trunk[47] (or posterior axillary fold) has been recognized in patients with BCRL, and it has been suggested that MLD might play an important role in such areas that are not conducive to compression therapy. In the present study an MMDC device was selected to measure and evaluate the water content in the skin at the level of the shoulder and trunk, as this device can be used to determine the tissue dielectric constant (in terms of the percentage of water content or PWC%), at any particular site of the body.[48, 49] However, only up to a depth of 2-3 mm this portable device allows measuring free and bounded water in the tissue through which the electromagnetic wave passes.[50] Therefore, questions arise whether the total accumulation of interstitial fluid can be taken into account using the MMDC device, as measurements are mainly

focused on the evaluation of epidermal edema (up to 2-3 mm) with only partly giving information regarding the subcutaneous area. Further secondary analyses in which changes in thickness of both skin layers (cutis and subcutis) are being evaluated using ultrasonography, should shed more light on this aspect.

b. Secondary outcome parameters

The first secondary outcome parameter being evaluated in our RCT, was the change in amount of *problems in lymphedema-related functioning*. Problems in functioning were evaluated using the Lymph-ICF-UL questionnaire. This revised version of the original questionnaire[6] in which the scoring system was amended from a visual analogue scale into a numeric rating scale (0-10), has shown to be valid and reliable in Chapter 5[7] as well as responsive in Chapter 6[9]. Also the French version of this questionnaire proved to be valid and reliable in Chapter 7.[10] The total score represents the total amount of problems in functioning using a percentage score between 0-100. The lower the total score, the lower the amount of problems in daily functioning due to the BCRL. As this total score is based on the individual scores of 29 questions that can be divided into 5 subdomains (problems in physical functioning, mental functioning, household activities, mobility activities and life and social activities), it provides opportunities to verify which aspects of functioning are being influenced by therapy and which are not.

Another secondary outcome parameter was the improvement in *overall quality of life*, which was captured through the McGill Quality of Life Questionnaire. This is a generic questionnaire originally developed for palliative patients, and was used in chronic diseases.[51] A few years ago, the questionnaire was validated in patients with BC and showed to be reliable as well.[52] The questionnaire counts 16+1 questions, which relate to the following domains: physical symptoms; physical wellbeing, psychological symptoms; existential wellbeing and support. Also a numeric rating scale with 11 possibilities (0-10) is used for the 16 questions and part D is an open question.[52] An advantage of using of this questionnaire is the fact that it is an existential questionnaire. Hence, patients can indicate up to three physical complaints or problems, of which they experience the most burden and impact on personal wellbeing. Especially in a BC population this can be beneficial, as it is characterized by various post treatment morbidities.[52] Clinical responsiveness of this questionnaire has not yet been investigated. Responsiveness is defined as the ability of a questionnaire to detect clinically important changes over time, even if these changes are small. As in our RCT, the quality of life remained stable in all patients during and after decongestive treatment, questions might arise about the sensitivity of this questionnaire to detect changes over time in a patient's quality of life. Nevertheless, as previous research also demonstrated that changes in arm volume are not predictive for changes in overall quality of life[53, 54], it is not entirely unexpected that the significant reduction of lymphedema volume

and lymphedema-related problems in functioning (such as physical, mental, social functioning) in the participants of our RCT, did not have impacted their general quality of life.

3. Methodological considerations of the project: limitations and strengths

Some methodological considerations regarding the conducted studies within this doctoral project should be mentioned.

The main project on which the entire PhD is founded, was the four-year randomized trial regarding the effectiveness of fluoroscopy-guided MLD (EFforT-BCRL trial).

First of all, a limitation of the RCT was that the inclusion of patients was ended before the project's predefined number of patients (n=201, incorporating 9 drop-outs) was reached. A first reason for the fact that the accrual rate was lower than anticipated, could have been the relatively strict inclusion and exclusion criteria together with the fact that participation in this trial required a great effort of patients (e.g. more than 30 trips to the hospital). With our research team, we decided that patients who had undergone a lymph node transplantation or lymphovenous shunt in the past, were excluded. The motivation for this decision was to be able to conclude, at the end of the trial, that the final treatment outcome was entirely obtained by the conservative treatment modalities that were provided during the trial. However, as during the past years surgical interventions (reconstructive and reductive) for BCRL have gained increased acceptance worldwide[20], a number of patients (*23 of the 391 screened patients*) that had undergone reconstructive surgery was no longer eligible for the present RCT (although they still showed at least 5% volume difference and signs of pitting). The second reason that might have impeded the inclusion rate, is the fact that less patients are developing arm lymphedema compared to a few years ago (see section 2.1 *"What is breast cancer-related lymphedema?"* – p. 345). Due to improved screening and awareness for BC over the past years, the proportion of patients with clinically negative axilla (cN0) has increased.[26] Taken together with the de-escalation in surgical axillary management, this implicates that throughout the last years, more and more SLNB's are being performed during surgery for BC without need for (completion) ALND. Consequently, the in 2013 reported pooled estimate for arm lymphedema incidence of 16.6%[2] might be overestimated, as less patients develop BCRL after a SLNB compared to an ALND (5.6% versus 19.9%).

However, a survey among 78 intervention studies showed that many studies face recruitment problems in Dutch primary care research: almost 40% of projects had to extend the fieldwork period

by at least 50%.[55] In studies in which the general practitioner or practice assistant was the first to inform the patient about the study, patient recruitment turned out to be less successful than when the patient received a letter by mail. Additionally, this study indicated that Lasagna's Law, a phenomenon coined by the American pharmacologist Louis Lasagna stating that medical investigators regularly overestimate the number of patients available for a research study[56], also holds in Dutch primary care research.[55] This might also have been the case in some of our trial's participating research centers, in which the recruitment was remarkably slower than estimated. Nevertheless, although the planned sample size was increased from 64 to 67 subjects per group to anticipate potential drop-out and the study was terminated earlier as there were fewer drop-outs than initially estimated (only 4 patients were lost to follow-up instead of 9 that were estimated), this did not jeopardize the final power of the primary analysis, since this analysis was still based on information from 194 subjects at baseline (65, 64, 65 in the 3 groups, respectively) and 190 subjects (63, 63, 64 in the 3 groups, respectively) after 3 weeks of intensive treatment.

Secondly, as a general limitation of an experimental design oftentimes is mentioned that the external validity is compromised. More specifically the fact that it can be difficult to export and generalize findings and conclusions outside the research setting, as during the trial the interventions and assessments all occurred in a very controlled manner. Indeed, the latter cannot be disputed. In our RCT, assessments and treatments occurred in a controlled and standardized manner to make sure each therapist offered the same treatment and, consequently, we would be able to draw proper conclusions. Nevertheless, the treatments we provided were according to the international recommendations on how treatments should be provided in clinical practice, based on guidelines published by experts in the field.

Thirdly, as the patients participating in our RCT did not receive a lymphoscintigraphic evaluation at baseline, one can postulate that some of the information is missing, since information regarding the lymphatic transport in the deep lymphatic system is lacking. However, as all patients included in this RCT were patients with arm lymphedema as a consequence of the treatment for BC, one can assume that particularly the superficial lymphatic system of these patients has been damaged. Therefore, it is not necessary to additionally expose all patients to a nuclear (ionizing) investigation, requiring a lot of time as well. Additionally, as mentioned earlier, the real-time imaging is an important advantage of a lymphofluoroscopic investigation as the lymphatic vessels and areas of disturbances are immediately being projected on the screen and these areas can be marked on the affected limb. In addition, the patient can immediately visualize the images which can help to understand his or her pathology better.

Next to these considerations, this RCT had several strengths. **First,** sample size calculations were performed in advance, randomization was concealed, both patients as well as assessors were blinded for the treatment allocation and the trial was placebo-controlled. **Second,** only 5 patients dropped out during the intensive treatment phase, of which 4 (2.1%) were lost to follow-up. Also long-term follow-up was good, as only 3 additional patients were lost to follow-up during the 6-monthly maintenance phase (7/194 patients in total during the entire study period or 3.6%). **Third,** patients in all three treatment groups received 13 intensive treatment sessions on average of the 14 sessions that were initially planned, and 17 maintenance treatment sessions on average of the 18 sessions that were initially planned. All therapists performed treatments in the intervention group as well as in the two control groups. In each study center, patients of all three treatment groups were treated by the same (team of) therapists who moved between the different centers. With exception of the type of MLD applied, all other components of the standard treatment were the same for each patient. Consequently, treatment programs were very similar between groups. **Fourth,** as five study centers participated in this trial, patients could be recruited in nearly all regions of Flanders. This way, as well as by including both men and women with unilateral BCRL for at least 3 months, with a lymphedema severity ranging between ISL stages I to IIb, and with at least 5% of volume excess, we believe a fairly degree of heterogeneity among the study participants could be achieved, making the study sample representative for a lot of patients with BCRL. Between the three groups, patient characteristics at baseline were comparable. **Fifth,** by educating patients a self-MLD that they needed to perform during the maintenance treatment phase on the days no treatment was provided by the therapist, we have tried to get the most out of the MLD treatment effect. Throughout the entire study period (except for the two weekends during the intensive treatment phase), MLD was applied on a daily basis. Additionally, during the entire study period, treatment adherence was evaluated by means of a diary that all patients needed to fill in. Of the patients that already have returned their diary, 79% (147/185) filled it in during the entire study period as requested. **At last,** the risk of performance bias (e.g. in patients receiving placebo MLD) was negligible, as more than 75% of the patients did not know their treatment allocation or indicated a wrong treatment group.

In addition to the RCT, seven other studies were conducted.

In Chapter 3, reliability, time-efficiency and clinical feasibility of five different and commonly used methods for evaluating excessive arm volume in patients with BCRL in clinical practice, were investigated and compared. To investigate intra- and inter-rater reliability, measurements were performed twice by the same assessor and once by a different assessor, in 30 study participants of the EFforT-BCRL trial. A methodological flaw in this design might have been the number of different raters

that were included in this study. In order to examine inter-rater reliability in particular, the inclusion of 30 assessors (instead of 2) and 3 patients (instead of 30), might have been interesting as well.[57] However, literature showed that the current methodology is the most commonly applied design in comparable reliability studies. Moreover, in most of the clinical practices in Belgium patients are being treated and consecutively evaluated by no more than two different edema therapists. A strength of the studies investigating the reliability of evaluation methods for swelling (Chapter 3) or water content (Chapter 4), is that reliability was analyzed by measuring both the edematous and the non-edematous limb, enabling that those results can be extrapolated to a population with lymphedema as well as to a healthy population or to a patient population without clinical representation of lymphedema.

Last, in Chapter 9, a longitudinal cost analysis was performed in order to provide an overview of the mean annual direct healthcare costs covered by the healthcare system, as well as of the out-of-pocket expenses paid by Belgian patients struggling with BCRL. In this study, 166 participants supplied nearly 13 months of cost data. Knowledge of costs related to BCRL not only improves the understanding of the economic burden of this morbidity, but also launches a baseline of comparison for future cost-analytic or cost-effectiveness studies.[58] Although, one should keep in mind that, as the present study did not compare the costs and the consequences of two or more interventions (as with a cost-effectiveness or cost-utility analysis), we should speak of a cost-descriptive study, rather than a *full* economic evaluation.[59] Despite the importance of this cost-descriptive study, some methodological considerations that could have implied an underestimation of healthcare costs should be mentioned. First, indirect costs were omitted in the current study, possibly inducing a narrow perspective bias.[60] A reason for this is the fact that, primarily, these costs may not be caused by the lymphedema but by the (previous) treatment for malignant disease.[61] However, they are important to take into consideration, knowing that for diseases in general, 70% of the total costs are direct and 30% are indirect.[62] Second, costs were administered through a retrospective cost questionnaire. Expenses during the past three months were reported by the patients, which relies on momentary recall that may induce some recall error.[63] Third, in case patients indicated to have no idea of the cost of their received physical therapy session and did not report the name or other contact details of the therapist, it was assumed that the participants visited an accredited physiotherapist. However, as 16% of the Belgian physiotherapists are not affiliated to the NIHDI convention, this might underestimate the actual (patient-borne) economic burden in Belgium. Lastly, any additional, individual insurances (e.g. for hospitalizations), were not encountered. However, as no patients reported any hospitalizations or surgical procedures, this should not have affected the present study results significantly. Nevertheless, a detailed collection of direct healthcare costs could be achieved in this study due to the approach of

both using billing prices of materials used during treatment, as well as the collection of additional costs made by patients by using a cost questionnaire. Therefore, this first available cost-descriptive study regarding direct healthcare costs for Belgian patients struggling with BCRL, provided important insights regarding the financial burden both for health insurers as for patients.

Noteworthy, a strength of this doctoral project in general is that in all studies patients with arm lymphedema were included, enabling that the study samples are fairly representative for all patients with BCRL stage I to IIb.

4. Clinical implications and future perspectives

As a respond to the call in literature emphasizing the need for randomized trials investigating the relative contribution of MLD to DLT[31], as well as to the quest for a patient-tailored MLD variant that could be (more) effective, a multi-center RCT was established.[3] The results of this trial and of the different subtrials, together with our clinical experience are translated into following recommendations.

First of all, results of the RCT showed that, regarding volume reduction and change in fluid accumulation (primary outcomes), as well as regarding reduction in amount of problems in lymphedema-related functioning and improvement in quality of life (secondary outcomes), **no additional effect of fluoroscopic MLD (as an adjunct to DLT)** could be demonstrated.

Despite the lack of evidence of an added value of fluoroscopic-guided MLD, a fluoroscopic investigation can still be useful in patients with a damaged superficial lymphatic network (as in case of BCRL) to optimize BCRL treatment. For example, in the prescription of appropriate compression hosiery, the compression can be adapted to the individual lymphatic (alternative) pathways. Areas with dermal backflow provide information regarding the locations where compression is needed. In addition, the more severe the degree of dermal backflow in a certain area, the higher the pressure that should be applied to that corresponding area. Furthermore, an absence of superficial lymphatic transport visualized by a fluoroscopic investigation, might highlight the importance of muscle pump activation (and consequently the indirect stimulation of the deep lymphatic system) even more. Nevertheless, despite its important opportunities in enhancing a patient-tailored approach, a lymphofluoroscopic investigation is not required in every patient with BCRL. We should acknowledge that it is still an investigation that needs to be performed in a medical setting requiring specific and expensive equipment. As a recent study based on the EFforT-BCRL trial's fluoroscopic data indicated that the results of a lymphofluoroscopy can be partially estimated by several clinical assessments, this

implicates that the lymphofluoroscopic investigation should not be necessary in all cases in order to provide an individualized treatment.[64] The most appropriate clinical measurements to estimate lymphatic transport disturbances in patients with ISL stage I to IIb lymphedema 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.[64] Nevertheless, information regarding (alternative) superficial draining pathways is only collected through fluoroscopic investigation. Consequently, in case of doubt, or when the provided treatment does not lead to the expected outcome, a fluoroscopic investigation may still be appropriate and desirable.

Secondly, results of this RCT not only failed to prove an additional effect of fluoroscopy-guided MLD, but of the **applied traditional MLD** as well, as the reduction in lymphedema volume (arm/hand) and the increase in fluid accumulation (shoulder/trunk) in both groups were not statistically significant different than in patients receiving a placebo MLD as an adjunct to DLT. No differences between the groups regarding the reduction in amount of problems in functioning or improvement in overall quality of life, were found either. This means that, for these clinical outcomes, the content of the treatment sessions should be reconsidered as there is no indication for including (time-consuming) MLD in the limited treatment time per session. Alternatively, more time should be spent on other, well-investigated and evidence-based treatment options of DLT such as compression therapy and exercise therapy, together with a great emphasis on education and self-management.[65] Future studies should investigate other secondary outcome parameters as well, such as the effect of (fluoroscopy-guided) MLD on hardness and fibrosis of the skin, water content, skin thickness and lymph transport in the long term, to see whether it may be beneficial for those clinical outcome measures to include MLD again as part of the standard treatment in DLT. In addition, sub-group analyses should be performed to investigate whether or not sub-groups of patients with specific characteristics (for instance based on the severity of volume differences, amount of pitting or dermal rerouting/backflow patterns) might show different outcomes regarding the clinical effect of (fluoroscopic-guided) MLD in addition to DLT. However, as these outcomes are secondary outcome parameters (without corrections being made for multiple testing), and therefore were not taken into account in the initial power calculations, single significant values should be interpreted with caution.

Next, evidence-based treatment should be accompanied by valid, reliable, rapid and easy-to-use evaluation methods that can be attributed to closely monitor the treatment results. To **evaluate excessive lymphedema volume** over time, it was shown that all five investigated volume measurements (i.e. traditional volumetry with overflow, volumetry without overflow, inverse volumetry, opto-electronic volumetry and calculated volume based on circumference measurements)

were reliable, but that the calculated arm volume based on circumference measurements was the most reliable (with highest ICC's and lowest SEM's) and most feasible method (with the least amount of limitations) to apply in clinical practice. Hereby, when measurements are performed by the same assessor, a test variation of more than 42ml should be considered as a change in excessive arm volume, exceeding the (potential) measurement error. In case the measurements are performed by different assessors, a test variation of more than 45ml exceeds the area of potential measurement errors. The device consists of materials with low costs, therefore it is easy to self-design a perimeter. For clinical centers having sufficient financial capacity, an opto-electronic volumeter can also be considered. However, a disadvantage of both methods is the fact that hand volume is not taken into account. Therefore, hand volume should be measured separately, for example by making use of a hand volumeter or figure-of-eight method.[66] We opted for a circumference measurement method that made use of a perimeter instead of separate girth measurements (using a tapeline), since it comprises several advantages compared to separate girth measurements. Future studies should compare reliability and correlate these two circumference measures, to investigate whether they could be used interchangeably. Furthermore, besides the already investigated concurrent validity of all five methods, research regarding the criterion validity of these methods is warranted to ascertain whether the measured arm volume fully corresponds the actual arm volume.[4]

Besides swelling, also other lymphedema characteristics can be evaluated over time such as water content in the skin. **To evaluate the water content in the skin** over time, it was demonstrated that the MMDC device is a reliable device to use, both by the same assessor as by different assessors. When single measurements are performed by the same assessor, a test variation of more than 5.23 PWC% (range between 1.77 PWC% and 5.23 PWC%, according to the location at the edematous limb) or 0.17 (range between 0.07 and 0.17) in case inter-limb ratios are calculated, should be considered as a change in local tissue water, exceeding the measurement error at the edematous limb. In case the measurement is performed by different assessors, a test variation of more than 5.34 PWC% (range between 2.31 PWC% and 5.34 PWC%, according to the location at the edematous limb) or 0.16 (range between 0.05 and 0.16) in case inter-limb ratios are calculated, exceeds the area of measurement error. Consequently, if 2 MMDC measurements differ more than 5.23 PWC% or 5.34 PWC%, respectively (or less, depending on the exact location), the difference can be interpreted as an identifiable difference in local tissue water which is not related to a standard error of the measurement. Additionally, this study showed that the pitting test has a very strong intra-rater agreement at well-nigh all measurement points, but a rather questionable inter-rater agreement, especially at the medial elbow and the breast. Therefore, follow-up evaluations over time incorporating the pitting test should be performed by the same assessor per patient. Furthermore, one

should keep in mind that in both methods different parts of the skin are being assessed. MMDC measurements are mainly focused on the evaluation of epidermal edema (up to 2-3 mm) with only partly giving information regarding the subcutaneous area, whereas the pitting test does provide information concerning both skin layers. Further research should focus on the amount of pressure necessary to evaluate the skin tissue correctly and to improve the standardization of the pitting test. More evidence regarding what exactly is being measured up to which depth, is needed. In addition, after standardization of this test is completed, future studies that examine concurrent and criterion validity of the pitting test and the MMDC device, for instance by comparing obtained results with ultrasound images representing skin thickness, are warranted to increase the clinical relevance of both tools.[5]

Additionally, BCRL does not only induce physical and functional impairments such as swelling or heaviness, but also psychosocial problems.[67] Given the large role on subjective complaints in lymphedema, paying attention to only physical edema characteristics such as swelling and water content is not enough to outline a holistic, patient-centered follow-up with tailored treatment and support.[65] **To monitor long-term treatment effects on problems in functioning, activity restrictions and participation problems** due to the edema, valid and reliable lymphedema-specific questionnaires should be used. The Dutch Lymph-ICF questionnaire using a VAS scoring system already proved to be valid and reliable.[6] As patients mentioned that a scoring system making use of a numeric rating scale would be easier, the scoring system of the questionnaire was adapted. This revised Lymph-ICF-UL questionnaire is also a reliable and valid Dutch questionnaire, using a simplified and clearer scoring procedure to assess problems in functioning of patients with arm lymphedema developed after BC treatment. By making use of this questionnaire, tailored treatment goals can be set. Thereafter, the questionnaire may be used to monitor long-term results of this treatment and self-care as it was shown that the Lymph-ICF-UL questionnaire is responsive to change after DLT in patients with BCRL. Based on the GPE outcome as anchor-based method, an MCID of 9% in total score indicates a clinically relevant change. However, no correlation between Lymph-ICF-UL change scores and GPE was found, indicating that the questionnaire showed a reduced ability to discriminate between the amount of changes in Lymph-ICF-UL scores and the actual clinical improvement as reported by participants. As in our opinion this is mainly due to the strict protocol in which this investigation occurred, a future investigation should be continued in a clinical setting, enabling a greater amount of variability between the study participants and consequently, in their treatment responses.[9] Additionally, also in French-speaking patients with BCRL of the arm/hand the amount of problems in lymphedema-related functioning can be assessed, as the Lymph-ICF-UL questionnaire was translated into French. This French version also showed to be valid and reliable. Other researchers have translated the Lymph-ICF-UL questionnaire

into Danish[68], Turkish[69], and German / Thai / Chinese / Italian / Greek / Swedish (these latter versions have not yet been published).

Lastly, besides evidence regarding evaluation methods and treatment modalities in order to limit the physical, mental and/or psychosocial burden of BCRL, little was known about the **financial burden of BCRL and its sequelae**. Our systematic review regarding direct and indirect costs related to the treatment of BCRL and its sequelae revealed that there is a lack of economic analyses associated with BCRL in particularly European countries. Therefore, we conducted a longitudinal study which showed that BCRL imposes a significant economic burden to the health insurers as well as to patients. Three weeks of intensive DLT and 12 months of maintenance DLT, requires € 2279.10 per patient on average, without considering the direct non-medical and indirect costs. Of this amount, € 1827.36 (80%) on average is borne by the health insurer, and € 451.74 (20%) is borne by the patient. The main cost drivers for health insurers and patients were the costs for physical therapy sessions comprising MLD (on average € 1 014.17 (55.5%) and € 188.36 (41.7%) respectively) and for compression sleeves/gloves (on average € 806.93 (44.2%) and € 188.31 (41.7%) respectively). During the intensive treatment phase, a crucial treatment modality that precedes wearing compression stockings, is multi-layer bandaging. The mean cost for this equipment was € 60.44 per patient. Unfortunately, despite its necessity, these costs are entirely borne by patients in our country.

These insights into the financial impact of BCRL are important to inform decision makers (e.g. policy makers and insurers) about the burden of this disease, which may assist them to inaugurate evidence-based public health policies and guidelines. Future studies on the effectiveness of specific treatment modalities for BCRL should consider defining health economic analyses a priori in order to be able to withdraw proper high quality conclusions based on cost-effectiveness outcomes such as the Incremental Cost-Effectiveness Ratio (ICER) and/or quality adjusted life-years (QALY).[60] Full economic evaluations (taking into consideration the consequences of treatment) can provide well-founded answers on efficacy questions.[59] To do so, it is suggested to include a generic health-related quality of life questionnaire (e.g. the EQ-5D-5L) and utility instrument to allow comparisons across interventions and populations.[60] An appropriate time-horizon (≥12 months) should be defined and both incremental (direct and indirect) cost elements from a patient and societal perspective should be considered and collected prospectively.

5. Conclusions

With this doctoral project we have contributed to the current knowledge on BCRL treatment and evaluation options. In clinical practice, many time is spent on MLD as a treatment modality for BCRL. In scientific literature however, pooled data demonstrated only a limited non-significant additional value of MLD, which was not confirmed by randomized data yet. The results of this PhD project support previous findings that intensive DLT significantly reduces the lymphedema volume, and improves daily functioning in patients with BCRL. However, the results of our RCT do not support the hypotheses that, after 3 weeks of intensive DLT treatment, additional fluoroscopy-guided MLD will provide a greater volume reduction at the level of the arm/hand, or less accumulation of lymph at the level of the shoulder/trunk, than traditional of placebo MLD. Also, the amount of problems in lymphedema-related functioning improved significantly after DLT in all treatment groups, regardless of the type of MLD provided, and thus without statistical differences between treatment groups. General health-related quality of life remained stable in all groups over time. This means that, for all these clinical outcomes, there is **no indication** to include (time-consuming) MLD in the limited treatment time per session. Alternatively, more time should be spent on other, well-investigated and evidence-based treatment options such as compression therapy and exercise therapy, together with a great emphasis on education and self-management. Future studies will investigate other secondary outcome parameters as well, such as the effect of (fluoroscopy-guided) MLD on hardness and fibrosis of the skin, water content, skin thickness and lymph transport in the long term, to see whether MLD could be of any (relevant) benefit for those clinical outcome measures.

Several reliable evaluation tools are available to monitor treatment response over time. To evaluate excessive lymphedema volume of the arm, calculated volume based on arm circumferences (perimetry) showed to be the most reliable and most feasible method. In addition, hand volume should be assessed separately. To evaluate water content in the skin, the MMDC device can be used as a reliable tool to assess the epidermal water content. To evaluate water content in both the cutis and subcutis, the pitting test is an easy-to-use test that is reliable when repeatedly performed and rated by the same assessor per patient. To evaluate problems in daily functioning in both Dutch and French-speaking patients with BCRL, the Lymph-ICF-UL questionnaire (in both its Dutch and French language version) is an appropriate and useful tool characterized by good clinimetric properties, that can be utilized.

At last, BCRL is acknowledged as a troublesome morbidity as it is accompanied by physical, functional and psychosocial hardships. Besides that, due to the chronicity of lymphedema, it entails a tremendous financial impact on both the health insurer as well as on the patient.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA: a cancer journal for clinicians. 2012;62(1):10-29.
2. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol. 2013;14(6):500-15.
3. De Vrieze T, Vos L, Gebruers N, Tjalma WAA, Thomis S, Neven P, et al. Protocol of a randomised controlled trial regarding the effectiveness of fluoroscopy-guided manual lymph drainage for the treatment of breast cancer-related lymphoedema (EFforT-BCRL trial). European journal of obstetrics, gynecology, and reproductive biology. 2017.
4. De Vrieze T GN, De Groef A, Dams L, Van der Gucht E, Nevelsteen I, Devoodt N. Reliability and time efficiency of five different methods to determine arm volume in patients with breast cancer-related lymphoedema. 2019.
5. De Vrieze T, Gebruers N, Nevelsteen I, De Groef A, Tjalma WAA, Thomis S, et al. Reliability of the MoistureMeterD Compact Device and the Pitting Test to Evaluate Local Tissue Water in Subjects with Breast Cancer-Related Lymphedema. Lymphatic research and biology. 2019.
6. Devoogdt N, Van Kampen M, Geraerts I, Coremans T, Christiaens MR. Lymphoedema Functioning, Disability and Health questionnaire (Lymph-ICF): reliability and validity. Physical therapy. 91. United States2011. p. 944-57.
7. De Vrieze T, Vos L, Gebruers N, De Groef A, Dams L, Van der Gucht E, et al. Revision of the Lymphedema Functioning, Disability and Health Questionnaire for Upper Limb Lymphedema (Lymph-ICF-UL): Reliability and Validity. Lymphatic research and biology. 2019.
8. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2010;19(4):539-49.
9. De Vrieze T, Gebruers N, Nevelsteen I, Tjalma WAA, Thomis S, De Groef A, et al. Responsiveness of the Lymphedema Functioning, Disability, and Health Questionnaire for Upper Limb Lymphedema in Patients with Breast Cancer-Related Lymphedema. Lymphatic research and biology. 2020:10.1089/lrb.2019.0073.
10. De Vrieze T, Frippiat J, Deltombe T, Gebruers N, Tjalma WAA, Nevelsteen I, et al. Cross-cultural validation of the French version of the Lymphedema Functioning, Disability and Health Questionnaire for Upper Limb Lymphedema (Lymph-ICF-UL). Disabil Rehabil. 2020:1-8.
11. De Vrieze T, Nevelsteen I, Thomis S, De Groef A, Tjalma WAA, Gebruers N, et al. What are the economic burden and costs associated with the treatment of breast cancer-related lymphoedema? A systematic review. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2020;28(2):439-49.
12. Ancukiewicz M, Miller CL, Skolny MN, O'Toole J, Warren LE, Jammallo LS, et al. Comparison of relative versus absolute arm size change as criteria for quantifying breast cancer-related lymphedema: the flaws in current studies and need for universal methodology. Breast cancer research and treatment. 2012;135(1):145-52.
13. Cormier JN, Xing Y, Zaniletti I, Askew RL, Stewart BR, Armer JM. Minimal limb volume change has a significant impact on breast cancer survivors. Lymphology. 2009;42(4):161-75.
14. Armer J. The Problem of Post-Breast Cancer Lymphedema: Impact and Measurement Issues. Cancer investigation. 2005;23(1):76-83.
15. Smoot BJ, Wong JF, Dodd MJ. Comparison of diagnostic accuracy of clinical measures of breast cancer-related lymphedema: area under the curve. Archives of physical medicine and rehabilitation. 2011;92(4):603-10.
16. Armer JM, Stewart BR. A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. Lymphatic research and biology. 2005;3(4):208-17.

17. Dylke ES, Schembri GP, Bailey DL, Bailey E, Ward LC, Refshauge K, et al. Diagnosis of upper limb lymphedema: development of an evidence-based approach. Acta oncologica (Stockholm, Sweden). 2016;55(12):1477-83.
18. Paskett ED, Dean JA, Oliveri JM, Harrop JP. Cancer-related lymphedema risk factors, diagnosis, treatment, and impact: a review. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(30):3726-33.
19. Kosir MA, Rymal C, Koppolu P, Hryniuk L, Darga L, Du W, et al. Surgical outcomes after breast cancer surgery: measuring acute lymphedema. The Journal of surgical research. 2001;95(2):147-51.
20. The Diagnosis and Treatment of Peripheral Lymphedema: 2020 Consensus Document of the International Society of Lymphology. Lymphology. 2020;53(1):3-19.
21. Hidding JT, Viehoff PB, Beurskens CH, van Laarhoven HW, Nijhuis-van der Sanden MW, van der Wees PJ. Measurement Properties of Instruments for Measuring of Lymphedema: Systematic Review. Physical therapy. 2016;96(12):1965-81.
22. Gebruers N, Verbelen H, De Vrieze T, Vos L, Devoogdt N, Fias L, et al. Current and future perspectives on the evaluation, prevention and conservative management of breast cancer related lymphoedema: A best practice guideline. European journal of obstetrics, gynecology, and reproductive biology. 2017;216:245-53.
23. Gebruers N, Truijen S, Engelborghs S, De Deyn PP. Volumetric evaluation of upper extremities in 250 healthy persons. Clinical physiology and functional imaging. 2007;27(1):17-22.
24. Devoogdt N, Geraerts I, Van Kampen M, De Vrieze T, Vos L, Neven P, et al. Manual lymph drainage may not have a preventive effect on the development of breast cancer-related lymphoedema in the long term: a randomised trial. J Physiother. 2018;64(4):245-54.
25. Specht MC, Miller CL, Russell TA, Horick N, Skolny MN, O'Toole JA, et al. Defining a threshold for intervention in breast cancer-related lymphedema: what level of arm volume increase predicts progression? Breast cancer research and treatment. 2013;140(3):485-94.
26. Zahoor S, Haji A, Battoo A, Qurieshi M, Mir W, Shah M. Sentinel Lymph Node Biopsy in Breast Cancer: A Clinical Review and Update. Journal of breast cancer. 2017;20(3):217-27.
27. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. Cancer. 2006;106(1):4-16.
28. Bergmann A, da Costa Leite Ferreira MG, de Aguiar SS, de Almeida Dias R, de Souza Abrahao K, Paltrinieri EM, et al. Physiotherapy in upper limb lymphedema after breast cancer treatment: a randomized study. Lymphology. 2014;47(2):82-91.
29. Gradalski T, Ochalek K, Kurpiewska J. Complex Decongestive Lymphatic Therapy With or Without Vodder II Manual Lymph Drainage in More Severe Chronic Postmastectomy Upper Limb Lymphedema: A Randomized Noninferiority Prospective Study. J Pain Symptom Manage. 2015;50(6):750-7.
30. Tambour M, Holt M, Speyer A, Christensen R, Gram B. Manual lymphatic drainage adds no further volume reduction to Complete Decongestive Therapy on breast cancer-related lymphoedema: a multicentre, randomised, single-blind trial. Br J Cancer. 2018;119(10):1215-22.
31. Ezzo J, Manheimer E, McNeely ML, Howell DM, Weiss R, Johansson KI, et al. Manual lymphatic drainage for lymphedema following breast cancer treatment. Cochrane Database Syst Rev. 2015(5):Cd003475.
32. Huang TW, Tseng SH, Lin CC, Bai CH, Chen CS, Hung CS, et al. Effects of manual lymphatic drainage on breast cancer-related lymphedema: a systematic review and meta-analysis of randomized controlled trials. World J Surg Oncol. 2013;11:15.
33. Foldi E. Massage and damage to lymphatics. Lymphology. 1995;28(1):1-3.
34. Eliska O, Eliskova M. Are peripheral lymphatics damaged by high pressure manual massage? Lymphology. 1995;28(1):21-30.
35. Lopera C, Worsley PR, Bader DL, Fenlon D. Investigating the Short-Term Effects of Manual Lymphatic Drainage and Compression Garment Therapies on Lymphatic Function Using Near-Infrared Imaging. Lymphatic research and biology. 2017;15(3):235-40.

36. Medina-Rodríguez ME, de-la-Casa-Almeida M, Martel-Almeida E, Ojeda-Cárdenes A, Medrano-Sánchez EM. Visualization of Accessory Lymphatic Pathways, before and after Manual Drainage, in Secondary Upper Limb Lymphedema Using Indocyanine Green Lymphography. Journal of clinical medicine. 2019;8(11).
37. Belgrado JP, Vandermeeren L, Vankerckhove S, Valsamis JB, Malloizel-Delaunay J, Moraine JJ, et al. Near-Infrared Fluorescence Lymphatic Imaging to Reconsider Occlusion Pressure of Superficial Lymphatic Collectors in Upper Extremities of Healthy Volunteers. Lymphatic research and biology. 2016;14(2):70-7.
38. Tan IC, Maus EA, Rasmussen JC, Marshall MV, Adams KE, Fife CE, et al. Assessment of lymphatic contractile function after manual lymphatic drainage using near-infrared fluorescence imaging. Archives of physical medicine and rehabilitation. 2011;92(5):756-64.e1.
39. Mihara M, Hara H, Araki J, Kikuchi K, Narushima M, Yamamoto T, et al. Indocyanine green (ICG) lymphography is superior to lymphoscintigraphy for diagnostic imaging of early lymphedema of the upper limbs. PloS one. 2012;7(6):e38182.
40. Pallotta OJ, van Zanten M, McEwen M, Burrow L, Beesley J, Piller N. Development and validation of a custom made indocyanine green fluorescence lymphatic vessel imager. Journal of biomedical optics. 2015;20(6):066003.
41. Weiler M, Kassis T, Dixon JB. Sensitivity analysis of near-infrared functional lymphatic imaging. Journal of biomedical optics. 2012;17(6):066019.
42. Granoff MD, Johnson AR, Lee BT, Padera TP, Bouta EM, Singhal D. A Novel Approach to Quantifying Lymphatic Contractility during Indocyanine Green Lymphangiography. Plast Reconstr Surg. 2019;144(5):1197-201.
43. Gjorup C, Zerahn B, Hendel HW. Assessment of volume measurement of breast cancer-related lymphedema by three methods: circumference measurement, water displacement, and dual energy X-ray absorptiometry. Lymphatic research and biology. 2010;8(2):111-9.
44. Yamamoto T, Yamamoto N, Hara H, Mihara M, Narushima M, Koshima I. Upper extremity lymphedema index: a simple method for severity evaluation of upper extremity lymphedema. Annals of plastic surgery. 2013;70(1):47-9.
45. Levenhagen K, Davies C, Perdomo M, Ryans K, Gilchrist L. Diagnosis of Upper Quadrant Lymphedema Secondary to Cancer: Clinical Practice Guideline From the Oncology Section of the American Physical Therapy Association. Physical therapy. 2017;97(7):729-45.
46. Taylor R, Jayasinghe UW, Koelmeyer L, Ung O, Boyages J. Reliability and validity of arm volume measurements for assessment of lymphedema. Physical therapy. 2006;86(2):205-14.
47. Roberts CC, Levick JR, Stanton AW, Mortimer PS. Assessment of truncal edema following breast cancer treatment using modified Harpenden skinfold calipers. Lymphology. 1995;28(2):78-88.
48. Nuutinen J, Ikaheimo R, Lahtinen T. Validation of a new dielectric device to assess changes of tissue water in skin and subcutaneous fat. Physiological measurement. 2004;25(2):447-54.
49. Mazor M, Smoot BJ, Mastick J, Mausisa G, Paul SM, Kober KM, et al. Assessment of local tissue water in the arms and trunk of breast cancer survivors with and without upper extremity lymphoedema. Clinical physiology and functional imaging. 2019;39(1):57-64.
50. Mayrovitz HN, Arzanova E, Somarriba S, Eisa S. Reference Values for Assessing Localized Hand Lymphedema Using Interhand Tissue Dielectric Constant Ratios. Lymphatic research and biology. 2018;16(5):442-5.
51. Cohen SR, Mount BM, Strobel MG, Bui F. The McGill Quality of Life Questionnaire: a measure of quality of life appropriate for people with advanced disease. A preliminary study of validity and acceptability. Palliat Med. 1995;9(3):207-19.
52. De Vrieze T, Coeck D, Verbelen H, Devoogdt N, Tjalma W, Gebruers N. Cross-cultural Psychometric Evaluation of the Dutch McGill-QoL Questionnaire for Breast Cancer Patients. Facts Views Vis Obgyn. 2016;8(4):205-9.
53. Dawes DJ, Meterissian S, Goldberg M, Mayo NE. Impact of lymphoedema on arm function and health-related quality of life in women following breast cancer surgery. Journal of rehabilitation medicine. 2008;40(8):651-8.

54. Hormes JM, Bryan C, Lytle LA, Gross CR, Ahmed RL, Troxel AB, et al. Impact of lymphedema and arm symptoms on quality of life in breast cancer survivors. Lymphology. 2010;43(1):1-13.
55. van der Wouden JC, Blankenstein AH, Huibers MJ, van der Windt DA, Stalman WA, Verhagen AP. Survey among 78 studies showed that Lasagna's law holds in Dutch primary care research. Journal of clinical epidemiology. 2007;60(8):819-24.
56. JAL G. Initial preparation for clinical trials. In: Harris EL FJ, editor. The principles and practice of clinical trials. Edinburgh/London: Livingstone; 1970.
57. Tidhar D, Armer JM, Deutscher D, Shyu CR, Azuri J, Madsen R. Measurement Issues in Anthropometric Measures of Limb Volume Change in Persons at Risk for and Living with Lymphedema: A Reliability Study. Journal of personalized medicine. 2015;5(4):341-53.
58. Shih YC, Xu Y, Cormier JN, Giordano S, Ridner SH, Buchholz TA, et al. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(12):2007-14.
59. Goossens ME, Evers SM, Vlaeyen JW, Rutten-van Molken MP, van der Linden SM. Principles of economic evaluation for interventions of chronic musculoskeletal pain. European journal of pain (London, England). 1999;3(4):343-53.
60. Evers SM, Hiligsmann M, Adarkwah CC. Risk of bias in trial-based economic evaluations: identification of sources and bias-reducing strategies. Psychology & health. 2015;30(1):52-71.
61. Gutknecht M, Herberger K, Klose K, Purwins S, Dietz D, Blome C, et al. Cost-of-illness of patients with lymphoedema. Journal of the European Academy of Dermatology and Venereology : JEADV. 2017;31(11):1930-5.
62. Dean LT, Moss SL, Ransome Y, Frasso-Jaramillo L, Zhang Y, Visvanathan K, et al. "It still affects our economic situation": long-term economic burden of breast cancer and lymphedema. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2018.
63. Goossens ME, Rutten-van Molken MP, Vlaeyen JW, van der Linden SM. The cost diary: a method to measure direct and indirect costs in cost-effectiveness research. Journal of clinical epidemiology. 2000;53(7):688-95.
64. Thomis S, Dams L, Fourneau I, De Vrieze T, Nevelsteen I, Neven P, et al. Correlation Between Clinical Assessment and Lymphofluoroscopy in Patients with Breast Cancer-Related Lymphedema: A Study of Concurrent Validity. Lymphatic research and biology. 2020.
65. Damstra RJ, Halk AB. The Dutch lymphedema guidelines based on the International Classification of Functioning, Disability, and Health and the chronic care model. Journal of vascular surgery Venous and lymphatic disorders. 2017;5(5):756-65.
66. Borthwick Y, Paul L, Sneddon M, McAlpine L, Miller C. Reliability and validity of the figure-of-eight method of measuring hand size in patients with breast cancer-related lymphoedema. European journal of cancer care. 2013;22(2):196-201.
67. Pusic AL, Cemal Y, Albornoz C, Klassen A, Cano S, Sulimanoff I, et al. Quality of life among breast cancer patients with lymphedema: a systematic review of patient-reported outcome instruments and outcomes. Journal of cancer survivorship : research and practice. 2013;7(1):83-92.
68. Grarup KR, Devoogdt N, Strand LI. The Danish version of Lymphoedema Functioning, Disability and Health Questionnaire (Lymph-ICF) for breast cancer survivors: Translation and cultural adaptation followed by validity and reliability testing. Physiotherapy theory and practice. 2019;35(4):327-40.
69. Kostanoglu A, Hosbay Z, Tarakci E. Lymphoedema functioning, disability and health questionnaire Turkish version: translation, cross-cultural adaptation and validation. Journal of physical therapy science. 2016;28(6):1728-32.
70. Kwan ML, Cohn JC, Armer JM, Stewart BR, Cormier JN. Exercise in patients with lymphedema: a systematic review of the contemporary literature. Journal of cancer survivorship : research and practice. 2011;5(4):320-36.
71. Rogan S, Taeymans J, Luginbuehl H, Aebi M, Mahnig S, Gebruers N. Therapy modalities to reduce lymphoedema in female breast cancer patients: a systematic review and meta-analysis. Breast cancer research and treatment. 2016;159(1):1-14.

SUMMARY

Breast cancer (BC) is the most common cancer among women, worldwide. The Belgian Cancer Registry reported 10 627 new BC diagnoses among women in 2017. Although breast cancer-related lymphedema (BCRL) is not the most prevalent complication after treatment for BC, it is internationally recognized as one of the most burdensome morbidities. The introduction of more effective treatment modalities has increased the number of BC survivors. Consequently, the amount of patients dealing with long-term side effects, such as lymphedema, has risen likewise. Today, pooled data reveals a BCRL incidence rate of 16.6%.

Manual lymph drainage (MLD) has been widely applied to treat BCRL, but its effectiveness and true merit remains unclear. Pooled data only demonstrated a limited non-significant additional value of 7% on lymphedema volume reduction, which should be confirmed by randomized data. A possible explanation is that MLD has been applied blind in previous studies, without knowledge of patient-specific lymphatic routes of transport, and according to a normal lymphatic anatomy. In addition, the MLD hand maneuvers used by the therapists in previous studies, possibly did not stimulate the lymphatic transport optimally. Near-infrared fluorescence imaging (or lymphofluoroscopy) has been introduced to visualize the superficial lymphatic network which allows MLD at the most needed location. A physiological effect after one session of fluoroscopy-guided MLD (using higher pressure gliding techniques on areas with evidence of dermal backflow instead of lower pressure pumping techniques that are applied in a 'blind' way) has already been demonstrated. However, evidence of a clinical and long-lasting effect is still lacking. Therefore, the main objective of this PhD was to investigate the effectiveness of fluoroscopy-guided MLD additional to the other modalities of decongestive lymphatic therapy (DLT) and compared to a traditional and a placebo drainage in the treatment of BCRL.

Given the extent of the project, this first aim was subdivided into the development of the protocol of this randomized, controlled, double-blind multi-center trial that was published in 2017 **(Chapter 1)**, and in a separate paper reporting study results and conclusions **(Chapter 2)**. The results of this RCT indicated that patients receiving fluoroscopy-guided MLD during the intensive treatment phase, did not show 1) a significantly greater decrease in lymphedema volume at the level of the arm/hand, or 2) significantly less accumulation of lymph at the level of the shoulder/trunk, than patients receiving the traditional MLD or placebo MLD (primary outcomes). Neither did patients receiving fluoroscopy-guided MLD during the intensive treatment phase show 1) a significantly greater reduction in amount of problems in lymphedema-related functioning, or 2) a significantly greater improvement in overall quality of life (secondary outcomes).

Seven other studies were performed in addition to this RCT. First of all, since an overview was lacking regarding the best method to evaluate excessive arm volume over time in patients with BCRL, a comparison between five different and commonly used volume measurements was made concerning reliability, time-efficiency and clinical feasibility (**Chapter 3)**. Results indicated that the calculated volume based on arm circumferences method is the best measurement method for evaluating excessive arm volume over time in terms of reliability, low error rate, low cost, few limitations, and time spent. Additionally, reliability of the MoisturemeterD Compact® (MMDC) device and the pitting test were investigated in order to evaluate local tissue water in the skin over time in patients with BCRL **(Chapter 4)**. MMDC measurements yielded moderate to very strong intra- (ICC 0.648-0.947) and inter-rater (ICC 0.606-0.941) reliability, depending on the measurement location on the edematous limb. The pitting test showed a very strong intra-rater agreement at nearly all defined points, but a weak inter-rater agreement, especially at the medial elbow and the breast. Consequently, the study supports the MMDC device and pitting test as being useful tools in the clinical evaluation of BCRL.

These former methods are all measurement tools used to objectively assess physical outcomes such as the extent of swelling and characteristics of the lymphedema. However, patients suffering from BCRL do not only experience purely physical impairments but also experience difficulties with performing household activities or show psychosocial problems. Therefore, in order to offer an improved tool that can be applied in clinical practice to assess problems in lymphedema-related functioning in patients with BCRL, reliability and validity of the revised Lymph-ICF-UL questionnaire using a numeric scoring system, was investigated **(Chapter 5)**. Results showed that the Lymph-ICF-UL is a reliable and valid questionnaire using a simplified and clearer scoring procedure to assess impairments in function, activity limitations, and participation restrictions of patients with BCRL. Next, further scrutiny continued regarding the responsiveness of this questionnaire, of which findings revealed that the Lymph-ICF-UL is also responsive to change after DLT. However, as no correlations were found between the Lymph-ICF-UL change scores and the Global Perceived Effect of change (GPE), future studies should be conducted in a clinical setting, allowing more variability between participants and their treatment responses **(Chapter 6)**. Additionally, this questionnaire was originally developed in Dutch and could not be applied to native French-speaking patients. A cross-cultural translation into French was therefore achieved, which proved to be valid and reliable as well **(Chapter 7)**.

At last, to generate an overview of the economic impact of BCRL and its sequelae, a systematic review was carried out on the amount of direct and indirect costs related to the conservative treatment of BCRL and its sequelae **(Chapter 8)**. It was stated that BCRL imposes a substantial economic burden on patients and Health Care, with yearly directs costs borne by patients ranging between US $2 306 and US $2 574 on average. However, the need for economic analyses associated with BCRL in particularly

European countries became apparent while reviewing the literature. Accordingly, a longitudinal financial evaluation of direct healthcare costs related to BCRL and its sequelae was conducted to address this gap in literature **(Chapter 9)**. Results showed that BCRL treatment is accompanied by a high amount of direct treatment costs as total direct healthcare costs per patient were €2279.10 on average, after three weeks of intensive treatments and 12 months of maintenance DLT. Within these direct costs, €1827.36 (80%) were accounted for statutory health insurances and €451.74 (20%) were out-of-pocket expenses for patients.

In conclusion, this project contributed to the knowledge on the treatment and evaluation of BCRL. Reliability, validity and clinical feasibility of different objective evaluation methods for assessing the amount and characteristics of lymphedema were thoroughly investigated, as well as for evaluating the impact of lymphedema on daily functioning. Additionally, it was indicated that BCRL treatment is accompanied by a high amount of direct treatment costs and that one of the main cost drivers for health insurers and patients were the costs for physical therapy sessions comprising MLD (55.5% of the direct costs paid by health insurers and 41.7% of the direct costs paid by patients). However, main findings of our RCT failed to prove an additional effect of MLD to the other components of DLT, regarding lymphedema volume reduction at the level of the arm/hand, fluid accumulation at the level of the shoulder/trunk, reduction of amount of problems in functioning and improvement of quality of life. Future research should investigate other secondary outcome parameters such as the effect of (fluoroscopy-guided) MLD on lymph transport in the long term, hardness and fibrosis of the skin, water content and skin thickness to examine any potential (relevant) added value of MLD on these outcomes. Meanwhile, there is no indication to still include time-consuming MLD in the limited treatment time per session. Alternatively, more time should be spent on other, well-investigated and evidence-based treatment options such as compression therapy and exercise therapy, together with a comprehensive education regarding self-management.

Borstkanker is de meest voorkomende kankersoort bij vrouwen wereldwijd. In 2017 rapporteerde het Belgische Kanker Register 10 627 nieuwe diagnoses van borstkanker bij vrouwen. Hoewel borstkanker-gerelateerd lymfoedeem niet de meest voorkomende complicatie is na de behandeling van borstkanker, wordt het internationaal erkend als een van de meest belastende morbiditeiten. De introductie van effectievere behandelmodaliteiten hebben het aantal overlevenden van borstkanker doen stijgen. De voorbije jaren is bijgevolg ook het aantal patiënten gestegen die te kampen hebben met langdurige bijwerkingen (zoals lymfoedeem). Vandaag de dag laten gepoolde gegevens een incidentie van borstkanker-gerelateerd lymfoedeem zien van 16,6%.

Manuele lymfedrainage (MLD) wordt sinds geruime tijd toegepast ter behandeling van borstkanker-gerelateerd lymfoedeem, maar de effectiviteit en meerwaarde ervan blijven tot op heden onduidelijk. Gepoolde data laten slechts een beperkte, niet-significante meerwaarde zien van 7% volumereductie, dewelke bovendien nog bevestigd moet worden door gerandomiseerde studies. Een mogelijke verklaring hiervoor is dat in voorgaande studies MLD op een 'blinde' manier werd uitgevoerd, namelijk zonder enige voorkennis te hebben van de patiënt-specifieke transportroutes van het lymfevocht en gebaseerd op een normale anatomie van het lymfestelsel. Bovendien zorgden de handmanoeuvres uitgevoerd door therapeuten in voorgaande studies mogelijk niet voor een optimale stimulatie van het lymfetransport. Enkele jaren geleden werd de lymfefluoroscopie geïntroduceerd ter visualisatie van het oppervlakkige lymfatische netwerk, dewelke het mogelijk maakt om MLD toe te passen op de meest noodzakelijke regio's. Een fysiologisch effect na één sessie fluoroscopie-gestuurde MLD (waarbij glijdende technieken aan hogere druk toegepast worden op regio's met een aangetoond verstoord transport, in tegenstelling tot pompende bewegingen aan lagere druk die 'blind' worden toegepast) werd reeds aangetoond. Bewijs voor een klinisch effect op langere termijn is echter nog niet voorhanden. Om die reden werd het de hoofddoelstelling van dit doctoraat om de effectiviteit van fluoroscopie-gestuurde MLD ter behandeling van borstkanker-gerelateerd lymfoedeem, additioneel aan de andere componenten van de decongestieve lymfatische therapie (DLT), en vergeleken met een traditionele en een placebo drainage, te onderzoeken.

Gezien de omvang van het project werd dit eerste doel onderverdeeld in enerzijds de ontwikkeling van het protocol van deze gerandomiseerde, gecontroleerde, dubbel-geblindeerde multicentrische studie (RCT) dewelke gepubliceerd werd in 2017 **(Hoofdstuk 1)** en anderzijds een apart artikel waarbij de resultaten en conclusies van de studie gerapporteerd werden **(Hoofdstuk 2)**. De resultaten van deze RCT toonden aan dat patiënten die de fluoroscopie-gestuurde MLD kregen tijdens de intensieve behandelfase 1) geen significant grotere vermindering vertoonden in lymfoedeemvolume ter hoogte van de hand/arm, of 2) geen significant mindere mate van vochtaccumulatie ter hoogte van de schouder/romp vertoonden, dan patiënten die de traditionele of placebo MLD kregen (primaire

uitkomstmaten). Ook vertoonden de patiënten die de fluoroscopie-gestuurde MLD kregen tijdens de intensieve behandelfase 1) geen significant grotere vermindering in het aantal functioneringsproblemen in het dagelijkse leven omwille van het lymfoedeem, of 2) geen significant grotere verbetering in algemene levenskwaliteit, dan patiënten die een traditionele of placebo MLD kregen (secundaire uitkomstmaten).

Additioneel aan deze RCT werden zeven andere studies uitgevoerd. Aangezien er een gebrek was aan een duidelijk overzicht aangaande de beste methode om het excessieve armvolume doorheen de tijd te evalueren bij patiënten met borstkanker-gerelateerd lymfoedeem, werd er eerst en vooral een vergelijking gemaakt tussen vijf verschillende en veelgebruikte volumemetingen voor wat betreft hun betrouwbaarheid, tijdsefficiëntie en klinische haalbaarheid **(Hoofdstuk 3)**. Resultaten toonden aan dat de methode waarbij het volume berekend werd aan de hand van omtrekmetingen de beste manier is om het excessieve volume te evalueren doorheen de tijd op vlak van betrouwbaarheid, grootte van de meetfout, aantal beperkingen, en de benodigde tijd voor de uitvoering van de meting. Ook werd de betrouwbaarheid van het MoisturemeterD Compact® (MMDC) toestel en de pitting test, ter evaluatie van de hoeveelheid weefselvocht in de huid, onderzocht bij patiënten met borstkanker-gerelateerd lymfoedeem **(Hoofdstuk 4)**. MMDC metingen vertoonden een gemiddelde tot zeer sterke intra- (ICC 0.648-0.947) en inter-beoordelaarsbetrouwbaarheid (ICC 0.606-0.941), afhankelijk van de meetlocatie op het oedemateuze lidmaat. De pitting test vertoonde een zeer sterke intra-beoordelaarsbetrouwbaarheid op nagenoeg alle meetlocaties, maar een zwakke inter-beoordelaarsbetrouwbaarheid, voornamelijk ter hoogte van de mediale elleboog en de borst. Bijgevolg onderschrijft deze studie het MMDC toestel en de pitting test als zijnde nuttige hulpmiddelen in de klinische evaluatie van borstkanker-gerelateerd lymfoedeem.

De voorgaande methodes worden aangewend om de hoeveelheid zwelling en de karakteristieken van het lymfoedeem objectief te evalueren. Echter ervaren patiënten met borstkanker-gerelateerd lymfoedeem niet enkel en alleen fysieke stoornissen, maar ook ondervinden ze bijvoorbeeld hinder bij het uitvoeren van huishoudelijke taken of ervaren ze psychosociale problemen. Om een geoptimaliseerd hulpmiddel te kunnen aanbieden dat in de klinische praktijk aangewend kan worden ter evaluatie van de oedeem-gerelateerde functioneringsproblemen bij patiënten met borstkanker-gerelateerd lymfoedeem, werd het scoringsyteem van de Lymph-ICF-UL vragenlijst aangepast, waarna de betrouwbaarheid en validiteit van deze aangepaste versie werd onderzocht **(Hoofdstuk 5)**. Resultaten toonden aan dat de Lymph-ICF-UL vragenlijst een valide en betrouwbare vragenlijst is die gebruik maakt van een vereenvoudigde en duidelijkere scoringsprocedure om stoornissen in functies, activiteitsbeperkingen en participatieproblemen in kaart te brengen en te evalueren. Verder werd ook de responsiviteit van deze vragenlijst nagegaan waarbij werd aangetoond dat de Lymph-ICF-UL

responsief is voor verandering na DLT. Echter, gezien er geen verband werd gevonden tussen de verandering in Lymph-ICF-UL scores en de algemeen ervaren verandering na behandeling, zou verder onderzoek hiernaar verricht moeten worden in een klinische setting die meer variabiliteit toelaat tussen deelnemers en hun behandelrespons **(Hoofdstuk 6)**. Bovendien, gezien deze vragenlijst initieel in het Nederlands werd ontwikkeld en daardoor niet aangewend kon worden voor patiënten die Franstalig zijn, werd de vragenlijst vertaald naar het Frans en werd ook deze Franstalige versie valide en betrouwbaar bevonden **(Hoofdstuk 7)**.

Als laatste werd een systematische literatuurstudie uitgevoerd om een overzicht te verkrijgen van de economische impact van borstkanker-gerelateerd lymfoedeem en zijn bijwerkingen **(Hoofdstuk 8)**. Er werd samengevat dat borstkanker-gerelateerd lymfoedeem een aanzienlijke financiële last met zich meebrengt voor zowel patiënten als voor de maatschappij, met jaarlijkse directe kosten betaald door de patiënt die gemiddeld variëren tussen US $2 306 en US $2 574. Wat echter duidelijk werd, was het huidige gebrek aan economische analyses geassocieerd met borstkanker-gerelateerd lymfoedeem in voornamelijk Europese landen. Om hieraan tegemoet te komen, werd een longitudinale financiële evaluatie uitgevoerd van de directe gezondheidszorg-gerelateerde kosten die geassocieerd zijn met borstkanker-gerelateerd lymfoedeem in België **(Hoofdstuk 9)**. Resultaten gaven aan dat de behandeling van borstkanker-gerelateerd lymfoedeem in België geassocieerd is met een hoog aantal directe kosten, gezien deze in totaal per patiënt gemiddeld €2 279.10 bedroegen na een periode van drie weken intensieve DLT en 12 maanden onderhoudsbehandelingen. Van dit bedrag valt gemiddeld €1 827.36 (80%) ten laste van de wettelijke ziekteverzekering en gemiddeld €451.74 ten laste van de patiënt.

Met dit project willen we bijdragen tot de kennis over de behandeling en evaluatie van borstkanker-gerelateerd lymfoedeem. Betrouwbaarheid, validiteit en klinische haalbaarheid van verschillende objectieve evaluatiemethodes werden grondig onderzocht om enerzijds de omvang en karakteristieken van het lymfoedeem in kaart te brengen en anderzijds om de impact van lymfoedeem op het dagelijks functioneren na te gaan. Bovendien werd ook aangetoond dat de behandeling van borstkanker-gerelateerd lymfoedeem gekenmerkt wordt door een hoog aantal directe behandelkosten en dat één van de belangrijkste kostenfactoren zowel voor de ziekteverzekering (55.5%) als voor de patiënt (41.7%) de kost voor kinesitherapeutische behandelsessies omvat (tijdens de onderhoudsfase hoofdzakelijk bestaande uit MLD). Echter konden de resultaten van onze RCT geen additioneel effect aantonen van MLD bovenop de andere componenten van DLT, aangaande volumereductie ter hoogte van arm/hand, vermindering van vochtaccumulatie ter hoogte van de schouder/romp, vermindering in mate van functioneringsproblemen in het dagelijkse leven en verbetering van de algemene levenskwaliteit.

Verder onderzoek zou de meerwaarde van (fluoroscopie-gestuurde) MLD moeten onderzoeken ten aanzien van andere (secundaire) uitkomstparameters zoals het lymfetransport op lange termijn, de hardheid en fibrosering van de huid en de hoeveelheid water en dikte van de huid. In tussentijd is er echter geen indicatie om deze (tijds-invasieve) MLD nog steeds deel te laten uitmaken van het behandelpakket. De beperkte tijd zou veeleer gespendeerd moeten worden aan andere onderzochte en op evidentie-beruste behandelopties zoals compressietherapie en oefentherapie, samengaand met een grondige educatie op vlak van zelfmanagement.

APPENDICES

- More than ever exercise proved to be medicine in oncology. However, as only between 30% and 47% of all cancer survivors have shown to meet the current physical activity recommendations, a call for action from several stakeholders is needed in order to make exercise assessment, guidance and referral of cancer patients common practice.

- The rising perks of domestic pets in cardiovascular rehabilitation: acquisition of cats may represent a novel approach for reducing the risk of cardiovascular diseases in high-risk patients, whereas dog ownership might induce better outcomes after a major cardiovascular event.

- To counter gender bias in academia, only *increasing* the number of women in (for instance) evaluation committees is not convenient. All members should be actively *informed and trained* to recognize implicit bias.

About the author

Tessa De Vrieze was born on March 24th 1992 in Edegem (Antwerp), Belgium. In 2010 she graduated from High School at Sint-Rita College in Kontich (Antwerp), Belgium. Thereafter, in 2015, she graduated magna cum laude as Master in Rehabilitation Sciences and Physiotherapy (specialization in Musculoskeletal Physiotherapy) at the University of Antwerp (UAntwerpen) and Vrije Universiteit Brussel, Belgium. Thereby, she received the award "Best Master's thesis University of Antwerp 2014-2015" and the "Amonis Research Award 2015". In June 2016, she graduated magna cum laude as Master in Manual Therapy at the Vrije Universiteit Brussel. Meanwhile, in February 2016, she started as a doctoral researcher at the Department of Rehabilitation Sciences in the Research Group for Rehabilitation in Internal Disorders at KU Leuven, and at the Department of Rehabilitation Sciences and Physiotherapy in the Research Group MOVANT at UAntwerpen, under coordination of prof. dr. Nele Devoogdt, prof. dr. Nick Gebruers and prof. dr. Ines Nevelsteen. This doctoral project focused on investigation of the effectiveness of fluoroscopy-guided manual lymph drainage in the treatment of breast cancer-related lymphedema. Meanwhile, she finished the interuniversity course "Edema Therapy" organized by the interuniversity educational and research group 'OEDEMA' (KU Leuven, UAntwerpen, UGent). Additionally, she completed the course 'Educational Professionalization (ECHO)' at UAntwerpen. Besides the research within her doctoral project, she was engaged in teaching activities within the Bachelor program of Rehabilitation Sciences and Physiotherapy at KU Leuven, and within the interuniversity group 'OEDEMA'. During her PhD, she was mentor and co-promotor of theses of 1st and 2nd Master students at KU Leuven and The Berekuyl Academy (The Netherlands). In 2019, she was awarded with a presidential prize for *Young Lymphologists* at the 27th International Congress of Lymphology in Buenos Aires, Argentina.

Nao sou nada.	*Ik ben niets.*
Nunca serei nada.	*Niets zal ik ooit zijn.*
Nao posso querer ser nada.	*Noch kan ik meer zijn dan niets.*
A parte isso, tenho em mim todos os sonhos do mundo.	*Afgezien daarvan, draag ik alle dromen van de wereld in mij.*

-Fernando Pessoa-

Publications

Publications in international journals with peer review

1. Zhao H, Wu Y, Tao Y, Zhou C, **De Vrieze T**, Li X, Chen L. Psychometric Validation of the Chinese Version of the Lymphedema Functioning, Disability, and Health Questionnaire for Upper Limb Lymphedema in Patients With Breast Cancer-Related Lymphedema. Cancer Nursing 2020. (IF most recent: 1.84)

2. De Groef A, **De Vrieze T**, Dams L, Penen F, Van der Gucht E, Van Assche B, Verhaeghe V, Devoogdt N. Reliability and validity of a Dutch Lymphoedema Questionnaire: Cross-cultural validation of the Norman Questionnaire. European Journal of Cancer Care (Engl) 2020. (IF most recent: 1.60)

3. Thomis S, Dams L, Fourneau I, **De Vrieze T**, Nevelsteen I, Neven P, Gebruers N, Devoogdt N. Correlation Between Clinical Assessment and Lymphofluoroscopy in Patients with Breast Cancer-Related Lymphedema: A Study of Concurrent Validity. Lymphatic Research and Biology 2020. (IF most recent: 1.49)

4. **De Vrieze T**, Gebruers N, Nevelsteen I, Tjalma W.A.A., Thomis S, De Groef A, Dams L, Van der Gucht E, Devoogdt N. Physical activity level and age contribute to functioning problems in patients with breast cancer-related lymphedema: a multicentre cross-sectional study. Supportive Care in Cancer 2020. (IF most recent: 2.75)

5. **De Vrieze T**, Frippiat J, Deltombe T, Gebruers N, Tjalma WAA, Nevelsteen I, Thomis S, Vandermeeren L, Belgrado J-P, De Groef A, Devoogdt N. Cross-cultural validation of the French version of the Lymphedema Functioning, Disability and Health Questionnaire for Upper Limb Lymphedema (Lymph-ICF-UL). Disability and Rehabilitation 2020. (IF most recent: 2.05)

6. **De Vrieze T**, Gebruers N, Nevelsteen I, Tjalma W.A.A., Thomis S, De Groef A, Dams L, Devoogdt N. Responsiveness of the Lymphedema Functioning, Disability, and Health Questionnaire for Upper Limb Lymphedema in Patients with Breast Cancer related Lymphedema. Lymphatic Research and Biology 2019. (IF most recent: 1.49)

7. Van der Gucht E, Dams L, Meeus M, Devoogdt N, Beintema A, Penen F, Hoelen W, **De Vrieze T**, De Groef A. Kinesiophobia contributes to pain-related disability in breast cancer survivors: a cross-sectional study. Supportive Care in Cancer 2020. (IF most recent: 2.75)

8. Verbelen H, **De Vrieze T**, Van Soom T, Meirte J, Van Goethem M, Hufkens G, Tjalma W, Gebruers N. Development and clinimetric properties of the Dutch Breast Edema Questionnaire (BrEQ-Dutch version) to diagnose the presence of breast edema in breast cancer patients. Quality of Life Research 2019. (IF most recent: 2.49)

9. **De Vrieze T**, Nevelsteen I, Thomis S, De Groef A, Tjalma WAA, Gebruers N, Devoogdt N. What are the economic burden and costs associated with the treatment of breast cancer-related lymphoedema? A systematic review. Supportive Care in Cancer 2019. (IF most recent: 2.75)

10. **De Vrieze T**, Gebruers N, Nevelsteen I, De Groef A, Tjalma WAA, Thomis S, Dams L, Van der Gucht E, Penen F, Devoogdt N. Reliability of the MoistureMeterD Compact Device and the Pitting Test to Evaluate Local Tissue Water in Subjects with Breast Cancer-Related Lymphedema. Lymphatic Research and Biology 2019. (IF most recent: 1.49)

11. **De Vrieze T**, Gebruers N, Tjalma WA, Nevelsteen I, Thomis S, De Groef A, Dams L, Van der Gucht E, Belgrado JP, Vandermeeren L, Devoogdt N. What is the best method to determine excessive arm volume in patients with breast cancer-related lymphoedema in clinical practice? Reliability, time efficiency and clinical feasibility of five different methods. Clinical Rehabilitation 2019, 33(7), 1221-1232. (IF most recent: 2.74)

12. **De Vrieze T**, Vos L, Gebruers N, De Groef A, Dams L, Van der Gucht E, Nevelsteen I, Devoogdt N. Revision of the Lymphedema Functioning, Disability and Health Questionnaire for Upper Limb Lymphedema (Lymph-ICF-UL): Reliability and Validity. Research and Biology 2019, 17(3):347-355 (IF most recent: 1.49)

13. Devoogdt N, Geraerts I, Van Kampen M, **De Vrieze T**, Vos L, Neven P, Vergote I, Christiaens MR, Thomis S, De Groef A. Manual lymph drainage may not have a preventive effect on the development of breast cancer-related lymphoedema in the long term: a randomised trial. Journal of Physiotherapy 2018, 64(4), 245-254. (IF most recent: 5.55)

14. **De Vrieze T**, Gebruers N, Devoogdt N. Concerning quality of life questionnaires in breast cancer-related lymphedema patients: review of the literature by Cornelissen et al. Lymphatic Research and Biology 2018, 16(4), 421-422. (IF most recent: 1.49)

15. **De Vrieze T**, Gebruers N, Devoogdt N. Can manual lymph drainage be improved or not: that's the question! A response letter. European Journal of Obstetrics and Gynecology and Reproductive Biology 2018, 229, 200-202. (IF most recent: 2.02)

16. De Groef A, Meeus M, **De Vrieze T**, Vos L, Van Kampen M, Geraerts I, Devoogdt N. Unraveling Self-reported signs of central sensitization in breast cancer survivors with upper limb pain: prevalence rate and contributing factors. Pain Physician 2018, 21(3): E247-E256. (IF most recent: 2.94)

17. **De Vrieze T**, Vos L, Gebruers N, Devoogdt N. Letter to the editor. British Journal of Community Nursing 2018, 23(4): S34

18. De Groef A, Van Kampen M, Dieltjens E, De Geyter S, Vos L, **De Vrieze T**, Geraerts I, Devoogdt N. Identification of myofascial trigger points in breast cancer survivors with upper limb pain: interrater reliability. Pain Medicine 2017. (IF most recent: 2.76)

19. Gebruers N, Verbelen H, **De Vrieze T**, Vos L, Devoogdt N, Fias L, Tjalma W. Prediction formulas to determine breast cancer treatment related lymphedema do have a clinical relevance. European Journal of Obstetrics and Gynecology and Reproductive Biology 2018, 225, 256-257. (IF most recent: 2.02)

20. **De Vrieze T**, Vos L, Gebruers N, Tjalma W, Thomis S, Neven P, Nevelsteen I, De Groef A, Vandermeeren L, Belgrado JP, Devoogdt N. Protocol of a randomised controlled trial regarding the effectiveness of fluoroscopy-guided manual lymph drainage for the treatment of breast cancer-related lymphoedema (EFforT-BCRL trial). European Journal of Obstetrics and Gynecology and Reproductive Biology 2018, 221, 177-188. (IF most recent: 2.02)

21. Gebruers N, Verbelen H, **De Vrieze T**, Vos L, Devoogdt N, Fias L, Tjalma W. Current and future perspectives on the evaluation, prevention and conservative management of breast cancer related lymphoedema: a best practice guideline. European Journal of Obstetrics and Gynecology and Reproductive Biology 2017, 216, 245-253. (IF most recent: 2.02)

22. De Groef A, Van Kampen M, Vervloesem N, Dieltjens E, Christiaens MR, Neven P, Vos L, **De Vrieze T**, Geraerts I, Devoogdt N. Effect of myofascial techniques for treatment of persistent arm pain after breast cancer treatment: randomised controlled trial. Clinical Rehabilitation 2017, 31(12), 1625-1635. (IF most recent: 2.74)

23. De Groef A, Van Kampen M, Vervloesem N, De Geyter S, Christiaens MR, Neven P, Vos L, **De Vrieze T**, Geraerts I, Devoogdt N. Myofascial techniques have no additional beneficial effects to a standard physical therapy programme for upper limb pain after breast cancer surgery: a randomized controlled trial. Clinical Rehabilitation 2017. (IF most recent: 2.74)

24. De Groef A, Meeus M, **De Vrieze T**, Vos L, Van Kampen M, Christiaens MR, Neven P, Geraerts I, Devoogdt N. Pain characteristics as important contributing factors to upper limb dysfunctions in breast cancer survivors at long term. Musculoskeletal Science and Practice 2017, 29, 52-59. (IF most recent: 1.73)

25. De Groef A, Van Kampen M, Vervloesem N, Dieltjens E, Vos L, **De Vrieze T**, Christiaens MR, Neven P, Geraerts I, Devoogdt N. Effect of myofascial techniques for treatment of upper limb dysfunctions in breast cancer survivors: randomized controlled trial. Supportive Care in Cancer 2017. (IF most recent: 2.51)

26. **De Vrieze T**, Coeck D, Verbelen H, Devoogdt N, Tjalma W, Gebruers N. Cross-cultural psychometric evaluation of the Dutch McGill-QOL Questionnaire for breast cancer patients. Facts Views and Vision in Obstetrics and Gynaecology 2016, 8(4), 205-209.

27. Gebruers N, Verbelen H, **De Vrieze T**, Coeck D, Tjalma W. Incidence and time path of lymphedema in sentinel node negative breast cancer patients: a systematic review. Archives of Physical Medicine and Rehabilitation 2015, 96(6):1131-9. (IF most recent: 2.70)

Publications in international journals without peer review

1. **De Vrieze T**, Gebruers N, De Groef A, Dams L, Van der Gucht E, Nevelsteen I, Devoogdt N. Revisie van de Lymf-ICF vragenlijst voor borstanker-gerelateerd lymfoedeem van de bovenste lidmaat (Lymph-ICF-UL): betrouwbaarheid en validiteit. Magazine 'Nederlandse Vereniging voor Fysiotherapie binnen de Lymfologie en Oncologie (NVFL)', O^2 Oedeem & Oncologie, volume 23, number 2, June 2020, pages 6-10

2. **De Vrieze T**, Gebruers N, Nevelsteen I, De Groef A, Tjalma W, Thomis S, Dams L, Van der Gucht E, Penen F, Devoogdt N. Betrouwbaarheid van het MoistureMeterD Compact toestel en de pitting test ter evaluatie van weefselvocht in patiënten met borstkanker-gerelateerd lymfoedeem. Magazine 'Nederlandse Vereniging voor Fysiotherapie binnen de Lymfologie en Oncologie (NVFL)', O^2 Oedeem & Oncologie, volume 22, number 4, December 2019, pages 7-8

3. Gebruers N, Verbelen H, Saeys W, Van Soom T, Van Breda E, **De Vrieze T**. Hoe omgaan met een perifeer oedeem na een CVA? Magazine 'Nederlandse Vereniging voor Fysiotherapie binnen de Lymfologie en Oncologie (NVFL)', O^2 Oedeem & Oncologie, volume 22, number 2, June 2019, pages 5-7

Oral presentations at <u>international</u> congresses

1. **De Vrieze T**, Thomis S, Gebruers N, Tjalma W, Nevelsteen I, De Groef A, Vandermeeren L, Belgrado J-P, Devoogdt N. The EFforT-BCRL trial: first results regarding changes amount of problems in functioning and QoL. 27th World Congress 2019 International Society of Lymphology. Buenos Aires (Argentina), September 2019.

2. **De Vrieze T**, Thomis S, Gebruers N, Tjalma W, Nevelsteen I, De Groef A, Vandermeeren L, Belgrado J-P, Devoogdt N. The EFforT-BCRL trial: first results regarding changes in absolute lymphedema volume at the hand/arm and fluid stagnation at the level of the shoulder/trunk. 27th World Congress 2019 International Society of Lymphology. Buenos Aires (Argentina), September 2019.

3. Gebruers N, **De Vrieze T**, Cannaerts S, Vorselmans S, Devoogdt N, Tjalma W, Thomis S. Does a decongestive treatment for upper limb lymphedema change the pathological severity assessed by lymphofluoroscopy – first results of the EFforT-BCRL trial. 27th World Congress 2019 International Society of Lymphology. Buenos Aires (Argentina), September 2019.

4. Gebruers N, **De Vrieze T**, Thomis S, Tjalma W, Nevelsteen I, Vandermeeren L, Belgrado J-P, Devoogdt N. Do we need to change our thoughts on the use and effectiveness of MLD as part of the conservative therapy for upper limb lymphedema – EFforT-BCRL trial. 27th World Congress 2019 International Society of Lymphology. Buenos Aires (Argentina), September 2019.

5. Verbelen H, van Breda E, **De Vrieze T**, Van Soom T, Tjalma W, Gebruers N. The Breast edema Questionnaire (BrEQ), a new tool for the diagnostic assessment and follow-up of patients suffering from breast edema. 27th World Congress 2019 International Society of Lymphology. Buenos Aires (Argentina), September 2019.

6. Van der Gucht E, Dams L, Meeus M, Devoogdt N, Beintema A, Penen F, Hoelen W, De **Vrieze T**, De Groef A. Kinesiophobia Contributes to Pain-Related Disability in Breast Cancer Survivors. EFIC Congress. Valencia (Spain), September 2019.

7. **De Vrieze T**, Gebruers N, Nevelsteen I, Thomis S, Tjalma W, Belgrado J-P, Vandermeeren L, Devoogdt N. What is the best method to determine excessive arm volume in patients with breast cancer-related lymphoedema in clinical practice? Reliability, time-efficiency and clinical feasibility of five different methods. 9th International Lymphoedema Framework co-hosted by the American Lymphedema Framework Project. Chicago (USA), June 2019.

8. **De Vrieze T**, Gebruers N, Nevelsteen I, Thomis S, Tjalma W, Neven P, Belgrado J-P, Vandermeeren L, Devoogdt N. Protocol of the EFforT-BCRL trial: Effectiveness of fluoroscopy-guided manual lymph drainage in the treatment of breast cancer-related lymphoedema. 9th International Lymphoedema Framework co-hosted by the American Lymphedema Framework Project. Chicago (USA), June 2019.

9. Devoogdt N, **De Vrieze T**, Gebruers N, Thomis S. Reliability of the MoisturemeterD Compact Device and the pitting test to determine local tissue water in patients with breast cancer-related lymphoedema. 9th International Lymphoedema Framework co-hosted by the American Lymphedema Framework Project. Chicago (USA), June 2019.

10. **De Vrieze T**, Vos L, De Groef A, Gebruers N, Devoogdt N. Revision of the Lymphoedema Functioning, Disability and Health Questionnaire for upper Limb Lymphoedema (Lymph-ICF-UL): Validity and Reliability. 8th International Lymphoedema Framework Conference. Rotterdam (The Netherlands), June 2018.

11. Thomis S, Devoogdt N, Vos L, **De Vrieze T**, Suchaneka K, Fourneau I. Effect of Decongestive Lymphatic Therapy on Dermal Backflow Pattern Visualised by Lymphofluoroscopy. 8th International Lymphoedema Framework Conference. Rotterdam (The Netherlands), June 2018.

Oral presentations at <u>national</u> congresses and symposia

1. Invited lecture: The EFforT-BCRL trial: protocol and preliminary results, Symposium Breast Clinic for physiotherapists. Symposium Breast Clinic AZ Groeninge Hospital for physiotherapists. Kortrijk (Belgium), 5th November 2019.

2. Fluoroscopie-gestuurde manuele lymfedrainage voor de behandeling van borstkanker-gerelateerd lymfoedeem. Proclamation pre-master Lymphology & Oncology at The Berekuyl Academy and Vrije Universiteit Brussel. Brussels Health Campus Jette, Brussels (Belgium), 21th September 2018.

3. De rol van manuele lymfedrainage. Lunch seminar organized by the University Hospitals of Leuven. Leuven (Belgium), 16th May 2017.

Poster presentations at national and international congresses and symposia

1. Vos L, **De Vrieze T**, Devoogdt N. Normative values of the MoisuremeterD Compact for the assessment of local tissue water content of the skin in breast cancer-related lymphedema. 8th International Lymphoedema Framework Conference. Rotterdam (The Netherlands), June 2018.

2. **De Vrieze T**, Gebruers N, Nevelsteen I, Thomis S, Tjalma W, Belgrado J-P, Vandermeeren L, Devoogdt N. De EFforT-BCRL studie: Protocol. Lunch seminar organised by the University Hospitals of Leuven. Leuven (Belgium), May 2017.

Collaborations on Master dissertations

1. Arno Vandenhoeck (2020)*: Wearables to measure physical activity in patients with lymphedema of the lower limbs.* Part 2 - KU Leuven. (Co-supervisor)

2. Anita Verdegaal en Sarah Hoenderdos (2020): *Predictieve factoren voor verandering van het arm-lymfoedeem-volume na een intensieve behandeling van borstkanker-gerelateerd lymfoedeem gedurende 3 weken*. Part 1 - The Berekuyl Academy & Vrije Universiteit Brussel. (Co-supervisor)

3. Nicolas Meert and Bregt Defossez (2019): *Concurrent validity and sensitivity of Bio-Impedance Analysis and Bio-Impedance Spectroscopy for the assessment of breast cancer-related lymphedema.* Part 2 - KU Leuven. (Co-supervisor)

4. Arno Vandenhoeck (2019)*: Wearables to measure physical activity in patients with lymphedema of the lower limbs.* Part 1 - KU Leuven. (Co-supervisor)

5. Eléonore Fonck and Andreas Ryckebusch (2019): *Predictive factors for functional impairments in patients with breast cancer-related* lymphedema. Part 2 - KU Leuven. (Co-supervisor)

6. Yasemine Vandeputte (2018): *Predictive factors for the response of decongestive lymphatic therapy in breast cancer-related lymphedema of the upper limb and trunk.* Part 1 - KU Leuven. (Mentor)

7. Eléonore Fonck and Andreas Ryckebusch (2018): *Predictive factors for functional impairments in patients with breast cancer-related lymphedema.* Part 1 - KU Leuven. (Mentor)

8. Sofie Van De Steene and Annelore Van Hoof (2018): *Research on reliability and time efficiency of five different methods to determine arm volume in patients with breast cancer-related lymphedema.* Part 2 - KU Leuven. (Mentor)

9. Sofie Van De Steene and Annelore Van Hoof (2017): *Research on reliability and time efficiency of five different methods to determine arm volume in patients with breast cancer-related lymphedema*. Part 1 - KU Leuven (Mentor)

Evaluations of Master dissertations (external jury)

1. Lianne Blonk and Lisanne Van Lieshout (2020): *Correlatie tussen armvolume en bepaalde symptomen bij patiënten met borstkanker gerelateerd lymfoedeem*. Vrije Universiteit Brussel.

2. Astrid De Keersmaeker and Gitte Janssens (2019): *A comparative study between different compression systems (Coban and CoFlex) for the treatment of edema of the lower limbs*. University of Antwerp.

3. Eline Smits and Kira Versmesse (2019): *The influence of patient-related factors on the development of breast edema in breast cancer patients undergoing radiotherapy: a prospective cohort study.* University of Antwerp.

4. Bram Jacob and Dorien Dombrecht (2019): *Treatment-related factors provoking breast edema in breast cancer patients following breast conserving surgery and radiotherapy: a prospective cohort study.* University of Antwerp.

5. Anke Van Espen (2019): *The influence of breast edema on activities of daily living in patients.* University of Antwerp.

6. Valerie Boonen and Lisa Maris (2018): *Breast edema in breast cancer patients after breast conserving surgery and radiation therapy.* University of Antwerp.

7. Fleur Theunissen and Melissa Camberlin (2018): *Prevention of breast edema by means of a compression bra.* University of Antwerp.

8. Matthias Lenaerts and Ferre Fierens (2018): *Het effect van skin care op de waterinhoud van de huid onder compressie.* University of Antwerp.

9. Valerie Boonen and Lisa Maris (2017): *The impact of lymphedema on activities of daily living.* University of Antwerp.

10. Fleur Theunissen and Melissa Camberlin (2017): *The effect of breast cancer treatment on physical activity.* University of Antwerp.

11. Olga Blok, Katharina Portheine-Schmutzler (2017): *Reference values and the concurrent validity of the MoistureMeter D compact for the assessment of local tissue water content of the skin in breast cancer patients with lymphedema.* The Berekuyl Academy & Vrije Universiteit Brussel.

Instructional courses, teaching (in addition to KU Leuven's practical courses)

2018-2019 'Praktijkles klinisch evalueren van oedeem' - Interuniversitaire permanente vorming Oedeemtherapie (OEDEMA), Leuven - Antwerp - Ghent (Belgium), September 2018.

ORCiD

ResearchGate

Scientific acknowledgements

This research received funding from the Agency for Innovation by Science and Technology, applied Biomedical Research (IWT 150178). In order to arrange such financing, a separate collaboration agreement has been signed by the KU Leuven and the beneficiaries.

The author of this manuscript gratefully acknowledges the colleagues of the group 'Rehabilitation in Internal Disorders' from the department of Rehabilitation Sciences at the Katholieke Universiteit Leuven as well as the nurses and medical staff of the multidisciplinary breast and lymphedema centers of the different participating hospitals (UZ Leuven, UZ Antwerpen, UMC Sint-Pieter Brussel, UZ Gent, AZ Groeninge), for their help in the recruitment of patients in the included studies. Also she is truly grateful to all the research relatives of the participating centers collaborating in this project, as well as all study participants.

Personal contribution

The author of this manuscript was responsible for data collection and contributed to the conception, execution, analysis and reporting of all included studies and chapters in this doctoral thesis manuscript. She was assisted by her (co-)supervisor(s) prof. dr. Nele Devoogdt (who was principal investigator of the IWT-TBM research project), prof. dr. Nick Gebruers and prof. dr. Ines Nevelsteen. All co-authors of the different chapters critically revised the papers for important intellectual content and approved the final manuscripts before submission.

Conflict of interest statement

We declare that none of the authors mentioned throughout this doctoral thesis manuscript has any conflict of interests to report. The funding source was not involved in the design, execution, analysis and reporting of any of the studies included in this doctoral thesis.

DANKWOORD

Na 4 jaar en 7 maanden, is de dag aangebroken waarbij ik hier vooraan mag staan en ons werk mag komen voorstellen. Dat de tijd ongelooflijk snel gaat, is een cliché dat ook ik kan bevestigen. Ik herinner me nog levendig de dag waarop ik voor het eerst vanuit Antwerpen naar campus Gasthuisberg toegereden kwam, en ik niet alleen al op de parking verloren gereden was, maar ook op weg naar en in "ON4" hopeloos verdwaald was geraakt. Gelukkig kon ik rekenen op het geduld en de hulp van mijn nieuwe collega's om me wegwijs te maken in deze nieuwe, grote universiteit. Vandaag, ontelbare kilometers en een nieuwe wagen later, begin ik eindelijk goed en wel het verschil te kennen tussen Toledo, KU Loket, Scone en Intranet.

Tijd om nog één van de moeilijkste taken te volbrengen, en dat is proberen iedereen te bedanken die deel heeft uitgemaakt van dit grote multicentrische project. Dit gezien er heel veel mensen zijn die het verdienen om erkend te worden voor de "Effort" die ook zij in dit doctoraatsproject hebben gestoken.

Uiteraard kan ik niet anders dan te starten met de personen die op de werkvloer gedurende de hele periode op de eerste rij hebben gestaan met het ondersteunen en begeleiden van mijn onderzoek: mijn promotoren. **Nele**, de passie voor wetenschap die jij bezit werkt voor velen van ons enorm aanstekelijk. Je veelzijdigheid, doorzettingsvermogen en perfectionisme in alles wat je doet maken van jou een heel inspirerende wetenschapper en een clinicus door wie elke oedeempatiënt behandeld wil worden. De manier waarop jij een balans kan vinden tussen een veeleisende job en rijk privéleven, boordevol ambities maar toch met het juiste relativeringsvermogen, is slechts voor weinigen weggelegd. Ondanks het vele werk, lijkt het alsof jij de wereld aankan en niets je te veel is. Bedankt voor alle kansen die ik de voorbije jaren gekregen heb, om me overal mee op sleeptouw te nemen, en voor de constructieve feedback die ervoor gezorgd heeft dat ik vandaag de dag onderzoek door een heel andere bril kan bekijken. **Nick**, op jouw begeleiding heb ik al 3 jaar langer mogen beroep doen, sinds het allereerste wetenschappelijk werk ooit in de kine-opleiding: de bachelorproef, zo'n 7 jaar geleden. Bedankt voor de mooie jaren, voor de verschillende kansen die ik allemaal heb gekregen tijdens deze hele periode, om ten allen tijde een luisterend oor te willen bieden, en voor al de kennis die je mij hebt bijgebracht. Niet alleen heb ik via jou de microbe voor wetenschap en oedeemtherapie te pakken gekregen, maar ook kon ik dankzij jou meermaals thuis uitpakken met enkele interessante weetjes over Schotse whisky of moto's. **Ines**, ook jij heel erg bedankt om in je drukke agenda telkens tijd te hebben willen vrijmaken voor het verschaffen van feedback en kennis die me heel wat hebben bijgeleerd. Bedankt voor de kansen die ik heb gekregen om operatieve ingrepen van dichtbij te kunnen bijwonen, waardoor mijn inzicht in de pathologie, diagnostiek en behandeling van borstkanker naar een hoger niveau getild kon worden.

Naast mijn promotoren, hebben ook heel wat andere experts me bijgestaan en geholpen om dit werk te realiseren. Dank aan mijn interne juryleden**, Prof. dr. Eric Van den Kerckhove**, **Prof. dr. Inge Fourneau** en **Prof. dr. Ann Smeets**. De voorbije jaren tijdens dit doctoraatsproject hebben jullie gezorgd voor de nodige kritische reflecties en bijsturing. Graag wil ik ook **Prof. dr. Simon Brumagne** bedanken als voorzitter, om de verschillende bijeenkomsten doorheen dit traject in goede banen te leiden. **Prof. dr. Stroobants** en **dr.**

Damstra, hartelijk dank voor jullie constructieve feedback en interessante discussiepunten die geholpen hebben om dit finale resultaat nog meer op punt te zetten.

Bedankt **Jean-Paul** en **Liesbeth**, voor de mogelijkheid om dit project mede onder jullie begeleiding te kunnen waarmaken. De verschillende 'opleidingsmomenten' in Brussel waren enorm verhelderend om inzicht te krijgen in de lymfofluoroscopie en de bijhorende fill & flush-technieken, die jullie uiteraard als geen ander kennen. Ook **Prof. dr. Tjalma** zou ik willen bedanken voor de begeleiding, de constructieve feedback, en de vele interessante tips gedurende de voorbije jaren. Niet alleen tijdens deze doctoraatsperiode, maar ook gedurende de jaren voorheen tijdens het uitvoeren van onze masterproeven.

Uiteraard zou ik een project als dit nooit alleen hebben kunnen uitvoeren. Gelukkig konden we beroep doen op heel wat studiemedewerkers die veel tijd en moeite gespendeerd hebben in deze studie. **Lore**, bedankt om de voorbije jaren zoveel energie te investeren in het behandelen en evalueren van de patiënten, ook al moest je hiervoor soms ettelijke uren in de auto vertoeven. Verkouden of niet, jij stond er ook altijd, en dat apprecieerde in enorm. Bedankt daarvoor! Ik wens je nog heel veel succes in de toekomst, zowel op werkgebied als in je privéleven nu jullie samen een nieuw, eigen stekje hebben gevonden. **Roxane** en **Lien**, ook jullie oprecht bedankt om zo'n sympathiek behandelteam te vormen. Bedankt voor jullie advies in het uitwerken van de behandel- en meetprotocollen, en om samen met Lore een vaste waarde te zijn voor onze patiënten. Ook een welgemeende *merci* aan **An-Kathleen**, om te allen tijde in de bres te willen springen om patiënten heel vroeg of laat na je eigen werkdag er nog bij te willen nemen en deze van een behandeling te willen voorzien. Jouw inzet en flexibiliteit was voor ons van onschatbare waarde. Bedankt **dr. Thomis**, om de voorbije jaren een onmisbare schakel binnen onze studie te willen zijn. Zonder jou, geen fluoroscopisch onderzoek, en dus geen Effort-studie. Bedankt voor alle tijd en moeite die je in de studie hebt geïnvesteerd, en voor de flexibiliteit om je ook naar Antwerpen en Kortrijk te hebben willen verplaatsen voor de fluoroscopische onderzoeken. Heel veel succes nog de komende periode met het finaliseren van jouw eigen onderzoeksproject.

Daarnaast zijn er nog zoveel andere studiemedewerkers die ik uiteraard heel graag zou willen bedanken. **Elke, Steven** en **Nick R**, heel erg bedankt voor al de energie die jullie in ons project gestoken hebben. Niets was jullie te veel, en jullie staken er werkelijk jullie hart en ziel in om het perfecte compressiemateriaal voor onze patiënten uit te werken. Aan iedereen uit de buurt die op zoek is naar een top bandagist, slechts één adres: Bandagisterie Heverlee! **Shanah**, bedankt om de voorbije jaren de metingen zo enthousiast en gedisciplineerd te hebben willen uitvoeren in Gent en Kortrijk. **Kevin D**, *merci beaucoup* voor de vaste schakel te zijn in het Sint-Pieters ziekenhuis in Brussel en voor al je (vertaal)hulp tijdens de studie. **Sophie V**, hartelijk dank voor de moeite tijdens de fluoroscopische onderzoeken in Brussel. **Dr. Hanssens** en **Ellen C**, heel erg bedankt voor alle mogelijkheden om ook in Kortrijk patiënten te hebben kunnen rekruteren en behandelen binnen de studie. Ik ben enorm blij de kans gekregen te hebben om in AZ Groeninge te kunnen behandelen. Het was extra vroeg opstaan en een eindje rijden, maar ik ging er telkens met veel plezier

naartoe. Bedankt om ons zo enthousiast te ontvangen in jullie ziekenhuis, en voor jullie hulp en advies bij alle praktische vragen die zich voordeden. **Dr. Monten** en **Rita H**, ook aan jullie een welgemeende dank u om ook in UZ Gent de studie te introduceren en voor jullie enthousiasme en gedrevenheid om zoveel mogelijk oedeempatiënten te kunnen helpen via de studie. We konden jullie altijd op een hele directe en toegankelijke manier benaderen bij vragen of problemen, en ook dat is van onschatbare waarde in een multicentrisch project.

Daarnaast gaat uiteraard ook veel DANK uit naar de vele **indirecte studiemedewerkers** die ervoor gezorgd hebben dat patiënten doorverwezen werden naar onze studie: de artsen, therapeuten en verpleegkundigen van het MBC en centrum voor lymfoedeem in UZ Leuven; maar ook de artsen, kinesitherapeuten en (borst)verpleegkundigen in UZ Antwerpen, UMC Sint Pieter Brussel, UZ Gent en AZ Groeninge, en alle andere externe artsen of therapeuten die potentiële kandidaten hebben doorverwezen naar ons.

Zonder **proefpersonen**, geen onderzoeksresultaten. Daarom ben ik alle personen die hebben deelgenomen aan onze studies enorm dankbaar. **Christa**, dankzij jou werd niet alleen mijn wereldkennis maar ook mijn kennis over literatuur en cultuur naar een hoger niveau gebracht. Zelfs vandaag de dag, enkele jaren na je deelname, sta je nog altijd paraat met interessante tips en adviezen en sta je op de eerste rij om op de hoogte te blijven van onze meest recente onderzoeksresultaten. Heel erg bedankt daarvoor, en voor alle steun die ik van jou gekregen heb (en nog steeds krijg)! Ook wil ik graag alle **masterproefstudenten** van de afgelopen jaren bedanken voor de hulp bij onze onderzoeken.

Tijdens de voorbije 4 jaren heb ik geluk gehad om, naast de collega's binnen de studie, ook heel wat andere collega's te hebben mogen ontmoeten. **An**, bedankt om vanaf dag één bij mijn aankomst op ON4 mij telkens verder te helpen bij mijn praktische vragen en problemen. Ik voelde me in het begin soms een weerloos lammetje in een grote (voor mij onbekende) universiteit, maar het feit dat ik bij jou terecht kon met al mijn vragen, is een grote hulp geweest. Jouw gedrevenheid, discipline en werkijver zijn werkelijk verbluffend en een inspiratiebron voor iedereen op de werkvloer. Heel veel succes gewenst nog in de verdere carrière, ik ben er zeker van jij het nog heel ver zal schoppen. **Elien**, **Lore D**, **Anne** en **Vincent**, bedankt voor de gezellige babbels tussendoor aan het bureau, of in de flexplek. Heel veel succes gewenst nog met jullie doctoraatsproject, ik hoor het graag wanneer ik voor jullie kan komen supporteren binnenkort. Niet alleen in Leuven, maar ook in Antwerpen heb ik de kans gehad om zeer leuke collega's (beter) te leren kennen. **Hanne**, bedankt om altijd klaar te staan met advies wanneer het nodig was en heel erg bedankt voor de mogelijkheid om een stukje te mogen bijdragen binnen je onderzoeksproject. Proficiat met je doctoraat eerder dit jaar; ik wens je nog heel veel succes toe met je nieuwe job en talloze mooie belevenissen met je gezinnetje. **Timia**, als er iemand is die je niet meer moet leren hoe sfeer en leven in de brouwerij te brengen, dan ben jij het wel. Ik heb er zelf niet "fysiek" gezeten, maar ik kan me voorstellen dat werken aan een bureau in jouw buurt dagelijks een feest moet zijn. Blijf altijd je spontane zelve, en nog

heel veel succes gewenst met je doctoraat. Ik hoor het wel wanneer ik kan komen supporteren voor jouw verdediging.

Ook aan de collega's binnen **Oedema** een welgemeende dank u voor de verschillende kansen die jullie me hebben gegeven de laatste jaren. Dankzij jullie heb ik ontzettend veel bijgeleerd, en samenwerken met jullie werkt enorm aanstekelijk en inspirerend. Bedankt daarvoor!

En dan wil ik uiteraard ook heel graag mijn geweldige vrienden en familie bedanken. De liefste **kiné-vriendinnen**: Charlie, Dodo, Marie, Lisa, Sien, Wolfke, Looverbos, Eline; bedankt voor de vele gezellige avonden en weekenden de voorbije jaren! Jullie zijn allemaal heldinnen die ik voor geen geld ter wereld meer zou kunnen missen. De liefste **Sint-Rita bende**: Karen, Marlies, Sofie, Schminne, Kim, Chloé, Nicky, Cotch, Jannik; we go way back! Wat ben ik blij met zo'n schatten van vrienden als jullie. Merci voor de vele gezellige etentjes, zotte avonden, en sinds de laatste maanden: de Skype-apero's. Op naar de volgende! De liefste **Zetel-vriendinnen**: Lynn, Anneleen, Ines, Paula & Laura; mijn kennis over wereldkeukens is dankzij jullie nog nooit zo uitgebreid aanwezig geweest. Bedankt voor de vele heerlijke en fijne avondjes, jullie zijn mijn toppers van Wilrijk (en omstreken)! En uiteraard ook bedankt aan de tofste **BET & WEP-leden** (de afkortingen zal ik in dit boekje maar beter niet voluit schrijven 😉) voor de zovele sfeervolle (dans)avondjes, etentjes, terrasjes, padel-wedstrijden, fietstochtjes, … en zoveel meer.

Mama en papa, **oma en opa**, **Kevin, Henne**, **Emiel en Mia**, bedankt voor de vele gezellige familiemomenten, de lekkerste mosselsoupers, en voor jullie onvoorwaardelijke steun in alles wat ik doe. Mama en papa, dankzij de kansen die ik van jullie heb gekregen, heb ik dit doctoraat kunnen waarmaken. Bedankt voor al jullie hulp in alles! **Luc en Veronique**, **Tine en Amparo**, **Yari en Hannes**, ook aan jullie heel veel dank voor de gezellige momenten, de culinair hoogstaande etentjes en de warme ontvangst die jullie me al vanaf dag één geboden hebben.

Last but not least, ***Stiggie***, bedankt om de afgelopen jaren mijn allertrouwste supporter en rots in de branding te zijn. Bedankt voor alle hulp en om me op tijd en stond eens achter mijn computer weg te sleuren. Zonder jou aan mijn zijde zou ik hier vandaag niet staan, dus een welgemeende DANK U voor alles!

Tessa De Vrieze

Wilrijk, september 2020