Does manual lymphatic drainage add value in reducing arm volume in patients with breast cancer–related lymphedema?

## Title page

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| ***Title*** | **Effectiveness of manual lymph drainage, in addition to decongestive lymphatic therapy, for the treatment of breast cancer-related lymphoedema: secondary outcomes of a multi-centre randomised controlled trial (EFforT-BCRL trial)** |
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***Tessa De Vrieze:*** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing. ***Nick Gebruers:*** Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Supervision; Validation; Visualization; Writing - review & editing. ***Ines Nevelsteen:*** Conceptualization; Supervision; Visualization; Writing - review & editing. ***Sarah Thomis:*** Data curation; Investigation; Methodology; Validation; Visualization; Writing - review & editing. ***An De Groef:*** Data curation; Methodology; Validation; Visualization; Writing - review & editing. ***Wiebren AA Tjalma:*** Conceptualization; Methodology; Resources; Supervision; Validation; Writing - review & editing. ***Jean-Paul Belgrado:*** Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Resources; Software; Supervision; Validation; Visualization; Writing - review & editing. ***Liesbeth Vandermeeren:*** Conceptualization; Methodology; Resources; Validation; Writing - review & editing. ***Chris Monten:*** Data curation; Investigation; Project administration; Supervision; Validation; Writing - review & editing. ***Marianne Hanssens:*** Investigation; Project administration; Supervision; Validation; Writing - review & editing. ***Anne Asnong:*** Investigation; Validation; Writing - review & editing. ***Lore Dams:*** Investigation; Validation; Writing - review & editing. ***Elien Van der Gucht:*** Investigation; Validation; Writing - review & editing. ***An-Kathleen Heroes:*** Investigation; Validation; Writing - review & editing. ***Nele Devoogdt:*** Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing.

**Contributors**

ND was principal investigator of the project. ND, NG, JPB and TDV designed the study. ND, IN, ST, NG, WT, MH, CM, JPB, LV, Rita Hietbrink, Ellen Callens and Kevin Dusart, provided patients in the different study centres. Lore Vos, Shanah Van den Bosch, Kevin Dusart and TDV performed all assessments. Lore Vos, Roxane Van Hemelrijck, Lien Billiet, AKH and TDV performed all treatments. ST, CM and Sophie Vankerckhove performed all lymphofluoroscopic investigations, always assisted by ND, NG or Kevin Dusart. TDV and ND analysed and interpreted the data. ADG randomized all study participants. TDV wrote the manuscript, assisted by ND, NG and IN. TDV is guarantor. All authors read, modified

and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

**Competing interests**

Declarations of interest: none

**Ethics approval**

The EFforT-BCRL trial has been approved 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 centres (CME reference S58689, EudraCT Number 2015-004822-33). The study has been registered in clinicaltrials.gov (NCT02609724).

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**Transparency statement**

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and if relevant registered) have been explained.

**Data sharing**

Relevant patient level data, a full dataset and statistical analyses are available from the corresponding author (tessa.devrieze@kuleuven.be) upon reasonable request.

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**Abstract**

**Objective:** To investigate the effectiveness of fluoroscopy-guided MLD, compared to traditional and placebo MLD, additional to decongestive lymphatic therapy (DLT), for the treatment of breast cancer-related lymphoedema (BCRL) on the suprafascial accumulation of lymphatic fluid and skin elasticity.

**Methods:** Multi-centre, three-arm, double-blinded randomised controlled trial (EFforT-BCRL trial). 194 participants (mean age 61 (±10) years) with unilateral BCRL were recruited. All participants received standardized DLT (education, skin care, compression therapy, exercises) and were randomised to either fluoroscopy-guided, traditional or placebo MLD. Participants daily received 60min of treatment during the 3-week intensive phase, and 18 sessions of 30min during the 6-months maintenance phase. Patients were instructed to wear compression garment, to perform exercises and to perform a self-MLD once daily. Present study comprises secondary analyses of the EFforT-BCRL trial. Outcomes were the amount of fluid accumulation in the suprafascial tissues (local tissue water, extracellular fluid and thickness of the skin and subcutaneous tissue) and skin elasticity, at the level of the arm and trunk. Measurements were performed at baseline, after intensive treatment, after 1, 3 and 6 months of maintenance treatment and after 6 months of follow-up.

**Results:** At the level of the arm, there was a significant improvement over time in the three groups for most of the outcomes. At the level of the trunk, no remarkable improvement was noted within the individual groups. No significant interaction effects *(between-group differences)* were present. Only skin elasticity at the level of the arm, evaluated through palpation, showed a significant interacting effect.

**Conclusions:** All three groups showed a similar improvement as a response to DLT, irrespective of the type of MLD that was added. The merit of MLD additionally to the other components of DLT in reducing local tissue water, extracellular fluid or skin thickness, and in improving skin elasticity and fibrosis in patients with chronic BCRL, is limited.

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

**Key-words:** Breast Neoplasms; Lymphoedema; Manual Lymphatic Drainage; Local tissue water; Skin thickness; Extracellular fluid

**IMPACT STATEMENT**

Although it has been applied all over the world since many years, evidence regarding the added value of manual lymphatic drainage (MLD) in reducing arm volume in patients with breast cancer-related lymphedema (BCRL), is lacking. Results of this RCT show that the merit of MLD, additionally to the other components of decongestive lymphatic therapy, in reducing local tissue water, extracellular fluid or skin thickness, and in improving skin elasticity and fibrosis in patients with chronic BCRL, is limited as well. To date, there is no clinical indication to still include time-consuming MLD in the physical therapy sessions of patients with chronic BCRL.

## Introduction

Worldwide, breast cancer is diagnosed in 2.3 million women each year and is therefore the most common cancer in women.[1] Improved treatment strategies have resulted in increased survival rates.[2] Consequently, more and more survivors are confronted with the impact of treatment-related problems, including breast cancer-related lymphoedema (BCRL). More than 16% of these patients develop BCRL.[3]

According to the recommendations of the International Society of Lymphology, lymphoedema needs to be treated with decongestive lymphatic therapy (DLT) consisting of a two-phase treatment.[4] During the intensive phase, lymphoedema is maximally reduced. This phase consists of skin care, manual lymph drainage (MLD), multi-layer bandaging and exercise therapy (under compression). The second or maintenance phase aims to conserve and optimize the results obtained in the first phase. It consists of skin care and education regarding self-management, a compression sleeve, exercises and MLD. Although it has been applied all over the world for many years (since 1930), a meta-analysis/ Cochrane systematic review including six RCTs could not demonstrate an added value of MLD (further called 'traditional MLD' throughout this paper) beside the other components of DLT in reducing arm volume.[5, 6] Four additional RCTs that have been published were also unable to demonstrate an added effect of traditional MLD in reducing lymphoedema volume in patients with BCRL.[7-10]

A decade ago, it has been shown that near-infrared fluorescence imaging or lymphofluoroscopy can be used to map the regions with dermal rerouting and the superficial remaining collecting vessels. This way, MLD can be tailored to the individual patient, possibly improving its effect. In addition, by altering the MLD techniques through 1) performing a resorption technique with the thumb instead of the whole hand, and 2) by gliding with the hand over the skin instead of using pumping techniques to stimulate the lymphatic transport, the resorption and transport through the lymph collectors and regions with dermal rerouting is improved.[11] The combination of these adapted manoeuvres being applied on the patient-specific lymphatic system, is hypothesized to be an optimised method of MLD to improve the clinical situation of the patient, and is throughout the paper called 'fluoroscopy-guided MLD'.

Recently, primary analyses of the EFforT-BCRL trial showed that neither fluoroscopy-guided MLD nor traditional MLD could show an additional effect on arm/hand volume reduction, reduction in local tissue water at the level of the shoulder/trunk, improvement in amount of lymphoedema-related problems in functioning or overall quality of life, compared to placebo MLD, and in addition to the other components of DLT.[12] Consequently, these findings are in line with previous systematic reviews having reported that the added effects of traditional MLD on volume reduction were limited to 75ml[5] and 7%[6] ($p>0.05$).

Previous studies merely focused on change in lymphoedema volume as an outcome measure to investigate the merit of MLD. Although worldwide considered as the gold standard in evaluating lymphoedema, volume measures are not capable of distinguishing between total limb volume and suprafascial lymph volume, nor to describe the tissue composition of affected limbs.[13] Volume measures represent an indirect measurement of the entire limb, by taking into account both the supra- and subfascial tissues (including muscle tissue, bones, fat). To date, plenty of methods are available that objectively quantify the **accumulation of fluid** in only the suprafascial tissues in a direct manner:

the *amount of local tissue* water can be measured in a reliable way[14] using a MoistureMeterD Compact® device which is able to represent the percentage of water content (PWC%) at any particular site of the body. Another direct indicator of the accumulation of tissue water is the *amount of extracellular fluid* in the limb by means of bioimpedance measurements (such as Bioimpedance Spectroscopy (BIS)). This method showed to be capable to monitor changes in the extracellular fluid with greater sensitivity than offered by indirect measurements such as circumference measures.[15-17] Additionally, as thickening of cutis and subcutis is associated with the development of lymphoedema, the accumulation of fluid in terms of *thickness of the skin and subcutaneous tissue* can be evaluated through palpation by performing a pinch test and comparing the skin fold thickness with the non-affected side.[18] More objectively, the thickness of the cutis and subcutis can directly be measured using ultrasonography.[19] Additionally, besides direct quantifications of the accumulation of fluid in the suprafascial tissues, it is of utmost importance to also evaluate the impact of lymphoedema on **skin characteristics** such as *skin elasticity and fibrosis*. As the oedema progresses, the skin and subcutaneous tissue gradually harden and become fibro-sclerotic due to the high protein concentration and due to repeated infections and inflammatory responses.[20] This can hinder movements of the limb or can induce subjective complaints such as feelings of hardness and heaviness of the skin.[20] In clinical practice, skin elasticity and presence of fibrosis can be evaluated subjectively by means of palpation. Alternatively, the SkinFibroMeter® is a portable device that can be used to objectively measure skin elasticity or skin stiffness (which in turn reflects the presence and severity of skin fibrosis) in terms of short-term resistance of the skin to an external force that is applied by the instrument.[21]

As little is known about the possible merit of MLD on outcome parameters other than change in arm volume, further research is highly warranted. Therefore, the aim of the present trial is to investigate the effectiveness of an hypothesized optimised MLD method (i.e. fluoroscopy-guided MLD) vs. traditional MLD and placebo MLD, added to DLT, for the treatment of BCRL on the accumulation of fluid in only the suprafascial tissues (in terms of the *changes in amount of local tissue water, extracellular fluid and thickness of the skin and subcutaneous tissue*) as well as on skin elasticity and fibrosis (in terms of *change in skin elasticity*).

## Material and methods

### *Study design and setting*

The EFforT-BCRL trial is a multi-centre, double-blind RCT. The design of the RCT is described in detail elsewhere.[22] Briefly, participants received an intensive treatment during 3 weeks, followed by a maintenance treatment for 6 months. Additional follow-up of another 6 months was established. All participants received a standardized DLT treatment consisting of education, skin care, compression therapy, and exercises. Only MLD differed among the three equally allocated groups: the intervention group received fluoroscopy-guided MLD, the first control group received traditional MLD and the second control group received placebo MLD. 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 (FU). Primary outcomes of this trial related to the arm volume and accumulation of lymph at the level of the trunk, and a set of secondary outcomes related to quality of life, were presented elsewhere.[12]

Participants were recruited in five hospitals in Belgium: the University Hospitals of Leuven (UH Leuven), Antwerp University Hospital (UH Antwerp), Saint-Pierre University Hospital in Brussels (UH Saint-Pierre), Ghent University Hospital (Ghent UH) and General Hospital Groeninge (GH Groeninge) in Kortrijk.
This trial had been approved by the Ethical Committees of all participating centres (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 lymphoedema of the arm and/or hand, developed after treatment for breast cancer, 2) chronic lymphoedema stage I to IIb (duration of >3 months), 3) at least 5% difference between both arms (= excessive volume) adjusted for limb dominance, and/or between both hands, and 4) no active metastases at the moment of inclusion. Patients were excluded when one of the following criteria were present: 1) age <18y, 2) oedema of the upper limb from another cause than breast cancer treatment, 3) inability to participate during the entire study period, 4) mental or physical inability to participate in the study, 5) allergy for Indocyanine Green, iodine, or sodiumiodine, 6) increased activity of the thyroid gland; benign tumours of the thyroid gland, 7) lymph node transplantation or lymphovenous shunt in the past, 8) bilateral axillary lymph node dissection.

Only patients who signed the informed consent document prior to the start of the study were included.

*Intervention*

All participants received a standard DLT consisting of skin care, compression therapy (multilayer bandaging followed by a compression sleeve and hand glove), exercises under compression and education regarding self-management.[4] The only treatment modality that differed among the three groups was the application of MLD. Patients wore their compression garment during daytime (sleeve and glove) and performed their exercises under compression twice per day at home. Patients were instructed to perform daily self-MLD, except on the days when treatment was provided by the therapist. For all details regarding the treatment and the different treatment modalities, we refer to the publication of the trial's protocol.[22]

All treatments were provided by five different physical therapists: RVH, LB, LV, AKH in UH Leuven; LV and TDV in UH Saint-Pierre, GH Groeninge and GUH; and TDV in UH Antwerp. All physical therapists

were experts in oedema therapy. Per patient, the same therapist provided DLT as well as MLD. To limit any subjective influences of the therapist, a standardized treatment protocol had been developed after consensus with our expert panel. To make the therapists familiar with this protocol and to ensure that the treatments given by each therapist were identical, multiple trainings were performed prior to the start and during the course of the trial.

*Assessments*

All participants received a standardised **lymphofluoroscopic assessment** at baseline (B0), post-intensive (P) and post-maintenance phase (P6). The baseline lymphofluoroscopy was used to determine the tailored procedure of MLD (i.e. which hand manoeuvres at which location[11]) in the group receiving fluoroscopy-guided MLD. **Clinical assessments** were performed 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). During the intensive and maintenance treatment phases, adherence to the self-management protocol was captured through a diary. For a detailed description regarding the fluoroscopic and different clinical assessments, see the protocol of the EFforT-BCRL trial.[22]

All lymphofluoroscopic assessments were performed by three doctors (ST, LV, CM) assisted by physical therapists (ND, NG, KD). Clinical assessments were performed by four assessors (TDV, LV, KD, SVDB). Participants were evaluated by the same assessor per centre. All of them were trained and experienced in performing these assessments.

*Outcome measures*

Patient-related data were collected to describe the baseline characteristics of our patient population. Body height and weight, pitting at the level of hand, of ventral and dorsal lower and upper arm, at elbow, shoulder, trunk and breast (0= no, 1= doubt; 2= clear) and lymphoedema stage were obtained through evaluation. Duration of lymphoedema was collected though interview. Information related to the age of the patient and the breast cancer and its treatment was searched in the medical file of the patient.

Details of the outcome measures, their measurement methods and procedures are presented in Table 1. The outcome measures covered in this paper for evaluating the *accumulation of fluid in the suprafascial tissues* involve the amount of local tissue water in the skin measured by the MoistureMeterD® Compact (MMDC) device (Delfin Technologies, Kuopio, Finland)[14], the amount of extracellular fluid measured using BioImpedance Spectroscopy[17, 24], the skin thickness (cutis and subcutis) assessed using ultrasound[19] and by using a clinical palpation test (pinch test). *Skin elasticity* was evaluated through palpation and was also measured using the SkinFibrometer® (Delfin Technologies, Kuopio, Finland)[21].

Measurements occurred at nine reference points along the upper limb and trunk (see Table 1, Annex I). Given the fact that compression therapy (i.e. bandaging during the intensive treatment phase and wearing a compression sleeve and glove during the maintenance treatment phase) was only applied at

the level of the arm and hand, this might have induced fluid accumulation at the level of the shoulder and trunk. Therefore, as we are interested in the clinical merit of MLD on (for example) fluid retention due to its stimulating effect on lymphatic fluid, we investigated the effect of DLT on the different outcome parameters at the level of the arm and trunk, separately.

Consequently, with the exception of the change in extracellular fluid (represented by an L-Dex score for the entire upper limb), the analyses for all other outcomes were performed for the arm (including 6 reference points at the hand, lower and upper arm) and trunk (including 3 reference points at the shoulder, trunk and breast) separately.

*Please insert here Table 1*

*Hypotheses*

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

1) a significantly greater reduction in amount of local tissue water;
2) a significantly greater reduction in amount of extracellular fluid;
3) a significantly greater reduction in thickness of the skin (cutis and subcutis);
4) a significantly greater improvement in elasticity of the skin;

than patients receiving **traditional MLD** or **placebo MLD** after three weeks of intensive treatment (P) and after one (P1), three (P3), six (P6) and twelve (P12) months of maintenance treatment.

*Sample size calculation*

A sample size calculation had been performed for the primary outcome measures of the EFforT-BCRL trial: 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 lymphoedema 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[25], a drop-out rate of 5% was estimated (or 9 patients). However, no sample size calculation occurred for the outcome parameters analyzed in the present paper as the these are secondary outcome measures of the EFforT-BCRL trial.

*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 based on type of MLD. The allocation to the groups was concealed and performed by an independent physical therapist (ADG). 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. Furthermore, all 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*

Baseline participant characteristics were reported descriptively.

Analyses for change in *amount of local tissue water by means of PWC% inter-limb arm/ trunk ratios*, for change in *thickness of the skin and subcutaneous tissue by means of ultrasound inter-limb arm/ trunk ratios*, and change in *skin elasticity by means of the induration force inter-limb arm/ trunk ratios* were performed on log-transformed ratios and not on (excess) percentages (reflected by the untransformed ratios). Analyses for change in *amount of extracellular fluid by means of L-Dex scores*, and change in *skin thickness and skin elasticity by means of palpation arm/ trunk outcome scores*, were performed on raw outcomes, without performing a log-transformation.

For all secondary outcome analyses, a **multivariate linear model for longitudinal measures** was used in order to compare the evolution of the log-ratios or the raw outcomes between the three groups. An unstructured covariance matrix was used for the 6x6 covariance matrix of the repeated measures over time (B0, P, P1, P3, P6, P12), except for the change in thickness of the skin and subcutaneous tissue measured by ultrasound where a 4x4 covariance matrix of the repeated measures was used (B0, P, P6, P12). Due to a right-skewed distribution of the model residuals, the outcome representing skin elasticity by means of palpation was log-transformed after adding a constant value.

Changes versus baseline were calculated at each time point and compared between the three groups. P-values for the overall interaction (group x time) effect are presented. 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). 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 IBM SPSS Statistics software, version 27 for Windows.

*Role of the funding source*

The funder played no role in the design, conduct, or reporting of this study.

**Results**

*Flow of participants and participant characteristics*

The flow of participants during the trial is presented in Figure 1. Of the 391 screened patients, 194 were included after giving written consent. Mean age was 61 (±10) years and mean absolute/relative excessive arm volume at baseline was 521.5 ml/24.66%, respectively (Table 2).

*Please insert here Figure 1*

*Please insert here Table 2*

During the intensive treatment phase, patients received on average 13 (±1) of the 14 treatment sessions (lasting 60 min) that were initially planned. The maintenance treatment phase lasted for 6 months, in which patients received on average 17 (±1) treatment sessions (lasting 30 min) of the 18 that were initially planned.

*Outcomes*

Tables 3-5 and Appendices 1-3 (Supplementary Material) display the results regarding the investigated outcome measures.

***Evaluation of the accumulation of fluid in suprafascial tissues***

*At the level of the arm*

As shown in Table 3, the amount of local tissue water, the thickness of the subcutis and the thickness of the cutis + subcutis together improved significantly over time in all three groups (*within-group differences*) ($p<0.05$). Only the change in thickness of the cutis did not significantly change over time in any of the groups. When looking at the overall interaction-term (groups x time), no significant effects could be detected ($p<0.05$), resulting in no *between-group differences*.

*At the level of the trunk*

As shown in Table 4, the amount of local tissue water and the thickness of the cutis, subcutis and cutis + subcutis evaluated with ultrasonography or by palpation did not improve remarkably over time at the level of the trunk (*within-group differences*). Neither were there any significant changes between the groups *(between-group differences)* regarding these outcome measures as there was no significant interaction-effect.

*At the level of the entire upper limb*

As shown in Table 5, the amount of extracellular fluid decreased significantly in all three groups over time (*within-group differences*) ($p<0.05$). Nevertheless, no statistically significant differences in reduction were present between the three groups ($p>0.05$).

***Evaluation of skin elasticity***

*At the level of the arm*

As presented in Table 3D, skin elasticity measured with the SkinFibrometer® improved significantly over time in all three groups (*within-group differences*) ($p<0.05$). No significant interaction-effect was present ($p<0.05$). The elasticity of the skin evaluated through palpation (Table 3E) showed some variation in the results. All groups showed a significant change over time, more specific an improvement in the

fluoroscopy-guided MLD group and a deterioration in the other two groups) (*within-group differences*) ($p<0.05$). Since a significant interaction-effect was present ($p=0.023$), *between-group differences* could be explored. Statistical differences between the groups (i.e. between the fluoroscopy-guided MLD group and the traditional MLD groups, as well as between the fluoroscopy-guided MLD group and the placebo MLD group) are present, however, are varying depending on the time of measurement. After the intensive treatment phase, there was a significant difference in change between the fluoroscopy-guided MLD group (decrease in skin hardness) and the placebo MLD group (increase in skin hardness), and during/after the maintenance treatment phase, a significant difference in change between the fluoroscopy-guided MLD group (decrease in skin hardness) and both the traditional and placebo MLD groups (increase in skin hardness) was noted.

*At the level of the trunk*

Skin elasticity (both evaluated with the SkinFibrometer® as well as through palpation) did not significantly improve over time (*within-group differences*). Neither was there a significant interaction-effect or significant changes between the groups *(between-group differences)* regarding these outcome measures ($p>0.05$).

*Please insert here Tables 3-5*

## Discussion

To our knowledge, this is the first RCT that investigated the merit of an optimised method of MLD (i.e. fluoroscopy-guided MLD) compared to traditional MLD and placebo MLD, additional to the other components of DLT, for the treatment of BCRL in terms of change in accumulation of fluid in suprafascial tissues, as well in change of skin elasticity. In contrast with previous trials[7-10, 26-30], the present study investigated the additional effect of MLD on outcome parameters other than change in arm volume, including not only the arm but also the trunk. In the Cochrane systematic review of Ezzo and colleagues, it was indeed recommended that future trials should include volumetric outcomes beyond solely arm volume.[6] The Cochrane review included only one trial that incorporated skin thickness (objectified with modified Harpenden skinfold calipers) at the trunk, and skin thickness (measured with a 20 MHz ultrasound scanner) at four sites on the edematous arm and trunk. The trial showed that MLD according to Vodder did not statistically reduce caliper creep on the affected side after three weeks of intensive treatment (MLD + compression sleeve) (p=0.06).[38]

In the present study, hardly any between-group differences were found. At the **level of the arm**, only for skin elasticity evaluated through palpation, a significant interaction effect was detected. However, the results are varying depending on the time of measurement. After the intensive treatment phase, there was a significant difference in change between the fluoroscopy-guided MLD group *(decrease in skin hardness)* and the placebo MLD group *(increase in skin hardness)*, and during/after the maintenance treatment phase, a significant difference in change between the fluoroscopy-guided MLD group *(decrease in skin hardness)* and both the traditional and placebo MLD groups *(increase in skin hardness)* was noted. Nevertheless, one should be skeptical about the clinical relevance regarding these changes in skin elasticity, as the changes in mean outcome values are minor and are based on a subjective therapist-reported palpation test with a relatively insensitive way of scoring this outcome (in terms of presence versus absence of skin fibrosis at each measurement point). Moreover, this was the only significant interaction at 0.05 level and it would not remain significant after considering a correction for multiple testing. Consequently, significant p-values should be interpreted with caution as the effect disappears if a correction for multiple testing had been carried out. At the **level of the trunk**, the different outcomes did not show remarkable improvements within each group over time at the level of the trunk, nor were there any other significant differences in changes over time *between* the groups. This is not surprising, as during the treatment sessions compression therapy (i.e. bandaging during the intensive treatment phase and wearing a compression sleeve and glove during the maintenance treatment phase) was only applied at the level of the arm. This might have induced some fluid accumulation at the level of the shoulder and trunk. However, as we hypothesized that the application of MLD could diminish this fluid retention due to its stimulating effect on lymphatic fluid, we were interested to investigate the effect of DLT on the different outcome parameters at the level of the arm and trunk, separately.

For none of the considered outcomes there was evidence for a clinically relevant difference in evolution between the three groups. Consequently, a clinical benefit of MLD in reducing the amount of local tissue water, skin thickness and skin elasticity at the level of the arm and trunk could not be shown in the

present study. Additionally, a clinical benefit of MLD in reducing the amount of extracellular fluid in **the entire upper limb**, could not be retrieved either. As an overall result, none of the predefined hypotheses regarding the outcome measures could be retained. Since other studies have not included outcome measures such as the amount of local tissue water, extracellular fluid or skin elasticity, we are not able to compare our results.

This study has several strengths. First of all, with five study centres participating, patients could be recruited in almost all regions of Flanders. Randomization was concealed and both patients and assessors were blinded for patients' treatment allocation. Also, treatments were performed by the same experienced therapists in all centres to ensure standardization of the treatment sessions. The risk of performance bias was negligible – a testing demonstrated that more than 75% of the patients did not know what treatment was given or indicated the wrong treatment allocation.[12] Second, drop-out rate was low. By educating patients to perform self-MLD during the maintenance treatment phase when no treatment was provided by the therapist, the present study tried to get the most out of the MLD treatment effect. 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. Lastly, in contrast to most trials, [8, 9] maintenance DLT treatment phase was included in the trial design. Compared to the other most recent RCT's[8-10], the present trial comprises a 6-months FU period together with a sufficiently large sample size empowering the trial. As a limitation, it should be mentioned that no corrections for multiple testing were considered for the EFforT-BCRL trial's secondary outcomes (as we considered two primary outcomes and two pairwise primary comparisons in our sample size calculation). Hence, single significant p-values should be interpreted with caution as the effect disappears if a correction for multiple testing is being carried out.

*Clinical implications and future research*

Literature emphasized the urgent need for randomised trials investigating the relative contribution of MLD to DLT on other outcome parameters than arm volume.[6] This multi-centre RCT showed that, in line with the results on the previously investigated outcome measures[12], fluoroscopy-guided MLD is not superior to the traditional MLD (in addition to DLT), for reducing the amount of local tissue water, extracellular fluid, skin thickness, and for improving skin elasticity in patients with chronic BCRL. Moreover, both fluoroscopy-guided and traditional MLD were not superior to a placebo MLD in addition to DLT. This means that, for these investigated clinical outcomes in patients with chronic BCRL, 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[31-33] and exercise therapy (under compression)[33, 34], together with a greater emphasis on education and self-management.[35]

Future analyses should be performed to investigate the role of (fluoroscopy-guided) MLD on lymphatic transport in the long term, and should explore the role and long-term clinical benefit of MLD in other types of oedema, e.g. in patients with dynamic (instead of obstructive) lymphatic disorders such as an

increased filtration rate. Additionally, more research on the effectiveness of MLD in patients with midline and lower limb lymphoedema is highly needed.

## Conclusions

The present findings could not demonstrate an added value of different types of MLD, in addition to the other modalities of DLT, for the treatment of chronic BCRL in terms of reducing the amounts of local tissue water and extracellular fluid, reducing skin thickness, and improving skin elasticity at the level of the arm and trunk. Therefore, a paradigm shift regarding the content (rather than the amount) of the treatment sessions for patients with chronic BCRL, is highly needed.

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## References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021.
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. 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.
4. The diagnosis and treatment of peripheral lymphedema: 2020 Consensus Document of the International Society of Lymphology. Lymphology. 2020;53(1):3-19.
5. 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.
6. 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.

7. 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.
8. 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.
9. 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. British journal of cancer. 2018;119(10):1215-22.
10. Sen EI, Arman S, Zure M, Yavuz H, Sindel D, Oral A. Manual Lymphatic Drainage May Not Have an Additional Effect on the Intensive Phase of Breast Cancer-Related Lymphedema: A Randomized Controlled Trial. Lymphat Res Biol. 2020.
11. 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.
12. De Vrieze TG, N; Nevelsteen, I; Fieuws, S; Thomis, S; Tjalma, W; Belgrado, J-P; Vandermeeren, L; Monten, C; Hanssens, M; Devoogdt, N. Effectiveness of manual lymph drainage, in addition to decongestive lymphatic therapy, for the treatment of breast cancer-related lymphoedema: a multi-centre randomised controlled trial (EFforT-BCRL trial). Submitted.
13. Kim L, Jeon JY, Sung IY, Jeong SY, Do JH, Kim HJ. Prediction of treatment outcome with bioimpedance measurements in breast cancer related lymphedema patients. Ann Rehabil Med. 2011;35(5):687-93.
14. 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. Lymphat Res Biol. 2019.
15. York SL, Ward LC, Czerniec S, Lee MJ, Refshauge KM, Kilbreath SL. Single frequency versus bioimpedance spectroscopy for the assessment of lymphedema. Breast cancer research and treatment. 2009;117(1):177-82.
16. Hayes S, Cornish B, Newman B. Comparison of methods to diagnose lymphoedema among breast cancer survivors: 6-month follow-up. Breast Cancer Res Treat. 2005;89(3):221-6.
17. Dylke ES, Ward LC. Three Decades of Bioelectrical Impedance Spectroscopy in Lymphedema Assessment: An Historical Perspective. Lymphat Res Biol. 2021;19(3):206-14.
18. International Lymphoedema Framework I. Best Practice for the Management of Lymphoedema: International Consensus2006.
19. Devoogdt N, Pans S, De Groef A, Geraerts I, Christiaens MR, Neven P, et al. Postoperative evolution of thickness and echogenicity of cutis and subcutis of patients with and without breast cancer-related lymphedema. Lymphat Res Biol. 2014;12(1):23-31.
20. Clodius L, Deak L, Piller NB. A new instrument for the evaluation fo tissue tonicity in lymphoedema. Lymphology. 1976;9(1):1-5.
21. 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. Lymphat Res Biol. 2017;15(1):70-6.
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 lymphoedema (EFforT-BCRL trial). Eur J Obstet Gynecol Reprod Biol. 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. Shah C, Vicini FA, Arthur D. Bioimpedance Spectroscopy for Breast Cancer Related Lymphedema Assessment: Clinical Practice Guidelines. Breast J. 2016;22(6):645-50.
25. 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 lymphoedema related to breast cancer: randomised controlled trial. Bmj. 2011;343:d5326.
26. 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.
27. 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.
28. Andersen L, Hojris I, Erlandsen M, Andersen J. Treatment of breast-cancer-related lymphedema with or without manual lymphatic drainage--a randomized study. Acta Oncol. 2000;39(3):399-405.
29. Sitzia J, Harlow W. Lymphoedema 4: research priorities in lymphoedema care. Br J Nurs. 2002;11(8):531-41.
30. 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 Res Treat. 2004;86(2):95-106.
31. Damstra RJ, Partsch H. Compression therapy in breast cancer-related lymphedema: A randomized, controlled comparative study of relation between volume and interface pressure changes. J Vasc Surg. 2009;49(5):1256-63.
32. 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. Support Care Cancer. 2012;20(5):1031-6.
33. 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 Res Treat. 2016;159(1):1-14.
34. Kwan ML, Cohn JC, Armer JM, Stewart BR, Cormier JN. Exercise in patients with lymphedema: a systematic review of the contemporary literature. J Cancer Surviv. 2011;5(4):320-36.
35. Damstra RJ, Halk AB. The Dutch lymphedema guidelines based on the International Classification of Functioning, Disability, and Health and the chronic care model. J Vasc Surg Venous Lymphat Disord. 2017;5(5):756-65.
36. 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.
37. 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.
38. 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.
39. 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. Lymphat Res Biol. 2009;7(3):153-8.
40. 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.
41. Cuschieri S. The CONSORT statement. Saudi J Anaesth. 2019;13(Suppl 1):S27-s30.

## Tables

**Table 1.** Overview of the measurement methods and procedures

| ***Evaluation of the accumulation of fluid in suprafascial tissues*** | | | |
|---|---|---|---|
| Outcome | | Measurement method | Procedure |
| **1** | *Local tissue water in arm and trunk (inter-limb ratio of %PWC)* | **Measurement of % water content** (PWC%)[36]<br><br>Material<br>MoistureMeter D Compact (Delfin Technologies)[37-39]<br><br>Reference points<br>See infra (Appendix)<br><br>Method<br>If skin is recently hydrated, dehydrate skin<br>Sensor is placed perpendicular on the reference points with a pressure that is indicated by the device<br>High electromagnetic wave is sent through the skin which will only be absorbed by water<br>Degree of reflection (i.e. % water content) can be read on the display of MoistureMeter D Compact | Relative excessive local tissue water (inter-limb ratio PWC%) = PWC% affected side / PWC% healthy side<br><br><u>Arm:</u> Reference points 1, 2, 3, 5, 6, 7 (Appendix) where after a mean ratio PWC% is calculated<br><u>Trunk:</u> Reference points 4, 8, 9 (Appendix) where after a mean ratio PWC% is calculated<br><br>Change of excessive local tissue water at level of arm/ trunk = Comparison between mean inter-limb ratio PWC% arm/ trunk time 1 and mean inter-limb ratio PWC% arm/ trunk time 2 in analysis |

| | | | |
|---|---|---|---|
| **2** | *Extracellular fluid in the upper limb (L-Dex score)* | Bioimpedance Spectroscopy (BIS)[24, 36, 40]<br><br>Material<br>Impedimed L-Dex U400<br><br>Reference points<br>On each hand, one double electrode is placed on dorsum of hand<br>On the right foot, one double electrode is placed on dorsum of foot<br><br>Method<br>Subject is in lying position; arms and legs spread<br>Measurements are generated by a low frequency electrical signal transmitted to the patient (3-1000 kHz frequency range)<br>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<br>One measurement at each side is performed in order to calculate one L-Dex score | Amount of extracellular fluid = represented by L-Dex score<br>This outcome is calculated and displayed on the BIS device, and represents the difference in the amount of extracellular fluid in the affected upper limb compared to the unaffected upper limb.<br><br>Change of extracellular fluid at level of the upper limb = Comparison between L-Dex time 1 and L-Dex time 2 in analysis |
| **3** | *Thickness of cutis and subcutis of arm and trunk (inter-limb ratio of mm thickness, and dichotomous outcome pinch test)* | Measurement of thickness of cutis and subcutis[19]<br><br>1. Thickness of skin and subcutaneous tissue using ultrasound<br><br>Material<br>Sonoscape S8 Portable ultrasound device<br><br>Reference points<br>See infra (Appendix)<br><br>Method<br>Subject is seated according to which reference point is being evaluated (see Appendix)<br>A high frequency linear probe (10-5 MHz) is used<br>Probe is placed perpendicular to the skin; reference point is located in the middle of the probe<br>Minimal amount of pressure needs to be given<br>Thickness of the cutis and subcutis is determined in mm<br>Images of every reference point are saved with its indicated thicknesses at both sides using a patient-specific code | Analyses for change in thickness of cutis (1), subcutis (2) and cutis + subcutis (3) were performed:<br>1. Relative excessive thickness of the cutis (inter-limb ratio of cutis in mm) =<br>Thickness of cutis (mm) affected side / thickness of cutis (mm) healthy side<br><u>Arm:</u> Reference points 1, 2, 3, 5, 6, 7 (Appendix) where after a mean ratio thickness of cutis is calculated<br><u>Trunk:</u> Reference points 4, 8, 9 (Appendix) where after a mean ratio thickness of cutis is calculated<br><br>2. Relative excessive thickness of the subcutis (inter-limb ratio of cutis in mm) =<br>Thickness of subcutis (mm) affected side / thickness of subcutis (mm) healthy side<br><u>Arm:</u> Reference points 1, 2, 3, 5, 6, 7 (Appendix) where after a mean ratio thickness of cutis is calculated |

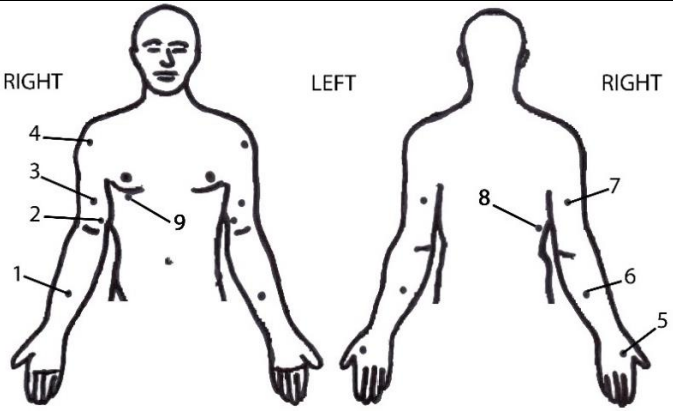
| | | | |
|---|---|---|---|
| | | | Trunk: Reference points 4, 8, 9 (Appendix) where after a mean ratio thickness of subcutis is calculated<br><br>3. Relative excessive thickness of the cutis + subcutis (inter-limb ratio of cutis + subcutis in mm) =<br>Thickness of cutis + subcutis (mm) affected side / thickness of cutis + subcutis (mm) healthy side<br>Arm: Reference points 1, 2, 3, 5, 6, 7 (Appendix) where after a mean ratio thickness of cutis + subcutis is calculated<br>Trunk: Reference points 4, 8, 9 (Appendix) where after a mean ratio thickness of cutis + subcutis is calculated<br><br>Change of excessive thickness of the (1) cutis, (2) subcutis and (3) cutis + subcutis at level of arm/ trunk = Comparison between mean inter-limb ratio thickness arm/ trunk of (1), (2) and (3) at time 1, and mean inter-limb ratio thickness arm/ trunk of (1), (2) and (3) at time 2 in analysis |
| | | 2. Skinfold thickness using pinch test<br><br>Material<br>None<br><br>Reference points<br>See infra (Appendix)<br><br>Method<br>Subject is seated according to which reference point is being evaluated (see Appendix)<br>Clinical test in which the ability to lift the skin and subcutaneous tissue is being measured, and where the skin fold thickness of the affected limb is being compared to the skinfold thickness of the non-affected limb | In total, nine reference points ( Appendix) are being evaluated and scored (0 or 1)<br>A reference point is scored with 1 in case the skin fold thickness at the affected side is increased compared to the reference point at the non-affected side<br>The final outcome for the arm score is the (cumulated) total score of six reference points 1, 2, 3, 5, 6, 7 (range 0-6)<br>The final outcome for the trunk score is the (cumulated) total score of three reference points 4, 8, 9 (range 0-3)<br><br>Change of increased skinfold thickness at level of arm/ trunk = Comparison between pinch test arm/ trunk score time 1 and pinch test arm/ trunk score time 2 in analysis |

| ***Evaluation of skin elasticity*** | | | |
|---|---|---|---|
| **4** | *Elasticity of skin and subcutaneous tissue of arm and trunk (inter-limb ratio of Newton value, and dichotomous outcome palpation test)* | 1. Measurement of induration (elasticity) of skin and subcutaneous tissue[21]<br><br>Material<br>SkinFibrometer® (Delfin Technologies)<br>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<br><br>Reference points<br>See infra (Appendix)<br><br>Method<br>First, the grey button is pressed to activate the device; if the display shows 'ready', the measurement can start<br>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<br>Each measurement is repeated 5 times at each reference point<br>The skin and subcutis resist deformation and induration and the induration force in Newton is determined by calculating the average resistance of 5 measurements<br>A lower value indicates less resistance or softer tissue<br><br>2. Evaluation of hardness (fibrosis) of the skin through palpation<br><br>Material<br>None<br><br>Reference points<br>See infra (Appendix)<br><br>Method<br>Subject is seated according to which reference point is being evaluated (see Appendix) | Relative difference in skin elasticity (induration force inter-limb ratio) = Skin elasticity affected side / skin elasticity healthy side<br><u>Arm:</u> Reference points 1, 2, 3, 5, 6, 7 (Appendix) where after a mean induration ratio is calculated<br><u>Trunk:</u> Reference points 4, 8, 9 (Appendix) where after a mean induration ratio is calculated<br><br>Change of difference in skin elasticity at level of arm/ trunk = Comparison between mean inter-limb arm/ trunk ratio induration force time 1 and mean inter-limb arm/ trunk ratio induration force time 2 in analysis<br><br>In total, nine reference points (Appendix) are being evaluated and scored (0 or 1)<br>A reference point is scored with 1 in case fibrosis of the skin is present<br>The final outcome for the <u>arm</u> score is the (cumulated) total score of six reference points 1, 2, 3, 5, 6, 7 (range 0-6)<br>The final outcome for the <u>trunk</u> score is the (cumulated) total score of three reference points 4, 8, 9 (range 0-3)<br><br>Change of fibrosis at level of arm/ trunk = Comparison between fibrosis arm/ trunk score time 1 and fibrosis arm/ trunk score time 2 in analysis |

| | | | |
|---|---|---|---|
| | | Clinical test in which the presence of skin fibrosis at different reference points is evaluated through palpation (yes/no) | |

Appendix

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)

**Reference points included in the 'arm' scores: 1, 2, 3, 5, 6, 7**
**Reference points included in the 'trunk' scores: 4, 8, 9**

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/ flank (8): Standing position, arms relaxed beside the body

Breast (9): Supine position

*Abbreviations: PWC% = Percentage of Water Content, BIS = BioImpedance Spectroscopy, mm =millimeter*

**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) or median (IQR)** | *N; mean (SD)* | *N; mean (SD)* | *N; mean (SD)* |
| **Body Mass Index (kg/m$^2$)** | 65; 27.6 (5.3) | 64; 28.8 (5.6) | 65; 27.8 (6.1) | 194; 28.1 (5.7) |
| **Age at baseline measurement (years)** | 65; 60.3 (10.8) | 64; 61.8 (9.5) | 65; 61.1 (9.0) | 194; 61.1 (9.8) |
| **Duration of lymphoedema (months)*** | 65; 29 (49) | 64; 28 (73) | 65; 16 (50) | 194; 24 (58) |
| **Absolute excessive lymphoedema arm volume (ml)*** | 65; 456.7 (390.5) | 64; 441.8 (464.4) | 65; 430.0 (510.8) | 194; 441.0 (442.3) |
| **Relative excessive lymphoedema 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%) |
| **Oedema 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 lymphoedema | 61/65 (93.9%) | 62/64 (96.9%) | 61/65 (93.9%) | 184/194 (94.9%) |
| Hand lymphoedema | 4/65 (6.2%) | 2/64 (3.1%) | 4/65 (6.2%) | 10/194 (5.2%) |
| **Lymphoedema 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 (9.2%) | 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** | 63/65 (96.9%) | 63/64 (98.4%) | 63/65 (96.9%) | 189/194 (97.4%) |
| **Chemotherapy** | 57/65 (83.1%) | 52/64 (81.2%) | 61/65 (93.8%) | 167/194 (86.1%) |
| **Hormonal therapy** | 51/65 (78.5%) | 53/64 (82.8%) | 48/65 (73.8%) | 152/194 (78.4%) |
| **Targeted therapy** | 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*, *(p or c)TNM: p= pathological, c= clinical, T= tumour stage, N= nodal stage , M= metastasis*

[a] *Calculated as a total score resulting from nine individual pitting test scores (with 0=no, 1= doubt; 2= clear) on the oedematous limb and trunk.*[14]

**Table 3.** Overview of (A) the mean amount of local tissue water (represented by PWC% inter-limb ratios), ($B_{1, 2, 3}$) the mean thickness of the skin and subcutaneous tissue (i.e. cutis, subcutis, and cutis + subcutis) (represented by inter-limb ratios), (C) the mean presence of thickened skin through palpation (represented by pinch test scores), (D) the mean skin elasticity (represented by induration force inter-limb ratios) and (E) the mean presence of skin fibrosis (represented by palpation test scores) **at the level of the arm** in each treatment group at the different time points, significance of relative changes versus baseline in each treatment group separately, p-values for the overall interaction-effect as well as comparisons of changes between the treatment groups in case of presence of a significant interaction-effect

| ***Evaluation of the accumulation of fluid in suprafascial tissues*** | | | | | | |
|---|---|---|---|---|---|---|
| ***(A) Local tissue water*** | | | | | | |
| | ***Fluoroscopy-guided MLD*** | | ***Traditional MLD*** | | ***Placebo MLD*** | *P-value for the overall interaction (group x time)* |
| | *Estimate (CI)* | | *Estimate (CI)* | | *Estimate (CI)* | ***0.665*** |
| B0 | 1.418 (1.365;1.473) | B0 | 1.354 (1.303;1.406) | B0 | 1.406 (1.354;1.459) | |
| P | 1.372* (1.326;1.419) | P | 1.292* (1.247;1.336) | P | 1.344* (1.300;1.391) | |
| P1 | 1.383 (1.328;1.438) | P1 | 1.315 (1.264;1.368) | P1 | 1.394 (1.340;1.449) | |
| P3 | 1.363 (1.309;1.420) | P3 | 1.288* (1.236;1.342) | P3 | 1.358 (1.303;1.415) | |
| P6 | 1.343* (1.290;1.399) | P6 | 1.298* (1.246;1.351) | P6 | 1.350* (1.297;1.405) | |
| P12 | 1.343* (1.305;1.383) | P12 | 1.332 (1.294;1.373) | P12 | 1.335* (1.297;1.374) | |
| Estimated mean (95% confidence interval). For the within-group differences, changes of the estimated mean versus baseline that were statistically significant are annotated with ** (p<.0001) or * (p<.05).<br>*Abbreviations: MLD = manual lymph drainage* | | | | | | |
| ***($B_1$) Thickness of cutis*** | | | | | | |
| | ***Fluoroscopy-guided MLD*** | | ***Traditional MLD*** | | ***Placebo MLD*** | *P-value for the overall interaction (group x time)* |
| | *Estimate (CI)* | | *Estimate (CI)* | | *Estimate (CI)* | ***0.422*** |
| B0 | 1.29 (1.22;1.36) | B0 | 1.27 (1.20;1.34) | B0 | 1.32 (1.24;1.35) | |
| P | 1.30 (1.23;1.37) | P | 1.29 (1.23;1.36) | P | 1.37 (1.31;1.44) | |
| P6 | 1.27 (1.20;1.34) | P6 | 1.30 (1.23;1.38) | P6 | 1.27 (1.21;1.35) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| P12 | 1.23 (1.16;1.30) | P12 | 1.28 (1.20;1.35) | P12 | 1.33 (1.25;1.41) | |

Estimated mean (95% confidence interval). For the within-group differences, changes of the estimated mean versus baseline that were statistically significant are annotated with ** (p<.0001) or * (p<.05).
*Abbreviations: MLD = manual lymph drainage*

| ***($B_2$) Thickness of subcutis*** | | | | | | |
|---|---|---|---|---|---|---|
| | ***Fluoroscopy-guided MLD*** | | ***Traditional MLD*** | | ***Placebo MLD*** | *P-value for the overall interaction (group x time)* |
| | *Estimate (CI)* | | *Estimate (CI)* | | *Estimate (CI)* | ***0.118*** |
| B0 | 1.62 (1.49;1.76) | B0 | 1.52 (1.40;1.65) | B0 | 1.52 (1.40;1.65) | |
| P | 1.38** (1.28;1.49) | P | 1.40* (1.30;1.51) | P | 1.36* (1.26;1.46) | |
| P6 | 1.38** (1.28;1.49) | P6 | 1.46 (1.36;1.58) | P6 | 1.30** (1.21;1.40) | |
| P12 | 1.34** (1.23;1.47) | P12 | 1.46 (1.34;1.60) | P12 | 1.25* (1.25;1.49) | |

Estimated mean (95% confidence interval). For the within-group differences, changes of the estimated mean versus baseline that were statistically significant are annotated with ** (p<.0001) or * (p<.05).
*Abbreviations: MLD = manual lymph drainage*

| ***($B_3$) Thickness of cutis + subcutis*** | | | | | | |
|---|---|---|---|---|---|---|
| | ***Fluoroscopy-guided MLD*** | | ***Traditional MLD*** | | ***Placebo MLD*** | *P-value for the overall interaction (group x time)* |
| | *Estimate (CI)* | | *Estimate (CI)* | | *Estimate (CI)* | ***0.180*** |
| B0 | 1.52 (1.42;1.63) | B0 | 1.44 (1.34;1.55) | B0 | 1.45 (1.35;1.56) | |
| P | 1.36* (1.27;1.27) | P | 1.38 (1.30;1.47) | P | 1.36 (1.28;1.45) | |
| P6 | 1.35** (1.27;1.44) | P6 | 1.40 (1.31;1.49) | P6 | 1.29** (1.21;1.37) | |
| P12 | 1.31** (1.22;1.41) | P12 | 1.40 (1.30;1.51) | P12 | 1.34* (1.24;1.44) | |

Estimated mean (95% confidence interval). For the within-group differences, changes of the estimated mean versus baseline that were statistically significant are annotated with ** (p<.0001) or * (p<.05).
*Abbreviations: MLD = manual lymph drainage*

| ***(C) Thickness of the skin and subcutis through palpation*** | | | | | | |
|---|---|---|---|---|---|---|
| | ***Fluoroscopy-guided MLD*** | | ***Traditional MLD*** | | ***Placebo MLD*** | *P-value for the overall interaction (group x time)* |
| | *Estimate (CI)* | | *Estimate (CI)* | | *Estimate (CI)* | ***0.889*** |
| B0 | 4.43 (4.01;4.85) | B0 | 4.03 (3.61;4.45) | B0 | 4.65 (4.23;5.07) | |
| P | 4.62 (4.23;5.00) | P | 4.23 (3.84;4.63) | P | 4.57 (4.18;4.96) | |
| P1 | 4.37 (3.96;4.78) | P1 | 4.25 (3.84;4.66) | P1 | 4.22 (3.81;4.62) | |
| P3 | 4.25 (3.82;4.68) | P3 | 4.19 (3.76;4.62) | P3 | 4.22 (3.79;4.64) | |
| P6 | 4.22 (3.77;4.67) | P6 | 4.03 (3.58;4.49) | P6 | 4.05* (3.60;4.50) | |
| P12 | 4.09 (3.61;4.57) | P12 | 3.92 (3.44;4.40) | P12 | 4.17 (3.69;4.65) | |
| Estimated mean (95% confidence interval). For the within-group differences, changes of the estimated mean versus baseline that were statistically significant are annotated with ** (p<.0001) or * (p<.05).<br>*Abbreviations: MLD = manual lymph drainage* | | | | | | |
| ***Evaluation of skin elasticity*** | | | | | | |
| ***(D) Skin elasticity*** | | | | | | |
| | ***Fluoroscopy-guided MLD*** | | ***Traditional MLD*** | | ***Placebo MLD*** | *P-value for the overall interaction (group x time)* |
| | *Estimate (CI)* | | *Estimate (CI)* | | *Estimate (CI)* | ***0.741*** |
| B0 | 1.28 (1.19;1.37) | B0 | 1.26 (1.17;1.35) | B0 | 1.41 (1.31;1.51) | |
| P | 1.11** (1.04;1.18) | P | 1.06** (1.0;1.13) | P | 1.14** (1.07;1.21) | |
| P1 | 1.15* (1.08;1.23) | P1 | 1.07** (1.01;1.14) | P1 | 1.18** (1.11;1.26) | |
| P3 | 1.16* (1.10;1.23) | P3 | 1.07** (1.01;1.14) | P3 | 1.15** (1.08;1.22) | |
| P6 | 1.13* (1.07;1.20) | P6 | 1.10* (1.04;1.17) | P6 | 1.14** (1.08;1.22) | |
| P12 | 1.19 (1.11;1.27) | P12 | 1.07** (1.01;1.14) | P12 | 1.15** (1.08;1.23) | |
| Estimated mean (95% confidence interval). For the within-group differences, changes of the estimated mean versus baseline that were statistically significant are annotated with ** (p<.0001) or * (p<.05).<br>*Abbreviations: MLD = manual lymph drainage* | | | | | | |

| ***(E) Skin elasticity (through palpation)*** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | ***Fluoroscopy-guided MLD*** | | ***Traditional MLD*** | | ***Placebo MLD*** | *P-value for the overall interaction (group x time)* | | |
| | | | | | | ***0.023**** | | |
| | | | | | | *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 | 0.49 (0.32;0.67) | B0 | 0.26 (0.12;0.41) | B0 | 0.24 (0.10;0.40) | | | |
| P | 0.40 (0.22;0.59) | P | 0.44 (0.26;0.64) | P | 0.56* (0.37;0.78) | 0.128 | 0.024* | 0.465 |
| P1 | 0.37 (0.21;0.55) | P1 | 0.52* (0.35;0.72) | P1 | 0.42 (0.26;0.61) | 0.026* | 0.073 | 0.657 |
| P3 | 0.17* (0.03;0.32) | P3 | 0.45 (0.29;0.64) | P3 | 0.50* (0.33;0.69) | 0.002* | <0.001* | 0.724 |
| P6 | 0.15* (0.05;0.25) | P6 | 0.23 (0.13;0.35) | P6 | 0.28 (0.17;0.40) | 0.026* | 0.007* | 0.621 |
| P12 | 0.22* (0.11;0.34) | P12 | 0.20 (0.09;0.32) | P12 | 0.24 (0.13;0.37) | 0.160 | 0.067 | 0.669 |

Estimated mean (95% confidence interval). For the within-group differences, changes of the estimated mean versus baseline that were statistically significant are annotated with ** (p<.0001) or * (p<.05).

*Abbreviations: MLD = manual lymph drainage*

**Table 4.** Overview of (A) the mean amount of local tissue water (represented by PWC% inter-limb ratios), ($B_{1, 2, 3}$) the mean thickness of the skin and subcutaneous tissue (i.e. cutis, subcutis, and cutis + subcutis) (represented by inter-limb ratios), (C) the mean presence of thickened skin through palpation (represented by pinch test scores), (D) the mean skin elasticity (represented by induration force inter-limb ratios) and (E) the mean presence of skin fibrosis (represented by palpation test scores) **at the level of the trunk** in each treatment group at the different time points as well as p-values for the overall interaction-effect

| ***Evaluation of the accumulation of fluid in suprafascial tissues*** | | | | | | |
|---|---|---|---|---|---|---|
| ***(A) Local tissue water*** | | | | | | |
| | ***Fluoroscopy-guided MLD*** | | ***Traditional MLD*** | | ***Placebo MLD*** | *P-value for the overall interaction (group x time)* |
| | *Estimate (CI)* | | *Estimate (CI)* | | *Estimate (CI)* | ***0.798*** |
| B0 | 1.09 (1.05;1.12) | B0 | 1.08 (1.05;1.11) | B0 | 1.12 (1.08;1.20) | |
| P | 1.11 (1.08;1.142) | P | 1.09 (1.06;1.12) | P | 1.12 (1.09;1.15) | |
| P1 | 1.14* (1.11;1.18) | P1 | 1.09 (1.06;1.129) | P1 | 1.12 (1.09;1.16) | |
| P3 | 1.10 (1.07;1.13) | P3 | 1.07 (1.04;1.10) | P3 | 1.10 (1.08;1.13) | |
| P6 | 1.09 (1.06;1.12) | P6 | 1.07 (1.04;1.09) | P6 | 1.09 (1.07;1.12) | |
| P12 | 1.10 (1.07;1.13) | P12 | 1.08 (1.03;1.10) | P12 | 1.10 (1.07;1.13) | |
| ***($B_1$) Thickness of cutis*** | | | | | | |
| | ***Fluoroscopy-guided MLD*** | | ***Traditional MLD*** | | ***Placebo MLD*** | *P-value for the overall interaction (group x time)* |
| | *Estimate (CI)* | | *Estimate (CI)* | | *Estimate (CI)* | ***0.743*** |
| B0 | 1.11 (1.06;1.17) | B0 | 1.09 (1.03;1.14) | B0 | 1.11 (1.06;1.17) | |
| P | 1.08 (1.02;1.15) | P | 1.09 (1.03;1.15) | P | 1.10 (1.04;1.16) | |
| P6 | 1.12 (1.04;1.20) | P6 | 1.07 (0.99;1.15) | P6 | 1.12 (1.04;1.20) | |
| P12 | 1.04* (0.98;1.10) | P12 | 1.08 (1.02;1.15) | P12 | 1.11 (1.04;1.17) | |
| ***($B_2$) Thickness of subcutis*** | | | | | | |

| | ***Fluoroscopy-guided MLD*** | | ***Traditional MLD*** | | ***Placebo MLD*** | *P-value for the overall interaction (group x time)* |
|---|---|---|---|---|---|---|
| | *Estimate (CI)* | | *Estimate (CI)* | | *Estimate (CI)* | ***0.252*** |
| B0 | 1.05 (0.99;1.12) | B0 | 1.01 (0.94;1.07) | B0 | 1.06 (0.99;1.13) | |
| P | 1.10 (1.03;1.16) | P | 1.01 (0.95;1.07) | P | 1.02 (0.96;1.08) | |
| P6 | 1.10 (1.02;1.19) | P6 | 1.05 (0.96;1.13) | P6 | 1.02 (0.94;1.10) | |
| P12 | 1.01 (0.95;1.07) | P12 | 1.03 (0.98;1.09) | P12 | 1.05 (0.99;1.11) | |
| ***($B_3$) Thickness of cutis + subcutis*** | | | | | | |
| | ***Fluoroscopy-guided MLD*** | | ***Traditional MLD*** | | ***Placebo MLD*** | *P-value for the overall interaction (group x time)* |
| | *Estimate (CI)* | | *Estimate (CI)* | | *Estimate (CI)* | ***0.283*** |
| B0 | 0.78 (0.72;0.85) | B0 | 0.79 (0.73;0.87) | B0 | 0.83 (0.76;0.90) | |
| P | 0.82 (0.76;0.89) | P | 0.81 (0.75;0.89) | P | 0.83 (0.76;0.90) | |
| P6 | 0.78 (0.71;0.86) | P6 | 0.80 (0.73;0.87) | P6 | 0.85 (0.78;0.93) | |
| P12 | 0.75 (0.69;0.81) | P12 | 0.82 (0.75;0.89) | P12 | 0.85 (0.78;0.92) | |
| ***(C) Thickness of the skin and subcutis through palpation*** | | | | | | |
| | ***Fluoroscopy-guided MLD*** | | ***Traditional MLD*** | | ***Placebo MLD*** | *P-value for the overall interaction (group x time)* |
| | *Estimate (CI)* | | *Estimate (CI)* | | *Estimate (CI)* | ***0.248*** |
| B0 | 1.17 (0.92;1.42) | B0 | 1.02 (0.76;1.27) | B0 | 1.31 (1.06;6.34) | |
| P | 1.39 (1.12;1.65) | P | 1.30 (1.03;1.56) | P | 1.40 (1.14;1.66) | |
| P1 | 1.28 (1.03;1.53) | P1 | 1.17 (0.92;1.42) | P1 | 1.08 (0.83;1.33) | |
| P3 | 1.34 (0.87;1.40) | P3 | 1.19 (0.92;1.46) | P3 | 1.14 (0.87;1.40) | |
| P6 | 1.31 (1.05;1.56) | P6 | 1.39* (1.33;1.65) | P6 | 1.00 (0.74;1.26) | |
| P12 | 1.15 (0.89;1.56) | P12 | 1.14 (0.88;1.41) | P12 | 1.06 (0.80;1.32) | |

Estimated mean (95% confidence interval). For the within-group differences, changes of the estimated mean versus baseline that were statistically significant are annotated with ** (p<.0001) or * (p<.05).
*Abbreviations: MLD = manual lymph drainage*

***Evaluation of skin elasticity***

***(D) Skin elasticity***

| | ***Fluoroscopy-guided MLD*** | | ***Traditional MLD*** | | ***Placebo MLD*** | *P-value for the overall interaction (group x time)* |
|---|---|---|---|---|---|---|
| | *Estimate (CI)* | | *Estimate (CI)* | | *Estimate (CI)* | ***0.857*** |
| B0 | 1.27 (1.16;1.39) | B0 | 1.15 (1.05;1.26) | B0 | 1.26 (1.15;1.38) | |
| P | 1.30 (1.18;1.42) | P | 1.19 (1.08;1.30) | P | 1.24 (1.14;1.36) | |
| P1 | 1.23 (1.13;1.33) | P1 | 1.20 (1.11;1.30) | P1 | 1.23 (1.14;1.34) | |
| P3 | 1.26 (1.16;1.37) | P3 | 1.14 (1.04;1.24) | P3 | 1.28 (1.17;1.39) | |
| P6 | 1.33 (1.22;1.45) | P6 | 1.15 (1.05;1.25) | P6 | 1.28 (1.18;1.39) | |
| P12 | 1.26 (1.15;1.38) | P12 | 1.19 (1.10;1.29) | P12 | 1.23 (1.13;1.34) | |

***(E) Skin elasticity through palpation***

| | ***Fluoroscopy-guided MLD*** | | ***Traditional MLD*** | | ***Placebo MLD*** | *P-value for the overall interaction (group x time)* |
|---|---|---|---|---|---|---|
| | *Estimate (CI)* | | *Estimate (CI)* | | *Estimate (CI)* | ***0.912*** |
| B0 | 0.17 (0.09;0.26) | B0 | 0.13 (0.05;0.21) | B0 | 0.14 (0.06;0.22) | |
| P | 0.20 (0.10;0.30) | P | 0.17 (0.08;0.27) | P | 0.22 (0.12;0.32) | |
| P1 | 0.21 (0.11;0.31) | P1 | 0.16 (0.07;0.25) | P1 | 0.22 (0.13;0.32) | |
| P3 | 0.18 (0.09;0.27) | P3 | 0.18 (0.09;0.28) | P3 | 0.22 (0.13;0.32) | |
| P6 | 0.14 (0.06;0.23) | P6 | 0.19 (0.10;0.28) | P6 | 0.23 (0.14;0.32) | |
| P12 | 0.11 (0.04;0.18) | P12 | 0.13 (0.06;0.20) | P12 | 0.11 (0.04;0.18) | |

Estimated mean (95% confidence interval). For the within-group differences, changes of the estimated mean versus baseline that were statistically significant are annotated with ** (p<.0001) or * (p<.05).
*Abbreviations: MLD = manual lymph drainage*

**Table 5.** Overview of the mean amount of extracellular fluid (represented by L-Dex scores) **at the level of the upper limb** in each treatment group at the different time points, significance of relative changes versus baseline in each treatment group at the different time points as well as the p-value for the overall interaction-effect

| ***Evaluation of the accumulation of fluid in suprafascial tissues*** | | | | | | |
|---|---|---|---|---|---|---|
| ***Extracellular fluid*** | | | | | | |
| | ***Fluoroscopy-guided MLD*** | | ***Traditional MLD*** | | ***Placebo MLD*** | *P-value for the overall interaction (group x time)* |
| | *Estimate (CI)* | | *Estimate (CI)* | | *Estimate (CI)* | ***0.950*** |
| B0 | 33.1 (26.1;40.1) | B0 | 32.3 (25.3;39.3) | B0 | 34.9 (28;41.8) | |
| P | 24.4* (19.1;29.6) | P | 25.4* (20.2;30.7) | P | 23.9** (18.7;29.1) | |
| P1 | 30.0 (22.2;37.8) | P1 | 29.5 (21.6;37.3) | P1 | 25.3* (17.6;33.0) | |
| P3 | 20.9** (16.6;25.2) | P3 | 22.2** (17.8;26.5) | P3 | 21.1** (16.8;25.4) | |
| P6 | 22.8** (17.1;28.5) | P6 | 22.6* (16.8;28.3) | P6 | 21.6** (16.0;27.3) | |
| P12 | 28.1 (20.0;36.2) | P12 | 24.1* (16.0;32.3) | P12 | 25.4* (17.3;33.4) | |

Estimated mean (95% confidence interval). For the within-group differences, changes of the estimated mean versus baseline that were statistically significant are annotated with ** (p<.0001) or * (p<.05).
*Abbreviations: MLD = manual lymph drainage*

## Figures

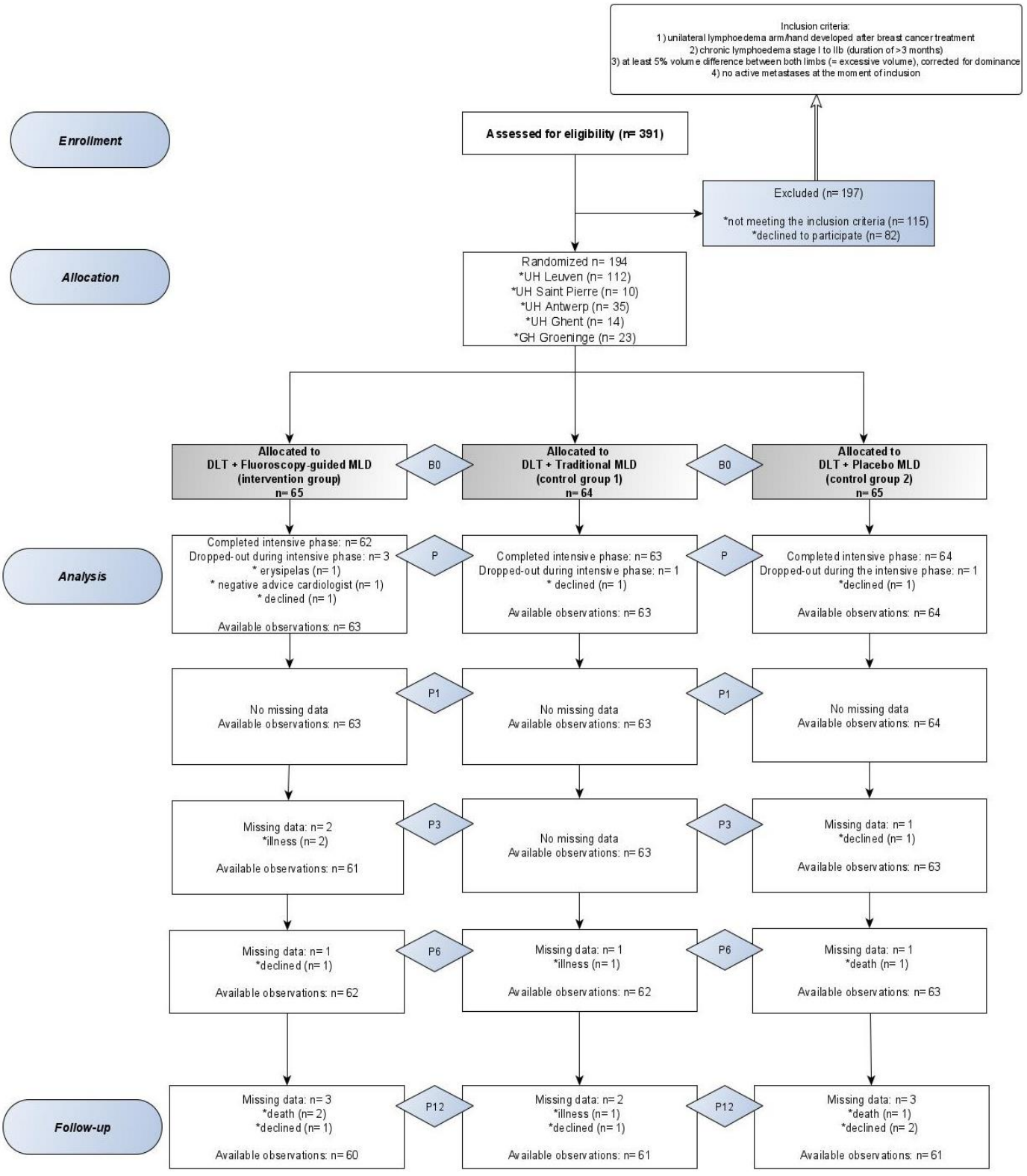



***Figure 1.*** *Flow chart of the EFforT-BCRL trial according to the Consort 2010 Flow diagram[41] Abbreviations: MLD = manual lymph drainage, B0 = baseline assessment, P = post-intensive assessment, P1 = 1 month post-intensive assessment, P3 = 3 months post-intensive assessment, P6 = 6 months post-intensive assessment (= end of maintenance phase), P12 = 12 months post-intensive phase (= after 6 months of follow-up).*