



Research

Manual lymphatic drainage with or without fluoroscopy guidance did not substantially improve the effect of decongestive lymphatic therapy in people with breast cancer-related lymphoedema (EforT-BCRL trial): a multicentre randomised trial

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KEY WORDS

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ABSTRACT

Questions: When added to decongestive lymphatic therapy (DLT), what is the effect of fluoroscopy-guided manual lymphatic drainage (MLD) versus traditional MLD or placebo MLD for the treatment of breast cancer-related lymphoedema (BCRL)? **Design:** Multicentre, three-arm, randomised controlled trial with concealed allocation, intention-to-treat analysis and blinding of assessors and participants. **Participants:** At five hospitals in Belgium, 194 participants with unilateral chronic BCRL were recruited. **Intervention:** All participants received standard DLT (education, skin care, compression therapy and exercises). Participants were randomised to also receive fluoroscopy-guided MLD (n = 65), traditional MLD (n = 64) or placebo MLD (n = 65). Participants received 14 sessions of physiotherapy during the 3-week intensive phase and 17 sessions during the 6-month maintenance phase. Participants performed self-management on the other days. **Outcome measures:** All outcomes were measured: at baseline; after the intensive phase; after 1, 3 and 6 months of maintenance phase; and after 6 months of follow-up. The primary outcomes were reduction in excess volume of the arm/hand and accumulation of excess volume at the shoulder/trunk, with the end of the intensive phase as the primary endpoint. Secondary outcomes included daily functioning, quality of life, erysipelas and satisfaction. **Results:** Excess lymphoedema volume decreased after 3 weeks of intensive treatment in each group: 5.3 percentage points of percent excessive volume (representing a relative reduction of 23.3%) in the fluoroscopy-guided MLD group, 5.2% (relative reduction 20.9%) in the traditional MLD group and 5.4% (relative reduction 24.8%) in the placebo MLD group. The effect of fluoroscopy-guided MLD was very similar to traditional MLD (between-group difference 0.0 percentage points, 95% CI -2.0 to 2.1) and placebo MLD (-0.2 percentage points, 95% CI -2.1 to 1.8). Fluid accumulated at the shoulder/trunk in all groups. The average accumulation with fluoroscopy-guided MLD was negligibly less than with traditional MLD (-3.6 percentage points, 95% CI -6.4 to -0.8) and placebo MLD (-2.4 percentage points, 95% CI -5.2 to 0.4). The secondary outcomes also showed no clinically important between-group differences. **Conclusion:** In patients with chronic BCRL, MLD did not provide clinically important additional benefit when added to other components of DLT. **Registration:** NCT02609724. [De Vrieze T, Gebruers N, Nevelsteen I, Fieuws S, Thomis S, De Groef A, Tjalma WAA, Belgrado J-P, Vandermeeren L, Monten C, Hanssens M, Devoogdt N (2022) Manual lymphatic drainage with or without fluoroscopy guidance did not substantially improve the effect of decongestive lymphatic therapy in people with breast cancer-related lymphoedema (EforT-BCRL trial): a multicentre randomised trial. *Journal of Physiotherapy* ■:■-■]

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Introduction

Worldwide, 2.3 million women are diagnosed with breast cancer every year.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, with > 16% of them developing breast cancer-related lymphoedema (BCRL).³

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According to the recommendations of the International Society of Lymphology, lymphoedema needs to be treated with decongestive lymphatic therapy (DLT) consisting of two-stage 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 optimise the results obtained in the first phase. It consists of skin care, education regarding self-management, a compression sleeve, exercises and MLD. Although it has been applied in many countries for decades, recent systematic reviews, including a Cochrane systematic review with six randomised trials, have not been able to demonstrate any added value of this method of MLD (subsequently called 'traditional MLD' throughout this paper).^{5,6} Four more-recent randomised trials were also unable to demonstrate any substantial effect of adding traditional MLD to DLT in reducing lymphoedema volume.⁷⁻¹⁰

One reason that traditional MLD did not show any added value in previous trials may be the 'blind' application without mapping of the lymphatic anatomy. After dissection of the axillary lymph nodes with or without irradiation, the lymphatic system of the upper limb is damaged. Lymph nodes are removed and often fibrosis of superficial lymphatics ensues.^{11,12} As a result, reverse flow of lymph fluid can occur (dermal backflow), arising from collecting vessels and moving through precollecting vessels in the direction of the initial dermal lymphatic vessels;¹³ importantly, this rerouting is patient-specific.¹⁴ Therefore, the effect of MLD might be improved by tailoring it to each individual patient.¹⁵ To tailor MLD, near-infrared fluorescence imaging or lymphofluoroscopy can be used to map the regions with dermal rerouting and the remaining superficial collecting vessels. Another reason that traditional MLD did not improve BRCL in previous trials may be the technique of MLD. The resorption of lymph by the initial lymphatics is better stimulated when the therapist performs a resorption technique with the thumb instead of the whole hand, and the transport of lymph through the lymph collectors and dermal rerouting is better stimulated when the therapist glides with the hand over the skin at a relatively higher pressure than when a pumping technique at relatively lower pressure is performed.¹⁵ These adapted manual manoeuvres applied to each patient's specific lymphatic system will subsequently be referred to as 'fluoroscopy-guided MLD' throughout this paper.

The lymphatic transport-stimulating effect of one session of fluoroscopy-guided MLD has been demonstrated in healthy volunteers and in patients with BCRL;^{15,16} however, no evidence exists on its long-term and clinical effects. In addition, patients report a positive subjective feeling after MLD,¹⁷ which may just be due to a placebo effect. Whether this is a real or placebo effect needs further investigation. The present study aimed to investigate the effect of fluoroscopy-guided MLD (versus traditional MLD or placebo MLD) added to DLT for the treatment of BCRL.

Therefore, the research question for this multi-centre randomised trial was:

When added to decongestive lymphatic therapy, what are the relative effects of fluoroscopy-guided manual lymphatic drainage versus traditional manual lymphatic drainage or placebo manual lymphatic drainage for the treatment of breast cancer-related lymphoedema?

Method

Study design

The EforT-BCRL trial is a multicentre, three-arm, randomised controlled trial with concealed allocation, intention-to-treat analysis and blinding of assessors and patients. The trial's design has been described in detail elsewhere.¹⁸ Briefly, participants were recruited at five hospitals in Belgium: University Hospitals of Leuven (UH Leuven), Antwerp University Hospital (UH Antwerp), Saint-Pierre University

Hospital in Brussels (UH Saint-Pierre), Ghent University Hospital (GUH) and General Hospital Groeninge (GH Groeninge) in Kortrijk. All participants received 3 weeks of intensive treatment followed by maintenance treatment for 6 months. Participants were followed up for 6 months beyond the end of the maintenance treatment. All participants received standardised DLT treatment consisting of education, skin care, compression therapy and exercises. Only MLD differed among the three randomly allocated groups: fluoroscopy-guided MLD, traditional MLD or placebo MLD. The random allocation sequence was computer-generated with permuted blocks of six. Allocation to the groups was performed by an independent person and concealed from participants and the researchers who performed the measurements. Participants were assessed: at 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. The study is reported according to the CONSORT statement.¹⁹

Participants

Inclusion criteria for the EforT-BCRL trial were: patients with unilateral lymphoedema of the arm and/or hand that developed after treatment for breast cancer; chronic lymphoedema stage I to IIb for > 3 months; excessive volume unilaterally, defined as $\geq 5\%$ difference between both arms adjusted for limb dominance and/or between both hands; and no active metastases at the moment of inclusion. Patients were excluded when one of the following criteria were present: aged < 18 years; oedema of the upper limb from another cause other than breast cancer treatment; inability to participate during the entire study period; mental or physical inability to participate in the study; allergy for indocyanine green, iodine or sodium iodide; increased activity of the thyroid gland; benign tumours of the thyroid gland; previous lymph node transplantation or lymphovenous shunt; and bilateral axillary lymph node dissection.

Intervention

For all details regarding the treatment and different treatment modalities, refer to the trial's published protocol;¹⁸ a brief summary is provided here. All participants received 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. All participants received 14 treatment sessions during the 3-week intensive treatment period. Each intensive treatment session lasted for 60 minutes: 30 minutes of standard treatment (skin care, bandaging, exercises) and 30 minutes of MLD. Treatment started with drainage of the shoulder and trunk, followed by removal of the bandage and circumference measurements of the arm using a perimeter. Afterwards, drainage of the arm (and hand), shoulder and trunk was continued. After MLD, skin care and bandaging were applied and the session ended with exercises.

During the subsequent 6-month maintenance period, participants received 18 sessions in decreasing frequency from two sessions per week initially down to one session per month during months 5 and 6. In the maintenance phase, therapeutic sessions lasted for 30 minutes because they only consisted of skin care and manual lymph drainage. Additionally, participants performed exercises at home and wore the compression sleeve and glove during the day.

The treatments were provided by five physiotherapists: RVH, LB, LV and AKH (at UH Leuven); LV and TDV (at UH Saint-Pierre, GH Groeninge and GUH); and TDV (at UH Antwerp); all were experts in oedema therapy. The same therapist provided DLT and MLD for any given participant. To limit any subjective influences of the therapist, a standardised treatment protocol was developed after consensus with the expert panel. To make the therapists familiar with this protocol and to ensure that the treatments given by each therapist were identical, multiple training sessions were given prior to the start and during the course of the trial.

Randomised MLD techniques

In the traditional MLD group, the therapist applied hand movements¹⁸ based on the normal anatomy of the lymphatic system (ie, without knowledge of the participant-specific lymphatic architecture) with pressure up to 40 mmHg. In the fluoroscopy-guided MLD

group, a similar regimen was used, except that baseline lympho-fluoroscopy was used to determine which hand movements would be applied at which location,¹⁵ some manual techniques differed¹⁸ and higher pressures (up to 80 mmHg) were applied in the regions with evidence of dermal backflow and/or rerouting. In the placebo MLD

Table 1

Overview of the measurement methods and procedures of the primary outcomes.

Outcome	Measurement method	Calculation procedure
Excess volume of the arm/hand: measurement at the level of the hand (this was the only outcome measure for participants with hand lymphoedema only)	<p>Water displacement method (ICC 0.99; SEM% 0.7%)³⁸</p> <p>Material Cylinder filled with 20 to 30 °C water, on a software-connected balance with 0.1 g accuracy^a on a 25-cm platform (Figure 1a)</p> <p>Reference point Lower ventral fold at level of wrist</p> <p>Method</p> <ul style="list-style-type: none"> Remove jewellery from arm/hand Participant stands beside cylinder Participant advised not to touch cylinder Hand enters the cylinder with axis perpendicular to water surface, until reference point reaches water Participant holds the hand stable and assessor activates software Software performs 10 volume measurements and calculates mean volume (volume of upward displaced water = mass of water/density of water^b) Software signals if mean volume or its SD is outside a pre-set range 	<p>Volume of hand = volume up to reference point at wrist.</p> <p>The volume of the non-dominant hand is on average 3.3% smaller than the dominant hand/arm;^{39,40} therefore, the volume of the hand/arm on the healthy side is corrected for hand dominance (multiply by 0.967 if the affected side is the dominant side; divide by 0.967 if the affected side is the non-dominant side).</p> <p>Relative excess lymphoedema volume of hand (ratio) = (volume affected side)/(corrected volume healthy side).</p> <p>Results are presented as % excess volume between oedematous and non-oedematous limb: [(oedematous/non-oedematous)*100] - 100.</p> <p>Change of relative excess lymphoedema volume of hand = comparison between ratio time 1 and ratio time 2 in analysis.</p> <p>To facilitate interpretation of the results, the <u>relative</u> percentage of volume reduction (ie, the change in excess arm volume before and after treatment relative to the baseline excess arm volume) is also reported in each group.</p>
Excess volume of the arm/hand: measurement at the level of the arm (hand volume was added to arm volume for participants with arm lymphoedema)	<p>Circumference measurements (ICC 0.99; SEM% 1.2%)^{38,41}</p> <p>Material Perimeter, which is a flexible stainless-steel bar with a tape measure fixed every 4 cm and a weight of 20 g at the end (Figure 1b)</p> <p>Reference point Upper border of olecranon</p> <p>Method</p> <ul style="list-style-type: none"> Remove jewellery from arm/hand Participant sits with 90° shoulder flexion, straight elbow and hand supported on table Arm circumferences measured at olecranon and at 4, 8, 12, 16 and 20 cm proximal and distal to the olecranon 	<p>Volume of whole arm = sum of volumes of all segments of arm.</p> <p>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 of 4 cm measured by a perimeter.</p> <p>The volume of the non-dominant hand/arm is on average 3.3% smaller than the dominant hand/arm;^{39,40} therefore, the volume of the arm at the healthy side is corrected for hand dominance (multiply by 0.967 if the affected side is the dominant side; divide by 0.967 if the affected side is the non-dominant side).</p> <p>Relative excessive lymphoedema volume of arm (ratio) = (volume arm + volume hand (compare above) affected side)/(corrected volume arm + corrected volume hand (compare above) healthy side).</p> <p>Results are presented as % excess volume between oedematous and non-oedematous limb: [(oedematous/non-oedematous)*100] - 100.</p> <p>Change of relative excess lymphoedema volume of arm = comparison between ratio time 1 and ratio time 2 in analysis.</p> <p>To facilitate interpretation of the results, the <u>relative</u> percentage of volume reduction (ie, the change in excess arm volume before and after treatment relative to the baseline excess arm volume) is also reported in each group.</p>
Excess fluid accumulation at the shoulder/trunk level	<p>Measurement of % water content (PWC%) (ICC 0.92)³⁸</p> <p>Material Skin hydration meter^c (Figure 1c)⁴²⁻⁴⁴</p> <p>Reference points Deltoid, 5 cm below lateral border of acromion Side of trunk, 5 cm below axillary crease</p> <p>Method</p> <ul style="list-style-type: none"> If skin is recently hydrated, dehydrate skin Sensor is placed perpendicular to the skin at the reference points with the pressure required by the device As the high electromagnetic wave is only absorbed by water, the device calculates water's relative presence, displayed as a percentage 	<p>Relative excessive fluid accumulation (ratio PWC%) = PWC% affected side/PWC% healthy side.</p> <p>Measured at the level of shoulder and trunk, after which a mean ratio PWC% is calculated.</p> <p>Results are presented as % excessive fluid accumulation between oedematous and non-oedematous side: [(PWC oedematous/PWC non-oedematous)*100] - 100.</p> <p>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.</p> <p>To facilitate interpretation of the results, the <u>relative</u> percentage of fluid accumulation (ie, the change in excess fluid accumulation before and after treatment relative to the baseline excess fluid accumulation) is also reported in each group.</p>

PWC% = percentage of water content.

^a KERN 572, Kern & Sohn GmbH, Balingen, Germany.

^b Density of water with temperature between 20 to 30 °C is 1.

^c MoistureMeter D Compact, Delfin Technologies, Kuopio, Finland.

group, deep massage was used, involving relaxing transverse movements on the muscles of the ipsilateral neck, back, shoulder, arm and hand. Each group received a plausible explanation for the type of MLD they received.

Outcome measures

Lymphofluoroscopic and clinical assessments

All participants received a standardised lymphofluoroscopic assessment at baseline, the end of the intensive treatment phase and the end of the maintenance phase. Baseline lymphofluoroscopy was used to determine the tailored procedure of MLD¹⁵ in the fluoroscopy-guided MLD group. Clinical assessments were performed at: baseline; after intensive treatment; after 1, 3 and 6 months of maintenance treatment; and after 6 months of follow-up. During the intensive and maintenance treatment phases, adherence to the self-management protocol was recorded. For a detailed description regarding the fluoroscopic and different clinical assessments, see the protocol of the EForT-BCRL trial.¹⁸ All lymphofluoroscopic assessments were performed by three doctors (ST, LV, CM) assisted by physiotherapists (ND, NG, KD). Clinical assessments were performed by four assessors (TDV, LV, KD, SVDB); all were experienced in performing these assessments. Participants were evaluated by the same assessor per centre.

To describe the characteristics of the sample, body height and weight (to calculate BMI), pitting at the level of hand and arm (to calculate the pitting score) and lymphoedema stage were obtained through evaluation. Duration of lymphoedema was collected through interview. Each participant's age, breast cancer characteristics and breast cancer treatment details were extracted from the medical files.

Primary outcomes

One primary outcome measure was the change in excess lymphoedema volume. The other primary outcome measure was the change in excess fluid accumulation at the level of the shoulder and trunk.²⁰ Further details are presented in [Table 1](#) and [Figure 1](#).

Secondary outcomes

Secondary outcome measures covered the clinical impact of lymphoedema: changes in extent of problems in functioning related to lymphoedema²¹ and change in overall quality of life.²² The numbers of participants reporting at least one episode of erysipelas and adverse effects related to the treatment or fluoroscopic examinations were also recorded during the entire study period and compared between the groups. Finally, at the last clinical evaluation after 6 months of follow-up, the overall treatment satisfaction and MLD-specific treatment satisfaction were assessed using a self-developed questionnaire and compared between the groups. Further details are presented in [Table 2](#).

Adherence

Participants' adherence to the self-management protocol (eg, self-MLD, wearing of compression materials, performance of exercises)

was recorded in a diary that participants were asked to complete ([Appendix 1](#) on the eAddenda).

Blinding

All participants were blinded to their allocation to one of the three MLD groups. To assess the blinding, participants' perceived treatment allocation was recorded on a self-developed questionnaire at the end of the follow-up period. All clinical and fluoroscopic assessments were performed by individuals who were blinded to the allocation of the different treatment groups, whereas the therapists were obviously informed on the treatment group allocation but blinded to the participant's outcome measurements.

Data analysis

Based on an alpha of 0.0125 (two primary outcomes and two pairwise primary comparisons) and power of 80%, the planned sample size for the study was 201 subjects or 67 subjects per group (taking into account potential loss to follow-up) 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 fluoroscopy-guided MLD on the one hand and traditional/placebo MLD on the other hand.¹⁸ The sought effect was determined from clinical results of the Leuven Lymphovenous Centre and by consulting experts in the field of lymphology, with an estimated reduction of 35% (SD 25) for the traditional MLD group, 50% (SD 25) for the fluoroscopy-guided MLD group and 20% (SD 25) for the placebo MLD group. Based on a previous longitudinal study with breast cancer patients,²³ a drop-out rate of 5% (or nine patients) was estimated.

Baseline participant characteristics were reported descriptively. Analyses for the primary outcomes were performed on log-transformed ratios because, for percentage change, the intervals between units are not equidistant. For example, the correct mean of an increase of 100% (ratio = 2) and a decrease of -50% (ratio = 0.5) should not be 25% but 0%. The latter is accomplished when taking the log of the ratios before calculating the mean and transforming the log-ratios back to the original scale. Evolution of the log-ratios between the three groups was calculated by a multivariate linear model for longitudinal measures. An unstructured covariance matrix was used for the 6×6 covariance matrix of the repeated measures over time (baseline; end of intensive treatment; after 1, 3 and 6 months of maintenance treatment; and after the 6-month follow-up). Given that a direct likelihood procedure was used, participants with incomplete outcome information were also included in the analysis. Results for the oedema/normal log-ratios were transformed back to the original scale (ratio) with a 95% CI. Note that these ratios have a direct interpretation of percent excess volume; for example, a ratio of 1.25 refers to 25% excess volume. From the model, changes in these log-ratios versus baseline were obtained at each time point and compared between the three groups. These differences versus baseline were reported as percentage point changes in excess volume. The time point for the assessment of the primary outcomes was at the end of the intensive treatment phase.



Figure 1. Equipment used in the measurement of (a) hand volume via the water displacement method, (b) volume of the arm via circumferential measurements (perimetry) and (c) percentage of water content at the shoulder and trunk. For further explanation, see [Table 1](#).

Table 2
Overview of the measurement methods and procedures of the secondary outcomes.

Outcome	Measurement method
Problems in functioning	Investigation of problems in functioning related to lymphoedema (ICC total score 0.93; SEM total score: 4.8) ⁴⁵ Material Lymph-ICF-UL Questionnaire (Dutch ^{21,46} and French ²⁷ versions) Method <ul style="list-style-type: none"> • At the end of each assessment, participants completed the questionnaire individually • The Lymph-ICF-UL has 29 questions in five domains: physical function, mental function, household activities, mobility activities, and life and social activities • Every question is scored between 0 and 10 • The overall score (<i>sum of the scores on 29 questions divided by 29, multiplied by 10</i>) and five different domain scores are calculated, each of them representing a score between 0 and 100 • A lower score indicates fewer problems in functioning
Quality of life	Investigation of quality of life for patients with a chronic disease (ICC total score: 0.93, SEM total score: 0.44) ²² Material McGill-QoL Questionnaire (Dutch and French versions) Method <ul style="list-style-type: none"> • At the end of each assessment, participants filled in the questionnaire individually • The McGill-QoL Questionnaire consists of 16 questions using a Likert scale and one open question in five domains: physical symptoms, physical well-being, psychological symptoms, existential well-being and support • Each question corresponds to a score between 0 (very bad) and 10 (excellent); a total score and five different domain scores are calculated and represent a score between 0 to 10 • A lower score indicates a lower quality of life
Difference in number of participants reporting at least one episode of erysipelas	Investigation of the number of participants reporting at least one episode of erysipelas during the 12-month study period (between baseline and the end of follow-up) Method <ul style="list-style-type: none"> • At the start of each assessment, participants were asked whether they had had an infection (erysipelas) during the past clinical assessment and the present date. If yes, participants had to specify how many times and when • Participants with no episodes of erysipelas during the 12 months scored 0; those with one or more episodes scored 1
Difference in overall treatment satisfaction and MLD-specific treatment satisfaction	Investigation of the overall treatment satisfaction and MLD-specific treatment satisfaction at the end of the trial Material Self-developed questionnaire Method <ul style="list-style-type: none"> • At the end of the last clinical assessment (ie, end of the follow-up phase), participants were asked to complete a survey, consisting of two elements • First, participants evaluated overall treatment satisfaction on a Likert scale (1 = very much better, 2 = much better, 3 = a little better, 4 = unchanged, 5 = a little worse, 6 = much worse and 7 = very much worse), based on change in complaints from before the study • Second, participants rated the perceived effect of MLD (MLD-specific treatment satisfaction) from 0 (no effect at all) to 10 (a lot of effect)

Lymph-ICF-UL = Lymphoedema Functioning, Disability and Health Questionnaire for Upper Limb Lymphoedema; McGill-QoL = McGill-Quality of life.

Analyses were performed by original assigned groups (intent-to-treat).

As with the primary outcomes, a multivariate linear model for longitudinal measures was used to compare the evolution of the scores of the first two secondary outcome parameters (problems in functioning and overall quality of life) between the three groups. Mean values with 95% CI were reported at each time point. Changes from baseline were calculated and compared between the three groups.

Difference in the number of participants reporting at least one episode of erysipelas was analysed with the χ^2 test and overall treatment and MLD-specific treatment satisfaction with the Kruskal-Wallis test. Commercial statistical software^{a,b} was used for all analyses.

Results

Compliance with the trial protocol

Inclusion of participants was ended before the project's pre-defined sample size ($n = 201$) was reached because there were fewer drop-outs than anticipated. This did not jeopardise the power of the performed primary analysis because the analysis was still based on information from 194 subjects at baseline and 190 subjects at the primary endpoint. Two secondary outcome measures were registered post hoc: overall treatment satisfaction and MLD-specific treatment satisfaction.

Flow of participants through the study

Between February 2016 and September 2019, 391 patients were screened and 194 participants were recruited. The flow of participants through the trial is presented in Figure 2. The baseline characteristics of the participants are presented in Table 3.

Adherence to the prescribed treatment sessions

During the intensive treatment phase, participants received a mean of 13 (SD 1) of the 14 treatment sessions that were initially planned. During the maintenance treatment phase, participants received on average 17 (SD 1) treatment sessions of the 18 that were initially planned. For details regarding the participants' adherence to the self-management protocol during the maintenance treatment phase, see Appendix 1 on the eAddenda.

Blinding

At the end of the 6-month follow-up period, 76 participants reported that they had no idea to which group they had been allocated and 63 guessed their allocated group incorrectly. Therefore, 139 of 180 participants (77%) could not identify their allocated group correctly, indicating successful blinding of participants.

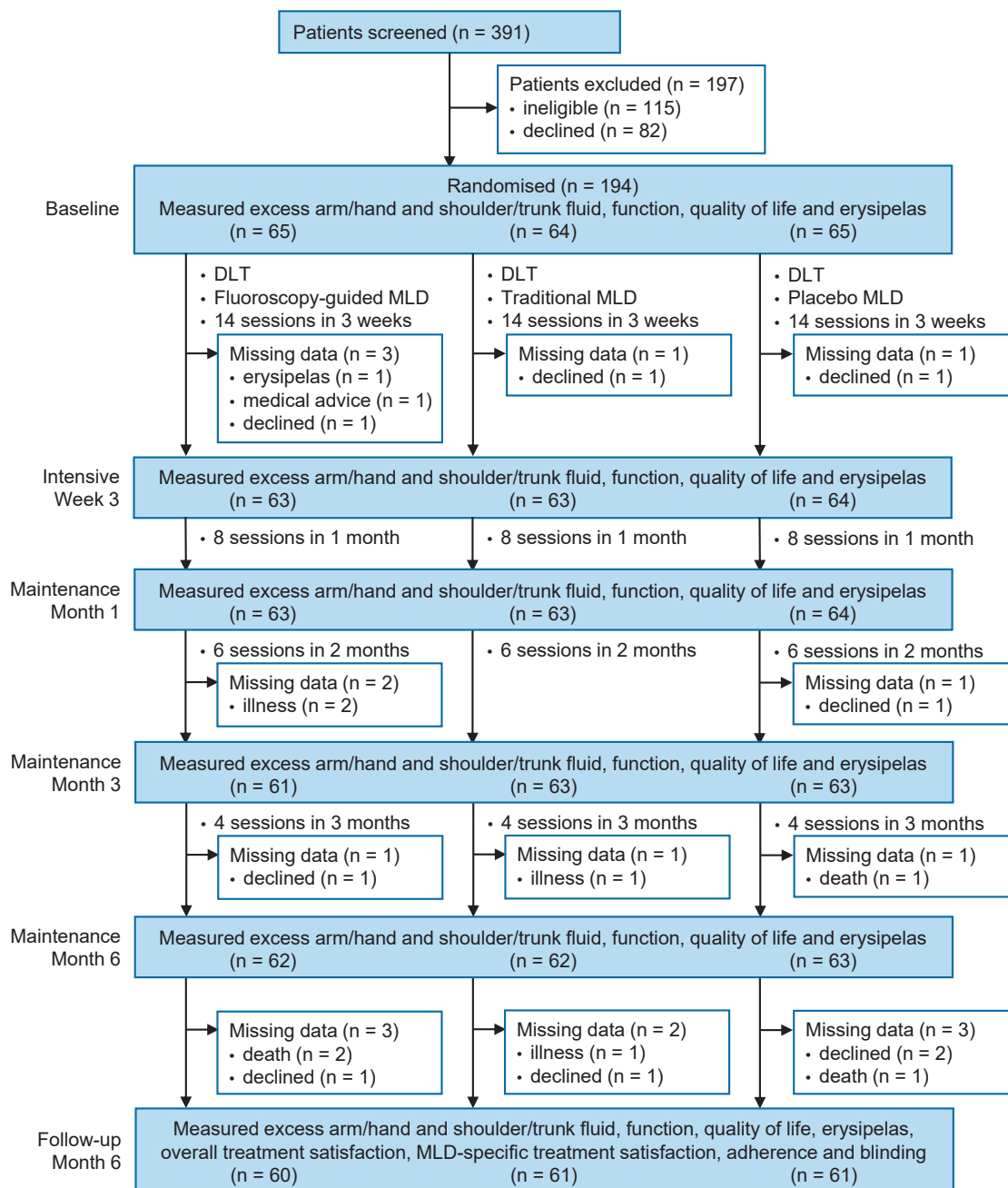


Figure 2. Flow of participants through the trial, according to CONSORT Statement.⁴⁷

Primary outcome

Excess lymphoedema volume at the arm/hand

After the intensive treatment phase, the excessive lymphoedema volume decreased in all three groups: fluoroscopy-guided MLD group (5.3% absolute excessive volume reduction (percentage points) or a relative reduction of 23.3%) and traditional MLD group (5.2% absolute reduction or 20.9% relative reduction), or between the fluoroscopy-guided MLD group and placebo MLD group (5.4% absolute reduction or 24.8% relative reduction). However, no clinically important differences in volume reduction were found between the groups, with all between-group differences and their CIs having a magnitude less than about 2 percentage points (Table 4 and Figure 3). Additional data are presented in Appendix 2 on the eAddenda.

Excess fluid accumulation at the shoulder/trunk

An increase in fluid accumulation at the level of the shoulder/trunk was present in all three treatment groups after the intensive treatment phase, with the change being most marked in the fluoroscopy-guided

MLD group at 4.4 percentage points (95% CI 2.4 to 6.4), which is a relative increase of 95.6%. In the traditional MLD group the change was an 0.8% absolute increase or a 15.7% relative increase, and in the placebo MLD group the change was a 2.0% absolute increase or a 35.1% relative increase. Although these differences in relative increases seem large, no clinically important differences in excess fluid accumulation were found between the groups, with all between-group differences and their CIs having a magnitude less than about 6 percentage points (Table 5 and Figure 3). Additional data are presented in Appendix 3 on the eAddenda.

Secondary outcomes

Problems in functioning related to lymphoedema

Changes in problems in functioning related to lymphoedema in each group and the corresponding between-group comparisons are presented in Table 6. The between-group differences were small (< 5 points on the Lymph-ICF-UL total score) with narrow CIs (~ 10 points

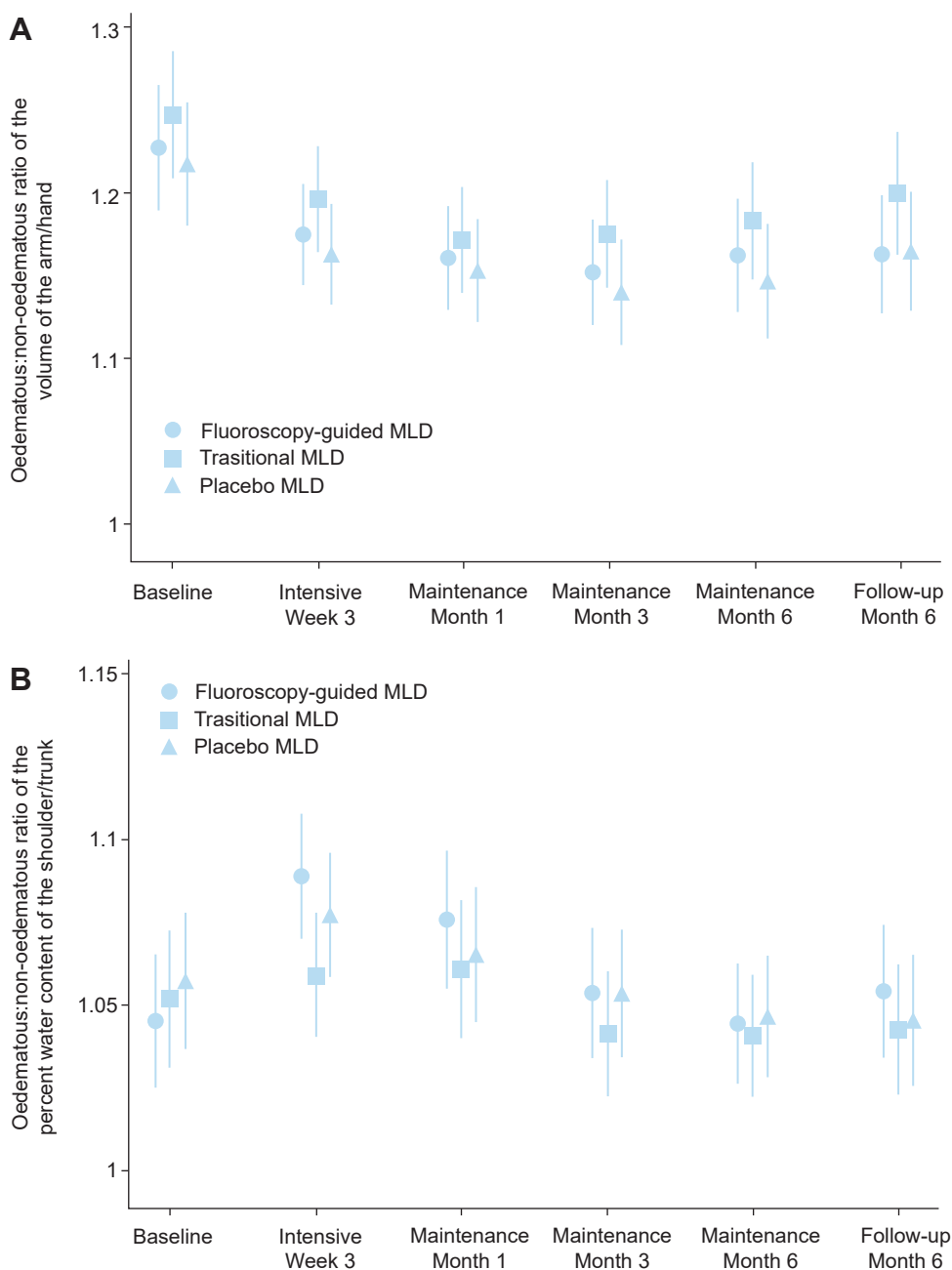


Figure 3. (a) Change in excessive lymphoedema volumes at the level of the arm/hand by means of the inter-limb ratio of volume (oedematous:non-oedematous) at different time points. (b) Change in excess fluid accumulation at the level of the shoulder/trunk by means of the mean inter-side ratio of percent water content (oedematous:non-oedematous) at different time points. In both graphs: the timepoint for analysis of the primary outcome is at week 3 of the intensive treatment period; all estimates are obtained from the multivariate linear model; and error bars depict the 95% CI.

or less), indicating negligible differences in effect between the three allocated interventions.

Quality of life

Changes quality of life in each group and the corresponding between-group comparisons are presented in Table 7. The between-group differences were small (< 0.5 points on the McGill-QoL total score) with narrow CIs (~1 point or less), indicating negligible differences in effect between the three allocated interventions.

Adverse events

Twenty participants had at least one case of erysipelas, with all episodes occurring after bacterial infection due to wounds, insect bites or scratches. The rates were similarly low in each group, leading to estimates of no important differences in risk of erysipelas among the three randomised interventions (Table 8). The participants

reported no adverse effects caused by the DLT or by the fluoroscopic examinations (intradermal injections of a solution of indocyanine green tracer^c diluted by saline water and pure water, reaching a final concentration of 0.016 mg indocyanine green per two injections of 0.2 ml indocyanine green-aqua-NaCl).

Overall treatment satisfaction

A total of 143 of 180 participants (79%) indicated that their complaints were slightly improved (n = 50), much improved (n = 64) or very much improved (n = 29) at the end of the follow-up phase, in comparison with the period prior to the start of the study. The number of participants indicating that their complaints were slightly improved, much improved or very much improved did not differ to a clinically important extent between the fluoroscopy-guided MLD group (80%), traditional MLD group (78%) and placebo MLD group (80%).

Table 3
Baseline characteristics of the study participants.

Characteristic	Fluoroscopy-guided MLD (n = 65)	Traditional MLD (n = 64)	Placebo MLD (n = 65)	All participants (n = 194)
Age (yr), mean (SD)	60 (11)	62 (10)	61 (9)	61 (10)
Gender, n (%)				
female	65 (100)	63 (98)	65 (100)	193 (99)
male	0 (0)	1 (2)	0 (0)	1 (1)
Body mass index (kg/m ²), mean (SD)	27.6 (5.3)	28.8 (5.6)	27.8 (6.1)	28.1 (5.7)
Lymphoedema duration (mth), median (IQR)	29 (5 to 54)	28 (6 to 78)	16 (5 to 54)	25 (5 to 62)
Excess lymphoedema arm volume				
absolute (ml), median (IQR)	457 (484 to 747)	442 (284 to 738)	430 (275 to 796)	441 (276 to 754)
relative (%), median (IQR)	22.8 (12.3 to 34.9)	21.9 (12.3 to 31.3)	21.3 (12.4 to 30.2)	21.7 (16.0 to 44.5)
Total pitting score (0 to 18) ^a , median (IQR)	5 (3 to 7)	5 (3 to 7)	4 (3 to 8)	5 (3 to 8)
Recruitment site, n (%)				
UH Leuven	39 (60)	36 (56)	37 (57)	112 (58)
UH Antwerp	9 (14)	10 (16)	16 (25)	35 (18)
UH Saint Pierre Brussels	6 (9)	2 (3)	2 (3)	10 (5)
GH Groninge Kortrijk	7 (11)	9 (11)	7 (11)	23 (12)
UH Ghent	4 (6)	7 (14)	3 (5)	14 (7)
Lymphoedema on dominant side, n (%)	31 (48)	21 (33)	33 (51)	85 (44)
Lymphoedema location, n (%)				
arm	61 (94)	62 (97)	61 (94)	184 (95)
hand	4 (6)	2 (3)	4 (6)	10 (5)
Lymphoedema stage, n (%)				
I	10 (15)	10 (16)	12 (19)	32 (17)
IIa	34 (52)	40 (63)	35 (54)	109 (56)
IIb	21 (32)	14 (22)	18 (28)	53 (27)
Type of surgery, n (%)				
mastectomy	36 (55)	40 (63)	39 (60)	115 (59)
breast-conserving surgery	29 (45)	24 (38)	26 (40)	79 (41)
Positive lymph nodes (n), n (%)				
0	12 (19)	19 (30)	17 (26)	48 (25)
1 to 3	35 (54)	24 (38)	28 (43)	87 (45)
4 to 10	13 (20)	11 (17)	14 (22)	38 (20)
> 10	5 (8)	9 (14)	6 (9)	20 (10)
Pathological tumour stage, n (%)				
1	19 (31)	19 (31)	17 (26)	55 (30)
2	32 (49)	29 (45)	43 (66)	104 (54)
3	6 (9)	9 (14)	3 (5)	18 (9)
4	7 (11)	5 (9)	2 (3)	14 (7)
Missing data (n = 3)				
Pathological nodal stage, n (%)				
0	12 (18)	16 (2)	15 (23)	45 (23)
1	36 (55)	32 (5)	34 (52)	99 (52)
2	11 (17)	8 (13)	7 (11)	26 (13)
3	6 (9)	8 (13)	9 (14)	23 (12)
Clinical metastases, n (%)				
0	64 (98)	64 (100)	63 (97)	191 (98)
1	1 (1)	0 (0)	2 (3)	3 (2)
Radiotherapy, n (%)	63 (97)	63 (98)	63 (97)	189 (97)
Chemotherapy, n (%)	54 (83)	52 (81)	61 (94)	167 (86)
Hormonal therapy, n (%)	51 (79)	53 (83)	48 (74)	152 (78)
Targeted therapy, n (%)	13 (20)	12 (19)	14 (22)	39 (20)

^a The total score is calculated as the sum of nine individual pitting test scores (0 = no, 1 = uncertain, 2 = obvious) on the oedematous limb and trunk.

MLD-specific treatment satisfaction

The median rating of the perceived effect of the MLD that participants received during the study was 7 (IQR 6 to 9) out of 10 (n = 181). The median score in the fluoroscopy-guided MLD group was 8 out of 10, the median score in the two other groups was 7 out of 10 (Table 9).

Discussion

It is believed that this is the first trial to investigate the merit of a patient-tailored method of MLD (ie, fluoroscopy-guided MLD) compared with traditional MLD or placebo MLD, additional to the other components of DLT, for the treatment of BCRL. It was necessary to try to develop a more effective method of MLD because several randomised trials could not demonstrate any added value of traditional MLD⁷⁻¹⁰ and MLD is applied worldwide, implying a large cost for healthcare systems.^{24,25} Unfortunately, a larger reduction in the excessive arm volume or less accumulation of lymph at the level of the shoulder/trunk was not identified in the group receiving fluoroscopy-guided MLD compared with the other two methods. Based on the width of the CIs for the between-group comparisons, it

can also be concluded that the mean between-group differences were not clinically relevant for the different investigated outcomes. The maximum difference in the excessive volume at the level of the arm and hand between the groups ranged between -3.5% and +4.7% at secondary endpoints. If this is transformed into an absolute excess volume difference, these numbers represent a range between -70 and 90 ml, which are not clinically relevant changes in the volume difference (ie, this is a small glass of water spread over the entire arm and hand). Moreover, a previous trial by this research group on the reproducibility of excess arm volume²⁶ found an SEM for the excess arm volume (based on the calculated volume from circumference measurements with the perimeter) of 45.3 ml. When calculating the smallest real difference (SRD) with the formula 'SRD = $\sqrt{2} \times 1.96 \times \text{SEM}$ ', an SRD for the excessive volume of 125.6 ml or of 4.96% was found (related to the volume of the non-oedematous limb with a volume of 2,532.0 ml). The CIs of the changes in excess volume between the groups were situated within the limits of the SRD (-4.96 to 4.96%).

Another trial by this research group on the reproducibility of tissue dielectric constant measures (in percent water content as well as in terms of inter-limb ratios)²⁰ found an SEM for the mean of the inter-limb ratios at the level of the shoulder and trunk (based on

Table 4

Percentage excess lymphoedema volume at the level of the arm/hand with 95% CIs in each group at each time point, within-group changes in percentage excess volume and between-group comparisons of these changes.

Time point	Excess volume (%) mean (95% CI)			Within-group change from baseline (<i>percentage point</i>), mean (95% CI)			Between-group difference mean (95% CI)		
	Fluoroscopy-guided MLD	Traditional MLD	Placebo MLD	Fluoroscopy-guided MLD	Traditional MLD	Placebo MLD	Fluoroscopy-guided MLD versus Traditional MLD	Fluoroscopy-guided MLD versus Placebo MLD	Traditional MLD versus Placebo MLD
Baseline	22.8 (19.0 to 26.6)	24.9 (21.1 to 28.8)	21.8 (18.1 to 25.6)						
Intensive week 3	17.5 (14.4 to 20.7)	19.7 (16.5 to 22.9)	16.4 (13.3 to 19.5)	-5.3 (-6.7 to -3.9)	-5.2 (-6.6 to -3.8)	-5.4 (-6.8 to -4.0)	0.0 (-2.0 to 2.1)	-0.2 (-2.1 to 1.8)	-0.2 (-2.2 to 1.8)
Maintenance month 1	16.1 (12.9 to 19.4)	17.2 (14.0 to 20.5)	15.3 (12.2 to 18.5)	-6.6 (-8.2 to -5.1)	-7.7 (-9.2 to -6.1)	-6.5 (-8.0 to -5.0)	-1.0 (-3.2 to 1.1)	0.2 (-2.0 to 2.3)	1.2 (-1.0 to 3.3)
Maintenance month 3	15.2 (12.0 to 18.5)	17.5 (14.2 to 20.9)	14.1 (10.9 to 17.3)	-7.5 (-9.4 to -5.7)	-7.3 (-9.2 to -5.4)	-7.7 (-9.5 to -5.9)	0.2 (-2.4 to 2.8)	-0.2 (-2.8 to 2.4)	-0.4 (-3.0 to 2.2)
Maintenance month 6	16.3 (12.8 to 19.8)	18.3 (14.8 to 22.0)	14.8 (11.3 to 18.3)	-6.5 (-8.5 to -4.4)	-6.6 (-8.7 to -4.5)	-7.0 (-9.1 to -5.0)	-0.1 (-3.0 to 2.9)	-0.5 (-3.4 to 2.3)	-0.5 (-3.4 to 2.5)
Follow-up month 6	16.3 (12.7 to 20.0)	20.0 (16.2 to 23.8)	16.5 (12.9 to 20.2)	-6.4 (-8.6 to -4.2)	-4.9 (-7.2 to -2.6)	-5.3 (-7.5 to -3.1)	1.5 (-1.7 to 4.7)	1.2 (-2.0 to 4.3)	-0.4 (-3.5 to 2.8)

Shaded cells indicate primary outcomes.

MLD = manual lymph drainage.

Table 5

Percentage excess fluid accumulation at level of the shoulder/trunk with 95% CIs in each group at each time point, within-group changes in percentage excess volume and between-group comparisons of these changes.

Time point	Excess fluid accumulation (%) mean (95% CI)			Within-group change from baseline (<i>percentage points</i>), mean (95% CI)			Between-group difference mean (95% CI)		
	Fluoroscopy-guided MLD	Traditional MLD	Placebo MLD	Fluoroscopy-guided MLD	Traditional MLD	Placebo MLD	Fluoroscopy-guided MLD versus Traditional MLD	Fluoroscopy-guided MLD versus Placebo MLD	Traditional MLD versus Placebo MLD
Baseline	4.5 (2.4 to 6.5)	5.1 (3.0 to 7.2)	5.7 (3.6 to 7.8)						
Intensive week 3	8.8 (6.9 to 10.8)	5.9 (4.0 to 7.7)	7.7 (5.8 to 9.6)	4.4 (2.4 to 6.4)	0.8 (-1.2 to 2.7)	2.0 (0.0 to 4.0)	-3.6 (-6.4 to -0.8) ^a	-2.4 (-5.2 to 0.4)	1.2 (-1.5 to 4.0)
Maintenance month 1	7.5 (5.4 to 9.6)	6.0 (4.0 to 8.1)	6.5 (4.4 to 8.5)	3.1 (1.0 to 5.1)	0.9 (-1.1 to 3.0)	0.8 (-1.2 to 2.8)	-2.1 (-5.0 to 0.8)	-2.3 (-5.2 to 0.6)	-0.1 (-3.0 to 2.7)
Maintenance month 3	5.3 (3.3 to 7.3)	4.1 (2.2 to 6.0)	5.3 (3.4 to 7.2)	0.8 (-1.2 to 2.9)	-1.0 (-3.0 to 1.0)	-0.4 (-2.4 to 1.7)	-1.8 (-4.7 to 1.0)	-1.2 (-4.1 to 1.7)	0.6 (-2.2 to 3.5)
Maintenance month 6	4.4 (2.5 to 6.3)	4.0 (2.2 to 5.9)	4.6 (2.8 to 6.5)	-0.1 (-1.9 to 1.8)	-1.1 (-2.9 to 0.8)	-1.1 (-2.9 to 0.8)	-1.0 (-3.6 to 1.7)	-1.0 (-3.6 to 1.7)	-0.0 (-2.6 to 2.6)
Follow-up month 6	5.3 (3.3 to 7.4)	4.2 (2.2 to 6.2)	4.5 (2.5 to 6.5)	0.9 (-1.2 to 3.0)	-0.9 (-3.0 to 1.2)	-1.2 (-3.3 to 0.9)	-1.8 (-4.7 to 1.2)	-2.1 (-5.0 to 0.9)	-0.3 (-3.2 to 2.6)

Shaded cells indicate primary outcomes.

MLD = manual lymph drainage

^a Note that when taking into account the multiplicity issue for the primary analysis, the CI (with alpha = 0.0125) would include the zero value.

Table 6

Mean Lymph-ICF-UL total score in each group at each time point, within-group change and between-group comparisons of these changes with 95% CIs.

Time point	Total Lymph-ICF-UL score mean (95% CI)			Within-group change from baseline mean (95% CI)			Between-group difference mean (95% CI)		
	Fluoroscopy-guided MLD	Traditional MLD	Placebo MLD	Fluoroscopy-guided MLD	Traditional MLD	Placebo MLD	Fluoroscopy-guided MLD versus Traditional MLD	Fluoroscopy-guided MLD versus Placebo MLD	Traditional MLD versus Placebo MLD
Baseline	38.0 (32.9 to 43.1)	35.7 (30.6 to 40.8)	38.1 (33.0 to 43.1)						
Intensive week 3	29.0 (24.3 to 33.6)	27.7 (23.0 to 32.4)	32.1 (27.5 to 36.7)	-9.0 (-12.8 to -5.3)	-8.0 (-11.7 to -4.2)	-6.0 (-9.7 to -2.2)	-1.1 (-6.3 to 4.2)	-3.1 (-8.3 to 2.2)	-2.0 (-7.3 to 3.3)
Maintenance month 1	27.8 (23.3 to 32.3)	24.6 (20.0 to 29.1)	28.8 (24.3 to 33.3)	-10.2 (-14.2 to -6.1)	-11.1 (-15.2 to -7.0)	-9.3 (-13.3 to -5.2)	0.9 (-4.8 to 6.6)	-0.9 (-6.6 to 4.8)	-1.8 (-7.5 to 3.9)
Maintenance month 3	23.3 (18.8 to 27.8)	25.4 (20.8 to 29.9)	25.2 (20.7 to 29.8)	-14.7 (-18.8 to -10.5)	-10.3 (-14.5 to -6.1)	-12.8 (-17.0 to -8.7)	-4.4 (-10.2 to 1.5)	-1.9 (-7.7 to 4.0)	0.6 (-5.2 to 6.5)
Maintenance month 6	25.3 (20.5 to 30.0)	24.5 (19.7 to 29.3)	27.5 (22.8 to 32.3)	-12.7 (-16.8 to -8.6)	-11.1 (-15.3 to -7.0)	-10.5 (-14.6 to -6.4)	-1.6 (-7.4 to 4.3)	-2.2 (-8.0 to 3.6)	-0.6 (-6.5 to 5.2)
Follow-up month 6	23.2 (18.5 to 27.9)	24.2 (19.5 to 28.9)	26.0 (21.3 to 30.7)	-14.8 (-18.9 to -10.7)	-11.5 (-15.6 to -7.3)	-12.1 (-16.2 to -8.0)	-3.4 (-9.2 to 2.4)	-2.7 (-8.5 to 3.1)	0.6 (-5.2 to 6.5)

Lymph-ICF-UL = Lymphoedema Functioning, Disability and Health Questionnaire for Upper Limb Lymphoedema, MLD = manual lymph drainage.

Table 7

Mean McGill-QoL total score in each group at each time point, within-group change and between-group comparisons of these changes with 95% CIs.

Time point	Total McGill-QoL score mean (95% CI)			Within-group change from baseline mean (95% CI)			Between-group difference mean (95% CI)		
	Fluoroscopy-guided MLD	Traditional MLD	Placebo MLD	Fluoroscopy-guided MLD	Traditional MLD	Placebo MLD	Fluoroscopy-guided MLD versus Traditional MLD	Fluoroscopy-guided MLD versus Placebo MLD	Traditional MLD versus Placebo MLD
Baseline	5.96 (5.58 to 6.35)	6.15 (5.75 to 6.54)	5.87 (5.48 to 6.26)						
Intensive week 3	6.06 (5.65 to 6.46)	6.18 (5.77 to 6.59)	5.82 (5.41 to 6.22)	0.09 (-0.35 to 0.54)	0.04 (-0.41 to 0.48)	-0.05 (-0.50 to 0.39)	0.06 (-0.57 to 0.69)	0.15 (-0.48 to 0.77)	0.09 (-0.54 to 0.72)
Maintenance month 1	6.14 (5.71 to 6.58)	6.21 (5.77 to 6.65)	5.98 (5.54 to 6.42)	0.18 (-0.23 to 0.59)	0.07 (-0.35 to 0.48)	0.11 (-0.30 to 0.53)	0.11 (-0.47 to 0.70)	0.07 (-0.52 to 0.65)	-0.05 (-0.64 to 0.54)
Maintenance month 3	5.85 (5.38 to 6.33)	6.10 (5.62 to 6.58)	5.82 (5.35 to 6.30)	-0.11 (-0.61 to 0.39)	-0.04 (-0.55 to 0.46)	-0.04 (-0.54 to 0.45)	-0.07 (-0.77 to 0.64)	-0.07 (-0.77 to 0.64)	-0.40 (-1.14 to 0.35)
Maintenance month 6	5.92 (5.43 to 6.41)	6.02 (5.53 to 6.52)	6.09 (5.60 to 6.58)	-0.05 (-0.56 to 0.46)	-0.12 (-0.64 to 0.39)	0.22 (-0.29 to 0.73)	0.07 (-0.65 to 0.80)	-0.27 (-0.99 to 0.45)	-0.34 (-1.07 to 0.38)
Follow-up month 6	5.96 (5.45 to 6.47)	5.69 (5.18 to 6.20)	5.81 (5.30 to 6.32)	-0.00 (-0.53 to 0.52)	-0.45 (-0.98 to 0.07)	-0.06 (-0.58 to 0.47)	0.45 (-0.29 to 1.19)	0.05 (-0.69 to 0.80)	-0.40 (-1.14 to 0.35)

McGill-QoL = McGill-Quality of life questionnaire, MLD = manual lymph drainage.

Table 8
Number (%) of participants with at least one episode of erysipelas and pairwise absolute risk differences with 95% CIs.

Outcome	Groups			Absolute risk difference (%) (95% CI)		
	Fluoroscopy-guided MLD	Traditional MLD	Placebo MLD	Fluoroscopy-guided MLD versus Traditional MLD	Fluoroscopy-guided MLD versus Placebo MLD	Traditional MLD versus Placebo MLD
≥ 1 episode of erysipelas ^a , n (%)	5/63 (8%)	8/63 (13%)	7/64 (11%)	-5 (-16 to 6)	-3 (-14 to 8)	2 (-10 to 14)
Reported complaints are improved ^b , n (%)	48/60 (80%)	46/59 (78%)	49/61 (80%)	2 (-13 to 16)	0 (-14 to 14)	-2 (-16 to 12)

MLD = manual lymph drainage.

^a Apparent discrepancies in subtraction are due to rounding of decimal places.

^b The categories of 'slightly improved', 'much improved' or 'very much improved' were combined to dichotomise this outcome into 'improved' or 'not improved'.

measures with the skin moisture meter^c at the same measurement points) of 0.06. When calculating an SEM for the mean of the percentage excess fluid accumulation at the level of the shoulder and trunk, this resulted in an SEM of 5.55% (results not included in the original paper). This entailed an SRD for excess fluid accumulation of 15.38%. The CIs of the changes in excess fluid accumulation between the groups were situated within the limits of the SRD (-15.40% to 15.40%).

For the degree of problems in functioning, the 95% CIs were also situated within the limits of the SRD (-15% to 15%).^{21,27} The same applied for quality of life, with limits of SRD of (-1.22 to 1.22).²² Treatment compliance was high and comparable between the groups. This means that the patient-tailored method of MLD based on fluoroscopic findings is not more effective than the (traditional) 'blind' method that has been performed for almost 100 years. In addition, fluoroscopy-guided MLD was not more effective than the (placebo) method, which was a simple and pleasant massage without a lymphatic transport-stimulating effect.

None of the previous randomised trials investigated the added value of fluoroscopy-guided MLD (to traditional MLD or placebo MLD) so the results were not directly comparable. However, during the last few decades, several systematic reviews of the literature investigated the effect of traditional MLD on volume reduction in patients with BCRL.^{5,6,28-31} They found a 75 ml or 7.11% ('non-significant') larger reduction in percentage points of excessive arm volume in the traditional MLD group (compared to no MLD), whereas the current study's estimate was an even smaller magnitude effect in the opposite direction (ie, 4% less reduction compared with placebo MLD), expressed in percentage points between the two relative arm volume reductions. The Cochrane systematic review of Ezzo recommended further additional high-quality research investigating the effect of MLD. As recommended, a clinically relevant volumetric outcome²⁶ was used and volumetric outcomes beyond arm volume were included by evaluating the volume at the level of the shoulder/trunk. A lymphoedema-specific QoL outcome (ie, Lymph-ICF-UL questionnaire)²¹ was included as a secondary outcome. Also, the participants were followed for a longer period (6 months of maintenance treatments after the intensive treatment phase, followed by a 6-month follow-up); this was also to investigate the long-term effect of MLD on skin thickness and fibrosis and impact on the lymphatic transport and superficial lymphatic anatomy (secondary outcomes, not reported in this paper).

There are several possible reasons why fluoroscopy-guided MLD and MLD in general applied to patients with chronic BCRL did not have added value to DLT, even though the lymphatic transport-stimulating effect has been demonstrated previously.^{15,16} First, MLD

was added to effective oedema-reducing modalities such as multi-layer bandaging and exercise therapy and was executed by experienced therapists. Also, lymphoedema progresses over time from pitting oedema, with accumulation of water in the skin/subcutaneous tissue, to form adipose tissue and fibrosis. The amount of adipose and fibrotic tissue cannot be reduced by lymphatic transport-stimulating treatment modalities such as MLD. Because fluoroscopy-guided MLD was applied specifically on the draining pathways (visualised by indocyanine green lymphofluoroscopy) at the level of the arm, shoulder and trunk by using fluoroscopy-guided hand manoeuvres, it was expected that it would result in less accumulation of lymph at the shoulder/trunk than the other two methods. However, there was a significant increase in the water content in this region in this MLD group (although this increase was very similar between the three groups); no explanation could be found for this phenomenon.

A limitation was that this study investigated (based on ethical considerations) the value of adding MLD to DLT and not the simple effect of MLD. Furthermore, the additional effect of MLD was investigated in participants with BCRL and not in those with other types of lymphoedema. Therefore, the study results imply that there is no indication for including (time-consuming) MLD in the limited treatment time per session in patients with chronic BCRL. Alternatively, more time could be spent on other evidence-based treatment options such as compression therapy³²⁻³⁴ and exercise therapy,^{34,35} together with great emphasis on education and self-management.³⁶

Nevertheless, fluoroscopic investigation can still be useful in patients with a damaged superficial lymphatic network (as in case of BCRL) to optimise BCRL treatment (eg, optimisation of compression hosiery, a guide for lymphatic surgery or to inform the patient about the seriousness of her reduced lymphatic transport).³⁷ In order to elucidate whether MLD might have an added effect on the other secondary outcome measures incorporated in the present trial, future studies investigating the short-term and long-term effects of (fluoroscopy-guided) MLD on lymphatic transport, hardness and fibrosis of the skin, water content and skin thickness should and will be conducted. In addition, sub-group analyses should be performed to investigate whether or not sub-groups of patients with specific characteristics may show different outcomes regarding the clinical effect of MLD in addition to DLT. Lastly, future randomised trials should be performed to investigate the added value of (fluoroscopy-guided) MLD in other types/areas of oedema (eg, in patients with midline oedema or lower limb lymphoedema). Taking into account the present findings, it is hypothesised that if fluoroscopy-guided MLD does have any (short-term) added value, this would probably mainly be in cases of non-fibrotic, watery oedema and in combination with an intact lymphatic

Table 9
Mean (SD) rating of MLD-specific treatment satisfaction in each group and pairwise between-group differences with 95% CIs.

Outcome	Groups			Between-group difference (95% CI) ^a		
	Fluoroscopy-guided MLD	Traditional MLD	Placebo MLD	Fluoroscopy-guided MLD versus Traditional MLD	Fluoroscopy-guided MLD versus Placebo MLD	Traditional MLD versus Placebo MLD
MLD-specific treatment satisfaction (0 to 10), median (IQR)	8 (7 to 9)	7 (5 to 8)	7 (5 to 9)	1 (0 to 1)	1 (0 to 1)	0 (-1 to 1)

MLD = manual lymph drainage.

^a Median differences (95% CI) for between-group comparisons were calculated using the Hodges-Lehman estimator.

system that still has the ability to resorb and transport fluid (eg, in patients with oedema due to chronic venous insufficiency); however the long-term clinical effect should also be investigated.

In conclusion, this trial supports previous findings that intensive decongestive physiotherapy significantly reduces lymphoedema volume and improves daily functioning in patients with BCRL. Additionally, the findings support the conclusions of systematic reviews and meta-analyses that the added value of MLD (compared with placebo/no MLD) to the other modalities of DLT for the treatment of BCRL is rather limited. Moreover, traditional MLD and fluoroscopy-guided MLD as adjuncts to DLT were not superior to placebo MLD in reducing arm/hand volume or fluid accumulation at the level of the shoulder/trunk in patients with chronic BCRL.

What was already known on this topic: For decades, manual lymph drainage has been widely used to treat breast cancer-related lymphoedema but its effectiveness remains unclear. Recently, manual lymph drainage has been optimised by making it patient-tailored using fluoroscopy.

What this study adds: In patients with chronic breast cancer-related lymphoedema, manual lymph drainage did not provide any clinically important additional benefits when added to other components of decongestive lymphatic therapy.

Footnotes: ^a SAS software V.9.4 for Windows, SAS Institute Inc, Cary, USA.

^b SPSS Statistics V.26.0 for Windows, IBM Corp., Armonk, USA.

^c ICG-PULSION® tracer, Pulsion Medical Systems, Munich, Germany.

eAddenda: Appendices 1 to 3 can be found online at <https://doi.org/10.1016/j.jphys.2022.03.010>.

Ethics approval: The Effort-BCRL trial was approved by the Ethical Committee of the University Hospitals of Leuven (main committee), with subsequent positive advice from the Ethical Committees of each other participating centre (CME reference S58689, EudraCT Number 2015-004822-33). All participants signed the informed consent document prior to their participation in the study.

Competing interests: Nil.

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References

- 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.
- 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;385:977–1010.
- 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;14:500–515.
- The diagnosis and treatment of peripheral lymphedema: 2020 Consensus Document of the International Society of Lymphology. *Lymphology*. 2020;53:3–19.
- 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.
- 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.
- 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;47:82–91.
- 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;50:750–757.
- 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. *Brit J Cancer*. 2018;119:1215–1222.
- 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.
- 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;7:1100–1115.
- Ahmed RL, Schmitz KH, Prizment AE, Folsom AR. Risk factors for lymphedema in breast cancer survivors, the Iowa Women's Health Study. *Breast Cancer Res Treat*. 2011;130:981–991.
- Weissleder H, Weissleder R. Lymphedema: evaluation of qualitative and quantitative lymphoscintigraphy in 238 patients. *Radiology*. 1988;167:729–735.
- 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. *Surg Oncol*. 2018;27:743–750.
- 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 Res Biol*. 2016;14:70–77.
- 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. *Arch Phys Med Rehabil*. 2011;92:756–764.e1.
- Williams AF, Vadgama A, Franks PJ, Mortimer PS. A randomized controlled cross-over study of manual lymphatic drainage therapy in women with breast cancer-related lymphoedema. *Eur J Cancer Care*. 2002;11:254–261.
- 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.
- Moher D, Schulz KF, Altman D. The CONSORT Statement: revised recommendations for improving the quality of reports of parallel-group randomized trials 2001. *Explore*. 2005;1:40–45.
- 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.
- 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. *Lymphat Res Biol*. 2019.
- 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;8:205–209.
- Devoogdt N, Christiaens MR, Geraerts I, Truijens 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.
- 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. *Support Care Cancer*. 2020;28:439–449.
- De Vrieze T, Gebruers N, Nevelsteen I, Tjalma WAA, Thomis S, De Groef A, et al. Breast cancer-related lymphedema and its treatment: how big is the financial impact? *Support Care Cancer*. 2020.
- De Vrieze T, Gebruers N, Tjalma WA, Nevelsteen I, Thomis S, De Groef A, et al. 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. *Clin Rehabil*. 2019;33:1221–1232.
- De Vrieze T, Fripiat 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.
- 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. *Eur J Obstet Gynecol Reprod Biol*. 2010;149:3–9.

29. 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;117:1136–1148.
30. Li L, Yuan L, Chen X, Wang Q, Tian J, Yang K, et al. Current Treatments for Breast Cancer-Related Lymphoedema: A Systematic Review. *Asian Pac J Cancer Prev*. 2016;17:4875–4883.
31. Shao Y, Zhong DS. Manual lymphatic drainage for breast cancer-related lymphoedema. *Eur J Cancer Care*. 2016.
32. 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;49:1256–1263.
33. 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;20:1031–1036.
34. 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;159:1–14.
35. 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;5:320–336.
36. 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;5:756–765.
37. Pigott A, Doig E, McCann A, Trevethan M. It was just mind blowing to be honest: a qualitative phenomenological study exploring cancer survivor's experiences of indocyanine green lymphography used to inform lymphedema therapy management. *Support Care Cancer*. 2021;29:6389–6397.
38. 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;96:1965–1981.
39. Gebruers N, Truijten S, Engelborghs S, De Deyn PP. Volumetric evaluation of upper extremities in 250 healthy persons. *Clin Physiol Funct Imaging*. 2007;27:17–22.
40. 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. *Eur J Obstet Gynecol Reprod Biol*. 2017;216:245–253.
41. 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. *Int Angiol*. 2010;29:401–407.
42. 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;25:447–454.
43. Czerniec SA, Ward LC, Kilbreath SL. Assessment of breast cancer-related lymphedema: a comparison of moisture meter and spot bioimpedance measurement. *Lymphat Res Biol*. 2015;13:10–19.
44. 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;7:153–158.
45. Devoogdt N, Van Kampen M, Geraerts I, Coremans T, Christiaens MR. Lymphoedema Functioning, Disability and Health questionnaire (Lymph-ICF): reliability and validity. *Phys Ther*. 2011;91:944–957.
46. 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. *Lymphat Res Biol*. 2020. <https://doi.org/10.1089/lrb.2019.0073>.
47. Cuschieri S. The CONSORT statement. *Saudi J Anaesth*. 2019;13:27–30.