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[Intervention Protocol]

Microsurgical versus complex physical decongestive therapy for chronic breast cancer-related lymphoedema

Yvonne Haas[1,2α], Olivia P Williams[2α], Jaume Masia[3], Gemma Pons[3], Erin M Taylor[4], Maria C. Katapodi[5,6], Daniel Staub[7], Steffen U Eisenhardt[8], Giuseppe Visconti[9], Benedetto Longo[10], Jan Plock[11], Florian Jung[12], Eduardo Gonzalez[13], Benedict Kaiser[1], Lea Zehnpfennig[14], Julia Stoffel[1,2], Florian S Halbeisen[15], Christian Appenzeller-Herzog[16], Laura Hilbig-Vlatten[17], Yvette Stoel[18], Raymund E Horch[19], Maria Mani[20], Karin Ribi[21], Joshua Vorstenbosch[22], Kathryn V. Isaac[23], Shan Shan Qiu[24], Björn Behr[25], Lars G Hemkens[5,26,27], Nicole Lindenblatt[28], Dirk J Schaefer[1,2], Katrin Seidenstuecker[29], Yves Harder[30,31], Christoph R. Hirche[32], Walter P Weber[2,33], Elisabeth A Kappos[1,2]

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of microsurgery versus complex physical decongestive therapy in people with chronic breast cancer-related lymphoedema.

BACKGROUND

Description of the condition

About one in eight women will develop breast cancer in their lifetime (Rojas 2016). Between 8.4% and 21.4% of breast cancer survivors will develop chronic breast cancer-related lymphoedema (BCRL) (DiSipio 2013), which significantly increases the burden of the disease. Lymphoedema (LE) is a localised condition characterised by tissue swelling, caused by abnormal retention of lymphatic fluid in the tissue due to compromised lymphatic pathways (Grada 2017; Mortimer 1998; Ridner 2013). Most people who develop BCRL do so within the first two years after breast cancer diagnosis or surgery (DiSipio 2013). The development and severity of chronic BCRL are associated with factors such as the extent of breast and/or axillary surgery, adjuvant radiation, (neo-) adjuvant chemotherapy, the number of removed positive lymph nodes, treatment in the dominant limb, and obesity (Byun 2021; DiSipio 2013; Gärtner 2010; International Society of Lymphology 2013; Kilbreath 2016; Langer 2007; McLaughlin 2008; Sayegh 2017; Shah 2011; Shaitelman 2017; Tsai 2009). BCRL is defined as chronic when related signs and symptoms last longer than three months; it can affect one or more areas of the breast and/or upper extremity (International Society of Lymphology 2013; National Cancer Institute 2023).

Out of all breast cancer sequelae, upper limb LE is described as one of the most underestimated and debilitating morbidities, especially in its chronic form (Chachaj 2009; Vassard 2010). Besides physical symptoms including limited range of motion, heaviness, pain, numbness in the upper extremity, and decreased grip strength (Boyages 2016; Chachaj 2009; Cidón 2011; Engel 2003; Fu 2014; Smoot 2010; Vignes 2020), chronic BCRL may also lead to psychological symptoms such as body dysmorphia, decreased self-confidence, sadness, anger, and anxiety (Fu 2013; Khan 2012; Vassard 2010). Furthermore, it can result in recurring skin infections (i.e. erysipelas) and the hardening and thickening of skin and subcutaneous tissue (i.e. soft-tissue fibrosis) (Chachaj 2009). All of these described symptoms can lead to a reduced quality of life in people with BCRL (Ridner 2005; Vassard 2010).

Description of the intervention

Surgical procedures that have been used to treat LE can be classified into two categories: ablative/reductive surgery and physiologic/reconstructive surgery (Park 2020). Ablative resection procedures are no longer routinely used to treat LE due to significant morbidities, except in rare and extreme cases of advanced LE (Park 2020). Two physiologic microsurgical procedures are mainly used to drain excess fluid trapped in lymphoedematous tissues into other lymphatic basins or the venous circulation, or both: lymphovenous anastomosis (LVA) and vascularised lymph node transfer (VLNT) (Coriddi 2020).

If the lymphatic vessels in the arm are still functional, LVA can be performed. LVA works through the surgical 'creation' of vascular bypasses between the lymphatic and venous systems. By connecting (i.e. anastomosing) lymphatic vessels to neighbouring subdermal venules, the lymphatic fluid can be successfully channelled into the venous system (Park 2020). If the lymphatic vessels in the arm are no longer functioning, VLNT is indicated. VLNT involves the microvascular relocation of the person's own vascularised lymph nodes (autologous) from an unaffected region of the body (donor site) to a specific region of the arm (usually armpit, sometimes region of the wrist). This procedure is followed by anastomosis of the blood vessels (artery and vein) of the flap to corresponding vessels at the recipient site, as it is routinely done in free flap surgery. In addition to these microsurgical procedures, liposuction can also be used, not only as a stand-alone procedure to reduce excessive volume (ablative/reductive surgery), but also in combination with the microsurgical procedures. Using appropriate cannulas, subcutaneous fatty tissue is removed from the LE-affected arm (Greene 2016).

Current treatment guidelines recommend conservative treatment with complex decongestive therapy (CDT), which includes gentle massage or manual lymphatic drainage (MLD), local compression, physical exercise, and meticulous skin care (Hirche 2019; NICE guidance 2022). MLD aims to stimulate the lymphatic system to enhance the removal of interstitial fluid. This is achieved by stretching the skin and subcutaneous tissues. External compression is also a crucial component of MLD because the lymphatic vessels are compromised in both function and structure. Furthermore, compression therapy maintains the decongestive effect of MLD, preventing re-accumulation of fluid. Simultaneously, it reduces venous pressure, thereby decreasing blood vessel ultrafiltration and increasing lymph flow in the remaining functional lymphatic vessels. Compression therapy includes both bandaging techniques and compression garments. During physical exercise, muscle and joint pumps are activated, leading to an increased flow of fluid through the lymphatic vessels (Flores 2021). Increased skin stress from LE results in skin changes, including reduced elasticity, functional deficits, and an increased risk of infection. Skin care is essential in maintaining skin integrity (Heinig 2015).

How the intervention might work

CDT is the gold standard in the treatment of BCRL. It aims to decrease interstitial fluid, thus facilitating lymphatic drainage and the prevention of progression to more severe stages of LE (Flores 2021). However, it is purely symptomatic and often not effective enough (Jeffs 2018). Based on the current evidence, microsurgical techniques are hypothesised to be superior to the current standard treatment with CDT alone (Coriddi 2020; Dionyssiou 2016; Forte 2020; Jorgensen 2018; Ozturk 2016; Rosian 2019; Scaglioni 2017; Tourani 2016; Winters 2017; Wolfs 2020).

The two microsurgical approaches – LVA and VLNT - are the most prevalent microsurgical reconstructive techniques performed in accordance with internationally accepted quality criteria (Hirche 2019; Hong 2018). In contrast to CDT alone, the microsurgical treatments target the pathophysiological mechanisms of chronic BCRL and, thus, the cause of LE. These treatments can lead to an improved outcome and reduction of symptoms, as shown in studies where both of the microsurgical treatments substantially improved patient quality of life compared to CDT alone (Coriddi 2020; Forte 2020; Ozturk 2016; Scaglioni 2017; Winters 2017). Incorporating conservative treatments of CDT remains a crucial component even after microsurgery; however, a significant number of patients experience substantial benefits from surgery in multiple aspects, leading to a potential reduction in the frequency and intensity of conservative treatments (Becker 2006; Dionyssiou 2016; Park 2020; Qiu 2020).

Why it is important to do this review

This review is important because BCRL, although among the most common and debilitating complications after breast cancer treatment, is one of the most underexplored areas in breast cancer research. Despite its substantial negative effect on patients' long-term quality of life, the current standard of care, CDT, is only symptomatic and not curative. While microsurgical treatment options such as VLNT or LVA are viable treatment options, they have not yet become part of standard clinical practice. There are no clinical trials of the highest level of evidence directly comparing these two therapies with each other to support the assumption that surgical treatment offers relevant improvement of patient-related outcomes. Despite promising surgical treatment options, most patients do not have access to these surgical interventions. This is due mostly to the lack of scientific evidence and the limited number of LE centres with trained reconstructive surgeons. Although systematic reviews on this topic exist (Markkula 2019), to our knowledge, there are none that compare microsurgical with conservative treatment that focus on patient-related outcomes in addition to arm volume reduction. We plan in this review to summarise and substantiate the existing evidence, raise awareness, and improve access to microsurgical LE treatment for those affected in the long term.

OBJECTIVES

To assess the effects of microsurgery versus complex physical decongestive therapy in people with chronic breast cancer-related lymphoedema.

METHODS

Criteria for considering studies for this review

Types of studies

We will include both randomised controlled trials (RCTs) and controlled non-randomised studies of interventions (NRSI) and exclude single-arm studies. We will consider quasi-RCTs, cluster-RCTs, and multi-arm studies. Quasi-randomised studies are defined as studies that use inadequate methods of sequence generation (e.g. based on date of birth, day of presentation) (Reeves 2024). We will include prospective and retrospective controlled NRSIs. Our review will encompass both published and unpublished studies.

Given that we aim to study the effects of a surgical intervention compared to a non-surgical one, RCTs on the topic are scarce. This may be due in part to strong patient preferences regarding the received treatment and the resulting challenges they pose to any randomisation process. Hence, we have decided to include quasi-RCTs and NRSIs provided they directly address our PICO (Population, Intervention, Control, Outcome) without critical risk of bias.

NRSIs must directly compare the outcomes of patients receiving at least one of the described microsurgical interventions with those of patients receiving the described comparator. To determine the eligibility of an NRSI or a quasi-RCT, we will use the classification of study features outlined in Reeves 2017 to determine study design rather than rely on study labels reported in potentially eligible studies.

- The intervention/comparator was provided to individuals.
- Outcome data are available at least once before and after the intervention/comparator for the same individuals.
- The intervention effect was estimated by the difference between groups.
- The researchers used methods to control for confounding.
- In this case, the method with which the participant groups were formed is most likely based on participant preference. Quasi-randomisation or allocation by healthcare practitioners will also be accepted.

Studies must report either quality of life or arm volume to be eligible for inclusion.

There will be no language restrictions. If no English or German translation is available, we will utilise artificial intelligence technology through DeepL (DeepL 2017).

Types of participants

We will include studies involving female or male participants aged 18 and older with chronic BCRL, encompassing unilateral and bilateral cases.

BCRL diagnosis relies on the former diagnosis of breast cancer, clinical assessment of the LE, measurement of arm volume, and imaging techniques such as lymphoscintigraphy or near-infrared fluorescence (NIRF) imaging (also known as indocyanine green (ICG) lymphography) (International Society of Lymphology 2020).

We will exclude studies involving participants with LE of other aetiology or LE affecting the lower extremities. If a study consists of a combination of eligible and ineligible participants – such as cases where LE is due to causes other than BCRL – we will aim to extract data specifically for the subset of eligible participants with BCRL. However, if such data cannot be separated, the study will be excluded and the reason for exclusion provided in the 'Characteristics of excluded studies' table.

Types of interventions

Surgical treatments for LE focus on physiologic procedures like lymphovenous anastomosis (LVA) and vascularised lymph node transfer (VLNT). LVA creates bypasses between lymphatic vessels and the venous system to drain excess fluid. VLNT involves transferring vascularised lymph nodes from a healthy part of the body to the affected area. Liposuction is also used to reduce excessive volume, either alone or in combination with microsurgical procedures. Current guidelines recommend conservative treatment with complex decongestive therapy (CDT) which includes manual lymphatic drainage (MLD), local compression, physical exercise, and meticulous skin care (Heinig 2015).

Interventions

Microsurgery, potentially combined with non-microsurgical liposuction, as follows.

- LVA
- LVA plus liposuction
- VLNT
- VLNT plus liposuction
- LVA plus VLNT

- LVA plus VLNT plus liposuction

Comparators

CDT (Heinig 2015), involving the following.

- Skincare (moisture-regulating agents in external product)
- MLD
- Exercises aimed at improvement of mobility/range of motion in the shoulder, elbow, or wrist joints
- Compression through circular bandaging or with customised elastic compression garment for the arm

The term CDT must be mentioned, or a conservative treatment synonymous with CDT must be described. There are no restrictions on interventions and comparators.

Pair-wise comparisons

- Microsurgical therapy versus CDT

Types of outcome measures

Based on a core outcome set (COS) proposed by Doubblestein 2024, we have decided to focus this review on a small selection of highly relevant outcomes listed below. We selected these outcomes because of their high practical relevance to decision makers and their importance for patients' experiences while also covering potential adverse effects. At least one of the listed primary outcomes must be reported for inclusion in this review. Although using outcomes as eligibility criteria is generally not recommended, we believe it is important that at least quality of life or arm volume is reported in order to properly answer our research question. Given that these are the standard outcomes of investigations in this field, they will be reported in any publication that measured them.

Primary outcomes

- Quality of life, measured using various validated questionnaires such as Upper Limb Lymphedema 27 (ULL-27) (Launois 2002), LYMQOL (Keeley 2010), LYMPH-ICF-UL (Devoogdt 2011), and LYMPH-Q (Klassen 2021). If one scale is mentioned in multiple studies, that scale will be prioritised.
- Arm volume, measured by a validated system for limb volume measurement (perometry, water displacement method, and tape measurement method) and defined as the percentage reduction in LE. Perometry and the water displacement method are the best evidence-based methods and will therefore be prioritised. However, if the tape measurement method is most commonly used in studies, it will be prioritised.

Secondary outcomes

- Number of cutaneous infections per year, reported by the participant through their medical history, and verified by a doctor in medical records if possible.
- Tissue consistency, measured by a physician by assessing tissue/skin resistance, with priority given to the pitting oedema test, fibrosis, induration.
- Pain, measured by a validated system (visual analogue scale (VAS) will be prioritised) (Hayes 1921).
- Upper quadrant function, measured through PROMs (Patient-Reported Outcome Measures) and the participant's movements (active range of motion prioritised).
- Upper extremity activity and motor control, assessed through PROMs the participant's neuromuscular function to initiate, modulate, and grade voluntary movements. If a particular PROM or measurement scale is referenced in multiple studies, that scale will be given priority.

Timing of outcome assessments

We will initially extract the outcome measurement time points as described in the studies. If not already homogenous, we will categorise them into defined intervals (e.g. < 6, < 12, and > 12 months) to increase comparability between studies in a second step.

Search methods for identification of studies

Electronic searches

An Information Specialist (CA-H) will develop the search strategies comprising database-specific subject headings and text words covering the concepts BCRL and BCRL treatment (surgical or conservative), which a second Information Specialist will peer-review.

We will search the following databases.

- The Cochrane Breast Cancer Group's (CBCG's) Specialised Register. Details of the search strategies used by the Group for the identification of studies and the procedure used to code references are outlined in the Group's module. The Specialised Register contains coded references published up to 6 October 2022. Trials with the keywords "RCT", "CCT", "breast cancer related lymphedema", "microsurgery", "lymphovenous anastomosis", "vascularized lymph node transfer", "liposuction", "lymphatic bypass procedure", "autologous lymph node transplant", "complete decongestive physiotherapy", "decongestive lymphatic therapy", "compression therapy", "manual lymphatic drainage", "therapeutic exercise", "negative pressure therapy" and "decongestive lymphatic therapy" will be extracted and considered for inclusion in the review.
- Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, from inception to present) (Appendix 1).
- MEDLINE (Ovid, from inception on 1 January 1946 to present) (Appendix 2).
- Embase (Embase.com, from inception on 1 January 1947 to present) (Appendix 3).
- Web of Science Core Collection (Editions = A&HCI, BKCI-SSH, BKCI-S, CCR-EXPANDED, ESCI, IC, CPCI-SSH, CPCI-S, SCI-EXPANDED, SSCI; webofscience.com, from inception to present) (Appendix 4).

Search syntax will be translated from Embase-Elsevier by publicly available macros (Bramer 2018) or by using the Polyglot Search Translator (Clark 2020). There will be no restrictions on language or publication dates. We will exclude conference abstracts.

We will also conduct a search for ongoing and completed trials in the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (Appendix 5) and ClinicalTrials.gov (Appendix 6).

Searching other resources

We will search for additional potentially relevant studies or publications by examining the reference lists of eligible studies and reviews on the same topic. Moreover, we will communicate with authors of unpublished studies to access information about ongoing or unpublished trials.

Data collection and analysis

Selection of studies

We will import search results into EndNote (EndNote 2021) and use Deduklick to remove duplicate records (Borissov 2022). Upon importing search results into Covidence (Covidence 2024), we will manually remove further duplicates. Two review authors (OPW, BK) will independently screen the title and abstract of each record in Covidence for potential relevance. We will obtain the full-text reports of those studies deemed potentially relevant, and two review authors (OPW, BK) will independently screen the full-text reports against the eligibility criteria and identify studies for inclusion. They will resolve any discrepancies that arise through discussion or in consultation with a third review author (EAK). We will contact study authors for any missing information needed to determine study eligibility. We will note the reasons for exclusion of excluded studies, and include a 'Characteristics of excluded studies' table for excluded studies that might be expected to have been included in the review. We will also prepare a ‘Characteristics of included studies’ table that will contain information on additional interventions performed that are not relevant to this review and will therefore not be included in the data analysis. We will record the study selection process in sufficient detail to complete a PRISMA flow diagram (Liberati 2009; Page 2021).

Data extraction and management

We will develop a data extraction form that two review authors (OPW, YHaa) will pilot on 10 studies. After resolving any inconsistencies by consensus and adapting the data extraction form as needed, at least two review authors (OPW, YHaa) will independently extract the study characteristics listed below.

- Study information: name author, contact author, institution author, country, publication date, language, sponsorship source, source of funding, authors’ conflicts of interest, setting, comments.
- Study characteristics: study design, study group, group differences, randomisation method, number of study centres, inclusion and exclusion criteria, subgroup analysis, statistical methods, time perspective of study, length and frequency of follow-up, start and end dates of enrolment, LE measurement tool, quality of life assessment tool, preoperative LE imaging, LE staging scale.
- Participant characteristics: number of participants, number of participants per study arm, age, minimum age, maximum age, gender, ethnicity, body mass index (BMI), previous treatment for BCRL, previous treatment for breast cancer, previous axilla surgeries, time between diagnosis to treatment, previous CDT, prophylactic antibiotics, American Society of Anesthesiologists (ASA) physical status classification system, number of withdrawals, dropout rate.
- Intervention characteristics: CDT, LVA, LVA and liposuction, VLNT, VLNT and liposuction, VLNT and LVA, VLNT and LVA and liposuction, CDT (frequency), VLNT (number of lymph nodes, donor site, recipient area, venous/arterial/lymphatic/amount of anastomosis), LVA (location, anastomosis, multiple/single, number of bypasses), co-interventions, surgery performed with a robot, one- or two-stage surgery, re-intervention, duration of treatment.
- Outcomes: primary and secondary outcomes, method of assessment and time point assessed.

Dealing with duplicate publications

In the case of duplicate publications or multiple reports on the same primary study, we will link publications to individual studies and consolidate the available data. We will utilise the most comprehensive dataset derived from all available publications, preferring those reporting the longest follow-up duration related to our primary or secondary outcomes.

Assessment of risk of bias in included studies

At least two review authors (OPW, YHaa) will independently perform a risk bias assessment for each outcome. In the case of disagreement, a final rating will be reached through consensus with the participation of the review author group. We will contact study authors for any missing information required to make risk of bias judgements.

We will apply the risk of bias tools to the following outcomes.

- Quality of life, measured using various validated questionnaires such as Upper Limb Lymphedema 27 (ULL-27) (Launois 2002), LYMQOL (Keeley 2010), LYMPH-ICF-UL (Devoogdt 2011), and LYMPH-Q (Klassen 2021).
- Arm volume, measured by a validated system for limb volume measurement and defined as the percentage reduction in LE.
- Number of cutaneous infections per year, reported by the participant through their medical history, and verified by a doctor in medical records if possible.
- Tissue consistency, measured by a physician by assessing tissue/skin resistance, with priority given to the pitting oedema test, fibrosis, induration.
- Pain, measured by a validated system (VAS will be prioritised) (Hayes 1921).
- Upper quadrant function, measured through PROMs and the participant's movements (active range of motion prioritised).
- Upper extremity activity and motor control, assessed through PROMs, the participant's neuromuscular function to initiate, modulate, and grade voluntary movements. If a particular PROMS or measurement scale is referenced in multiple studies, the outcomes reported using that scale will be given priority.

We will assess all reported time points between pre-intervention and 12 months post-intervention. As outcome measures for quality of life may vary between studies, we will perform the risk of bias assessment for all of them. We will apply the same method to all other outcomes, should outcome measures vary across studies.

Randomised controlled trials

At least two review authors (OPW, YHaa) will perform the risk of bias assessment, employing the RoB 2 Excel tool (Higgins 2019).

We will rate the risk of bias for each outcome as low risk of bias, some concerns, or high risk of bias based on the following domains.

- Bias arising from the randomisation process.
- Bias due to deviations from intended interventions. In this review we intend to address the effect of assignment to the intervention (microsurgical versus conservative treatment) at baseline and applying the RoB 2 tool as such. This will be estimated by an intention-to-treat analysis (ITT) that includes all randomised participants (Fergusson 2002).
- Bias due to missing outcome data.
- Bias in measurement of the outcome.
- Bias in selection of the reported result.

We will assess the overall risk of bias on the same scale as the individual domains, which will default to the highest level of risk identified among domains. In the case of multiple domains judged as some concerns, we will evaluate how they lower risk of bias for the overall result and assess the study as high risk of bias where appropriate.

Cluster-randomised trials

In the case of cluster-randomised trials, we will implement the RoB 2 tool for cluster-randomised trials (Eldridge 2021).

We will rate the risk of bias for each outcome as low risk of bias, some concerns, or high risk of bias based on the following domains.

- Bias arising from the randomisation process.
- Bias arising from the timing of identification or recruitment of participants in a cluster-randomised trial.
- Bias due to deviations from the intended interventions (effect of assignment to intervention).
- Bias due to missing outcome data.
- Bias in measurement of the outcome.
- Bias in selection of the reported result.

We will assess the overall risk of bias using the same method as above for RCTs.

Non-randomised studies

For NRSIs, two review authors (OPW, YHaa) will perform the risk of bias assessment using the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool (Sterne 2016), according to the following domains.

Pre-intervention

- Bias due to confounding, e.g. participant comorbidities (e.g. obesity), LE stage, socioeconomic status influencing participant selection of surgery or conservative treatment and therefore also their quality of life outcome (confounding bias).
- Bias due to selection of participants into the study (selection bias).

At intervention

- Bias in classification of interventions (information bias).

Post-intervention

- Bias due to deviation from intended interventions; as with RoB 2, our effect of interest is the effect of assignment to the intervention (confounding bias).
- Bias due to missing data (selection bias).
- Bias in measurement of outcomes (information bias).
- Bias in selection of the reported result (reporting bias).

It is important to note that likely co-interventions for participants receiving a microsurgical intervention include microsurgical breast reconstruction and liposuction. Previous/ongoing treatments for breast cancer may also vary between groups.

We will rate the risk of bias as low, moderate, serious or critical according to ROBINS-I. As with our assessment of RCTs, the overall risk of bias will be determined by the highest risk of bias given to any domain. In line with the RoB 2 tool, we will present the extent of risk of bias both narratively and in a risk of bias table generated in robvis (McGuinness 2020).

Measures of treatment effect

We will use the following measures of the effect of treatment.

- Dichotomous outcomes (i.e. surgical complications) will be extracted from the number of participants with surgical complications and the total number of participants in each arm, in order to estimate a risk ratio (RR) with 95% confidence interval (CI).
- Continuous data (i.e. quality of life, arm volume, and number of cutaneous infections per year) will be expressed as a mean difference (MD) or median (range) if the same scale has been used with a 95% CI. If studies use different scales to measure quality of life, we will report the treatment effects as a standardised mean difference (SMD) with 95% CIs. We will interpret SMDs using Cohen's effect sizes (Cohen 1988) and also by back-transforming SMDs to one of the original scales (Higgins 2019).

In the case of NRSIs presenting both unadjusted and adjusted intervention effects, we will favour the latter. In the case of multiple adjusted effect estimates, we will select the one deemed most effective at minimising confounding bias (Higgins 2019).

Unit of analysis issues

The unit of analysis will be the individual participant. We do not expect to identify cluster-randomised studies; however, if we do identify any, they will be included. To avoid false-positive conclusions of the effects of the interventions, clusters will not be treated the same as if individual participants had been randomised. We will adjust the effective sample size by accounting for the number of clusters randomised, total participants, and average cluster size. We will use outcome data as reported for individuals, and apply an intracluster correlation coefficient (ICC) for adjustment. If the ICC is unavailable, we will use a typical ICC from the literature. We will perform sensitivity analyses both with and without the adjustment for clustering to assess the robustness of the results, and acknowledge any limitations.

We will also include multiple-arm studies. We will identify which intervention groups are relevant to our systematic review and which specific meta-analysis they belong to, taking care to not

exclude relevant groups or double-count participants (Higgins 2024).

Dealing with missing data

We will retrieve the attrition rate. For dichotomous data, we will determine the withdrawal rate using the number of participants admitted. For continuous data, we will determine the missing data based on the number of participants enrolled.

We will attempt to contact study authors for missing information as needed. If this is not possible, we will analyse only the available data and perform a sensitivity analysis to assess the impact of including these studies in this review. Additionally, we will take into consideration whether the data are likely to be missing at random or not, with the former case being less likely to result in considerable bias from analysing only the available data, as suggested in Chapter 10, Section 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2023). Data assumed as not missing at random are 'not-ignorable' and will be treated with greater uncertainty; we will perform a separate sensitivity analysis to assess the extent of the resulting bias from including these studies.

Assessment of heterogeneity

We will determine the presence of heterogeneity through visual inspection of forest plots and by conducting Chi^2 tests, considering a P value of less than 0.1 as indicative of statistically significant heterogeneity. Additionally, we will quantify statistical heterogeneity among studies using the I^2 statistic.

We will interpret the I^2 value as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

In the case of substantial or considerable heterogeneity, we will explore potential sources of heterogeneity by conducting subgroup or sensitivity analyses.

Assessment of reporting biases

We will assess potential bias due to missing evidence for all meta-analyses listed in the summary of findings table with tests for funnel plot asymmetry, if more than 10 studies are available (Egger 1997).

Data synthesis

We anticipate significant heterogeneity due to the diverse methodologies, study designs, and patient populations in the included studies. Consequently, our primary strategy for data synthesis will involve random-effects models, utilising the inverse variance method to weight studies, incorporating between-study variation, and estimating this variation using the DerSimonian and Laird method (DerSimonian 1986). In the case of rare events within studies with binary outcomes, we will consider using conditional hypergeometric-normal generalised linear mixed model, providing a robust alternative in the presence of sparse data (Bakbergenuly 2018).

The primary analysis will only include RCTs and NRSIs with an overall low risk of bias. This will be followed by a sensitivity analysis including all studies except NRSIs with a critical risk of bias, which will be excluded from the analysis.

For outcomes with either absent numerical data or data measured inconsistently, we will use Synthesis Without Meta-analysis (SWiM) methods such as summarising effect estimates or vote-counting based on direction of effect as specified in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (McKenzie 2019). Following the SWiM guideline recommendations (Campbell 2020; McKenzie 2019), we will categorise studies by key characteristics such as population, outcome, and study design. Additionally, we will outline the standardised metrics, transformation methods, synthesis techniques employed, criteria for prioritising results, and synthesis limitations (Campbell 2020).

We will conduct all statistical analyses using RevMan software (RevMan 2024).

Subgroup analysis and investigation of heterogeneity

We plan to conduct an analysis of the following subgroups to investigate heterogeneity: LE stage of 0, I, II, III according to the International Society of Lymphology (ISL) (International Society of Lymphology 2013).

We have selected the above-mentioned subgroup for the following reasons. The selection of either conservative or surgical interventions is contingent upon variables such as the stage of LE. Typically, initial attempts involve conservative treatments, with surgical options contemplated when conservative approaches prove inadequate in addressing the condition. Meanwhile, there is emerging understanding suggesting that surgical therapy can also be beneficial in earlier stages of LE.

We will use primary and secondary outcomes for the subgroup analysis, which we will perform using the formal test for subgroup differences in RevMan (Borenstein 2013).

Sensitivity analysis

After the primary analysis, we plan to perform sensitivity analyses as described below to examine the robustness of our results as well as the impact of the sensitivity analyses on effect size. The sensitivity analyses will include all studies except NRSIs with a critical risk of bias.

- Limiting the analysis to trials with a low risk of bias.
- Excluding trials funded by for-profit entities.
- Excluding trials with missing data likely to induce bias.

Summary of findings and assessment of the certainty of the evidence

We will generate summary of findings tables using GRADEpro GDT software (GRADEpro GDT), according to methods described in the *Cochrane Handbook* (Schünemann 2023). We will include the following outcomes: quality of life, arm volume, tissue consistency, number of cutaneous infections per year, pain, upper extremity mobility, and upper extremity motor control. We will prioritise results reported within a timeframe of 12 months post-intervention.

We will generate tables for the pair-wise comparisons of different microsurgical therapies: LVA versus CDT, LVA plus liposuction versus

CDT, VLNT versus CDT, VLNT plus liposuction versus CDT, LVA plus VLNT versus CDT, and LVA plus VLNT plus liposuction versus CDT.

Two review authors (YHaa, OPW) will independently assess the certainty of the evidence for the outcomes as outlined in the GRADE Handbook (Schünemann 2023). We will resolve any differences in assessment through consensus or by involving another review author (EAK) if necessary. We will apply the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the evidence for studies contributing data to the meta-analyses of the prespecified outcomes. We will explain any decisions to down- or upgrade the certainty of the evidence and provide additional comments to enhance the reader's understanding of the review as needed. The overall risk of bias will inform the GRADE assessment.

We will conduct the review according to the published protocol. We will describe any deviations from it in detail in the 'Differences between protocol and review' section of the review.

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The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Nicola Rocco, Universita degli Studi di Napoli Federico II, Naples, Italy;
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Sue Marcus, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments, and supported the editorial team): Lisa Wydrzynski, Cochrane Central Editorial Service;
- Copy Editor (copy editing and production): Lisa Winer, Cochrane Central Production Service;
- Peer reviewers (provided comments and recommended an editorial decision): Erich Brenner, Institute of Clinical and Functional Anatomy, Medical University of Innsbruck, Austria (clinical/content review), Brian Duncan (consumer review), Clare Miles, Evidence Production and Methods Directorate (methods review), Jo Platt, Central Editorial Information Specialist (search review).

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APPENDICES

Appendix 1. CENTRAL

([mh ^"breast cancer lymphedema"] OR (([mh "breast neoplasms"] OR [mh mastectomy] OR ("breast cancer":ti,ab,kw OR "mammary cancer":ti,ab,kw OR ("breast" NEXT carcinoma*):ti,ab,kw OR ("mammary" NEXT carcinoma*):ti,ab,kw OR ("breast" NEXT tumor*):ti,ab,kw OR ("mammary" NEXT tumor*):ti,ab,kw OR ("breast" NEXT tumour*):ti,ab,kw OR ("mammary" NEXT tumour*):ti,ab,kw OR ("breast" NEXT neoplasm*):ti,ab,kw OR ("mammary" NEXT neoplasm*):ti,ab,kw OR ("breast" NEXT malignan*):ti,ab,kw OR ("mammary" NEXT malignan*):ti,ab,kw OR mastectomy:ti,ab,kw OR postmastectomy:ti,ab,kw OR postradiation:ti,ab,kw OR post-radiation:ti,ab,kw OR "breast amputation":ti,ab,kw OR "breast resection":ti,ab,kw OR mammectomy:ti,ab,kw OR postmammectomy:ti,ab,kw)) AND ([mh lymphedema] OR (lymphedema*:ti,ab OR lymphoedema*:ti,ab OR lymphooedema*:ti,ab OR ("large" NEXT arm*):ti,ab OR ("swollen" NEXT arm*):ti,ab OR edema:ti,ab OR oedema:ti,ab) ,kw.)) OR BCRL:ti,ab,kw)

AND

([mh ^"surgery, plastic"] OR [mh ^microsurgery] OR [mh "surgical flaps"] OR [mh ^lipectomy] OR [mh ^"anastomosis, surgical"] OR ("plastic surgery":ti,ab,kw OR "corrective surgery":ti,ab,kw OR ("plastic" NEXT reconstruction*):ti,ab,kw OR "reconstructive surgery":ti,ab,kw OR "preposthetic surgery":ti,ab,kw OR "reparative surgery":ti,ab,kw OR ("operative" NEXT reconstruction*):ti,ab,kw OR "reconstruction surgery":ti,ab,kw OR ("reconstructive surgical" NEXT procedure*):ti,ab,kw OR ("surgical" NEXT reconstruction*):ti,ab,kw OR microsurg*:ti,ab,kw OR micro-surg*:ti,ab,kw OR "microscale surgery":ti,ab,kw OR "microscopic surgery":ti,ab,kw OR supermicrosurg*:ti,ab,kw OR microvascular:ti,ab,kw OR micro-vascular:ti,ab,kw OR microanastomosis:ti,ab,kw OR "micro anastomosis":ti,ab,kw OR ("surgical" NEXT flap*):ti,ab,kw OR ("myocutaneous" NEXT flap*):ti,ab,kw OR ("deep inferior epigastric perforator" NEXT flap*):ti,ab,kw OR ("deep inferior epigastric artery perforator" NEXT flap*):ti,ab,kw OR ("DIEP" NEXT flap*):ti,ab,kw OR ("free" NEXT flap*):ti,ab,kw OR ("free" NEXT graft*):ti,ab,kw OR ("tissue" NEXT flap*):ti,ab,kw OR ("free tissue" NEXT graft*):ti,ab,kw OR "free tissue transfer":ti,ab,kw OR lipectom*:ti,ab,kw OR adipectom*:ti,ab,kw OR dermolipectom*:ti,ab,kw OR "fat excision":ti,ab,kw OR liposuction*:ti,ab,kw OR ((aspiration:ti,ab,kw OR suction:ti,ab,kw) AND (lipolysis:ti,ab,kw OR lipoplast*:ti,ab,kw)) OR "fat suction surgery":ti,ab,kw OR ((lymphaticovenous:ti,ab,kw OR "lymphatico venous":ti,ab,kw OR lymphaticovenular:ti,ab,kw OR lymphatico-venular:ti,ab,kw OR "lymphatic venous":ti,ab,kw OR lymphovenous:ti,ab,kw OR lymphadenovenous:ti,ab,kw) NEAR/3 (anastomos*:ti,ab,kw OR bypass:ti,ab,kw OR shunt*:ti,ab,kw OR communication:ti,ab,kw)) OR ("lymphatic bypass" NEXT

procedure*):ti,ab,kw OR LVA:ti,ab,kw OR ("lymph node":ti,ab,kw NEAR/3 (transfer*:ti,ab,kw OR transplant*:ti,ab,kw OR flap*:ti,ab,kw)) OR VLNT:ti,ab,kw OR ALNT:ti,ab,kw OR "charles procedure":ti,ab,kw OR "charle s procedure":ti,ab,kw OR "subcutaneous excision":ti,ab,kw))

AND

([mh "conservative treatment"] OR [mh massage] OR [mh ^bandages] OR [mh "compression bandages"] OR [mh "athletic tape"] OR [mh ^"physical therapy modalities"] OR [mh ^"exercise movement techniques"] OR [mh ^"exercise therapy"] OR [mh ^exercise] OR [mh ^"intermittent pneumatic compression devices"] OR [mh ^"extracorporeal shockwave therapy"] OR [mh ^"low-level light therapy"] OR [mh "acupuncture therapy"] OR [mh ^acupuncture] OR [mh ^"electric stimulation therapy"] OR (conservative*:ti,ab,kw OR non-operative*:ti,ab,kw OR nonoperative*:ti,ab,kw OR non-surgical:ti,ab,kw OR nonsurgical:ti,ab,kw OR drainage:ti,ab,kw OR decongesti*:ti,ab,kw OR massage:ti,ab,kw OR ("zone" NEXT therap*):ti,ab,kw OR massotherap*:ti,ab,kw OR compression:ti,ab,kw OR bandag*:ti,ab,kw OR sleeve*:ti,ab,kw OR ("elastic" NEXT dressing*):ti,ab,kw OR ("athletic" NEXT tap*):ti,ab,kw OR ("orthotic" NEXT tap*):ti,ab,kw OR ("kinesio" NEXT tap*):ti,ab,kw OR kinesiotap*:ti,ab,kw OR garment*:ti,ab,kw OR PlasmaFlow:ti,ab,kw OR VasoGrad:ti,ab,kw OR IPC:ti,ab,kw OR ("physical" NEXT therap*):ti,ab,kw OR physiotherap*:ti,ab,kw OR ("physio" NEXT therap*):ti,ab,kw OR ("physical" NEXT treatment*):ti,ab,kw OR exercise*:ti,ab,kw OR ("physical" NEXT activit*):ti,ab,kw OR kinesiotherap*:ti,ab,kw OR ("movement" NEXT therap*):ti,ab,kw OR ("motion" NEXT therap*):ti,ab,kw OR "A-V Impulse System":ti,ab,kw OR "ActiveCare DVT":ti,ab,kw OR AeroDVx:ti,ab,kw OR ArtAssist:ti,ab,kw OR BioTAB:ti,ab,kw OR "Flexitouch system":ti,ab,kw OR Flowtron:ti,ab,kw OR "intermittent pneumatic compression":ti,ab,kw OR "intermittent venous compression":ti,ab,kw OR Plexipulse:ti,ab,kw OR "pneumatic intermittent impulse":ti,ab,kw OR "SC-2004 Sequential Circulator PCD":ti,ab,kw OR "sequential venous compression":ti,ab,kw OR VascuEase:ti,ab,kw OR VasQcare:ti,ab,kw OR ("venous compression" NEXT system*):ti,ab,kw OR (pneumatic:ti,ab,kw NEAR/2 (stocking*:ti,ab,kw OR hose:ti,ab,kw)) OR (("shock wave":ti,ab,kw OR shockwave:ti,ab,kw OR HIFU:ti,ab,kw) NEAR/3 (therap*:ti,ab,kw OR treat*:ti,ab,kw)) OR "high-intensity focused ultrasound":ti,ab,kw OR ESWT:ti,ab,kw OR ("laser" NEXT therap*):ti,ab,kw OR ("laser" NEXT treatment*):ti,ab,kw OR ("light" NEXT therap*):ti,ab,kw OR ("light" NEXT treatment*):ti,ab,kw OR "laser biostimulation":ti,ab,kw OR "laser phototherapy":ti,ab,kw OR LLLT:ti,ab,kw OR LILT:ti,ab,kw OR "photo biomodulation":ti,ab,kw OR photo-bio-modulation:ti,ab,kw OR photobiomodulation:ti,ab,kw OR ("PBM" NEXT therap*):ti,ab,kw OR PBMT:ti,ab,kw OR acupuncture:ti,ab,kw OR shonishin:ti,ab,kw OR acupressure:ti,ab,kw OR Shiatsu:ti,ab,kw OR "Tui Na":ti,ab,kw OR electroacupuncture:ti,ab,kw OR pharmacoacupuncture:ti,ab,kw OR acupotom*:ti,ab,kw OR "acupoint stimulation":ti,ab,kw OR "burnt needle therapy":ti,ab,kw OR "fire needle therapy":ti,ab,kw OR "fire needling":ti,ab,kw OR thermoacupuncture:ti,ab,kw OR endermolog*:ti,ab,kw OR electrotherapy*:ti,ab,kw OR electro-therapy*:ti,ab,kw OR "electric stimulation":ti,ab,kw OR "electrical stimulation":ti,ab,kw OR electrostimulation:ti,ab,kw OR electro-stimulation:ti,ab,kw))

NOT "conference proceeding":pt

Appendix 2. MEDLINE (Ovid)

(breast cancer lymphedema/ OR ((exp breast neoplasms/ OR exp mastectomy/ OR (breast cancer OR mammary cancer OR breast carcinoma* OR mammary carcinoma* OR breast tumor* OR mammary tumor* OR breast tumour* OR mammary tumour* OR breast neoplasm* OR mammary neoplasm* OR breast malignan* OR mammary malignan* OR mastectomy OR postmastectomy OR postradiation OR post-radiation OR breast amputation OR breast resection OR mammectomy OR postmammectomy).ab,ti,kf.) AND (exp lymphedema/ OR (lymphedema* OR lymphoedema* OR lymphooedema* OR large arm* OR swollen arm* OR edema OR oedema).ab,ti,kw.)) OR BCRL.ab,ti,kf.)

AND

(surgery, plastic/ OR microsurgery/ OR exp surgical flaps/ OR lipectomy/ OR anastomosis, surgical/ OR (plastic surgery OR corrective surgery OR plastic reconstruction* OR reconstructive surgery OR preposthetic surgery OR reparative surgery OR operative reconstruction* OR reconstruction surgery OR reconstructive surgical procedure* OR surgical reconstruction* OR microsurg* OR micro-surg* OR microscale surgery OR microscopic surgery OR supermicrosurg* OR microvascular OR micro-vascular OR microanastomosis OR micro anastomosis OR surgical flap* OR myocutaneous flap* OR deep inferior epigastric perforator flap* OR deep inferior epigastric artery perforator flap* OR DIEP flap* OR free flap* OR free graft* OR tissue flap* OR free tissue graft* OR free tissue transfer OR lipectom* OR adipectom* OR dermolipectom* OR fat excision OR liposuction* OR ((aspiration OR suction) AND (lipolysis OR lipoplast*)) OR fat suction surgery OR ((lymphaticovenous OR lymphatico venous OR lymphaticovenular OR lymphatico-venular OR lymphatic venous OR lymphovenous OR lymphadenovenous) ADJ3 (anastomos* OR bypass OR shunt* OR communication)) OR lymphatic bypass procedure* OR LVA OR (lymph node ADJ3 (transfer* OR transplant* OR flap*)) OR VLNT OR ALNT OR charles procedure OR charle s procedure OR subcutaneous excision).ab,ti,kf.)

AND

(exp "conservative treatment"/ OR exp massage/ OR bandages/ OR exp "compression bandages"/ OR exp "athletic tape"/ OR "physical therapy modalities"/ OR "exercise movement techniques"/ OR "exercise therapy"/ OR exercise/ OR intermittent pneumatic compression devices/ OR extracorporeal shockwave therapy/ OR low-level light therapy/ OR exp acupuncture therapy/ OR acupuncture/ OR electric stimulation therapy/ OR (conservative* OR non-operative* OR nonoperative* OR non-surgical OR nonsurgical OR drainage OR decongesti* OR massage OR zone therap* OR massotherap* OR compression OR bandag* OR sleeve* OR elastic dressing* OR athletic tap* OR orthotic tap* OR kinesio tap* OR kinesiotap* OR garment* OR PlasmaFlow OR VasoGrad OR IPC OR physical therap* OR physiotherap* OR physio therap* OR physical treatment* OR exercise* OR physical activit* OR kinesiotherap* OR movement therap* OR motion therap* OR A-V Impulse System OR ActiveCare DVT OR AeroDVx OR ArtAssist OR BioTAB OR Flexitouch system OR Flowtron OR intermittent pneumatic

compression OR intermittent venous compression OR Plexipulse OR pneumatic intermittent impulse OR SC-2004 Sequential Circulator PCD OR sequential venous compression OR VascuEase OR VasQcare OR venous compression system* OR (pneumatic ADJ2 (stocking* OR hose)) OR ((shock wave OR shockwave OR HIFU) ADJ3 (therap* OR treat*)) OR high-intensity focused ultrasound OR ESWT OR laser therap* OR laser treatment* OR light therap* OR light treatment* OR laser biostimulation OR laser phototherapy OR LLLT OR LILT OR photo biomodulation OR photo-bio-modulation OR photobiomodulation OR PBM therap* OR PBMT OR acupuncture OR shonishin OR acupressure OR Shiatsu OR Tui Na OR electroacupuncture OR pharmacoacupuncture OR acupotom* OR acupoint stimulation OR burnt needle therapy OR fire needle therapy OR fire needling OR thermoacupuncture OR endermolog* OR electrotherapy* OR electro-therapy* OR electric stimulation OR electrical stimulation OR electrostimulation OR electro-stimulation).ab,ti,kf.)

NOT (exp animals/ NOT humans/)

Appendix 3. Embase

('breast cancer-related lymphedema'/exp OR (('breast tumor'/exp OR 'mastectomy'/exp OR 'patient history of mastectomy'/de OR ('breast cancer' OR 'mammary cancer' OR 'breast carcinoma*' OR 'mammary carcinoma*' OR 'breast tumor*' OR 'mammary tumor*' OR 'breast tumour*' OR 'mammary tumour*' OR 'breast neoplasm*' OR 'mammary neoplasm*' OR 'breast malignan*' OR 'mammary malignan*' OR mastectomy OR postmastectomy OR postradiation OR post-radiation OR 'breast amputation' OR 'breast resection' OR mammectomy OR postmammectomy):ab,ti,kw) AND ('lymphedema'/exp OR 'arm edema'/de OR (lymphedema* OR lymphoedema* OR lymphooedema* OR 'large arm*' OR 'swollen arm*' OR edema OR oedema):ab,ti,kw)) OR BCRL:ab,ti,kw)

AND

('plastic surgery'/de OR 'reconstructive surgery'/de OR 'microsurgery'/de OR 'microvascular surgery'/exp OR 'lipectomy'/exp OR 'liposuction'/exp OR 'skin graft'/de OR 'tissue flap'/exp OR 'surgical flaps'/exp OR 'lymphovenous anastomosis'/de OR 'lymphovenular anastomosis'/de OR 'anastomosis'/de OR 'microanastomosis'/de OR 'vein anastomosis'/de OR 'vein bypass'/de OR 'lymph node transplantation'/de OR 'lymph node transfer'/de OR 'charles procedure'/de OR 'vascularized lymph node transfer'/exp OR ('plastic surgery' OR 'corrective surgery' OR 'plastic reconstruction*' OR 'reconstructive surgery' OR 'preposthetic surgery' OR 'reparative surgery' OR 'operative reconstruction*' OR 'reconstruction surgery' OR 'reconstructive surgical procedure*' OR 'surgical reconstruction*' OR microsurg* OR micro-surg* OR 'microscale surgery' OR 'microscopic surgery' OR supermicrosurg* OR microvascular OR micro-vascular OR 'microanastomosis' OR 'micro anastomosis' OR 'surgical flap*' OR 'myocutaneous flap*' OR 'deep inferior epigastric perforator flap*' OR 'deep inferior epigastric artery perforator flap*' OR 'DIEP flap*' OR 'free flap*' OR 'free graft*' OR 'tissue flap*' OR 'free tissue graft*' OR 'free tissue transfer' OR lipectom* OR 'adipectom*' OR 'dermolipectom*' OR 'fat excision' OR liposuction* OR ((aspiration OR suction) AND (lipolysis OR lipoplast*)) OR 'fat suction surgery' OR ((lymphaticovenous OR 'lymphatico venous' OR lymphaticovenular OR lymphatico-venular OR 'lymphatic venous' OR lymphovenous OR lymphadenovenous) NEAR/3 (anastomos* OR bypass OR shunt* OR communication)) OR 'lymphatic bypass procedure*' OR LVA OR ('lymph node' NEAR/3 (transfer* OR transplant* OR flap*)) OR VLNT OR ALNT OR 'charles procedure' OR 'charle s procedure' OR 'subcutaneous excision'):ab,ti,kw)

AND

('conservative treatment'/de OR 'compression therapy'/exp OR 'drainage'/exp OR 'massage'/exp OR 'bandage'/exp OR 'athletic tape'/exp OR 'compression garment'/exp OR 'elastic tape'/exp OR 'physiotherapy'/exp OR 'exercise'/de OR 'kinesiotherapy'/de OR 'arm exercise'/de OR 'leg exercise'/de OR 'movement therapy'/de OR 'intermittent pneumatic compression device'/de OR 'intermittent pneumatic compression'/de OR 'intermittent pneumatic compression therapy'/de OR 'shock wave therapy'/de OR 'shock wave generator'/de OR 'low level laser therapy'/de OR 'photobiomodulation'/de OR 'acupuncture'/exp OR 'low frequency electrotherapy'/de OR (conservative* OR non-operative* OR nonoperative* OR non-surgical OR nonsurgical OR drainage OR decongesti* OR massage OR 'zone therap*' OR massotherap* OR compression OR bandag* OR sleeve* OR 'elastic dressing*' OR 'athletic tap*' OR 'orthotic tap*' OR 'kinesio tap*' OR kinesiotap* OR garment* OR PlasmaFlow OR VasoGrad OR IPC OR 'physical therap*' OR physiotherap* OR 'physio therap*' OR 'physical treatment*' OR exercise* OR 'physical activit*' OR 'kinesiotherap*' OR 'movement therap*' OR 'motion therap*' OR 'A-V Impulse System' OR 'ActiveCare DVT' OR 'AeroDVx' OR 'ArtAssist' OR 'BioTAB' OR 'Flexitouch system' OR Flowtron OR 'intermittent pneumatic compression' OR 'intermittent venous compression' OR 'Plexipulse' OR 'pneumatic intermittent impulse' OR 'SC-2004 Sequential Circulator PCD' OR 'sequential venous compression' OR 'VascuEase' OR 'VasQcare' OR 'venous compression system*' OR (pneumatic NEXT/2 (stocking* OR hose)) OR (('shock wave' OR shockwave OR HIFU) NEAR/3 (therap* OR treat*)) OR 'high-intensity focused ultrasound' OR ESWT OR 'laser therap*' OR 'laser treatment*' OR 'light therap*' OR 'light treatment*' OR 'laser biostimulation' OR 'laser phototherapy' OR LLLT OR LILT OR 'photo biomodulation' OR 'photo-bio-modulation' OR photobiomodulation OR 'PBM therap*' OR PBMT OR acupuncture OR shonishin OR acupressure OR Shiatsu OR 'Tui Na' OR electroacupuncture OR pharmacoacupuncture OR 'acupoint stimulation' OR acupotom* OR 'burnt needle therapy' OR 'fire needle therapy' OR 'fire needling' OR 'thermoacupuncture' OR endermolog* OR electrotherapy* OR electro-therapy* OR 'electric stimulation' OR 'electrical stimulation' OR electrostimulation OR electro-stimulation):ab,ti,kw)

NOT

(('animal'/de OR 'animal experiment'/exp OR 'nonhuman'/de) NOT ('human'/exp OR 'human experiment'/de))

NOT

[conference abstract]/lim

Appendix 4. Web of Science Core Collection

TS=((((("breast cancer" OR "mammary cancer" OR "breast carcinoma*" OR "mammary carcinoma*" OR "breast tumor*" OR "mammary tumor*" OR "breast tumour*" OR "mammary tumour*" OR "breast neoplasm*" OR "mammary neoplasm*" OR "breast malignan*" OR "mammary malignan*" OR mastectomy OR postmastectomy OR postradiation OR post-radiation OR "breast amputation" OR "breast resection" OR mammectomy OR postmammectomy) AND (lymphedema* OR lymphoedema* OR lymphooedema* OR "large arm*" OR "swollen arm*" OR edema OR oedema)) OR BCRL)

AND

("plastic surgery" OR "corrective surgery" OR "plastic reconstruction*" OR "reconstructive surgery" OR "preposthetic surgery" OR "reparative surgery" OR "operative reconstruction*" OR "reconstruction surgery" OR "reconstructive surgical procedure*" OR "surgical reconstruction*" OR microsurg* OR micro-surg* OR "microscale surgery" OR "microscopic surgery" OR supermicrosurg* OR microvascular OR micro-vascular OR "microanastomosis" OR "micro anastomosis" OR "surgical flap*" OR "myocutaneous flap*" OR "deep inferior epigastric perforator flap*" OR "deep inferior epigastric artery perforator flap*" OR "DIEP flap*" OR "free flap*" OR "free graft*" OR "tissue flap*" OR "free tissue graft*" OR "free tissue transfer" OR lipectom* OR "adipectom*" OR "dermolipectom*" OR "fat excision" OR liposuction* OR ((aspiration OR suction) AND (lipolysis OR lipoplast*)) OR "fat suction surgery" OR ((lymphaticovenous OR "lymphatico venous" OR lymphaticovenular OR lymphatico-venular OR "lymphatic venous" OR lymphovenous OR lymphadenovenous) NEAR/2 (anastomos* OR bypass OR shunt* OR communication)) OR "lymphatic bypass procedure*" OR LVA OR ("lymph node" NEAR/2 (transfer* OR transplant* OR flap*)) OR VLNT OR ALNT OR "charles procedure" OR "charle s procedure" OR "subcutaneous excision")

AND

(conservative* OR non-operative* OR nonoperative* OR non-surgical OR nonsurgical OR drainage OR decongesti* OR massage OR "zone therap*" OR massotherap* OR compression OR bandag* OR sleeve* OR "elastic dressing*" OR "athletic tap*" OR "orthotic tap*" OR "kinesio tap*" OR kinesiotap* OR garment* OR PlasmaFlow OR VasoGrad OR IPC OR "physical therap*" OR physiotherap* OR "physio therap*" OR "physical treatment*" OR exercise* OR "physical activit*" OR "kinesiotherap*" OR "movement therap*" OR "motion therap*" OR "A-V Impulse System" OR "ActiveCare DVT" OR "AeroDVx" OR "ArtAssist" OR "BioTAB" OR "Flexitouch system" OR Flowtron OR "intermittent pneumatic compression" OR "intermittent venous compression" OR "Plexipulse" OR "pneumatic intermittent impulse" OR "SC-2004 Sequential Circulator PCD" OR "sequential venous compression" OR "VascuEase" OR "VasQcare" OR "venous compression system*" OR (pneumatic NEAR/2 (stocking* OR hose)) OR (("shock wave" OR shockwave OR HIFU) NEAR/2 (therap* OR treat*)) OR "high-intensity focused ultrasound" OR ESWT OR "laser therap*" OR "laser treatment*" OR "light therap*" OR "light treatment*" OR "laser biostimulation" OR "laser phototherapy" OR LLLT OR LILT OR "photo biomodulation" OR "photo-bio-modulation" OR photobiomodulation OR "PBM therap*" OR PBMT OR acupuncture OR shonishin OR acupressure OR Shiatsu OR "Tui Na" OR electroacupuncture OR pharmacoacupuncture OR "acupoint stimulation" OR acupotom* OR "burnt needle therapy" OR "fire needle therapy" OR "fire needling" OR "thermoacupuncture" OR endermolog* OR electrotherapy* OR electro-therapy* OR "electric stimulation" OR "electrical stimulation" OR electrostimulation OR electro-stimulation))

NOT DT=(Meeting Abstract)

Appendix 5. WHO ICTRP

Basic searches:

1. breast cancer related lymphedema
2. breast cancer related lymphoedema
3. breast cancer related lymphedema AND compression therapy AND lymphatic surgery
4. breast cancer related lymphoedema AND compression therapy AND lymphatic surgery

Advanced searches:

1. Condition: (Breast cancer* OR breast neoplasm*) AND (lymphedema OR lymphoedema OR BCRL OR lymphatic oedema* OR lymphatic edema*)

Intervention:(compression OR compression therap* OR bandag* OR pneumatic compression* OR lymphedema therap* OR lymphoedema therap*) AND (liposuction OR lymph node transfer OR lymphaticovenular anastomosis OR LVA OR Lympathico-lymphatic bypass OR microsurgical lymphatic reconstruct*)
Recruitment status:All

2. Condition:(Breast cancer* OR breast neoplasm*) AND (lymphedema OR lymphoedema OR BCRL OR lymphatic oedema* OR lymphatic edema*)

Intervention: (compression garment* OR intermittent pneumatic compression device* OR sequential pneumatic compression OR massage OR negative pressure massage therap*) AND (anastomotic reconstruct* OR lymphatic surg* OR lymphatic reconstruct* OR axillary lymphadenectom* OR Lymph node flap*)

Recruitment status: All

3. Condition: (Breast cancer* OR breast neoplasm*) AND (lymphedema OR lymphoedema OR BCRL OR lymphatic oedema* OR lymphatic edema*)

Intervention:(laser therap* OR acupuncture OR athletic tap* OR athletic taping OR kinesio tap* OR kinesio taping OR lymph tap* OR lymph taping) AND (microvascular surg* OR micro anastomosis OR free tissue graft* OR free tissue transfer)

Recruitment status: All

4. Condition: (Breast cancer* OR breast neoplasm*) AND (lymphedema OR lymphoedema OR BCRL OR lymphatic oedema* OR lymphatic edema*)

Intervention:(therapeutic exercise OR yoga OR manual lymphatic drain* OR MLD OR complete decongestive therap*) AND (dermolipectom* OR autologous lymph node transplant* OR vascularised lymph node transfer* OR ALNT)

Recruitment status: All

Appendix 6. ClinicalTrials.gov

'New' interface search

1. Condition or disease: breast cancer related lymphedema

2. Condition or disease: breast cancer related lymphedema
Other terms: compression therapy AND lymphatic surgery

3. Condition or disease:breast cancer related lymphedema
Other terms:(compression OR compression therapy OR bandage OR pneumatic compression OR lymphedema therapy) AND (liposuction OR lymph node transfer OR lymphaticovenular anastomosis OR LVA OR Lympathico-lymphatic bypass OR microsurgical lymphatic reconstruction)

4. Condition or disease: breast cancer related lymphedema
Other terms: (compression garment OR intermittent pneumatic compression device OR sequential pneumatic compression OR massage OR negative pressure massage therapy) AND (anastomotic reconstruction OR lymphatic surgery OR lymphatic reconstruction OR axillary lymphadenectomy OR Lymph node flap)

5. Condition or disease: breast cancer related lymphedema
Other terms:(laser therapy OR acupuncture OR athletic tape OR kinesio tape OR lymph tape) AND (microvascular surgery OR micro anastomosis OR free tissue graft OR free tissue transfer)

6. Condition or disease:breast cancer related lymphedema
Other terms: (therapeutic exercise OR yoga OR manual lymphatic drainage OR MLD OR complete decongestive therapy) AND (dermolipectomy OR autologous lymph node transplant OR vascularised lymph node transfer OR ALNT)

*All studies (no recruitment filters) and All sexes used for each search strategy

CONTRIBUTIONS OF AUTHORS

Conceptualisation project: YHaa, OPW, EAK

Search strategy: CA-H

Statistical analysis strategy: FH

Writing protocol: YHaa, OPW

Revision protocol: JM, GP, EMT, MK, DS, SE, GV, BL, JP, FJ, EG, BK, LZ, JS, FH, C-AH, LH-V, YS, REH, MM, KR, JV, KVI, SSQ, BB, LGH, NL, DJS, KS, YHar, CRH, WW, EAK

If any of the review authors are also authors of included studies, they will not participate in the risk of bias or GRADE assessment of their own studies, in accordance with Cochrane's conflict of interest policy.

DECLARATIONS OF INTEREST

YHaa, OPW, JM, GP, EMT, MK, DS, GV, BL, FJ, EG, BK, LZ, JS, FSH, CA-H, LH-V, YS, REH, KR, JV, KVI, SSQ, LGH, DJS, KS, EAK: no conflict of interest.

MM: Elected representative at lymphoedema national evaluation group for lymphoedema care in Sweden, Microsure (scientific board member; development of robot for microsurgery), breast cancer association for research on lymphoedema (grant).

BB: Consultant for Julius Zorn GmbH.

SE: Deutsche Forschungsgemeinschaft (grant/contract).

YHar: Clinical consultant for device development, author *Modern Surgical Management of Chronic Lymphedema* (Thieme; ISBN: 9783132414280).

CRH: Advisory Board at 3M Company.

NL: Consultant and scientific advisor for Medical Microinstruments (MMI).

JP: Medical and Marketing Consultant for Kerecis Limited, Scientific Advisor and Speaker for Nanomedic.

WW: Speaking engagement for MSD.

SOURCES OF SUPPORT

Internal sources

- University Hospital of Basel, Switzerland

  Affiliated Center

External sources

- None, Other

  None