Review Article

Surgical treatment algorithm for breast cancer lymphedema—a systematic review

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Background: Various surgical treatments are increasingly adopted and gaining popularity for lymphedema treatment. However, challenges persist in selecting appropriate treatment modalities targeted for individual patients and achieving consensus on choice of treatment as well as outcomes. The systematic review aimed to create a treatment algorithm incorporating the latest scientific knowledge, to provide healthcare professionals and patients with a tool for informed decision-making, when selecting between treatments or combining them in a relevant manner. This systematic review evaluated and synthesized the evidence on the effectiveness of three surgical treatments for breast cancer-related lymphedema (BCRL): lymphovenous anastomosis (LVA), vascularized lymph node transfer (VLNT), and liposuction.

Methods: We conducted a systematic search of electronic databases on 18 June 2023, including Medline, Embase, Cochrane Library, Google Scholar, and ClinicalTrials.org. Eligible studies were randomized controlled trials, non-randomized comparative studies, and observational studies that assessed the outcomes of LVA, VLNT, or liposuction in managing BCRL. The primary results of interest were changes in arm volume, lymphatic flow, and quality of life. Two independent reviewers performed the study selection and data extraction. Following this, we systematically reviewed and conducted a risk of bias assessment. Results were qualitatively presented, and a treatment algorithm was developed based on the available data.

Results: We identified 16,593 papers, after removal of duplicates. Following assessment of studies, 73 articles met the inclusion criteria, including 2,373 patients. We were not able to conduct a meta-analysis due to considerable heterogeneity in the methodologies and outcome measures across the studies. Liposuction appears effective for patients presenting with non-pitting lymphedema. LVA indicates variable success rate, with some evidence indicating a reduction in limb volume and symptomatic relief amongst early stages of lymphedema. VLNT showed promising results for limb volume reduction and symptom improvement in patients presenting with mild and moderate lymphedema.

Conclusions: Liposuction, LVA, and VLNT seem to be effective treatments for BCRL, when targeted for the appropriate patient. Well-conducted high evidence clinical studies in the field are still lacking to uncover the efficacy of surgical treatment for BCRL.

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Keywords: Breast cancer-related lymphedema (BCRL); secondary lymphedema; lymphovenous anastomosis (LVA); vascularized lymph node transfer (VLNT); liposuction

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Introduction

Background

Breast cancer-related lymphedema (BCRL) is a debilitating condition that affects a substantial number of breast cancer survivors (1). Conservative treatment with compression therapy, manual lymphatic drainage, exercise, and skincare are widely recognized as the golden standard for managing lymphedema symptoms. While this treatment regime can offer a reduction in edema, alleviate pain, and slow down the progression of the disease, it remains primarily focused on relieving symptoms and is heavily dependent on patient compliance and resource availablility (2-4). However, it has its limitations, being most effective in the early stages of lymphedema, where the lymphatic system may still be stimulated to remove excess fluid. As the disease progresses, the lymphedematous tissue undergoes fibrosis and becomes less pliable, making conservative treatment less effective. Many individuals also find their daily activities restricted due to the use of compression garments. Further limitations include restrictions in activities of daily living due to the use of compression sleeves and the ongoing fitting issues, discomfort and economic burden of new or adjusted compression sleeves. Patients also face time-consuming travel between treatment centers, as the accessibility of lymphedema specialists is impacted by local resource availability (2-5).

Surgical interventions for BCRL include liposuction, lymphovenous anastomosis (LVA), and vascularized lymph node transfer (VLNT), have been available for several years (6-8). The field of lymphedema surgery is expanding swiftly, and studies are continuously published, showing promising results (9). However, there are still many questions that remain unanswered. These include the efficacy of the procedure, the optimal pre-operative planning, identifying the proper treatment for the individual, as well as choice of optimal post-operative management. Another challenge lie in the early lymphedema detection and the absence of standardized methods for diagnostic modalities and criteria, contributing to increased complexity, and thus likely resulting in delayed diagnosis and treatment (10,11).

Reviewing surgical treatments for BCRL is crucial to advance our understanding of the condition, improving patient care, and guiding future research and clinical practice by systematically evaluating the effectiveness of surgical interventions for managing BCRL, providing a comprehensive understanding of their outcomes, benefits, and limitation. This will allow for an evidence-

Highlight box

Key findings
- While promising, surgical lymphedema treatments require further high-quality studies to address uncertainties in breast cancer-related lymphedema (BCRL) management.
- Liposuction is a valuable treatment for non-pitting lymphedema patients, with significant volume reduction.
- Vascularized lymph node transfer seems effective, especially when combined with breast reconstruction.
- The efficacy of lymphovenous anastomosis remains uncertain, but it may be effective in early lymphedema stages.

What is known and what is new?
- Variability in outcomes following surgical treatments emphasized the need for careful patient selection when treating BCRL.
- New technologies and surgical techniques enable potentially more effective lymphedema surgery and patient-centered treatments. However, the efficacy of the surgical procedures are inadequatelty investigated.

What is the implication, and what should change now?
- Healthcare professionals should emphasize the importance of early detection and treatment of lymphedema, moving towards a proactive approach in the screening and early intervention within the BCRL care.
- The lack of uniform diagnostic and evaluation tools for lymphedema poses a significant challenge to provide consistent care and research transparency. Adopting standardized methods for classification and measurements will improve diagnosis accuracy, facilitate early detection, and enable comparison of outcomes across studies.
- Implementing a patient-centered treatment plan considering lymphedema stage, patient symptoms, and individual needs is essential for achieving the best possible outcomes and managing the disease effectively.

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Table 1 Search terms and strings for Medline search

1. exp Breast Cancer Related Lymphedema/
2. Breast Neoplasms/
3. Lymphedema/
4. ((Breast Cancer adj3 Lymphedema*) or (breast neoplasm* adj3 lymphedema*) or (postmastectomy adj3 lymphedema*) or (post-mastectomy adj2 lymphedema*) or (secondary adj3 lymphedema*) or (iatrogenic adj3 lymphedema*) or lymphoedema*).mp. [mp=title, abstract, original title, name of substance word, subject heading rod, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5. 1 or 2 or 3 or 4
6. Anastomosis, Surgical/
7. Lymph Nodes/
8. Lipectomy/
9. ((Lymph* adj3 anastomos*) or LVA or (lymph node adj3 transplant*) or (lymph* transplant*) or (lymph node adj3 transfer*) or VLNT or LNT or liposuction or debulking).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. 6 or 7 or 8 or 9
11. 5 and 10

Keywords, search strings, and Boolean operators were used. LVA, lymphovenous anastomosis; VLNT, vascularized lymph node transfer.

based synthesis and provide a broader understanding of patient outcomes. We believe this will aid future treatment guidelines and research prioritization.

Objective

The aim of this article was to conduct a systematic review on LVA, VLNT, and liposuction for treatment of BCRL to explore its efficacy on arm volume reduction, quality of life, lymph flow, and ultimately develop an optimal, evidence-based treatment algorithm based upon the patients' characteristics, symptoms and needs. We present this article in accordance with the PRISMA reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-503/rc) (12).

Methods

Search strategy

We conducted an electronic literature search in the five databases: EMBASE (Ovid), Medline (Ovid), Cochrane Library, Google Scholar, and ClinicalTrials.gov. The search was conducted on June 18, 2023. The search query included various keywords, such as: "Breast Cancer Related Lymphedema", "Breast Neoplasms", "Lymphedema", "Surgical Anastomosis", "Lymph Nodes", and "Lipectomy". See *Table 1* for search terms and string examples and Table S1 for the entire search string. No filter function nor time limit was applied to include all available articles, including non-peer-reviewed ones. All systematic reviews on surgical treatments for BCRL identified through our search strategy were also assessed for potentially relevant literature.

Inclusion and exclusion criteria

All original studies presenting outcomes of LVA, VLNT, or liposuction for patients with unilateral upper extremity lymphedema (UEL) secondary to breast cancer were included. Studies investigating a combination of treatments were excluded, except studies with combined breast reconstruction and VLNT. A model encompassing patient population, interventions, comparison, and outcomes of interests, known as the PICO model, was formulated. For full PICO criteria, see *Table 2*. Only articles written in English were included. Animal studies, conference abstracts, oral- or poster presentations, case reports, and interventional studies with a study population of less than ten patients in the intervention group were all excluded.

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Table 2 PICO model for the systematic review

PICO	Description of PICO model
Population	Patients with unilateral UEL secondary to breast cancer treatment
Intervention	LVA, VLNT, liposuction, or debulking procedure
Comparison	No comparison or comparison with other conservative and/or surgical interventions
Outcome	Changes in quality-of-life quantified by validated scores, the difference in limb volume measured on different scales, volumetric calculations, circumference measurements, water displacement, etc., and changes in lymph flow
Study design	Interventional studies (all kinds of interventional study designs, e.g., randomized controlled trials, cohort studies, case-control studies, self-controlled case series)

UEL, upper extremity lymphedema; LVA, lymphovenous anastomosis; VLNT, vascularized lymph node transfer.

Data extraction

Two independent reviewers conducted the title and abstract screening using Covidence software, followed by full-text review of selected articles. Disagreements were resolved through discussion or consultation with a third reviewer. The following study characteristics were collected in an excel spreadsheet: study design, year of publication, region/area of origin for the article, number of patients, intervention and comparison, lymphedema duration, lymphedema classification, type of surgery, surgery duration, number of performed anastomoses, number of transplanted lymph nodes, donor- and recipient site for VLNT, volume aspirated from liposuction, type of volume measure, arm volume measures, quality of life assessment, lymphatic flow evaluation, the significance of outcomes, complications and flap loss, post-operative management, follow-up duration.

Risk of bias and quality assessment

The quality of included studies was assessed using ROBINS-I for non-randomized studies and ROB2 for randomized controlled trials. For cross-sectional studies, we used a modified Newcastle-Ottawa Quality Assessment Scale, and for observational studies, we applied a systematic checklist to evaluate the risk of bias (13-16). The checklist assessed the reporting and risk of implementing bias in a study on its design, research question, selection of population and recruitment, their exposure- and outcome assessment, loss to follow-up, confounding domains, reporting and transparency, ethical considerations, study funding and conflicts of interest, and lastly the study's overall risk of bias. The scoring system ranged from zero to 32 points. Zero to eight points indicated a critical risk of bias, nine to sixteen points a serious risk of bias, seventeen to 24 a moderate risk of bias, and 25–32 a low risk of bias, while having in mind the nature of observational studies always has some degree of bias due to the natural design of the study.

Since the included papers did not provide adequate data for a combined analysis, an evaluation of the confidence in evidence from a data synthesis using the GRADE approach for randomized and non-randomized trials was not conducted in this review (17).

Statistical analysis

Due to the substantial heterogeneity observed among the included articles and the insufficient number of randomized and non-randomized controlled trials, no meta-analysis was performed. Heterogeneity in this context refers to the significant variation in study designs, patient populations, interventions, and outcome measurements across the included articles. This variation makes it challenging to pool the data and conduct a meaningful meta-analysis, as the results would be potentially misleading. As such, we will provide a qualitative synthesis of the findings, summarizing the key trends, patterns, and insights observed within the individual studies. The variation in outcomes across studies that reported the same measure of efficacy was analyzed using SPSS and quantified using the I^2 statistic to assess heterogeneity (18).

Results

The initial literature review revealed 16,593 articles after removing duplicates, of which 827 were included for full-text screening. After thoroughly evaluating full texts, 70

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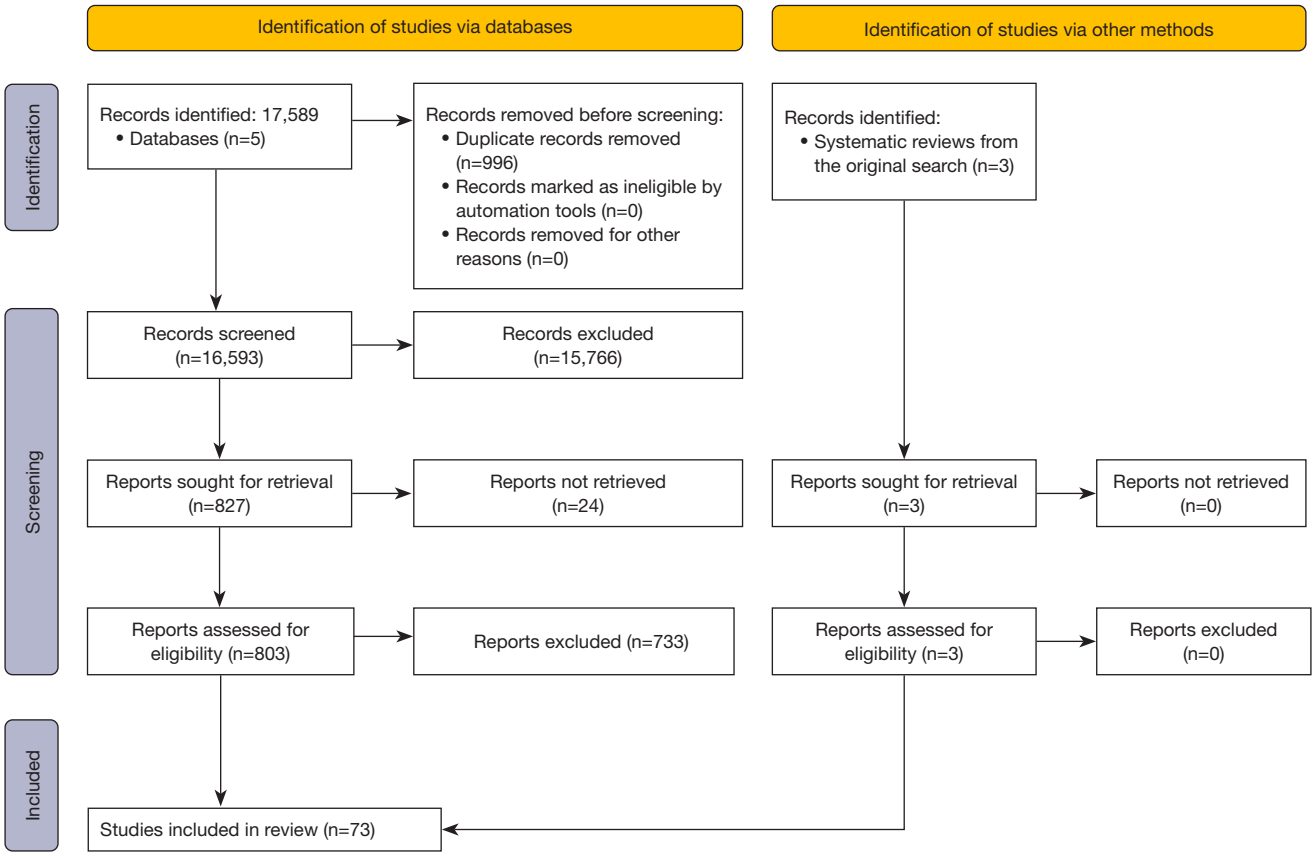

Figure 1 PRISMA flow chart presenting the screening process. Articles not retrieved refers to the articles that were initially identified and included for full text screening, but were not obtained or accessed for the review.

articles fulfilled our inclusion criteria and were selected for data extraction and analysis. An additional three articles were identified and included through relevant systematic reviews, resulting in 73 included articles. The 73 articles were subdivided according to subjects, 24 focused on LVA, 29 on VLNT, 12 on liposuction, and two described both LVA and VLNT, in addition to six ongoing clinical trials. See *Figure 1* for the entire screening process. Only three articles were randomized controlled trials, none of which were blinded (5,19,20). Overall, 2,373 patients were included in the study. International Society of Lymphology (ISL) was the most frequently used classification system to evaluate lymphedema stage. Other methods used included the Campisi staging of lymphedema, Cheng Lymphedema Grading System, lymphoscintigraphy, indocyanine green lymphography (ICG-L), Arm Dermal Backflow, M. D. Anderson Scale, and the pitting test, see *Table 3* (10,21-26). Amongst patients receiving LVA or VLNT, their lymphedema was classified primarily using ISL with 11.2% stage I, 71.3% stage II, and 17.5% stage III. ISL was not applied in liposuction articles, where the pitting-test was the predominant way of evaluating lymphedema.

The effect of LVA

LVA was described in a total of 26 articles, 33.8% of the included articles, presented the outcome of LVA for treatment of BCRL, see *Table 4*. The studies were published between 2009 and 2023, with a steady annual increase, reaching its peak in 2022, highlighting the continued relevance of the topic, as indicated in *Figure 2*.

Among the 26 articles, 16 (61.2%) were prospective studies (20,27-41), one being a randomized controlled trial (20), one single cross-sectional study (42), and nine (31.0%) followed a retrospective design (43-51). Geographically, the Netherlands (seven articles) (20,30,31,36,41,48,50) and Japan (six articles) (34,39,42,43,45,47) were the most represented regions/areas in the literature. Other

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Table 3 Overview of lymphedema classifications used in the included articles

Lymphedema classification	Classification description
ISL (10)	Classification of 5 classes:
	0: a subclinical state where swelling is not evident despite impaired lymph transport. This stage may exist for months or years before edema becomes evident
	1: early onset of the condition where there is accumulation of tissue fluid that subsides with limb elevation. The edema may be pitting at this stage
	2: limb elevation alone rarely reduces swelling, and pitting is manifested. Late 2: there may or may not be pitting, as tissue fibrosis is more evident
	3: the tissue is hard (fibrotic), and pitting is absent. Skin changes such as thickening, hyperpigmentation, increased skin folds, fat deposits, and warty overgrowths develop
Campisi staging of lymphedema (21)	Classification of 6 stages:
	1A: no edema with presence of lymphatic dysfunction (e.g., after mastectomy and axillary lymphadenectomy, without any difference in volume and consistency between the arms)
	1B: mild edema, reversible with declivous position and night rest
	2: persistent edema that regresses only partially with declivous position and night rest
	3: persistent and ingravescent edema (acute erysipeloid lymphangitis)
	4: fibrotic lymphedema (with initial lymphstatic verrucosis) and column-shaped limb
	5: elephantiasis with severe limb deformation, scleroindurative pachidermitis, and marked and widespread lymphstatic verrucosis
Cheng Lymphedema Grading System (22)	Classification of 5 stages:
	0: symptoms: reversible; circumferential difference: <10%; lymphoscintigraphy: partial occlusion; management: rehabilitation
	1: symptoms: mild; circumferential difference: 10–19%; lymphoscintigraphy: partial occlusion; management: LVA, liposuction, rehabilitation
	2: symptoms: moderate; circumferential difference: 20–29%; lymphoscintigraphy: total occlusion; management: VLNT, LVA, rehabilitation
	3: symptoms: severe; circumferential difference: 30–39%; lymphoscintigraphy: total occlusion; management: VLNT + additional procedures
	4: symptoms: very severe; circumferential difference: >40%; lymphoscintigraphy: total occlusion; management: Charles procedure + VLNT
M. D. Anderson Scale (23)	Classification of 5 stages:
	0: no dermal backflow
	1: many patent lymphatics and minimal dermal backflow
	2: moderate number of patent lymphatics and segmental dermal backflow
	3: few patent lymphatics with extensive dermal backflow
	4: dermal backflow involving the hand
	5: ICG does not move proximally to injection site

Table 3 (*continued*)

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Table 3 (*continued*)

Lymphedema classification	Classification description
Arm Dermal Backflow Scale (23)	Classification of 5 stages: 0: no dermal backflow 1: splash pattern around the axilla 2: stardust limited between olecranon and axilla 3: stardust distal to olecranon 4: stardust involving the hand 5: diffuse and stardust pattern involving the entire limb
Pitting test (24)	Pressure is applied with the thumb to the examined area for 60 seconds, and the depth of depression is measured in millimeters. The presence of pitting indicated the predominance of fluid in cases of lymphedema, while the absence of pitting suggests a dominance of adipose tissue
Tawian lymphoscintigraphy staging (22)	Classification of 7 classes, based upon lymphoscintigraphy findings: L-0: category: normal lymphatic drainage; proximal lymph nodes: +; intermediate lymph nodes: –; lymphatic ducts: +; dermal backflow: – P-1: category: partial obstruction; proximal lymph nodes: +/↓; intermediate lymph nodes: –; lymphatic ducts: +/distal; dermal backflow: – P-2: category: partial obstruction; proximal lymph nodes: ↓; intermediate lymph nodes: +/–; lymphatic ducts: distal/engorged; dermal backflow: + (proximal/distal) P-3: category: partial obstruction; proximal lymph nodes: –; intermediate lymph nodes: +; lymphatic ducts: –; dermal backflow: + (distal/entire) T-4: category: total obstruction; proximal lymph nodes: –; intermediate lymph nodes: –; lymphatic ducts: engorged/–; dermal backflow: + (distal) T-5: category: total obstruction; proximal lymph nodes: –; intermediate lymph nodes: –; lymphatic ducts: engorged/–; dermal backflow: + (enitre) T-6: category: total obstruction; proximal lymph nodes: –; intermediate lymph nodes: –; lymphatic ducts: –; dermal backflow: – Note: upper extremity: various degree of uptake and transportation of intradermal administered Tc-99m labeled sulfur colloid or human albumin in lymphoscintigraphies. Please see Cheng *et al.* for further details (22)
ICG-L (25)	Assessment of real-time video patterns of the lymphatic uptake of intradermal administered ICG. The lymphatic transport and function are evaluated, commonly used in lymphedema staging through classification scales, such as the M. D. Anderson Scale
Lymphoscintigraphy (26)	Evaluation of images from lymphatic uptake of intradermally administered Tc-99m labeled sulfur colloid or human albumin, focusing on evaluating lymphatic transport and function

ISL, International Society of Lymphology; LVA, lymphovenous anastomosis; VLNT, vascularized lymph node transfer; ICG, indocyanine green; ICG-L, indocyanine green lymphography.

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Table 4 Summary of included articles on LVA

Author	Year	Region/area	Study design	No. of patients	Method for lymphedema evaluation	Lymphedema duration (years)	Volume measurement method	Quality of life measure	Lymph flow measure	Follow-up duration (months)	Post-operative management	Complications
van Mulken TJM *et al.* (20)	2022	Netherlands	Randomized controlled trial	20	ISL, ADB	4 [1.8–6.0]; 7 [3.0–15.5]	Arm circumference (UEL index)	Lymph-ICF	–	12	No CCT or lymph drainage until 4 weeks after surgery	None
Visconti G *et al.* (27)	2022	Italy	Prospective	47	ISL	NA	Arm circumference (sum of arm circumference)	–	–	12	No strict protocol, CCT after surgery followed up with a physical therapist	NA
Rodriguez JR *et al.* (28)	2022	Chile	Prospective	47	ISL, lymphoscintigraphy	NA	Arm circumference (arm volume reduction)	–	–	14	CCT class III immediately after surgery 24 hours per day, until day 14, hereafter only during the daytime	NA
Boccardo F *et al.* (29)	2022	Italy	Prospective	63	ISL, lymphoscintigraphy	NA	NA (excess volume reduction)	–	Lymphoscintigraphy	60	CCT class II immediately after surgery for 6 months, hereafter 8–10 hours daily for another 6 months	NA
Wolfs JAGN *et al.* (30)	2020	Netherlands	Prospective	25	ISL, ICG-L	6.1±5.1	Arm circumference (UEL index)	Lymph-ICF	–	12	No CCT nor lymphatic drainage for the first month. After this period, individual consultations determined whether CCT was necessary for each patient	Infection in three patients
Qiu SS *et al.* (31)	2020	Netherlands	Prospective	85	ISL	NA	Arm circumference (UEL index)	Lymph-ICF	–	25	No CCT nor lymphatic drainage for the first month. After this period, individual consultations determined whether CCT was necessary for each patient	NA
Phillips GSA *et al.* (32)	2019	United Kingdom	Prospective	37	ICG-L	NA	Perometer (arm volume difference)	LYMQOL	–	12	Elevation of the arm and massage from dorsal to proximal towards the scars	None
Khan AA *et al.* (33)	2019	United Kingdom	Prospective	27	NA	3.5 [0.5–18]	Perometer (arm volume difference)	–	–	24	Limb elevation for 3 days, CCT 2 weeks after surgery as usual	NA
Mihara M *et al.* (34)	2018	Japan	Prospective	13	ISL, ICG-L, lymphoscintigraphy	6.4	Arm circumference (arm volume difference)	VAS	–	10.6	CCT after surgery	NA
Poumellec MA *et al.* (35)	2017	France	Prospective	31	Campisi staging of lymphedema	NA	Arm circumference (reduction in circumference)	–	–	12.7	CCT and lymph drainage 2 weeks after surgery	None
Cornelissen AJM *et al.* (36)	2017	Netherlands	Prospective	20	ISL	6 [2–30]	Arm circumference (UEL index)	Lymph-ICF	–	12	No CCT for 4 months after surgery	Skin irritation in two patients at the injection site of ICG
Chang DW *et al.* (37)	2013	United States	Prospective	89	Campisi staging of lymphedema	3.5 [1–10]	Perometer (arm volume difference)	–	–	12	Compression bandage immediately after surgery and arm elevation. After 4 weeks, patients could resume to their usual CCT	None
Ayestaray B *et al.* (38)	2013	France	Prospective	20	NA	3.4±2.52	Arm circumference (calculated cross-sectional area, and lymphedema volume)	–	–	6	NA	One patient with skin ulceration
Mihara M *et al.* (39)	2012	Japan	NA	10	ISL	NA	Arm circumference (sum of arm circumference)	–	–	2	CCT immediately after surgery	None

Table 4 (*continued*)

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Table 4 (*continued*)

Author	Year	Region/area	Study design	No. of patients	Method for lymphedema evaluation	Lymphedema duration (years)	Volume measurement method	Quality of life measure	Lymph flow measure	Follow-up duration (months)	Post-operative management	Complications
Chang DW *et al.* (40)	2010	United States	Prospective	20	Campisi staging of lymphedema	4.8 [1–17]	Perometer (arm volume difference)	–	–	12	Compression bandage immediately after surgery and arm elevation. After 4 weeks, patients could resume to their usual CCT	None
Damstra RJ *et al.* (41)	2009	Netherlands	Prospective	10	Campisi staging of lymphedema	5.3 [3–14]	Water displacement and arm circumference (arm volume difference)	SF-36	Lymphoscintigraphy	12	Compression bandage immediately after surgery and arm elevation. Patients resumed to their usual CCT during follow-up	NA
Brahma B *et al.* (42)	2021	Japan	Cross-sectional	70	ISL, lymphoscintigraphy	NA	Arm circumference (UEL index)	LeQOLiS	–	7.4	Elastic compression bandage immediately after surgery until wound healing, hereafter CCT class II followed up with a physical therapist	Infection, four patients with lymphedema progression
Roh S *et al.* (43)	2023	Japan	Retrospective	25	ISL	5 [1–16]	Arm circumference (interlimb volume ratio)	–	–	6	NA	NA
Ciudad P *et al.* (44)	2023	Peru	Retrospective	18	ISL	39.2±13	Arm circumference (CRRs)	–	–	12	CCT 5 days after surgery	None
Fuse Y *et al.* (45)	2022	Japan	Retrospective	23	ISL	37.5±24.488; 88.28±52.11	Arm circumference (arm volume difference)	–	–	8.5 12	CCT immediately after surgery	NA
Park JK *et al.* (46)	2022	Korea	Retrospective	80	ISL, lymphoscintigraphy	5.72±6.86	Arm circumference (arm volume reduction)	Lymph-ICF	Lymphoscintigraphy, ICG-L	12	CCT immediately after surgery	NA
Seki Y *et al.* (47)	2019	Japan	Retrospective	30	ISL	3.1 [0.3–10.3]; 1.6 [0.3–4.4]	Arm circumference (UEL index)	–	–	12; 12	CCT 1 week after surgery	NA
Winters H *et al.* (48)	2019	Netherlands	Retrospective	12	NA	7.8 [2–19]	Water displacement (arm volume difference)	LYMQOL	–	12	CCT immediately after surgery for 1 week, with elevation of the arm during nighttime. CCT continued for 3 months	None
Engel H *et al.* (49)	2018	Taiwan	Retrospective	23	Cheng Lymphedema Grading System	1.4	Arm circumference (arm volume difference)	–	–	9.7	Admittion for 3 days to decrease mobility. Two weeks rehabilitation program. CCT on month after surgery, continued for 2 months and then discontinued	NA
Winters H *et al.* (50)	2017	Netherlands	Retrospective	29	Campisi staging of lymphedema	9 [2–39]	Water displacement (arm volume difference)	LYMQOL	–	12	CCT immediately after surgery with elevation of the arm. CCT continued for 6 months	Cellulitis in two patients
Gennaro P *et al.* (51)	2016	Italy	Retrospective	40	ISL	4.4±4.1	Arm circumference (sum of circumference)	Self-developed QOL	–	12	Usual care continued immediately after surgery. Patients encouraged to undergo lymphatic drainage and CCT for 12 months following surgery	None

Unless otherwise stated, values are reported as mean ± standard deviation, median [interquartile range], or mean. LVA, lymphovenous anastomosis; ISL, International Society of Lymphology; ADB, arm dermal backflow; CCT, controlled compression therapy; NA, not available; ICG-L, indocyanine green lymphography; UEL, upper extremity lymphedema; LYMQOL, Lymphedema Quality of Life; VAS, Visual Analog Scale; IGC, indocyanine green; SF-36, Short Form-36; CRR, circumference reduction rate; QOL, quality of life.

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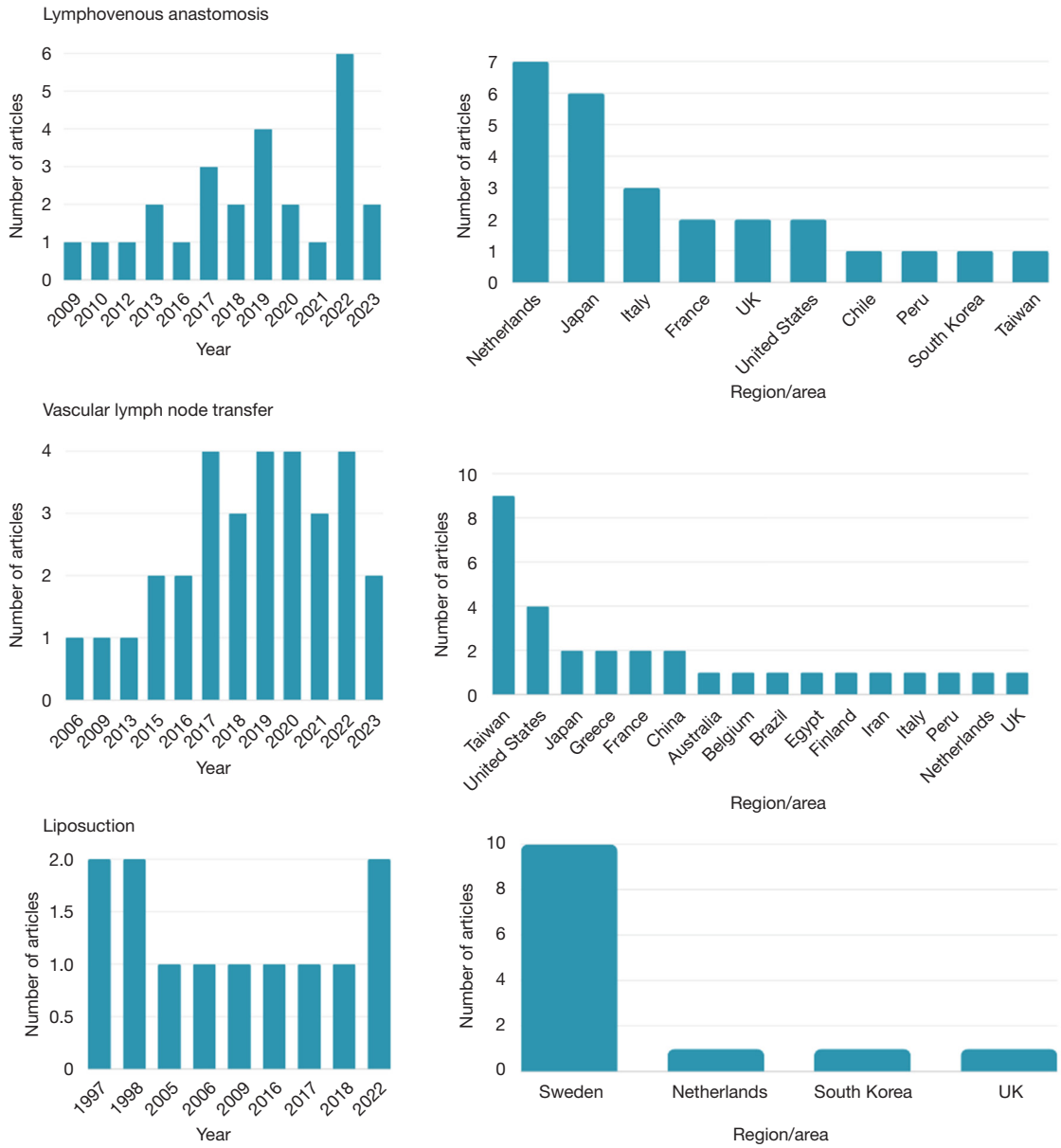

Figure 2 Graphical presentation of the geographical distribution amongst published data, and year of publication for studies on LVA, VLNT, and liposuction. LVA, lymphovenous anastomosis; VLNT, vascularized lymph node transfer.

contributing regions/areas included Italy (three articles) (27,29,51), France (two articles) (35,38), United Kingdom (two articles) (32,33), United States (two articles), Chile (one article) (28), Peru (one article) (44), Korea (one article) (46) and Taiwan (one article) (49), see *Figure 2*.

LVA surgery was performed in a total of 914 patients. Sample sizes ranged from 10 to 89 individuals. On average, the duration of lymphedema was 4.7±1.9 years, and the median follow-up period extended to 12 months, ranging from 6 to 60 months. The ISL classification system, utilized to evaluate lymphedema severity, was applied in 16 out of 26 articles (61.5%). In this classification, 12.2% of cases were ISL stage I, 73.3% stage II, and 17.7% stage III. A significant number of studies further divided stage II into sub-groups, with 42.1% classified as stage IIa and 25.3% as stage IIb. Other classifications systems employed, included the Campisi staging of lymphedema (n=5) (35,37,40,41,50), lymphoscintigraphy (n=5) (28,29,34,42,46), ICG-L (n=3)

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(30,32,34), Arm Dermal Backflow Scale (n=1) (20), and Cheng Lymphedema Grading System (n=1) (49).

Surgery was primarily performed using local anesthesia in 16 articles (76.2%). On average, there were 2.67±1.4 anastomoses performed per patient, and the mean surgery duration was 169.7±65.2 minutes. Ten articles reported no complications following LVA. Others reported the development of cellulitis (three articles) and lymphedema progression (one article).

All 26 articles evaluated the efficacy of LVA by monitoring changes in arm volume. Additionally, 11 articles provided insights into the patients' quality of life (20,30-32,34,36,41,42,46,48,50), and three articles examined alterations in lymphatic flow (29,41,46). Patients were followed for a mean period of 14 months, with the majority having a follow-up period of 12 months. The longest follow-up duration was 60 months, however results are presented as the mean volume reduction from combined 1-, 3-, and 5-year follow-ups (29), While they report sustained volume reduction over the 5-year study period, long-term data remains limited across the included studies.

Arm volume following LVA

Arm volume measurements in the included articles were conducted using three distinct methods: manual arm circumference (n=20) (20,27-31,34-36,38,39,42-47,49-51), perometer (n=4) (32,33,37,40), and water displacement (n=3) (41,48,50). Manual arm circumference measurements involved assessing the arm circumference at several predefined points to assess changes in arm circumferences or calculate total arm volume using the formula of a blunt cone. Some articles used this volume measure to calculate the excess arm volume, comparing the lymphedematous arm with the unaffected one. A perometer is a device that employs optical scanning or laser technology to capture limb contours and provide volume measurements (52). In contrast, the water displacement method is a volumetric technique that involves submerging the arm in a water basin. The volume of displaced water corresponds to the arm's volume measured in mL (53).

While arm volume is assessed using only three methods, the presentation of their findings exhibited substantial variability, with 20 different approaches. The UEL index, initially introduced by Yamamoto *et al.*, was the most common method for presenting arm volume (54). This index incorporates arm circumferences relative to the patient's body mass index (BMI):

$$\text{UEL index} = \frac{C_1^2 + C_2^2 + C_3^2 + C_4^2 + C_5^2}{\text{BMI}} \quad [1]$$

Here, C_{1-5} represents the circumferences in five areas of the upper extremity, and BMI is the patient's BMI. However, despite being the most frequently employed method, only six studies utilized this approach. The remaining articles present volume changes in various formats, including ratios, mL, cm^3, or percentages.

Upon conducting the data analysis, the initial assessment of the included studies indicated a notable variation in effect sizes amongst the articles that reported data for the UEL index. The I^2 statistic was calculated to quantify this heterogeneity, yielding a value of 0.89, indicating substantial heterogeneity among the studies. Consequently, it was determined that a meta-analysis was unsuitable for this review, and instead, a narrative synthesis was conducted. Across the six studies using the UEL index, the unweighted mean revealed a slight rise of 1.9±11.3. In contrast, studies focusing on percentage-based relative volume reduction presented an average decline of 27.6%±30.9% in excessive arm volume. Overall, the range of results across the reviewed studies was broad, spanning from an 87 mL increase to a 93.5% relative reduction in excess arm volume, underscoring both the diversity in outcomes and the varied methods of reporting within this research area.

Patients' quality of life after LVA

In evaluating patients' quality of life, the Lymph-ICF questionnaire was the predominant patient-reported outcome measure (PROM) used in five articles (20,30,31,36,46). Other PROMs included Lymphedema Quality of Life (LYMQOL) (n=2) (32,48), LymphQol (n=1) (50), LeQOLiS (n=1) (42), Short Form-36 (SF-36) (n=1) (41), Visual Analog Scale (VAS) (n=1) (34), and a self-developed questionnaire addressing clinical condition and quality of life (n=1) (51). Patient responses to the Lymph-ICF questionnaire generate a total score within each scale, ranging from 0 to 100, with 0 being the highest health-related quality of life and 100 reflecting the lowest. The smallest real difference has been calculated for each scale to assess clinically significant changes, establishing the minimum score change required to be clinically meaningful for the patients (55). Looking at the Lymph-ICF scores, the mean total score across the studies was 44.5±4.2 pre-operatively and 24.8±7.1 at follow-up, indicating a significant improvement of 19.7±6.8 points. physical function score changed from 48.5±0.7 to 23.0±14.1, mental function from 40.5±2.1 to 15.5±7.8 post-operative,

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mobility activities from 42.5±2.1 to 21.5±14.9 at follow-up, household activities from 48.5±5.0 to 31.0±0.0 post-operative, and life and social activities from 41.0±0.0 to 20.5±0.5, all non-significant. For a comprehensive overview of the PROMs and their outcomes in the included articles, please see Tables S2-S9.

Lymphatic flow following LVA

Only three articles within this review of LVA provided data on changes in lymphatic flow, evaluated with ICG-L or lymphoscintigraphy (29,41,46). The velocity of ICG was calculated from video recordings as the distance traveled divided by the time elapsed (cm/min) (46). In the case of lymphoscintigraphy, the lymphatic transport index (LyTI) was evaluated and compared to a scale where 0 was considered a completely normal condition and 45 a completely pathological condition (29,41). The ICG-L was only assessed prior to LVA, however, the article found a positive correlation between pre-operative ICG velocity and post-operative volume reduction, indicating that a higher velocity before surgery might lead to a better outcome following surgery (46). Boccardo *et al.* presented a significant improvement in lymph flow following LVA, with a decrease of LyTI from 31.7±9.4 to 11.2±1.9 at 18 months follow-up (29). On the other side, Damstra *et al.* reported no significant alteration in lymphatic flow with a decrease from 43.0 [28–45] to 42.2 [30–43] (41).

Patency of anastomoses

Four studies additionally assessed the patency of anastomoses during follow-up appointments, with 76.5% of the anastomoses confirmed as patent and at least one patent LVA found in 82.8% of the patients. These evaluations were performed using ICG-L, which involved observing the flow of ICG dye through the vessels beneath the surgical scars (20,30,48,49).

The effect of VLNT

Our review included 31 studies (40.3%) published between 2006 and 2023, examining VLNT for BCRL, see *Table 5*. The studies were globally diverse, with notable contributions from Taiwan (nine studies) (49,56-63), United States (four studies) (64-67), as detailed in *Figure 2*. The study designs comprised 14 retrospectives (8,44,49,56,60,61,68-75), 13 prospectives (57-59,62-67,76-79), two randomized controlled trials (5,19), and two of unspecified designs (80).

The study population involved 972 patients, ranging from ten to 100 per study, with a mean lymphedema duration of 3.9±1.6 years prior to surgery. Notably, one study included two male patients (65). For evaluating the degree of lymphedema, the primary classification was the ISL, used in 15 articles (5,19,44,58,61,64,65,68,70,72,77-81). Other grading systems included the Cheng Lymphedema Grading System (three studies) (49,56,60), M. D. Anderson Scale (one study) (67), Taiwan Lymphoscintigraphy Staging (one study) (59), a modified grading system without further specification (one study) (62), and self-developed classification (three studies) (8,69,74). None of the patients were ISL stage 0. The breakdown of stages was as follows: 11.1% stage I, 74.9% stage II, and 14.1% stage III. Among these, only two studies differentiated between the subcategories of stage II, reporting 6.8% of patients stage Iia, and 7.6% stage IIb.

The majority of studies, 29 studies, used the groin as donor site for vascular lymph nodes. Alternative donor sites included submental (six studies) (49,56,57,59,60,62), gastroepiploic (four studies) (44,61,64,73), subclavicular fossa (three studies) (61,64,77), and lateral thoracic vascularized lymph nodes (three studies) (64,71,81). The axilla was the primary recipient site, mentioned in 21 articles (5,8,19,44,64-72,74-81), followed by the wrist (14 studies) (19,44,49,56-63,68,77,78), elbow (five studies) (19,49,58,62,77), forearm (one study) (73), and unspecified (one study) (64). Fourteen studies combined VLNT with breast reconstruction, predominantly using the deep inferior epigastric perforator (DIEP) flap (10 studies) (19,44,49,67,70,75,76,78,80,81), with variations such as the DIEP or transverse rectus abdominis muscle (TRAM) flap (two studies) (66,69), DIEP or latissimus dorsi (LD) flap (one study) (72), and DIEP, TRAM, or superficial inferior epigastric artery (SIEA) flap (one study) (71). The average surgery duration was 210.7 minutes, ranging from 40.4 to 515 minutes, varying based on the inclusion of breast reconstruction and procedure. Each patient received, on average, 3.2 lymph nodes. Four articles described a partial flap loss in three patients and total flap loss in four (19,44,64,75). Patients were followed for a mean period of 36.3 months, ranging from 6 to 79 months.

However, in studies with extended follow-up, the access to long-term data remains limited, mainly due to substantial loss to follow-up and the observational character of the studies (71,72).

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Table 5 Summary of included articles on VLNT

Author	Year	Region/area	Study design	No. of patients	Method for lymphedema evaluation	Lymphedema duration (years)	Donor-site	Recipient-site	Volume measurement method	Quality of life measure	Lymph flow measure	Follow-up duration (months)
Dionyssiou D *et al.* (5)	2016	Greece	RCT	18	ISL	Inguinal	Inguinal	Axillary	Arm circumference	Self-developed	Lymphoscintigraphy	18
Becker C *et al.* (8)	2006	France	Retrospective	24	Self-developed	Few months n=5; 2.4, n=7; 7.4, n=11	Inguinal	Axillary	Not specified	NA	Lymphoscintigraphy	8.3
Abdelfattah U *et al.* (19)	2021	Egypt	RCT	15	ISL	3.2	Inguinal	Axillary, elbow, wrist	Arm circumference	VAS	NA	30.07±2.6
Ciudad P *et al.* (44)	2023	Peru	Retrospective	22	ISL	NA	Gastroepiploic, inguinal	Axillary, wrist	Arm circumference	NA	NA	12
Engel H *et al.* (49)	2018	Taiwan	Retrospective	45	Cheng Lymphedema Grading System	2.9	Inguinal, submental	Elbow, wrist	Arm circumference	NA	NA	19.1±5.3
Aljaaly H *et al.* (56)	2019	Taiwan	Retrospective	15	Cheng Lymphedema Grading System	2.4	Submental	Wrist	Arm circumference	LYMQOL	NA	17
Ho OA *et al.* (57)	2018	Taiwan	Prospective	A: 13; B: 30	Cheng Lymphedema Grading System	A: 3.3; B: 4.3	Inguinal, submental	Wrist	Arm circumference	NA	NA	NA
Cheng MH *et al.* (58)	2013	Taiwan	Prospective	10	ISL	NA	Inguinal	Wrist, elbow	Arm circumference	NA	NA	39.1
Lin CY *et al.* (59)	2020	Taiwan	Prospective	100	Taiwan Lymphoscintigraphy Staging	6.6	Inguinal, submental	Wrist	Arm circumference	LYMQOL, knowledge of lymphedema, PHCA-seeking behavior	NA	6
Francis EC *et al.* (60)	2022	Taiwan	Retrospective	10	Cheng Lymphedema Grading System	4.5	Inguinal, submental	Wrist	Arm circumference	LYMQOL	NA	78±34.2
Ciudad P *et al.* (61)	2020	Taiwan	Retrospective	29	ISL	NA	Inguinal, supraclavicular, gastroepiploic, ileocecal	Wrist	Arm circumference	NA	NA	24
Patel KM *et al.* (62)	2015	Taiwan	Prospective	15	Modified lymphedema grading	3.1	Inguinal, submental	Axillary	Arm circumference	LYMQOL	NA	12
Lin CH *et al.* (63)	2009	Taiwan	Prospective	29	NA	NA	Inguinal	Wrist	Arm circumference	NA	NA	11
Brown S *et al.* (64)	2022	United States	Prospective	65	ISL	NA	Gastroepiloic, lateral thoracic system, inguinal, supraclavicular	Axillary, distal placement	Arm circumference, perometer	LLIS, ULL-27	NA	24
Gratzon A *et al.* (65)	2017	United States	Prospective	50	ISL	4.9	Inguinal	Axillary	Arm circumference	LYMQOL	NA	12
Nguyen AT *et al.* (66)	2015	United States	Prospective	29	NA	3.3	Inguinal	Axillary	Perometer	NA	NA	12
Chang EI *et al.* (67)	2020	United States	Prospective	21	M. D. Anderson Scale	NA	Inguinal	Axillary	Perometer	NA	NA	23.3±17.5
Maruccia M *et al.* (68)	2019	Italy	Retrospective	A: 18; B: 21	ISL	A: 2.2; B: 2.1	Inguinal	Axillary, wrist	Arm circumference	LYMQOL	NA	24
Yang Z *et al.* (69)	2017	China	Retrospective	10	Self-developed	NA	Inguinal	Axillary	Arm circumference	Self-developed	NA	12
Winters H *et al.* (70)	2022	Netherlands	Retrospective	45	ISL	3.65	Inguinal	Axillary	Water displacement	ULL-27	NA	51.1
Rannikko EH *et al.* (71)	2021	Finland	Retrospective	67	NA	3.5	Inguinal	Axillary	Arm circumference	NA	Lymphoscintigraphy	70±17
Dionyssiou D *et al.* (72)	2021	Greece	Retrospective	64	ISL	NA	Inguinal	Axillary	Perometer	VAS	NA	36
Mousavi SR *et al.* (73)	2020	Iran	Retrospective	24	NA	5.6, n=18; 0.42, n=6	Gastroepiploic	Forearm	Arm circumference	NA	NA	48
Arriv L *et al.* (74)	2017	France	Retrospective	15	Self-developed	8	Inguinal	Axillary	Arm circumference	NA	NA	Not specified, maximum 42 months
De Brucker B *et al.* (75)	2016	Belgium	Retrospective	25	NA	3.5	Inguinal	Axillary	Arm circumference	ULL-27	NA	29
Akita S *et al.* (76)	2017	Japan	Prospective	A: 13; B: 14	NA	NA	Inguinal	Axillary	Arm circumference	NA	Lymphoscintigraphy	A: 18.5±1.9; B: 19.5±1.5
Ngo QD *et al.* (77)	2020	Australia	Prospective	10	ISL	2.6	Inguinal, supraclavicular fossa	Axillary, elbow	Arm circumference	NA	Lymphoscintigraphy, L-Dex	–
Montag E *et al.* (78)	2019	Brazil	Prospective	24	ISL	3.6	Inguinal	Axillary, wrist	Arm circumference	NA	NA	24
Liu HL *et al.* (79)	2018	China	Prospective	30	ISL	6	Inguinal	Axillary	Arm circumference	NA	Lymphoscintigraphy	22.1±7.8
Di Taranto G *et al.* (80)	2023	United Kingdom	Not specified	26	ISL	NA	Inguinal	Axillary	Arm circumference	LYMQOL	NA	42.5±25.6
Akita S *et al.* (81)	2022	Japan	NA	42	ISL	NA	Inguinal, lateral thoracic	Axillary	Arm circumference	NA	ICG-L	6

†, study population includes two men. Unless otherwise stated, values are reported as mean ± standard deviation or mean. VLNT, vascularized lymph node transfer; RCT, randomized controlled trial; ISL, International Society of Lymphology; NA, not available; VAS, Visual Analog Scale; LYMQOL, Lymphedema Quality of Life; PHCA, professional healthcare advice; LLIS, Lymphedema Life Impact Scale; ULL-27, Upper Limb Lymphedema 27; ICG-L, indocyanine green lymphography.

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Arm volume following VLNT

All studies, except for one, assessed the effectiveness of VLNT on arm volume. The main outcome measurement was manual arm circumferences, used in 28 articles, with additional methods like perometry (three studies) (66,67,72) and water displacement (one study) (70). Even though manual measurements are commonly used, the way of measuring the patient's arm, and hereafter presenting the data, differ amongst the studies. Most commonly, the arm circumferences were measured ten cm above and below the elbow, some also measured at the level of the axilla, wrist and mid-palm, however, studies are inconsistent. Most common, changes in arm volume were reported as circumference reduction rates (CRRs), calculated as follow (19):

$$\mathrm{CRR} = \left(1 - \frac{\Delta\text{Arm Circumference}_{\text{After surgery}}}{\Delta\text{Arm Circumference}_{\text{Before surgery}}}\right) \times 100\% \quad [2]$$

Where $\Delta\text{arm circumference}_{\text{before}}$ represents the difference in arm circumferences between the lymphedematous and unaffected arm before surgery, and $\Delta\text{arm circumference}_{\text{after surgery}}$ presents the difference in arm circumference between the lymphedematous and unaffected arm after surgery. Even though a substantial number of articles (nine papers) used the CRR (19,44,49,56,61,63,65,68,79), manual circumferences measures were overall performed in eleven different ways, with different circumference points, presenting either individual circumference differences or the sum of circumferences, for further calculations of the CRR. Even though a substantial number of articles reported their volumetric outcome as CRR, due to limited reporting of data in the included studies, no meta-analysis was conducted as available data was limited, making it impossible to conduct. An unweighted mean of their circumferential reduction rate, a mean relative volume reduction of 43.6%, was seen. However, this number should be interpreted with caution due to the potential risk of bias and unweighted mean.

Patients' quality of life following VLNT

A total of 14 studies examined the impact on quality of life (5,19,56,59,60,62-65,68-70,75,80), primarily evaluated using the LYMQOL questionnaire (seven studies) (56,59,60,62,65,68,80). Due to a considerable degree of heterogeneity in the reported outcomes, with an I^2 of 0.95, a meta-analysis was not conducted for LYMQOL scores. Other tools included the Upper Limb Lymphedema 27 (ULL-27) in two studies (64,75), two studies using VAS for pain, function, and arm heaviness (5,19), and the Lymphedema Life Impact Scale (LLIS) in one study (64). Custom-developed questionnaires were used in two studies, with one study also incorporating lymphedema knowledge and health-care seeking behavior questionnaires (59,63,69). Even though a meta-analysis was not possible, all articles reported an improvement in patient-reported outcomes, with an overall improvement of 3.7 points for total quality of life; computed as an unweighted mean for LYMQOL (20,30,31,36,46). Generally, patients were experiencing a greater overall quality of life, with improvement in their lymphedema symptoms, arm function, bodily appearance, and mood.

Lymphatic flow after VLNT

A total of seven articles evaluated the lymph flow following surgery, primarily through lymphoscintigraphy, ICG lymphography or L-Dex score (5,8,71,76,77,79,81). Lymphscintigraphy results were evaluated as activity in implanted lymph nodes, or semi-quantified as the transport index (TI). Articles showed an improvement in lymph flow, and a single article demonstrated an absolute improvement in TI of 3.3, with a significant decrease from 29.0±14.4 to 26.0±14.2 (71). For the results qualitatively described, "improved", "some improvement" or "effectiveness of lymph nodes" were used as their main outcome. A mean 66.6% of the patients were found to have some improvements or visible lymph nodes following surgery, evaluated by lymphschintigraphy findings. Looking at ICG-lymphangiography, articles mainly subjectively described improvements of dermal backflow patterns, without further description (76,81).

The effect of liposuction

Twelve (15.6%) of the included studies investigated the effect of liposuction on treating BCRL, see *Table 6*. The studies published in the period 1998 and 2023 had a geographical distribution between Sweden (10 studies) (82-91), the Netherlands (one study) (92), and South Korea (one study) (93), see *Figure 2*. Eleven out of 12 studies were prospective studies (82-92), while one was retrospective (93). The outcomes for efficacy assessment of liposuction were excessive arm volume reduction (12 articles) (82-93), improvement in health-related quality of life (two articles) (83,88), changes of soft-tissue composition (one article) (89), improvement in lymph flow (one article) (84), reduction in erysipelas incidents (two

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Table 6 Summary of included articles on liposuction

Author	Year	Region/area	Study design	Included patients, n	Method for lymphedema evaluation	Lymphedema duration (years)	Volume measurement method	Quality of life measure	Lymph flow measure	Follow-up time (months)	Post-operative management	Complications
Lee D *et al.* (82)	2016	Sweden	Prospective	130	NA	NA	Water displacement	NA	NA	6	NA	NA
Brorson H *et al.* (83)	2006	Sweden	Prospective	35	Pitting-test	8.4±7.4	Water displacement	VAS, NHP, PGWB, HAD	NA	12	CCT immediately after surgery	NA
Brorson H *et al.* (84)	1998	Sweden	Prospective	11	NA	7.5±6.2	Water displacement	NA	Indirect lymphoscintigraphy	12	CCT immediately after surgery	NA
Brorson H *et al.* (85)	1998	Sweden	Prospective	14	NA	7.8±6.8	Water displacement	NA	NA	12	CCT immediately after surgery	No complications
Karlsson T *et al.* (86)	2022	Sweden	Prospective	18	MD Anderson classification, ICG-L, Arm dermal backflow	9 [5–7]	Water displacement	NA	NA	12	CCT immediately after surgery	NA
Hoffner M *et al.* (87)	2018	Sweden	Prospective	105	Pitting-test	10±7.4	Plethysmography	NA	NA	60	CCT immediately after surgery	No complications
Hoffner M *et al.* (88)	2017	Sweden	Prospective	60	Pitting-test	10±1.3	Water displacement	SF-36	NA	12	CCT immediately after surgery	No complications
Bagheri S *et al.* (89)	2005	Sweden	Prospective	20	Pitting-test	11±8.7	Water displacement	NA	NA	12	CCT immediately after surgery	NA
Brorson H *et al.* (90)	1997	Sweden	Prospective	12	NA	6 [1–16]	Water displacement	NA	NA	12	CCT immediately after surgery	No complications
Brorson H *et al.* (91)	1997	Sweden	Prospective	28	NA	7 [1–23]	Water displacement	–	–	12	CCT immediately after surgery	Paraesthesia in operated arm (n=1), pneumonia (n=1), dyspnea (n=1), superficial abrasion caused by compression garment (n=2), erysipelas (n=2)
Damstra RJ *et al.* (92)	2009	Netherlands	Prospective	37	Pitting-test	8.2 [1–24]	Water displacement	NA	NA	12	CCT immediately after surgery	No complications
Kim RS *et al.* (93)	2022	South Korea	Retrospective	17	NA	NA	Arm circumference	NA	ICG-L	12	CCT immediately after surgery	NA

Unless otherwise stated, values are reported as mean ± standard deviation or median [interquartile range]. NA, not available; VAS, Visual Analog Scale; NHP, Nottingham Health Profile; PGWB, Psychological General Well-Being Index; HAD, Hospital Anxiety Depression Scale; CCT, controlled compression therapy; SF-36, Short Form-36.

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articles) (82,90), and improvement in tissue tonometry (one article) (89).

Sample sizes ranged from 12 to 130 patients, with a total of 487 patients undergoing liposuction. The mean duration of lymphedema was 9.3±2.0 years before surgery. Five studies applied the pitting test for lymphedema assessment. This test involves exerting pressure on the patient's arm for one minute (87). Subsequently, they assess whether a temporary indentation or pit forms in the skin and, if so, measure its depth in millimeters to quantify the degree of pitting. Only patients presenting with no- or minimal pitting were offered liposuction. Two studies used the M. D. Anderson Scale, ICG-L, and Arm Dermal Backflow Scale for evaluation (86,93).

A combination of dry liposuction, power-assisted liposuction, and tumescent liposuction was applied across all studies; overall, a mean total volume of 1,596±332.3 mL was aspirated during surgery. In recent times, power-assisted liposuction ad modum Brorson has become the most accepted method (94).

The I^2 statistic was calculated to quantify the heterogeneity of volume measures, yielding a value of 0.99, indicating substantial heterogeneity among the studies. Consequently, a meta-analysis was unsuitable. Across studies, an unweighted mean reduction of excess arm volume of 1,667.5±132.2 mL was accomplished. Arm volume was evaluated using the water displacement method in ten studies (82-86,88-92); a single study also used DEXA scans (86), another study used plethysmography (87), and the last study used arm circumference measures (93). Only one study presented the surgery duration with a median of 122 (range, 70–220) minutes (91).

A total of 10 studies followed their patients for 12 months (83-86,88-93); a single study had a follow-up time of only 6 months (82) and a single study for 5 years (87), all indicating effective reduction of arm volume, including long-term effects. Ten out of 12 articles described their post-operative routine, all involving immediate compression garments following surgery with minor variations. Brorson *et al.* also presented the consequences of discontinuing the compression garment with increased arm volume as a consequent (85). Only one study described complications, including paraesthesia in the operated arm, pneumonia, dyspnea, and superficial abrasion caused by compression garments and erysipelas (91). None the studies described any major complications.

One article investigated the effect of liposuction on lymphatic flow, and two articles presented the impact on quality of life, with significant improvements (83,88). Brorson *et al.* presented a study on patients' quality of life following liposuction with a statistically significant improvement in shoulder range of motion and a decrease in VAS score regarding pain, hand and arm swelling, and difficulties with activity of daily living (ADL) functions during 1-year follow-up. Regarding their results from Nottingham Health Profile, significant improvements were seen in total score, pain, and housework after 1 year. Looking at patients' answers from the Psychological General Well-Being Index and Hospital Anxiety Depression Scale, no significant improvements were seen; however, patients undergoing only conservative treatments had a significantly higher score regarding anxiety when compared to the liposuction group (83). Hoffner *et al.* evaluated the effect on the quality of life using the SF-36 questionnaire and presented a significant improvement at a 1-year follow-up regarding physical functioning, bodily pain, social functioning, mental health, and vitality. An improvement was also seen in their physical and mental component scores, which is an aggregation of the other domains. The results were also compared to normative data with the Swedish reference score from the SF-36 questionnaire, and no significant differences were detected after 1 year of follow-up regarding physical functioning, role physical, role emotional, and general health, indicating they were able to normalize the patient's quality of life (88).

Only a single study evaluated the changes in lymph flow following surgery, quantified as the clearance of injected activity during indirect lymphoscintigraphy. The study concluded no lymph flow change after liposuction and compression garments. At 12 months follow-up, there was a slight increase in activity of the upper arm; otherwise, no differences were found, indicating no further damage to the lymphatic system following liposuction (84).

Upon data evaluation, an initial assessment of the included studies revealed substantial heterogeneity in the effect size among the selected trials with normally distributed data (87,88). The heterogeneity assessment included calculating the I^2 statistics quantifying the proportion of total variation in effect sized due to heterogeneity rather than chance. In this analysis, the I^2 statistics yielded a value of 0.99, indicating significant heterogeneity between the two studies. It was determined that a meta-analysis was not appropriate for this review; instead, a narrative synthesis of the included studies was conducted.

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Table 7 Overview of data from included articles, most commonly used outcome measures and raw means

Data overview	LVA	VLNT	Liposuction
No. of patients	914	972	487
Lymphedema duration prior to surgery (years)	4.3	3.8	9.3
Lymphedema classification system	ISL	ISL	Pitting-test
	Stage I–III	Stage I–III	No or minimal pitting
Relative volume reduction (raw means)	27.6%	43.6%	113.7%
Method of volume measure (most frequent)	Arm circumference	Arm circumference	Water displacement
Quality of life measure (most frequent)	Lymph-ICF	LYMQOL	SF-36, VAS
Lymph flow measure	Lymphoscintigraphy	Lymphoscintigraphy	Lymphoscintigraphy
Number of RCT studies	1 (pilot study)	2	0

LVA, lymphovenous anastomosis; VLNT, vascularized lymph node transfer; ISL, International Society of Lymphology; LYMQOL, Lymphedema Quality of Life; ISL, International Society of Lymphology; VAS, Visual Analog Scale; RCT, randomized controlled trial.

Patient characteristics

The articles included in the present study focused on liposuction presented patients with only minimal or no pitting lymphedema, when selecting patients for the procedure. In contrast, studies exploring both LVA and VLNT primarily utilized the ISL classification system when evaluating patient's lymphedema. The range of patients included in these studies spanned from stage I to III, with variable results. Only two randomized controlled trials on VLNT, reported outcomes specific for patients in stage II or a combination of stages II and III, with significant volume reduction, improvement in symptoms, and reduction in infection rate. A single randomized controlled trial on manual or robotic-assisted LVA present no significant volume reduction following surgery, for patients classified primarily at stage II, with a single patient in stage I (20). However, it should be noted that this was a pilot study. See *Table* 7, for summarized data from studies on LVA, VLNT and liposuction.

Ongoing clinical trials

There are currently six ongoing trials investigating the effect of LVA and/or VLNT on BCRL (89,95-100). Two are designed as randomized controlled trials (95,98), three as randomized parallel assignments (97,99,100), and a single pilot study (96). Their outcomes include the effect on arm volume, arm circumference, quality of life, and shoulder mobility. The most extended follow-up planned is 10 years in a single study (100), which investigates the effect of LVA and VLNT on quality of life measured with LYMPH-ICF-UL, LYMPH-Q, EQ-5D-5L, and VAS questionnaires. The ongoing trials are geographically located in the Netherlands (95), Denmark (96), the United Kingdom (97), Sweden (98), Norway (99), and Switzerland (100).

Future perspectives

LVA

In the lastest articles from 2023 to 2021, a noticable difference was observed in planning methods for LVA surgery compared to the other articles. More studies utilized ultrasound, including a single study with ultra-high frequency ultrasound, in the planning of LVA surgery. Surgeons are using ISL more frequently for evaluation the lymphedema, and arm volume were evaluated with manual arm circumference. However, various outcomes were epmloyed when presenting results, including the UEL index, interlimb ratio, circumferenctial reduction rate, relative excess volume, among others. As for PROMs, different questionnaires were applied across the studies. Overall, articles shared a similar follow-up duration, except for one with longer follow-up with 60-month, reporting sustained arm volume reduction. However, specific results for this period were not provided, presenting challenges for a thorough assessment (29).

VLNT

The latest articles from 2023 to 2021 do not notably differ from the other articles in terms of measurement methods,

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planning methods, or patient populations. Two of the studies have the longest follow-up period among included articles, but due to substantial loss to follow-up, limites data is available to assess long-term effects. Most frequently, studies evaluate arm volume using arm circumferences however, measurements are still performed at different levels, and used to evaluate arm volume with different calculations and presentations.

Liposuction

Among the limited included articles, there is consistency in the reported results across all years of published data. The shift in surgical techniques has moved away from the "dry technique" trend, now favoring the tourniquet combined with the tumescence technique to minimize blood loss in (86,87). Regarding follow-up, outcome measures and patient population, no significant changes in trends has been observed in recent years.

Discussion

The surgical management of BCRL is rapidly evolving and showing promising results. However, the existing evidence is a product of studies with large heterogeneity limiting comparability and meta-analysis. Future studies should focus on building on the existing evidence in order to strengthen the evidence on the field of surgical BCRL treatment.

Liposuction

Liposuction has emerged as an effective method for volume reduction in non-pitting lymphedema, with a significant reduction in arm volume and improved quality of life, compared to compression therapy (83). Although the studies exhibit moderate to high risk of bias, the results are remarkable. Furthermore, a long-term study indicates a sustained reduction in volume, confirming the enduring effectiveness of liposuction for treating lymphedema (87). However, it is important to note that liposuction does not address the underlying lymphatic dysfunction. Consequently, continuous compression garment usage is necessary to maintain the reduced arm volume (85). Another key aspect is the observation that dry liposuction does not further exacerbate damage to the lymphatic channels of the lymphedematous arm, emphasizing its safety and efficiency (84).

Regarding the impacts on health-specific quality of life and its long-term result needs further investigation using disease-specific questionnaires to provide deeper insight into its effect, as studies have only been conducted using unspecific questionnaires (83,88).

VLNT

VLNT intend to rebuild the lymphatic pathways, improving lymphatic function. It aims to address the underlying pathophysiology of lymphedema; however, to our knowledge, whether the lymph node transfer lead to lymphangiogenesis and increased drainage has still not been shown or confirmed. Even though most studies are observational with a high risk of bias, the included studies indicated promising results in limb volume reduction and symptom relief, with significant improvement in two well-conducted randomized controlled trials (5,19). Patients experiencing substantial improvements originate from ISL stages II and III, a group covering patients with and without active pitting lymphedema. However, no statistical differences were found in limb reduction between patients at stages I, II, or III, which may indicate an effective procedure for both patients with mild to more developed stages of lymphedema (72). When combined with breast reconstruction, the effect on limb reduction may be significantly greater compared to transplanted lymph nodes alone (19,49). These results were derived as secondary outcomes from a sample of 15 patients in the randomized controlled trial (RCT) study (19). Additionally, an improved patient-reported quality of life and reduced rate of skin infections has been reported, further emphasizing the positive outcomes of the intervention. A cost analysis revealed that VLNT was significantly less expensive compared to lifelong conservative treatment with physiotherapy and compression. Additionally, the overall expenses increase when accounting for the costs associated with sick leave and antibiotics for recurring lymphedema-related infections (5). Therefore, an intervention like VLNT, which may reduce infection rates and potentially decrease sick leave, calls for further systematic studies to justify its use.

While the potential risk of donor site lymphedema from VLNT is a significant concern, the included studies only report two cases of lower extremity swelling as a complication of the procedure (57,66). The complications reported were primarily related to issues with the microvascular flap, such as flap necrosis, infections, and lymphorrhea, rather than lymphedema at the donor site. It is necessary to consider the possibility of reporting bias,

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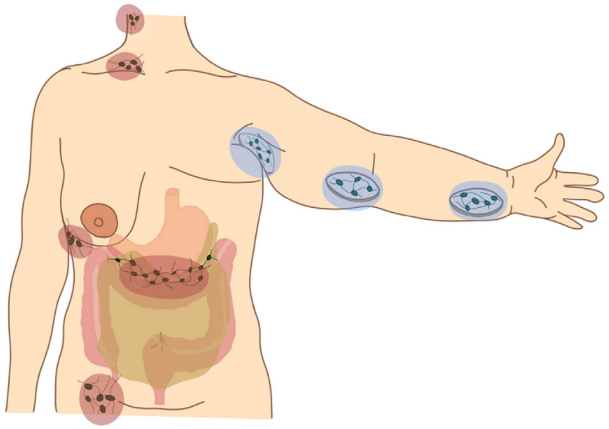

Figure 3 Illustration of the different donor sites (marked with red circles) and recipient sites (marked with blue circles) for VLNT. Donor sites include submental, supraclavicular, omentum, lateral thoracic and inguinal lymph nodes. Recipient sites include axil, elbow and wrist. VLNT, vascularized lymph node transfer.

as a limited number of studies reported an approach for evaluating donor-site lymphedema. Additionally, since our primary focus did not include complications, the articles were not selected based on their reporting of such issues. Thus, this review may not fully represent the actual rate of complications.

Another issue of great discussion is the preferred donor- and recipient site for lymph nodes, see *Figure 3*. Vascular submental lymph nodes may lead to a significantly greater volume reduction than inguinal lymph nodes (57). Furthermore, patients undergoing inguinal VLNT are at greater risk for donor-site lymphedema. In the study conducted by Ho *et al.*, lymphedema of the legs manifested in 7.7% of patients undergoing inguinal VLNT harvest in their study subjects, translating to two cases within a group of thirteen patients (57). Considering the available evidence from a study involving 43 patients, submental lymph nodes seem superior compared to the inguinal lymph nodes, unless other circumstances favor the groin, as the donor site, such as breast reconstruction combined with VLNT or if the patient prefers to avoid scarring on their neck (19,57). Examples on advantages and disadvantages regarding donor- and recipient sites as described in the literature are presented in *Table 8* (19,57,58,61,101).

Regarding the choice of recipient site for lymph node transfer, current studies do not show a significant difference in outcomes between proximal and distal locations. Axillary insertion combined with breast reconstruction appears to be a favorable option, in instances where this is not relevant, the patient's preference for scar placement should be the primary consideration, given the current evidence (19). Another reason that advocates for axillar placement is in cases of substantial axillary scarring with a restricted range of motion of the shoulder, where a skin flap with lymph nodes might be preferred, and may even aid in decreasing the compression of the axillary vein (68).

LVA

LVA is primarily designed to restore lymphatic drainage. However, as seen in various studies, its effectiveness has been inconsistent. Some studies report limb volume reduction and improvements in symptoms and quality of life, while others have not observed significant changes. Given that most of the data originates from studies with a high risk of bias, it is challenging to asses LVA's impact on arm volume reduction. Notably, there was a prominent improvement in quality of life and arm function in many studies, although not all reported significant volume reduction. Whether this is due to the placebo effect cannot be ruled out, as well-conducted RCT studies are lacking in this field of research. The actual effectiveness of LVA remains unclear, and further research is essential to elucidate its impact. Evidence suggests that LVA might be more effective in the early stages of lymphedema than in the advances stages (37). Most studies focused on patients in stages II and III, while only 12.2% of included patients were stage I, potentially overlooking the full potential of LVA due to selection bias. A potential hurdle involves recruiting patients in the initial stage of lymphedema, given that almost half of those assessed with lymphedema are unaware of their condition (42). This places an increased responsibility on clinicians to actively monitor our cancer patients, aiming to detect the condition early on and provide the opportunity for prompt intervention (59). The overall goal of lymphedema treatment also warrants discussion. While volume reduction is a key objective, symptom relief and improved functionality may be equally important. The only RCT study amongst the included studies did not show significant volume reduction but did report notable improvements in quality of life.

Most studies employed ICG-L before surgery to identify lymphatic vessels leading up to an area of dermal backflow for anastomosis. The technique has been shown to be superior to surgery without pre-operative guidance (27). A novel approach combines ultra-high frequency ultrasound

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Table 8 Overview of advantages and disadvantages regarding donor- and recipient sites for VLNT

VLNT	Donor site					Recipient site		
	Inguinal	Submental	Supraclavicular	Omentum	Lateral thoracic	Axillary	Elbow	Wrist
Advantages[†]	• Known anatomy	• Low risk of donor-site lymphedema	• Low risk of donor-site lymphedema	• No risk of donor-site lymphedema	• Substantial number of lymph nodes	• Possible more effective when combined with breast reconstruction	• Possibly more effective than axillary implantation	• Possibly more effective than axillary implantation
	• May be combined with vascularized free flap for breast reconstruction	• Acceptable scar		• No risk of nerve damage		• Scar is well-hidden		
	• Scar is well hidden			• Rich number of lymph nodes				
	• Substantial number of lymph nodes							
Disadvantages[‡]	• Risk of donor-site lymphedema	• Complex anatomy	Visible scar	• Intra-abdominal procedure with the risk of bowel perforation, pancreatitis, and internal bleeding	• Risk of nerve injury	• Complex anatomy, often impacted by scars from previous surgeries and exposure to radiation	• Visible scar	• Visible scar
	• Risk of seroma formation	• Small skin flap	• Risk of damage to axillary nerve and brachial plexus	• Risk of conversion to open procedure				
	• Bulky flap	• Risk of damage to the mandibular nerve	• Small skin flap	• No skin paddle				

[†], for donor site (57,61), for recipient site (19); [‡], for donor site (57,58,101). VLNT, vascularized lymph node transfer.

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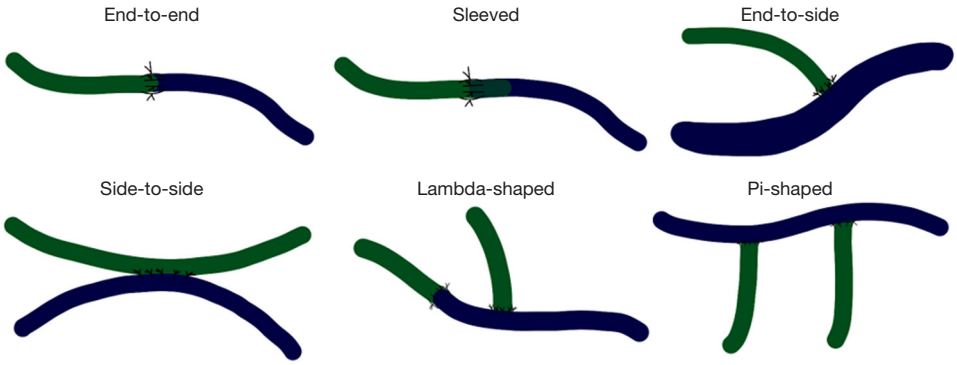

Figure 4 Illustration of different types of anastomoses between lymph vessels and venules, including end-to-end, sleeved, end-to-side, side-to-side, lambda-shaped and pi-shaped anastomoses.

and ICG-L to locate nearby venules. It could potentially optimize and shorten the duration of the procedure. None of the included articles indicated one anastomosis technique superior to another. Opting for end-to-side rather than end-to-end may be driven by variations in vessel caliber and the potential risk of venous backflow. The most frequent type of anastomoses performed was an end-to-end; see *Figure 4* for all types of anastomoses. There is insufficient evidence among the included studies to recommend one technique over the other. A single study indicates significantly greater volume improvements the more anastomoses formed; however, challenges lie in selecting the lymph vessels of dermal backflow and not performing anastomosis on already functioning lymph vessels without blockage.

A shared challenge among lymphedema classification systems is their dependence on subjective assessments and the inherently complex nature of lymphedema. The extent of a patient's lymphedema may vary depending on the region of the arm being evaluated. This variability adds layers of complexity to the accurate diagnosis of lymphedema, a fact echoed in the varied assessment techniques used in the research we examined. Although the pitting test is advantageous for its accessibility and straightforwardness in both execution and evaluation, it is noteworthy that this method was not used in any of the studies concerning LVA or VLNT we reviewed. Nevertheless, the ISL incorporates the pitting test in its lymphedema assessments, see *Table 3*. We would recommend maintaining consistency in using the same classification method in the future, facilitating data comparison.

Treatment algorithm

Based on the knowledge available, we have developed a treatment algorithm built upon evidence-based studies and approaches for optimal management and treatment of BCRL, see *Figure 5*.

Future perspectives

A significant challenge in lymphedema research is the diversity in lymphedema evaluation, measuring methods, and data reporting, making it difficult to compare results across studies. For future research, standardizing these aspects is crucial to better understand the interventions' actual effects. Transparent reporting of pre- and post-intervention data from well-conducted trials, including statistical details, will significantly enhance the research field, especially relevant for studies on LVA and VLNT. In simpler terms, there is an urgent need for thoroughly executed randomized trials with a well-reasoned and calculated study size. These studies should systematically explore the impact of surgery on arm volume and quality of life while providing comprehensive and accurate data reporting.

Other questions that still remain unanswered are the long-term outcome on arm volume following LVA and VLNT, the impact of LVA on earliest stage of lymphedema, the influence of liposuction on health-related quality of life, and a comparative analysis of VLNT and LVA to determine if patients should be recommended VLNT over LVA or combined approach. Lastly, the variations in outcomes based on different donor- and recipient-sites for VLNT remain to be fully explored.

Regarding measuring arm volume changes, reporting the absolute reduction in mL and percentage for arm differences would provide a more concrete metric

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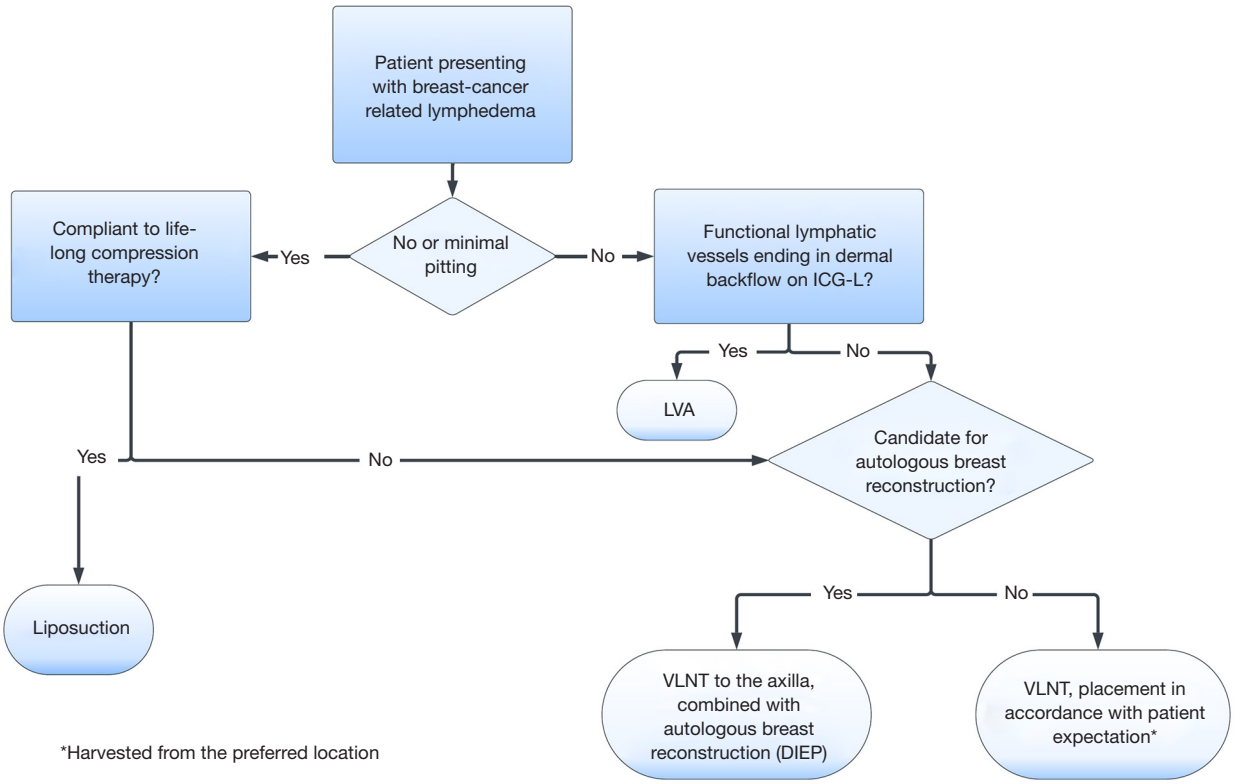

Figure 5 The proposed treatment algorithm based on the available knowledge. ICG-L, indocyanine green lymphography; LVA, lymphovenous anastomosis; VLNT, vascularized lymph node transfer; DIEP, deep inferior epigastric artery flap.

for clinicians and researchers. A systematic review by Hidding *et al.* recommends the utilization of water volumetry for assessing arm volume in breast cancer-related lymphedema (102). This method is highly reliable, exhibiting the lowest variance, standard error of the mean (SEM), and the smallest detectable change (SDC) when compared to tape measurements and perometers. Additionally, perometers are costly instruments compared to water displacement and tape measurements, making them less preferable for primary practice. Moreover, we highlight the importance of screening for BCRL following cancer treatment for early detection and intervention (102).

A COSMIN review identified deficiencies in existing questionnaires for lymphedema patients regarding the quality of life assessments. In response, Klassen *et al.* developed the LYMPH-Q Upper Extremity Module questionnaire to fill this gap and provide a tool with solid content validity for BCRL (103). None of the studies we reviewed utilized this questionnaire, likely because it was only developed in 2021. Nonetheless, we advocate for its future adoption in assessing the quality of life in patients with BCRL.

Conclusions

In conclusion, liposuction is a valuable option in treating BCRL for patients with non-pitting lymphedema, who can accept lifelong compression therapy, where excess volume is the primary concern. VLNT seems to be effective for patients presenting with both pitting- and non-pitting lymphedema and is especially preferred for patients who also are planning to undergo breast reconstruction, however more high evidence studies are needed to confirm the findings. The effect of LVA is more uncertain, but it seems essential to treat the patients in the early stages to achieve a potential impact. Data is based on articles with high risk of bias and is, therefore, of a low level of evidence.

Thus, to summarize, BCRL is a complex disorder with many uncertain elements. Surgical treatments can be effective in suitable patients, but well-conducted clinical studies in the field are still lacking to uncover several unanswered questions.

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Supplementary

Table S1 Search terms and strings for Medline, Embase, Cochrane Library, Google Scholar, and ClinicalTrials.org

Databases	Search terms
Medline	1. exp Breast Cancer Related Lymphedema/
	2. Breast Neoplasms/
	3. Lymphedema/
	4. ((Breast Cancer adj3 Lymphedema*) or (breast neoplasm* adj3 lymphedema*) or (postmastectomy adj3 lymphedema*) or (post-mastectomy adj2 lymphedema*) or (secondary adj3 lymphedema*) or (iatrogenic adj3 lymphedema*) or lymphoedema*).mp. [mp=title, abstract, original title, name of substance word, subject heading rod, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	5. 1 or 2 or 3 or 4
	6. Anastomosis, Surgical/
	7. Lymph Nodes/
	8. Lipectomy/
	9. ((Lymph* adj3 anastomos*) or LVA or (lymph node adj3 transplant*) or (lymph* transplant*) or (lymph node adj3 transfer*) or VLNT or LNT or liposuction or debulking).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identificer, synonyms]
	10. 6 or 7 or 8 or 9
	11. 5 and 10
Embase	1. exp breast cancer-related lymphedema/
	2. breast tumor/
	3. lymphedema/
	4. ((Breast Cancer adj3 Lymphedema*) or (breast neoplasm* adj3 lymphedema*) or (postmastectomy adj4 lymphedema*) or (post-mastectomy asj2 lymphedema*) or (secondary adj3 lymphedema*) or (iatrogenic adj3 lymphedema*) or lymphoedema*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
	5. 1 or 2 or 3 or 4
	6. anastmomsis/
	7. lymph node/
	8. lipectomy/
	9. (Lymph* adj3 anastomos*) or LVA or (lymph node adj3 transplant*) or (lymph* transplant*) or (lymph node adj3 transfer*) or VLNT or LNT or liposuction, or debulking).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
	10. 6 or 7 or 8 or 9
	11. 5 and 10
Cochrane Library	1. MeSH descriptor: [Breast Cancer Lymphedema] explode all trees
	2. MeSH descriptor: [Breast Neoplasms] explode all trees
	3. MeSH descriptor: [Lymphedema] explode all trees
	4. (Breast Cancer Lymphedema*) or (breast neoplasm* lymphedema*) or postmastetomy lymphedema*) or (Post-mastectomy lymphedema*) or (secondary lymphedema*) or (iatrogenic lymphedema*) or (lymphoedema*)
	5. MeSH descriptor: [Anastomosis, Surgical] explode all trees
	6. MeSH descriptor: [Lymph Nodes] explode all trees
	7. MeSH descriptor: [Lipectomy] explode all trees
	8. (Lympho* anastomos*) or LVA or (lymph node transplant*) or (lymph* transplant*) or (lymph node transfer*) or VLNT or LNT or liposuction og debulking
	9. 1 or 2 or 3 or 4
	10. 5 or 6 or 7 or 8
	11. 9 and 10
Google Scholar	Using the type bar, following search string were made: (Breast Cancer Lymphedema OR Breast Neoplasm OR Lymphedema) AND (lymphovenous anastomosis OR lymphaticovenular anastomosis OR LVA OR lymph node transfer OR LNT OR VLNT OR vascular lymph node transfer OR liposuction OR debulking)
	No search filter, no sorting by date
ClinicalTrial.org	Advanced search
	Condition or disease: lymphedema
	Other terms: breast cancer
	No further filters were used

Keywords, search strings, and Boolean operators were used. LVA, lymphovenous anastomosis; VLNT, vascularized lymph node transfer; MeSH, medical subject headings.

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Table S2 Overview of arm volume outcomes from included articles on LVA

Author	Presentation of volume	Pre-operative volume	Post-operative volume	Volume difference	Significant reduction, yes/no
Roh S *et al.* (43)	Interlimb volume ration = affected arm volume/unaffeced arm volume	1.29±0.12	1.21±0.15	0.08±0.04	Yes
Ciudad P *et al.* (44)	CRR (%) = [1 – (post-operative affected limb – nonaffected limb)]/(pre-operative affected limb – nonaffected limb) 100	NA	NA	56.5%±8.4%	NA
van Mulken TJM *et al.* (20)	UEL index = $(C_1^2 + C_2^2 + C_3^2 + C_4^2 + C_5^2)$/BMI	116.45 [101.1–131.8]; 122.7 [110.1–135.6]	122.7 [106.1–139.3]; 128.0 [114.7–141.4]	–6.2 [–38.2 to 25.7]; –5.3 [–31.1 to 20.9]	No
Fuse Y *et al.* (45)	Arm circumference difference = (circumference affected arm – circumference unaffected arm)/circumference unaffected arm	NA	NA	–0.25% [–3.35 to 2.25], 0.37% [–3.67 to 2.84], –2.45% [–6.22; to 0.27]; –2.78% [–8.14 to –1.87], –0.74% [–4.07 to 2.31], –2.54% [–6.40 to –0.75]	No
Visconti G *et al.* (27)	Difference in sum of arm circumferences (cm) = sum of arm circumferences pre-operative – sum of arm circumference post-operative	143.84±11.15	133.25±14.24	10.59±2.64	Yes
Rodriguez JR *et al.* (28)	Calculated limb volume using formula of a truncated cone, then presented as volume reduction rate (%)	NA	NA	67% [7–93%]	NA
Park JK *et al.* (46)	Calculated limb volume using formula of a truncated cone, then presented as volume reduction rate (%)	NA	NA	10.2%±7.7%	Yes
Boccardo F *et al.* (29)	Relative excess volume = pre-operative arm volume – (post-operative arm volume/pre-operative arm volume) 100	2,806±460	2,164±806	642±117.01	NA
Brahma B *et al.* (42)	UEL index = $(C_1^2 + C_2^2 + C_3^2 + C_4^2 + C_5^2)$/BMI	117.7±26.5	106.9±18.5	10.8	Yes
Wolfs JAGN *et al.* (30)	UEL index = $(C_1^2 + C_2^2 + C_3^2 + C_4^2 + C_5^2)$/BMI	16.2	15.8	0.4	No
Qiu SS *et al.* (31)	UEL index = $(C_1^2 + C_2^2 + C_3^2 + C_4^2 + C_5^2)$/BMI	119.8±13.8	116.8±15.9	–3.18±8.7	No
Seki Y *et al.* (47)	UEL index = $(C_1^2 + C_2^2 + C_3^2 + C_4^2 + C_5^2)$/BMI	NA	NA	10.23±6.16 [3.83–26.17]	No
				2.03±9.36 [–15.51 to 16.53]	Yes
Winters H *et al.* (48)	Volume reduction defined as the relative decrease in volume difference between the healthy and affected extremity	NA	NA	–32.3%	Yes
Phillips GSA *et al.* (32)	Relative volume reduction of excess limb volume (excess limb volume = volume affected arm – volume unaffected arm)	13.3% [–0.8% to 59.5%]	6.6% [3.5–36.4%]	23%	Yes
Khan AA *et al.* (33)	EVR = (volume of affected limb post-operative – volume of affected limb pre-operative)/(volume of affected limb pre-operative – volume of unaffected limb pre-operative) 100	NA	NA	9.2%±71.8%	No
Engel H *et al.* (49)	Circumferencial reduction = (pre-operative circumference arm differende – post-operative circumference arm difference)/pre-operative circumference arm difference	NA	NA	–17.3%±6.0%	NA
Mihara M *et al.* (34)	Change rate = (sum of pre-operative circumferences – sum of post-operative circumferences)/sum of pre-operativecircumference	NA	NA	–1.43%	No
Winters H *et al.* (50)	Arm volume differende (mL) = pre-operative arm volume – post-operative arm volume	701±435 mL	467±303 mL	234 mL or 23.5%	Yes
Poumellec MA *et al.* (35)	Arm circumference difference (cm) = pre-operative (circumference affected arm – circumference unaffected arm) – post-operative (circumference affected arm – circumference unaffected arm)	NA	NA	1.29; 1.00; 1.79 (22.5%; 21.32%; 20.24%)	NA
Cornelissen AJM *et al.* (36)	UEL index = $(C_1^2 + C_2^2 + C_3^2 + C_4^2 + C_5^2)$/BMI	14.92±8.01	12.99±7.47	–1.93	No
Gennaro P *et al.* (51)	Sum of diameters pre-operative and post-operative (cm), and the percentage of reduction	134.5±13.45 cm	125.3±12.37 cm	9.2±5.23 cm or 49.65%±19.98%	NA
Chang DW *et al.* (37)	Reduction in excess volume = (pre-operative volume differential – post-operative volume differential)/pre-operative volume differential Volume difference = (volume of affected limb – volume of unaffected limb)/volume of unaffected limb	32% excess volume	NA	42% reduction	Yes
Ayestaray B *et al.* (38)	CSA =pi $r^2 = C^2/4$ pi	NA	NA	22.8% [7.2–48.8%]	Yes
	The volume of lymphoedema [V = pi h $(C_1^2 + C_3^2 + C_1 \ C_3)/12$]				
	The reduction rate at percentage (%) and difference pre-operative and post-operative cross-sectional area (cm^3)				
Mihara M *et al.* (39)	Percentage reduction = (post-operative sum of four sites' circumference/pre-operative sum of four sites' circumference) 100	NA	NA	93.5% [90–97%]	NA
Chang DW *et al.* (40)	Reduction in excess volume = (pre-operative volume difference – post-operative volume difference)/pre-operative volume difference The volume difference = (volume of affected arm – volume of unaffected arm)/ volume of unaffected arm	NA	NA	35%	NA
Damstra RJ *et al.* (41)	Volume difference = volume of affected arm – volume of unaffected arm	988 [532–1,400] mL	1,075 [500–1,856] mL	87 mL	NA
	Presented as mean volume difference between both arms pre- and post-operative (%)	35.2% [20–50%]	33.5% [18–49%]	1.7%	NA

Unless otherwise stated, values are reported as mean ± standard deviation, median [interquartile range], or mean. LVA, lymphovenous anastomosis; CRR, circumference reduction rate; NA, not available; UEL, upper extremity lymphedema; BMI, body mass index; EVR, excess volume reduction; CSA, cross-sectional area.

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Table S3 Overview of outcomes for PROMs from included articles on LVA

Author	PROM	Scale	Pre-operative score	Post-operative score	Change in score
van Mulken TJM *et al.* (20)	Lymph-ICF	Total score	38 [25–50]	22 [8–35]	–16
			49 [38–59]	26 [16–37]	–23
Park JK *et al.* (46)	Lymph-ICF	Average	NA	NA	–34.4±38
Wolfs JAGN *et al.* (30)	Lymph-ICF	Total score	47.5	31.5	16.0*
		Hand functioning score	NA	NA	NA*
		Mental function score	NA	NA	NA*
		Household activities score	NA	NA	NA
		Mobility activities score	NA	NA	NA*
		Life and social activities score	NA	NA	NA
Qiu SS *et al.* (31)	Lymph-ICF	Total score	43.9±19.9	30.6±20.2	–13.3*
		Physical function score	49	33	–16*
		Mental function score	39	22	–17*
		Household activities score	45	34	–11
		Mobility activities score	44	32	–12
		Life and social activities	41	30	–11
Cornelissen AJM *et al.* (36)	Lymph-ICF	Total score	44	14	–30*
		Physical function score	48	13	–35*
		Mental function score	42	11	–31*
		Household activities score	52	28	–24*
		Mobility activities score	41	11	–30*
		Life and social activities	41	11	–30*
Winters H *et al.* (48)	LYMQOL	Overall QOL	5.8	7.3	1.4 [0–3]*
		Function	2.2	1.7	–0.5*
		Appearance	2.6	1.9	–0.7*
		Symptoms	2.8	1.9	–0.9*
		Mood	2.2	1.5	–0.7*
Phillips GSA *et al.* (32)	LYMQOL	Overall QOL	NA	NA	9*
		Function			25*
		Appearance			18*
		Symptoms			28*
		Mood			14*
Brahma B *et al.* (42)	LeQOLiS	Overall dissatisfaction cause by lymphedema	5.6±2.4	3.7±2.6	–38%*
		Distention	6.1±2.5	3.2±2.2	–47%*
		Heaviness	5.7±2.8	3.0±2.3	–47%*
		Pain	4.7±3.3	2.9±2.8	–37%*
		Dysesthesia	4.8±3.3	2.7±2.6	–44%*
		Appearance distortion	5.6±2.5	3.3±2.5	–41%*
		Motor dysfunction	4.6±3.1	2.8±2.5	–39%*
		Limitation in daily activity	4.8±2.8	3.3±2.4	–32%*
		Influence in social activity	4.3±3.0	2.9±2.6	–32%*
		Distress cause by compression therapy	4.6±3.0	3.7±2.8	–18%
Mihara M *et al.* (34)	VAS	–	3.5 [0–8]	0.59 [0–3]	*
Winters H *et al.* (50)	LymphQoL	Overall QOL	5.8±1.1	4.7±0.7	*
		Function	2.2	1.8	*
		Appearance	2.6	1.9	*
		Symptoms	2.8	1.8	*
		Mood	2.7	1.5	*
Damstra RJ *et al.* (41)	SF-36	NA	NA	NA	Subjective relief of complaints in 5 patients
Gennaro P *et al.* (51)	Self-developed	A 4-point scale measuring patients' satisfaction level, with 1 representing the lowest satisfaction, and 4 being the highest	NA	3.7	NA

Values are reported as mean ± standard deviation, median [interquartile range], or mean. *, statistical significant. PROM, patient-reported outcome measure; LVA, lymphovenous anastomosis; NA, not available; LYMQOL, Lymphedema Quality of Life; QOL, quality of life.

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Table S4 Presenting post-operative management and complications in included studies of VLNT

Author	Post-operative management	Complications
Di Taranto G *et al.* (80)	NA	Dehiscence of wound on abdomen, seroma, hernia
Ciudad P *et al.* (44)	CCT 14 days after surgery	Venous congestion n=1, partial flap loss n=1, seroma n=3, delayed wound healing n=2, complete flap loss n=1
Winters H *et al.* (70)	NA	Infected heamatoma n=1, revision of anastomosis n=2, infected seroma n=2, wound dehiscence on the abdomen n=3, seroma n=2
Francis EC *et al.* (60)	Admission to microsurgical intensive care unite for 5 days, then transferred to regular ward. No CCT at any stage post-operatively. Retrograd manual lymphatic drainage was recommender three times daily starting from post-operative day 14. Gradual return to normal activity level as tolerated	No major
Brown S *et al.* (64)	No nasogastric tubes. Discharge at day 3, with compression wrapping and manual lymphatic drainage until volume plateau. Hereafter CCT	NA
Akita S *et al.* (81)	NA	No major
Abdelfattah U *et al.* (19)	NA	Partial flap loss n=1, seroma n=1
Rannikko EH *et al.* (71)	CCT for 6 months. Manual lymphatic drainage 4 weeks after surgery	Haematoma n=16, reanastomosis n=5, partial flap necrosis n=11, total flap loss n=1, poor wound healing n=10, infection n=5, loss of sensation in the upper thigh n=2, seroma n=10
Dionyssiou D *et al.* (72)	Manual lymphatic drainage for 30 days, followed by CCT of 20 mmHg for 5 months	No major. One flap failure excluded from the study
Ngo QD *et al.* (77)	Prophylactic antibiotics for 3 days. Doppler monitoring of the flap. Surgical drains at both donor- and recipient site. CCT avoided for 2 weeks. After 2 weeks, patients were advised to wear CCT for at least 12 months. Limb elevation and rest were advised. After discharge at day 4–7, manual lymph drainage was permitted. No pressure on the lymph node flap for the first 4 weeks	No major
Mousavi SR *et al.* (73)	NA	None
Ciudad P *et al.* (61)	NA	NA
Chang EI *et al.* (67)	Flap monitored every 2 hours for first 48 hours post-operative, then every 4-hour until discharge. LMWH daily from first porsoperative day. Percutaneus drains left in place until production less than 33 mL/day for 2 consecutive days. Intravenous antibiotics during hospitalization. No CCT or conservative treatments for 1 month after surgery	Delayed wound healing n=3, skin flap necrosis n=1, pulmonary embolus n=1
Maruccia M *et al.* (68)	Monitored for 5 days	NA
Aljaaly H *et al.* (56)	Microsurgical care unit for 5 days, discharged at day 7. Restricted finger movement was encouraged from day 3. No CCT. Manual lymphatic massage was encouraged. Return to normal activity gradually as tolerated	–
Ho OA *et al.* (57)	50.9±31.4; 28.6±6.7	46.2% had complications in group A, 38.5% in group B
Engel H *et al.* (49)	NA	NA
Montag E *et al.* (78)	Plaster cast for 21 days with wrist in neutral position. Monitoring flap every 3 hours for 48 hours, then every 6-hour until discharge. CCT after 30 days post-operative	NA
Lin CY *et al.* (59)	NA	NA
Liu HL *et al.* (79)	Bed rest for 2 days with arm abducted. Immediate after surgery, arm bandage and manual lymphatic massage	NA
Akita S *et al.* (76)	NA	Seroma n=2
Yang Z *et al.* (69)	Flap monitoring every 2 hours for first 72 hours. Leg placed in knee and hip flexion for 2 weeks. CCT continuously for 1 year, avoiding the transplanted axilla	Fat necrosis n=1
Gratzon A *et al.* (65)	Immediately short stretch CCT, adjusted after 1 day. Continue wear at day and nights for 1 month. Hereafter, only when symptoms of swelling, pain, or heaviness occurred	Seroma n=6, wound dehiscence n=6, infection n=6, hematoma n=1, non-healing wound n=1, bleeding n=1
Arriv L *et al.* (74)	NA	NA
Dionyssiou D *et al.* (5)	NA	Mild discomfort at donor site n=2, lymphorrhea at donor site n=2
De Brucker B *et al.* (75)	Removal of drains 1–2 days post-operative. CCT initiated 10 days post-operative	Seroma n=3, wound problems n=4, infection n=1, total flap loss n=1
Patel KM *et al.* (62)	Flap monitoring for 2 weeks, hereafter discharged with encouragement to ambulate, slowly increasing the daily activity and eliminate any previous CCT	None
Nguyen AT *et al.* (66)	NA	Delayed wound healing n=9, partial flap necrosis n=1, venous thrombosis n=1, abdominal bulge n=1, seroma n=1, swelling of lower extremity n=1
Cheng MH *et al.* (58)	NA	NA
Lin CH *et al.* (63)	Microsurgical intensive care unit for 5 days, discharged after 7–10 days. Upper limb elevation with wrist in neutral position with splinting for 2 weeks. Finger flexion and extension encouraged upon day 3 post-operative	Venous congestion n=1, infection n=1
Becker C *et al.* (8)	Manual lymphatic massage daily for the first 3 months. Hereafter twice a week for another 3 months. No CCT. Acetylsalicylates were administered during the post-operative period	Lymphorrhea n=8, infection n=18

VLNT, vascularized lymph node transfer; NA, not available; CCT, controlled compression therapy; LMWH, low molecular weight heparin.

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Table S5 Overview of volume measures for included studies on VLNT

Author	Volume method	Pre-operative excess volume	Post-operative excess volume	Volume change (reduction)	Significant reduction, yes/no
Di Taranto G *et al.* (80)	Arm circumference (circumferences at deltoid insertione, above elbow, below elbow, mid-forearm, and wrist)	NA	NA	46.1±52.3, 39±42.3, 47.5±53.5, 39.2±52.4, 33.6±50.1 cm at the deltoid insertion, above the elbow, below the elbow, at the mid-forearm and wrist respectively	No
Ciudad P *et al.* (44)	Arm circumference {CRR = [1 – (post-operative affected – post-operative nonaffected)/(pre-operative affected – pre-operative nonaffected)] 100}	NA	NA	54.4%±10.2% for GE group 56.5%±3.9% for DIEP group	NA
Winters H *et al.* (70)	Water displacement [arm volume difference = (volume_lymphedema_arm – volume_healthy_arm)]	407 mL	406 mL	1 mL	No
Francis EC *et al.* (60)	Arm circumference [circumference measured 10 cm above elbow, 10 below elbow; limb difference = (pre-lymf – pre-healthy)/pre-healthy]	25.6±11.5 cm	8.3±4.2 cm	NA	Yes
Brown S *et al.* (64)	Arm circumference, perometer (arm volumes calculated by circumferences at 4 cm intervals from the wrist to 44 cm proximally then using the truncated cone formula; perometer to calculate limb volume)	30.2±15.4 mL	25.5±11.9 mL	15.6%	Yes
Akita S *et al.* (81)	Arm circumference (arm volume calculated using forumla of a blunt cone; arm circumference at wrist, forearm, elbow, and upper arm)	NA	NA	142.9±89.4 cm in good blood flow group 62.1±55.0 cm cm in poor blood flow group	NA
Abdelfattah U *et al.* (19)	Arm circumference (10 cm below and above elbow, both limbs)	NA	NA	38.8±16.1	Yes
Rannikko EH *et al.* (71)	Arm circumference (arm volume calculted from forumla of blunt cone; the arm circumference was measured at 4 cm intervals from the distal end of the ulna to proximal direction of both upper limbs on 12 different sites in these patients; the edema volume was calculated using Brorson's truncated cone model)	416±432 mL 3.2±2.6 cm	267±285 mL 2.5±1.7 cm	NA NA	No No
Dionyssiou D *et al.* (72)	Perometer [VD (%) = (affected limb volume – unaffected limb volume)/unaffected limb volume 100; mVDR not further specified]	NA	NA	55.7%	NA
Ngo QD *et al.* (77)	Arm circumference [excess volume = (affected limb volume – unaffected limb volume)/unaffected limb volume; arm volume calculated using forumla of a blunt cone. Arm circumference at 4 cm interval]	498 mL	573 mL	74.32 (increase)	NA
Mousavi SR *et al.* (73)	Arm circumference (circumference above elbow, below elbow; not further specified)	33.4%±12.6% above elbow 30.6%±12.2% below elbow	12.5%±11.1% above elbow 15.1%±17.9% below elbow	NA	Yes
Ciudad P *et al.* (61)	Arm circumference {circumference measured 10 cm below the elbow, 10 cm above the wrist, and at the midhand; CRR (%) = [1 – (post-operative lymphedema – healthy)]/(pre-operative lymfedema – healthy) 100}	NA	NA	28.6%±5.6%	Yes
Chang EI *et al.* (67)	Perometer [VD (%) = (affected limb volume – unaffected limb volume)/unaffected limb volume 100]	NA	NA	57.8%	Yes
Maruccia M *et al.* (68)	Arm circumference {arm circumference above and below elbow; used to CRR = [(pre_circumference _lymphedem – pre_circumference_healthy) – (post _circumference_lymphedem – post_circumference_healthy)]/(pre_circumference_lymphedem – pre_circumference_ healthy)}	NA	NA	51.2%±6.3% axillary recipient site 34.8%±5.8% wrist as recipient site	Yes Yes
Aljaaly H *et al.* (56)	Arm circumference {arm circumference 10 cm above and 10 cm below elbow; used to CRR = [(pre_circumference_lymphedem – pre_circumference_ healthy) – (post_circumference_lymphedem – post_ circumference_healthy)]/(pre_circumference_lymphedem – pre_circumference_healthy)}	33.5±15.6 31.5±10.6	16.2±9.2 16.8±16.7	54.3%±35.5% 30.1%±23.7%	Yes
Ho OA *et al.* (57)	Arm circumference (cm, not further specified)	NA	NA	48.4%±23.9% 55.5%±23.9%	Yes Yes
Engel H *et al.* (49)	Arm circumference {circumference difference = (circumference affected – nonaffected)/nonaffected; CRR = [(pre-operative circumference affected – nonaffected)/nonaffected] – [(post-operative circumference affected – nonaffected)/nonaffected]/[(pre-operative circumference affected – nonaffected)/nonaffected]}	NA	NA	34%±6.9% lymph node transplantation; 34.9%±10.0% lymph node transplantation combined with DIEP	NA (significantly greater reduction when combined with DIEP)
Montag E *et al.* (78)	Arm circumference [arm volume calculated from formula of truncated cone; circumferences of the wrist, 5 and 10 cm above wrist, the elbow, 5 and 10 cm above elbow; compared means before and after (difference)]	426 [300–774] cm^3	425 [192–661] cm^3	20.1%±44.89%	Yes
Lin CY *et al.* (59)	Arm circumference (circumference 10 cm above and below the elbow; not further specified)	NA	NA	7.8%±3.9%	Yes
Liu HL *et al.* (79)	Arm circumference {arm circumference to calculate reduction rate = [(pre-lymphedema circumference – pre-healthy circumference) – (post-lymphedema circumferende – post-healthy circumference)]/(pre-lymphedema circumference – pre-healthy circumference)}	NA	NA	47.06%±27.92%	NA
Akita S *et al.* (76)	Arm circumference [UEL index = $(C_1^2 + C_2^2 + C_3^2 + C_4^2 + C_5^2)$/BMI]	NA	13.9±4.1; 13.2±1.5	NA	NA
Yang Z *et al.* (69)	Arm circumference (arm circumference, the palm of the hand between the thumb and the index finger, the wrist, the median of the forearm, the elbow through the olecranon, and the median and the root of the upper arm.)	25.34±1.24; 22.49±0.69; 32.19±1.09; 30.37±1.66; 36.88±1.45; 39.88±3.16	23.34±1.04; 23.40±0.73; 29.15±1.45; 27.75±1.43; 33.15±1.17; 38.10±2.65	NA	Yes
Gratzon A *et al.* (65)	Arm circumference {arm circumference to calculate volume; circumferential reduction rate was calculated using forumla: [(A2 – N2) – (A1 – N2)]/(A1 – N1) 100; A1, affected arm volume pre-operative; A2, affected arm volume at reassessment; N1, nonaffected arm volume pre-operative; N2, affected arm at reassessment}	NA	NA	57.68	No
Arriv L *et al.* (74)	Arm circumference (reduction in cm; circumferential measures four levels, 5 cm above wrist, 10 cm above the wrist, 5 cm above elbow, 10 cm above elbow)	19,45±3.0; 27.91±5.3; 31.09±5.6; 22.91±4.7	17.91±2.9; 25.36±5.0; 29.27±5.0; 21.72±4.3	1.545±1.293; 2.455±1.508; 2.182±1.662; 1.818±1.601	NA
Dionyssiou D *et al.* (5)	Arm circumference [4 cm intervals; excess volume calculated as arm difference/unaffected limb 100 (%)]	36.61%	15.72%	20.88%	Yes
De Brucker B *et al.* (75)	NA	NA	NA	NA	NA
Patel KM *et al.* (62)	Arm circumference [arm circumference measured 10 cm proximal to the elbow and 10 cm below the elbow; the circumferential differentiation = (the circumference of unaffected arm – the circumference of the affected arm)/the circumference of the healthy arm]	18.1±4.2	21.1±5.3	6 cm or 24.4%±14.7%	Yes
Nguyen AT *et al.* (66)	Perometer [excess volume = (affected limb volume – unaffected limb volume)/unaffected limb volume]	21%	10%	11% absolute volume reduction; 48% relative volume reduction	NA
Cheng MH *et al.* (58)	Arm circumference (10 cm above elbow)	NA	NA	7.3%±2.7% ccircumferential differentiation; 40.4%±16.1% mean circumferential reduction rate	Yes (significantly greater reduction when recipient site was wrist compared to elbow)
Lin CH *et al.* (63)	Arm circumference {measured 10 cm above elbow; CRR of the lymphedematous arm = [(a – b) – (c – d)]/(a – b); a, pre-operative lesion of the arm; b, pre-operative healthy arm; c, post-operative lesion of the arm; d, post-operative healthy arm}	33.3±5.3	29.7±5.3	50.55±19.26	Yes
Becker C *et al.* (8)	Measurements (not further explained)	NA	NA	Returned to normal in 10 cases, unchanged in 2 cases, decreased more than 50% in 6 patients and led than 50% in 6 patients	NA

Unless otherwise stated, values are reported as mean ± standard deviation or mean. VLNT, vascularized lymph node transfer; NA, not available; CRR, circumference reduction rate; GE, gastroepiploic lymph nodes; DIEP, deep inferior epigastric perforator; VD, volume differential; mVDR, mean volume differential reduction; UEL, upper extremity lymphedema; BMI, body mass index.

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Table S6 Overview of outcomes for PROMs from included articles on VLNT

Author	PROM	Scale	Pre-operative score	Post-operative score	Change in score
Di Taranto G *et al.* (80)	LYMQOL	Overall QOL	6.7±1.7	8.6±1.4	1.9*
		Function	1.57±0.48	1.21±0.16	0.36*
		Appearance	2.33±0.81	1.15±0.4	1.18*
		Symptoms	2.5±0.68	1.34±0.38	1.16*
		Mood	2±0.85	1.33±0.43	0.67*
Francis EC *et al.* (60)	LYMQOL	Overall QOL	3.9±1.1	7.4±0.5	3.5*
		Function	30.6±2.8	14.5±2.5	16.1*
		Appearance	18.2±1.9	8.5±2.1	9.7*
		Symptoms	30.4±5.9	10.9±1.0	19.5*
		Mood	29.2±4.4	10.7±1.0	18.5*
Maruccia M *et al.* (68)	LYMQOL	Function	37.9 (Group A)	19.7 (Group A)	18.2
			38.0 (Group B)	20.6 (Group B)	17.4
		Appearance	20.1 (Group A)	11.4 (Group A)	8.7
			20.0 (Group B)	12.0 (Group B)	8.0
		Symptoms	23.6 (Group A)	15.0 (Group A)	8.6
			23.8 (Group B	15.5 (Group B)	8.3
		Mood	23.6 (Group A)	14.7 (Group A)	8.9
			23.4 (Group B)	15.2 (Group B)	8.2
Aljaaly H *et al.* (56)	LYMQOL	Overall QOL	NA	NA	NA*
		Function	NA	NA	NA*
		Appearance	NA	NA	NA*
		Symptoms	NA	NA	NA*
		Mood	NA	NA	NA*
Lin CY *et al.* (59)	LYMQOL	Overall QOL	3.9	8.6	4.7*
		Function	37	15	22*
		Appearance	18	8	10*
		Symptoms	22	9	13*
		Mood	18	10	8*
Gratzon A *et al.* (65)	LYMQOL	Overall QOL	5.72	7.79	2.07*
		Function	2.41	1.5	0.91*
		Appearance	2.99	1.5	1.49*
		Symptoms	2.69	1.6	1.09*
		Mood	2.23	1.4	0.83*
		Pain	3.97	0.38	3.59*
		Heaviness	5.52	1.67	3.85*
Patel KM *et al.* (62)	LYMQOL	Overall QOL	2.1±0.5	5.8±0.7	3.7*
		Function	37.9±0.5	19.3±4.4	18.6*
		Appearance	19.9±0.5	12.1±2.9	7.8*
		Symptoms	23.9±0.5	15.3±2.8	8.6*
		Mood	23.9±0.5	14.4±2.9	9.5
Winters H *et al.* (70)	ULL-27	Total ULL-27	NA	NA	12.66*
		Physical	NA	NA	13.65*
		Psychological	NA	NA	11.11*
		Social	NA	NA	9.50*
Brown S *et al.* (64)	ULL-27	Total ULL-27	51.5±19.7	69.1±14.7	17.6*
		Physical	49.4±23.5	68.8±17.4	19.4*
		Psychological	49.7±20.3	65.3±16.9	15.6*
		Social	60.9±20.7	75.7±16.1	14.8*
	LLIS	LLIS total impairment	47.5±18.1	31.5±16.1	16.0*
		Physical	12.3±4.7	8.0±5.2	4.3*
		Psychological	10.9±5.3	7.5±4.5	3.4*
		Functional	9.2±4.5	5.9±2.9	3.3*
De Brucker B *et al.* (75)	ULL-27	Total ULL-27	44±18	26±16	18±17*
		Physical	NA	20±19	NA*
		Psychological	NA	12±16	NA*
		Social	NA	19±21	NA*
Abdelfattah U *et al.* (19)	VAS	Infection	2.46	0.0	2.46*
		Pain	5.2	0.73	4.47*
		Heaviness	6.2	0.93	5.27*
		Function	6.73	1.06	5.67*
Dionyssiou D *et al.* (72)	VAS	Infection	1.94	0.277	1.663*
		Pain	5.38	0.61	4.77*
		Heaviness	6.33	0.94	5.39*
		Function	5.5	1.22	4.28*

Unless otherwise stated, values are reported as mean ± standard deviation or mean. *, significant. PROM, patient-reported outcome measure; VLNT, vascularized lymph node transfer; LYMQOL, Lymphedema Quality of Life; QOL, quality of life; NA, not available; ULL-27, Upper Limb Lymphedema 27; LLIS, Lymphedema Life Impact Scale; VAS, Visual Analog Scale.

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Table S7 Overview of outcomes from included articles on liposuction

Author	Volume method	Volume aspirated (mL)	Pre-operative excess volume	Post-operative excess volume	Volume change (reduction)
Karlsson T *et al.* (86)	Water displacement	1,323 [1,230–1,828]	1,213 [1,014–1,676] mL	–73 [–180 to –59] mL	1,286 mL
Kim RS *et al.* (93)	Arm circumference	500 [300–600]	0.41 [0.22–0.53] (excess volume ratio)	0.13 [0.10–0.28] (excess volume ratio)	–0.13 [–0.28 to –0.12]
		550 [437.5–762.5]	0.41 [0.33–0.51] (excess volume ratio)	0.32 [0.25–0.46] (excess volume ratio)	–0.04 [–0.09 to –0.02]
Hoffner M *et al.* (87)	Plethysmography	1,831±599	1,573±645 mL	–188±300 mL	1,761 mL
Hoffner M *et al.* (88)	Water displacement	1,361±66	1,365±73 mL	–213±35 mL	1,574 mL
Lee D *et al.* (82)	Water displacement	NA	1,607 [570–3,950] mL	–43 [–945 to –1,390]	1,650 mL
Damstra RJ *et al.* (92)	Water displacement	2,124 [945–4,070]	1,540 [765–3,090] mL	–149 [–876 to –473]	1,689 mL
Brorson H *et al.* (83)	Water displacement	NA	1,781 [1528–2,080] mL	–21 [–118 to –112]	1,802 mL
Bagheri S *et al.* (89)	Water displacement	1,724	1,648 [765–3,090] mL	112 [580–410]	1,536 mL
Brorson H *et al.* (84)	Water displacement	NA	1,610 [570–2,950] mL	–230 [–655 to –235]	1,840 mL
Brorson H *et al.* (85)	Water displacement	NA	1,790 [570–3,914] mL	52 [–655 to –1,135]	1,738 mL
Brorson H *et al.* (90)	Water displacement	2,060 [1,000–3,850]	1,745 [810–3,915] mL	60 [–445 to –135]	1,685 mL
Brorson H *et al.* (91)	Water displacement	2,250 [1,000–3,858]	1,845 [570–3,915] mL	30 [–655 to –1,135]	1,815 mL

Unless otherwise stated, values are reported as mean ± standard deviation, median [interquartile range], or mean. NA, not available.

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Table S8 Overview of outcomes for PROMs from included articles on liposuction

Author	PROM	Scale	Pre-operative score	Post-operative score	Change in score
Hoffner M *et al.* (88)	SF-36	Physical functioning	67±2.4	75±2.5	8*
		Role physical	65±5.3	67±4.8	2
		Bodily pain	65±3.4	79±3.2	14*
		Social functioning	83±3.2	90±2.3	7*
		Role emotional	71±5.1	78±4.7	7
		Mental health	74±2.5	82±2.1	8*
		General health	68±2.9	69±2.7	1
		Vitality	66±2.7	72±2.4	6*
		Physical component score	43±1.3	45±1.2	2*
		Mental component score	49±1.3	52±1.2	3*
Brorson H *et al.* (83)	VAS	Pain	25 [9–35]	3 [2–5]	22*
		Swelling of hand	39 [27–48]	12 [8–22]	31*
		ADL	41 [31–51]	4 [2–8]	37*
		Reduces mobility	63	20	43*
		Swollen arm	94	14	80*
		Heavy arm	89	11	78*
		Fatigue/weakness	51	14	37*
		Numbness/prick. sens.	37	23	14
		Total score	9 [5–23]	8 [2–14]	1*
	NHP	Emotions	5 [0–14]	0 [0–8]	5
		Sleep	17 [6–28]	11 [6–21]	6
		Lack of energy	0 [0–30]	0 [0–12]	0
		Pain	11 [5–26]	0 [0–13]	11*
		Physical mobility	7 [4–14]	5 [0–10]	2
		Social isolation	0 [0–13]	0 [0–0]	0
		House work	51	29	22*
		Social life	9	9	0
		Family life	3	6	3
		Hobbies	31	34	3
		Holidays	26	29	3
		Total score	107 [100–113]	109 [100–118]	2
		Anxiety	26 [24–27]	26 [24–28]	0
	PGWB	Depressed mood	16 [16–17]	16 [15–17]	0
		Well-being	17 [16–18]	17 [16–19]	0
		Self-control	17 [16–17]	17 [15–17]	0
		General health	15 [13–16]	16 [14–17]	1
		Vitality	18 [17–20]	20 [17–21]	2
	HAD	Anxiety	5 [4–6]	4 [3–6]	1
		Depression	3 [2–4]	3 [1–4]	0

Unless otherwise stated, values are reported as mean ± standard deviation, median [interquartile range], or mean. *, significant. PROM, patient-reported outcome measure; SF-36, Short Form-36; VAS, Visual Analog Scale; ADL, activity of daily living; NHP, Nottingham Health Profile; PGWB, Psychological General Well-Being Index; HAD, Hospital Anxiety Depression Scale.

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Table S9 Overview of risk of bias assessment for included studies in the systematic review

Author	Risk of bias
Articles on LVA	
Roh S *et al.* (43)	Serious
Ciudad P *et al.* (44)	Serious
van Mulken TJM *et al.* (20)	Moderate
Fuse Y *et al.* (45)	Serious
Visconti G *et al.* (27)	Serious
Rodriguez JR *et al.* (28)	Serious
Park JK *et al.* (46)	Serious
Boccardo F *et al.* (29)	Serious
Brahma B *et al.* (42)	Critical
Wolfs JAGN *et al.* (30)	Serious
Qiu SS *et al.* (31)	Serious
Seki Y *et al.* (47)	Serious
Winters H *et al.* (48)	Serious
Phillips GSA *et al.* (32)	Serious
Khan AA *et al.* (33)	Serious
Engel H *et al.* (49)	Serious
Mihara M *et al.* (34)	Serious
Winters H *et al.* (50)	Serious
Poumellec MA *et al.* (35)	Serious
Cornelissen AJM *et al.* (36)	Serious
Gennaro P *et al.* (51)	Critical
Chang DW *et al.* (37)	Critical
Ayestaray B *et al.* (38)	Critical
Mihara M *et al.* (39)	Critical
Chang DW *et al.* (40)	Critical
Damstra RJ *et al.* (41)	Serious
Articles on lymph node transfer	
Di Taranto G *et al.* (80)	Serious
Ciudad P *et al.* (44)	Critical
Winters H *et al.* (70)	Serious
Francis EC *et al.* (60)	Serious
Brown S *et al.* (64)	Serious
Akita S *et al.* (81)	Serious
Abdelfattah U *et al.* (19)	Some concerns
Rannikko EH *et al.* (71)	Critical
Dionyssiou D *et al.* (72)	Serious
Ngo QD *et al.* (77)	Serious
Mousavi SR *et al.* (73)	Serious
Ciudad P *et al.* (61)	Serious
Chang EI *et al.* (67)	Serious
Maruccia M *et al.* (68)	Moderate
Aljaaly H *et al.* (56)	Moderate
Ho OA *et al.* (57)	Moderate
Engel H *et al.* (49)	Serious
Montag E *et al.* (78)	Serious
Lin CY *et al.* (59)	Moderate
Liu HL *et al.* (79)	Serious
Akita S *et al.* (76)	Moderate
Yang Z *et al.* (69)	Moderate
Gratzon A *et al.* (65)	Critical
Arriv L *et al.* (74)	Serious
Dionyssiou D *et al.* (5)	Some concerns
De Brucker B *et al.* (75)	Serious
Patel KM *et al.* (62)	Serious
Nguyen AT *et al.* (66)	Serious
Cheng MH *et al.* (58)	Moderate
Lin CH *et al.* (63)	Critical
Becker C *et al.* (8)	Critical
Articles on liposuction	
Karlsson T *et al.* (86)	Moderate
Kim RS *et al.* (93)	Moderate
Hoffner M *et al.* (87)	Moderate
Hoffner M *et al.* (88)	Moderate
Lee D *et al.* (82)	Moderate
Damstra RJ *et al.* (92)	Serious
Brorson H *et al.* (83)	Moderate
Bagheri S *et al.* (89)	Serious
Brorson H *et al.* (84)	Critical
Brorson H *et al.* (85)	Serious
Brorson H *et al.* (90)	Moderate
Brorson H *et al.* (91)	Moderate

Overall, articles were primarily evaluated as high risk of bias, some being at moderate risk. No study presented with low risk of bias. LVA, lymphovenous anastomosis.

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