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Surgical Treatment for Primary Lymphedema: A Systematic Review of the Literature

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Abstract

This is a retrospective review of surgical management for primary lymphedema. Data were extracted from 55 articles from PubMed MEDLINE, Web of Science, SCOPUS, and Cochrane Central Register of Controlled Trials between the database inception and December 2022 to evaluate the outcomes of lymphaticovenous anastomosis (LVA) and vascularized lymph node transfer (VLNT), and outcomes of soft tissue extirpative procedures such as suction-assisted lipectomy (SAL) and extensive soft tissue excision. Data from 485 patients were compiled; these were treated with LVA ($n = 177$), VLNT ($n = 82$), SAL ($n = 102$), and excisional procedures ($n = 124$). Improvement of the lower extremity lymphedema index, the quality of life (QoL), and lymphedema symptoms were reported in most studies. LVA and VLNT led to symptomatic relief and improved QoL, reaching up to 90 and 61% average circumference reduction, respectively. Cellulitis reduction was reported in 25 and 40% of LVA and VLNT papers, respectively. The extirpative procedures, used mainly in patients with advanced disease, also led to clinical improvement from the volume reduction, as well as reduced incidence of cellulitis, although with poor cosmetic results; 87.5% of these reports recommended postoperative compression garments. The overall complication rates were 1% for LVA, 13% for VLNT, 11% for SAL, and 46% for extirpative procedures. Altogether, only one paper lacked some kind of improvement.

Primary lymphedema is amenable to surgical treatment; the currently performed procedures have effectively improved symptoms and QoL in this population. Complication rates are related to the invasiveness of the chosen procedure.

Keywords
- lymphedema
- primary lymphedema
- congenital lymphedema
- lymphovenous anastomosis
- lymph node transplant

Lymphedema is a pathological entity characterized by volume enlargement of a body part caused by the accumulation of lymphatic fluid due to an affected lymphatic system; its causes are varied. When the blockage of lymphatic flow is due to surgery, trauma, radiation, or infection, the condition is termed secondary lymphedema; 1 in 1,000 people is affected.[1] Conversely, primary lymphedema entails a preexisting anomaly of the lymphatic system in patients with a

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family history or a genetic background for the disease.[2] The prevalence of primary lymphedema is 1.15 in 100,000 individuals[3] and involves either the lower extremity (91%) or upper extremity (9%).[2,4,5]

Primary lymphedema has been classified into praecox to designate an early development of the disease, affecting mainly female patients aged from 10 to 24 years, and congenital, present at birth, and subdivided into simple and familial (Milroy's disease).[4] The term lymphedema *tarda* was subsequently introduced to designate the late presentation of the disease, which usually occurs after 35 years of age.[6]

In the wide spectrum of congenital vascular malformations, primary lymphedema can appear as an isolated entity or be accompanied by other anomalies such as venous malformations or lymphangioma.[7] Also, primary lymphedema is an accompanying clinical feature of several syndromes with identified genetic associations: Hennekam syndrome (CCBE1), Noonan syndrome 1 (PTPN11), Emberger syndrome (GATA2), hypotrichosis-lymphedema-telangiectasia syndrome (SOX18), oculodentodigital dysplasia (GJA1), among others.[8] The usual clinical presentation in isolated primary lymphedema frequently shows an extremity with a woody, brawny texture, prominent veins, deep toe creases, "sky-jump" toenails, and papillomatosis (most severe over the second toe), and episodes of cellulitis and/or lymphangitis.[9]

Various underlying pathological features have been identified in primary lymphedema, including hypoplasia, dilatation, and aplasia of the lymphatic trunks in 55, 24, and 14% of patients, respectively,[6] as well as diseased lymph nodes.[10] Magnetic resonance lymphangiography has confirmed defects of inguinal lymph nodes with mild or moderate dilatation of afferent lymph vessels in 17% of cases, lymphatic vascular anomalies (aplasia, hypoplasia, or hyperplasia) with no obvious defect of the draining lymph nodes in 32% of cases, and involvement of both lymph vessels and lymph nodes in 51% of cases.[11] These findings can potentially correlate to clinical features, considering the affected levels of the limb and the involvement of lymphatic hypoplasia.[11,12] It has been recognized that the defective development occurs in the later stage of lymphangiogenesis.[13] All these severe structural abnormalities have traditionally led primary lymphedema to be considered an incurable disease, unlike secondary lymphedema where originally the lymphatic structure and anatomy are normal, and continue to be until advanced stages, and the basic principle of surgical treatment is the restoration of flow in the severed lymphatic channels.[3]

Hence, for the past 20 years, lymphaticovenous anastomosis (LVA) and its derivative mechanism through supermicrosurgery have become a popular physiological treatment modality for lymphedema[14]; nevertheless, few studies have focused on the treatment of primary cases.[15,16] In consequence, nonsurgical treatment, compression therapy being the cornerstone, is critical in treating lymphedema, providing symptom relief, and halting the progression of the disease.[17,18] The results of these conservative therapies have been moderately successful: decreases in absolute limb volume (around 30%), decreases in body mass index, and improvement in quality of life (QoL) assessed through patient-reported outcome measures have been published.[19]

Despite the above, several surgical treatment modalities are available nowadays. The vascularized lymph node transfer (VLNT) for primary lymphedema with hypoplastic lymph vessels has proven to be a beneficial physiological procedure[16,20–22]; this modality works mainly in two ways: as a source for vascular endothelial growth factor, stimulating lymphangiogenesis in the affected limb, and drawing lymph forth into the venous circulation through a pressure gradient.[23] These fluid dynamics are further complicated by the role of the endothelial glycocalyx layer functioning as a monitor of fluid filtration from blood capillaries, causing most interstitial fluid to be reabsorbed by lymphatic rather than venous capillaries, as is now dictated by the revised Starling's principle.[24,25]

Conversely, excisional and debulking procedures have been used as palliative surgeries for lymphedema. These include the Charles procedure, which is performed predominantly for advanced stages of lymphedema, resulting in evident scarring with tissue breakdown and poor cosmetic results, as well as lymphorrhea, recurrence, and residual distal edema[26,27]; and suction-assisted lipectomy (SAL), which started as a conjunct procedure for compression-resistant lymphedema.[28,29]

Although lymphedema has been an object of special attention in recent years, the special considerations of primary lymphedema etiopathology, concurrently with the unavoidable long-standing progression of the disease before an accurate diagnosis is made, have altogether contributed to the current lack of well-established protocols in the surgical treatment for this condition. Indeed, primary lymphedema is considered a rare or orphan disease.[30] Therefore, in this study, we aimed to perform a systematic review of the literature focusing on the reported outcomes of surgical treatment in the context of primary lymphedema of the extremities.

Methods

Protocol and Search Strategy

This review was performed commensurate with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PRISMA Checklist available online).[31,32] A comprehensive search design by author J.M.E. across PubMed MEDLINE, Web of Science, SCOPUS, and Cochrane Central Register of Controlled Trials was performed from database inception through December 2022. The terms "Lymphedema," "Primary," "Hereditary," "Congenital," "Praecox," "Tarda," "Meige's syndrome," "Milroy's disease," "Lymph node transfer," "Lymphovenous anastomosis," "Liposuction," "Lipectomy," "lymph node transplant," "Excision," and "radical reduction preservation perforators" were used as keywords with Boolean operators in several combinations (see ►**Supplementary Table S1** [available in the online version only], which exhibits the specific search terms used for the different databases).

Inclusion and Exclusion Criteria

We included original articles written in English, reporting outcomes and surgical techniques for the management of primary lymphedema of extremities in human patients.

Preclinical studies and survey studies were excluded. Studies reporting outcomes where multiple patients with primary and secondary lymphedema were included when the outcomes of primary lymphedema were explicitly distinguished from the analysis. Otherwise, studies dealing with primary and secondary lymphedema where data were aggregated without distinction were excluded. Studies reporting outcomes of the surgical management of exclusively lymphatic malformations, malignancies secondary to lymphedema, or genital lymphedema, were excluded.

Study Selection and Data Extraction

Once duplicated citations were excluded, two independent authors (B.H.K-C. and J.M.E) evaluated the included references based on the title and abstract. Subsequently, a full-text assessment was accomplished in the remaining studies. Disagreements through this two-step process were solved by a third author (M.A.G-G.). Two authors performed data extraction independently. Extracted data included author and year, location, number of patients, age, lymphedema stage, duration of lymphedema, associated syndromes or comorbidities, surgical technique, adjuvant procedures, postoperative protocol, outcomes, complications, and follow-up. Cumulative estimates were calculated as weighted means.

Quality Assessment and Risk of Bias

Appraisal of the levels of evidence was performed independently by two reviewers (J.M.E. and M.A.G-G.) using the Oxford Centre for Evidence-Based Medicine (OCEBM) (►**Supplementary Table S2** [available in the online version only]).[33] The risk of bias was evaluated by operating the Newcastle–Ottawa Scale (NOS; ►**Supplementary Table S3** [available in the online version only]) for observational cohort studies, and the Methodological Quality Assessment Tool (MQAT) for case reports and case series (►**Supplementary Table S4** [available in the online version only]).[34,35]

Results

Literature Search

Overall, 2,033 citations were identified during the electronic bibliographic search. After duplicated references were eliminated, 1,777 records were screened, and 1,203 were excluded based on the title and abstract review. Following a full-text review, 55 articles met the inclusion criteria and were selected for data extraction. The PRISMA flow chart can be seen in ►**Fig. 1**.[5,21,22,26,36–84]

An overview of the studies' characteristics is displayed in ►**Table 1**.

Quality Assessment

All studies had a level of evidence of 4 using the OCEBM instrument (►**Table 1**), indicating that most studies included were case series and poor-quality cohort and case–control studies. Most case series and case reports had a moderate risk of bias when using the MQAT as 12 studies scored 5, 19 scored 4, and 3 scored 3. The evaluation of the methodological quality of cohort studies was as follows: 12 studies had an NOS score of 6, and 9 scored 5, which showed a low-to-moderate risk of bias.

Demographic and Clinical Characteristics

This review included 485 patients with primary lymphedema. The average age was 36.44 years and ranged from 1 to 94 years, reported in 52 studies. Seven (12%) and 53 (96%) articles reported the surgical management for upper extremity lymphedema and lower extremity lymphedema, respectively. The average follow-up was 24.74 months (range, 1–324 months), reported in 47 studies. The average duration of lymphedema before the surgical intervention reported in the articles was 14.2 years (range, 1 month–52 years), reported in 365 patients. Different lymphedema staging systems were reported in the included studies; the most common was the International Society of Lymphology (ISL) scale ($n = 17$), followed by the Cheng's lymphedema grading scale ($n = 7$) and the Campisi staging system ($n = 5$). See ►**Table 1**.

Several congenital malformations and syndromes were associated with primary lymphedema including Milroy's disease ($n = 16$), Klippel–Trenaunay syndrome ($n = 7$), Meige's disease ($n = 3$), Turner syndrome ($n = 1$), spina bifida with hydrocephalus ($n = 1$), absence of the thoracic duct ($n = 1$), congenital vascular lesions ($n = 3$), and complex lymphatic malformations ($n = 1$).

Lymphaticovenous Anastomosis

This procedure has been reported since 2003. Twenty-four studies adequately reported the surgical outcomes of 177 patients with primary lymphedema treated with LVAs. Most studies reported LE (91%) surgical outcomes, and only two reported outcomes of the UE (8%). Staging of lymphedema was heterogeneously reported among studies. The most common stages treated with LVAs were ISL II ($n = 130$) and ISL I ($n = 13$). Only seven patients with lymphedema stage III were treated using this modality. When using Cheng's classification, most patients were in stage II to III (n = 58). When using the Campisi staging system, most patients were in stage II ($n = 4$), followed by stage III ($n = 3$) and IV ($n = 1$).

The average number of LVAs per patient was 3.44 (range, 1–9), reported in 174 patients. The most common LVA techniques were the end-to-side, end-to-end, or side-to-end technique; nonetheless, several studies reported the use of π-shaped LVAs, octopus LVAs, and side-to-end anastomosis through temporary lymphatic expansion. An overview of the results is displayed in ►**Table 2**. Surgical outcomes were not homogeneously reported. In most studies, an improvement of the LE lymphedema index, the QoL, and lymphedema symptoms, as well as a reduction of the cross-sectional area, episodes of cellulitis, the need for compression garments, and circumferential measures were reported. Some papers reported marginal improvements, for example, Mihara et al reported an average reduction rate of 2.7% in limb circumference,[69] while the same author had previously reported average size reductions of around 90%.[51] In contrast, Auba et al reported an increment in the limb perimeter in comparison to preoperative measures.[53] Hara et al also reported that the LE circumference increased following LVA

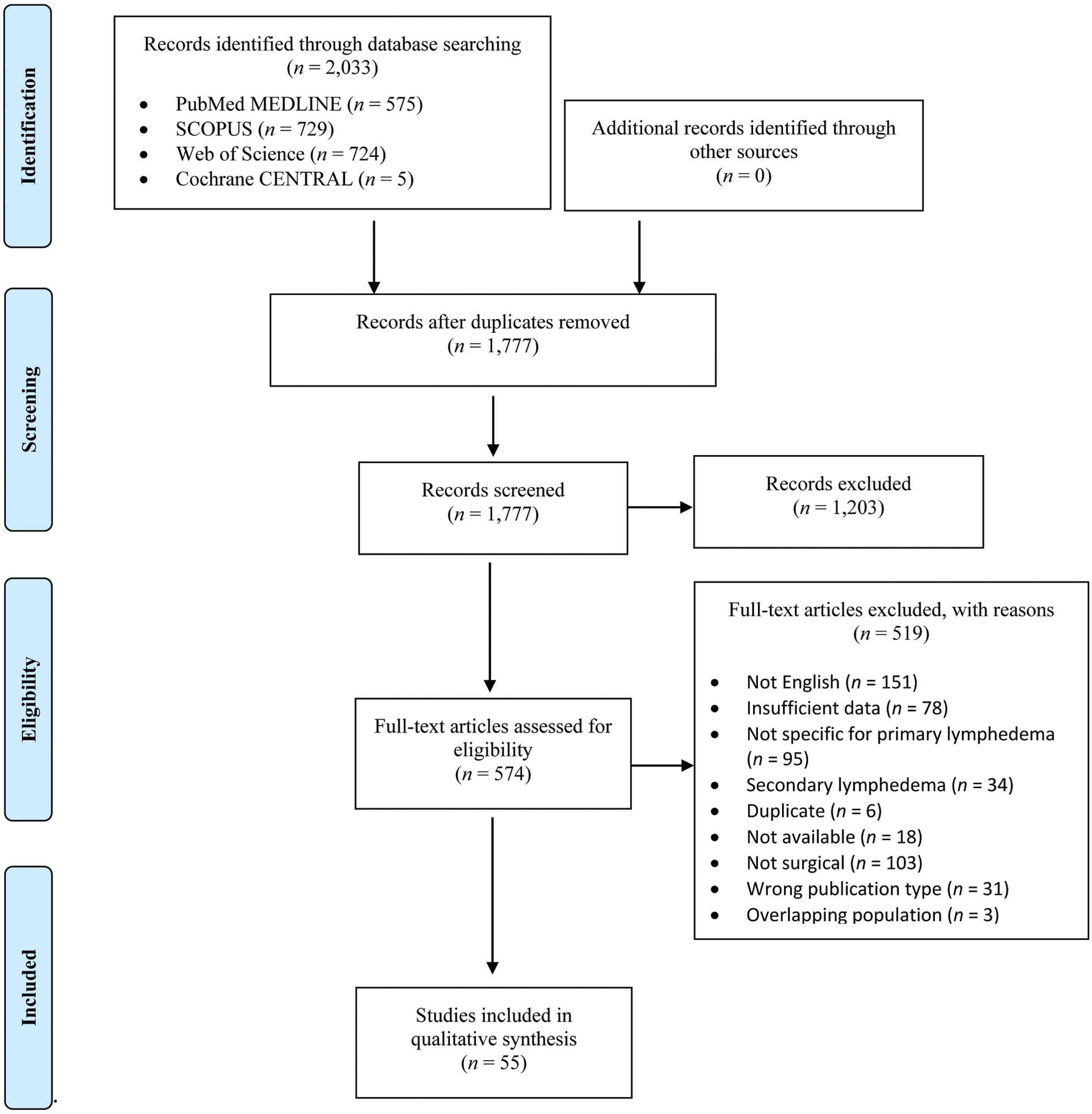

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart. CENTRAL, Central Register of Controlled Trials.

treatment in patients with an onset age of <11 years; but significantly decreased in patients with an onset age of >11 years.[15] QoL improvement was represented by diminution or absence of cellulitis episodes with less need for compression garments[77]; reported explicitly in at least 25% of papers. Systematic assessment of the QoL was seldom reported using the Lymphoedema Quality of Life Questionnaire (LYMQoL).[16] The overall complication rate was 1%. The most common complications reported were several episodes of a lymphatic fluid leak in one patient and failure of the anastomosis.[52,55]

Vascularized Lymph Node Transfer

We found 12 articles reporting outcomes of VLNT for primary lymphedema, accounting for 82 treated patients. An overview of the results is displayed in ►**Table 3**. This technique was used mainly for the treatment of LE lymphedema. Pedicled VLNTs were described in two series. Fonkalsrud et al[37] reported an omentum transposition as described by Goldsmith[37], while Borz et al reported modified enteromesenteric bridging.[72] The remaining eight studies reported the use of free VLNT, including the submental-VLNT (SM-VLNT; 33.33%), groin-VLNT (8.3%), vascularized omental lymph node transfer (8.3%), gastroepiploic-VLNT (16.6%), lateral thoracic-VLNT (16.6%), and the first web space-VLNT (8.3%).

The outcomes were not reported uniformly; however, some reports stated that the average circumference reduction rate ranged from 17.2 to 61%, tonicity was reduced by 6.8 ± 0.8%, and the episodes of cellulitis decreased by 2.67 to 3 times/year during a follow-up ranging from 16 to 63 months. As a whole, a reduction in cellulitis episodes was reported explicitly in at least 40% of papers. Qualitatively, most studies reported improved symptoms and

Table 1 Overview and quality assessment of included studies reporting surgical outcomes of primary lymphedema

Author, year	Journal	Location	OCEBM	NOS	Patients (n)	Age (years)	Site	Grading	Lymphedema duration (years)	Syndrome or comorbidities	Follow-up (months)
MacKmull et al, 1950	Plastic and Reconstructive Surgery	Philadelphia, Pennsylvania	4	5[a]	1	25	LE	NR	25	NR	8
Fonkalsrud et al, 1969	Journal of Pediatric Surgery	Los Angeles, California	4	3[a]	4	(Range, 3–15)	LE	NR	NR	NR	>6
Tilley et al, 1974	The Canadian Medical Association Journal	Toronto, Canada	4	4[a]	1	40	LE	III ISL	26	NR	10
Dellon et al, 1977	Plastic and Reconstructive Surgery	Baltimore, Maryland	4	4[a]	9	31 (range, 22–40)	LE	NR	Range, 12–18	NR	127 (range, 14–277)
					1	1.5	UE	NR	1.45	NR	216
Feins et al, 1977	Journal of Pediatric Surgery	Boston, Massachusetts	4	5	38	Range, 1–19	LE ($n = 36$) UE ($n = 2$)	NR	NR	NR	Range, 1–60
Smeltzer et al, 1985	Pediatrics	Rochester, Minnesota	4	5	16	NR	NR	NR	NR	Milroy's disease ($n = 1$) Meige's disease ($n = 3$)	Range, 0–324
Louton et al, 1989	Annals of Plastic Surgery,	Charleston, South Carolina	4	3[a]	1	26	LE	NR	13	NR	NR
Mavili et al, 1994	Lymphology	Ankara, Turkey	4	4[a]	4	NR	LE	NR	NR	NR	Range, 12–36
Dumanian et al, 1996	Lymphology	Pittsburgh, Pennsylvania	4	4[a]	1	35	LE	NR	15	NR	180
Koshima et al, 2003	Journal of Reconstructive Microsurgery	Okayama, Japan	4	4[a]	4	33 (range, 12–53)	LE	NR	9.25 (range, 2–24)	NR	93 (range, 60–108)
Fraga et al, 2004	Lymphology	São Paulo, Brazil	4	4[a]	1	21	UE	NR	15	NR	0.5
Hosnuter et al, 2006	Medical Science Monitor	Zonguldak, Turkey	4	4[a]	1	47	LE	III ISL	16	NR	12
Greene et al, 2006	Plastic and Reconstructive Surgery	Boston, Massachusetts	4	4[a]	1	34	LE	NR	10	Spina bifida Paraplegia Hydrocephalus Ventriculoperitoneal shunt	18
Espinosa et al, 2009	Journal of Vascular Surgery	Mexico City, Mexico	4	4[a]	1	26	LE	III ISL	10	NR	14
Eryilmaz et al, 2009	Aesthetic Plastic Surgery	Ankara, Turkey	4	5[a]	1	29	LE	NR	20	NR	22
van der Walt et al, 2009	Annals of Plastic Surgery	Cape Town, South Africa	4	5	8	34.8 (range, 13–57)	LE	NR	17.6 (range, 12–31)	NR	27.3 (range, 12–90)
Karonidis et al, 2010		Kaohsiung, Taiwan	4	6	8		LE	Advanced		NR	36

Table 1 (*Continued*)

Author, year	Journal	Location	OCEBM	NOS	Patients (*n*)	Age (years)	Site	Grading	Lymphedema duration (years)	Syndrome or comorbidities	Follow-up (months)
	Annals of Plastic Surgery					21.6 (range, 16–51)			6.37 (range, 3–10)		
Pereira et al, 2010	International Journal of General Medicine	São José do Rio Preto, Brazil	4	3[a]	2	59 (range, 65–64)	LE	III ISL	NR	NR	3
Mihara et al, 2011	Clinical Radiology	Tokyo, Japan	4	4[a]	2	52	LE	II ISL	NR	NR	23.6
Yamamoto et al, 2011	Journal of Plastic, Reconstructive and Aesthetic Surgery	Tokyo, Japan	4	4[a]	2	20 (range, 15–25)	LE and scrotum	NR	20 (range, 15–25)	NR	34 (range, 15–53)
Auba et al, 2012	Microsurgery	Pamplona, Spain	4	4[a]	1	52	LE	III Campisi	24	NR	18
Suehiro et al, 2012	Surgery Today	Yamaguchi, Japan	4	4[a]	1	25	LE and scrotum	NR	12	Absence of the thoracic duct and dilated iliac lymph trunks	12
Yamamoto et al, 2013	PLoS ONE	Tokyo, Japan	4	6	6	Range, 25–71	LE	I II III ISL	Range, 0.75–18	NR	6
Ayestaray et al, 2014	Journal of Reconstructive Microsurgery	Evry, France	4	5[a]	1	34	LE	NR	23	Turner syndrome	12
Gómez Martín et al, 2014	Journal of Plastic, Reconstructive and Aesthetic Surgery	Madrid, Spain	4	4[a]	1	57	LE	NR	5	NR	5
Qiu et al, 2014	Plastic and Reconstructive Surgery - Global Open	Taoyuan, Taiwan	4	4[a]	1	13	LE	NR	NR	Klippel–Trenaunay	3
Akita et al, 2015	Annals of Plastic Surgery	Chiba, Japan	4	6	1	34	LE	NR	13	NR	12
Hara et al, 2015	Plastic and Reconstructive Surgery	Tokyo, Japan	4	6	62	42 (range, 10–90)	LE	1 ($n=8$) 2a ($n=23$) 2b ($n=46$) 3 ($n=2$) ISL	10.6 (range, 0.1–52)	NR	19.5 (range, 5.6–54.3)
Koshima et al, 2015	Journal of Reconstructive Microsurgery	Tokyo, Japan	4	5[a]	2	17.5 (range, 15–20)	LE	NR	2.25 (range, 2–2.5)	NR	3.5 (range, 3–4)
Chen et al, 2015	Journal of Reconstructive Microsurgery	Iowa City, Iowa	4	5[a]	1	50	LE	IV Campisi	NR	NR	Range, 6–9

(*Continued*)

Table 1 (*Continued*)

Author, year	Journal	Location	OCEBM	NOS	Patients (*n*)	Age (years)	Site	Grading	Lymphedema duration (years)	Syndrome or comorbidities	Follow-up (months)
Ito et al, 2016	Microsurgery	Taoyuan, Taiwan	4	5[a]	2	32.5 (range, 29–36)	LE	1.5 Cheng's	8 (range, 2–14)	NR	10.5 (range, 3–19)
Gennaro et al, 2016	European Review for Medical and Pharmacological Sciences	Siena, Italy	4	6	8	42 (range, 16–56)	LE	I ($n=1$) II ($n=6$) III ($n=1$) ISL	7.85 (range, 2–15)	NR	36
					1	48	UE	III ISL	4	NR	36
Greene et al, 2016	Annals of Plastic Surgery	Boston, Massachusetts	4	4[a]	8	41.87 (range, 17–66)	LE	NR	NR	NR	36
Lee et al, 2016	Lymphology	Los Angeles, California	4	5[a]	1	65	LE	NR	35	NR	15
Yamamoto et al, 2016	Journal of Plastic Reconstructive and Aesthetic Surgery	Tokyo, Japan	4	5[a]	1	49	LE	NR	5	NR	18
Chen et al, 2016	Journal of Reconstructive Microsurgery	Iowa City, Iowa	4	6	4	54.5 (range, 50–62)	LE	III ($n=1$) IV ($n=3$) Campisi	NR	NR	12
Mihara et al, 2016	Plastic and Reconstructive Surgery	Saitama, Tokyo	4	5	15	Range, 24–94	LE	I–III ISL	NR	NR	Range, 6–51
Lamprou et al, 2017	British Journal of Surgery	Drachten, The Netherlands	4	6	47	43.6 (range, 12–4)	LE	"End stage"	20 (range, 10–33)	NR	12
Lee et al, 2017	Microsurgery	Seoul, South Korea	4	5[a]	7	37 (range, 11–58)	LE	II ($n=4$) III ($n=3$) Campisi	6.78 (range, 1–15)	NR	24
Stewart et al, 2018	Journal of Plastic Reconstructive and Aesthetic Surgery	Dundee, United Kingdom	4	6	42	41 (range, 20–68)	LE	II–III ISL	20 (range, 4–45)	NR	16 (range, 6–48)
Borz et al, 2018	Annali Italiani di Chirurgia	Munes, Romania	4	4[a]	18	18	LE and scrotum	NR	14	Praecox	3
Cheng et al, 2018	Plastic and Reconstructive Surgery - Global Open	Taoyuan, Taiwan	4	6	17	31.5 (range, 2–57)	LE	I ($n=2$) II ($n=10$) III ($n=2$) IV ($n=5$) Cheng's	4.51 (range, 0.25–9.6)	Klippel–Trenaunay ($n=4$)	18.2 ± 8.9
Sachanandani et al, 2018	Journal of Surgical Oncology	Taoyuan, Taiwan	4	5[a]	3	25 (range, 13–43)	LE	I ($n=1$) IV ($n=4$) Cheng's	13 (range, 8–18)	Klippel–Trenaunay ($n=2$) Concomitant vascular lesions ($n=3$)	23 (range, 19–30)

Table 1 (*Continued*)

Author, year	Journal	Location	OCEBM	NOS	Patients (*n*)	Age (years)	Site	Grading	Lymphedema duration (years)	Syndrome or comorbidities	Follow-up (months)
Giacalone et al, 2019	Journal of Clinical Medicine	Mechelen, Belgium	4	4[a]	1	27	LE	NR	27	Complex lymphatic malformation	4
Maruccia et al, 2019	Microsurgery	Bari, Italy	4	5[a]	1	32	LE	III ISL	3	NR	3
AlJindan et al, 2019	Plastic and Reconstructive Surgery	Taoyuan, Taiwan	4	6	15	NR	LE ($n=14$) UE ($n=1$)	1.2 Cheng's	NR	NR	14.2 (range, 12.3–16.1)
Bolleta et al, 2020	Journal of Surgical Oncology	Taichung, Taiwan	4	5	15	16 ± 0.8	LE	II–III Cheng's	16 ± 0.8	Milroy's disease	20.2 ± 2.8
Robertson et al, 2020	Journal of Vascular Surgery	Cincinnati, Ohio	4	4[a]	2	42.5 (range, 35–50)	LE	NR	4.5 (range, 3–6)	NR	12
Damstra et al, 2020	Journal of Clinical Medicine	Drachten, The Netherlands	4	6	28	44.7 (range, 32–66)	LE	III ISL	27.5 (range, 6–36)	NR	54 (range, 36–60)
Ciudad et al, 2020	Microsurgery	Taichung, Taiwan	4	6	11	(range, 26–53)	LE and UE	II and III ISL	3.5 (range, 0.6–6.3)	NR	32.8 (range, 24–49)
Cheng et al, 2020	Microsurgery	Taoyuan, Taiwan	4	5[a]	9	9.2 (range, 2–19)	LE	2.6 ± 1.6 Cheng's	9.3 (range, 2–19)	NR	38.4 (range, 16–63)
Drobot et al, 2021	Journal of Vascular Surgery	Hiroshima, Japan	4	5	22	34	LE	II ISL	7.3	NR	9 (range, 3–24)
Onoda et al, 2021	Journal of Vascular Surgery	Kagawa, Japan	4	5	2	46 (range, 30–62)	LE	II ISL	NR	NR	31 (range, 6–48)
Scaglioni et al, 2021	Microsurgery	Lucerne, Switzerland	4	5	1	46	LE	III Campisi	NR	NR	9
					2	4.5 (range, 2–7)	UE	2.5 Cheng's	4 (range, 3–5)	NR	37 (range, 31-43)
Hayashi et al, 2022	Journal of Clinical Medicine	Chiba, Japan	4	5	26	44.2 (range, 16–82)	LE	1 ($n=3$) 2a ($n=15$) 2b ($n=14$) 3 ($n=1$) ISL	8.6 (0.8–29)	NR	17.5 (range, 6–36)

Abbreviations: ISL, International Society of Lymphology; LE, lower extremity; OCEBM, Oxford Centre for Evidence-Based Medicine: Levels of Evidence; NOS, Newcastle–Ottawa Scale; NR, not reported; UE, upper extremity.

[a]Case reports and case series in which the Methodological Quality Assessment Tool proposed by Murad et al[34] was used.

Table 2 Studies reporting surgical outcomes of primary lymphedema using lymphaticovenous anastomosis

Author, year	Patients (*n*)	Site	Surgical technique	Other procedures	Postoperative treatment	Outcomes	Complications
Koshima et al, 2003	4	LE	LVA Number of anastomoses (mean): 4.25 (range, 2–5)	Fat flap	Compression garments	Remarkable reduction in the circumference (8 cm each in the B/L lower legs) Patients achieved a 55.6% reduction of the excess circumference	NR
Mihara et al, 2011	2	LE	LVA Number of anastomoses (mean): 3.5 (range, 3–4)	NR	NR	The average size reduction was 90.15% Degree of limb hardness decreased from 2 to 1	NR
Yamamoto et al, 2011	2	LE and scrotum	Multisite LVA Number of anastomoses (mean): 6 (range, 3–9)	NR	NR	No recurrence ($n = 2$)	Several episodes of lymphorrhea ($n = 1$)
Auba et al, 2012	1	LE	LVA	NR	Limb elevation	The average preoperative limb perimeter increased from 32.1 to 32.9 cm	–
Suehiro et al, 2012	1	LE and scrotum	LVA ($n = 2$)	NR	Medium-chain triglycerides supplement Compression therapy	2,000-mL reduction from the initial presentation Episodes of cellulitis decreased from every month to none	NR
Yamamoto et al, 2013	6	LE	SEATTLE ($n = 2$) Standard LVA ($n = 4$)	NR	NR	The LEL index decreased 18.2 ± 15.9 in patients with primary lymphedema LEL index reduction in SEATTLE group was significantly greater that in non-SEATTLE group	11% of LVAs resulted in anastomosis failure
Bekara et al, 2014	1	LE	LVA π-shaped Number of anastomoses: 4	NR	NR	The circumferential reduction rate was 17% Cross-sectional area reduction rate was 32.2% Average volume reduction rate was 36.5%	No complications
Akita et al, 2015	1	LE	Multiple LVA	NR	NR	LEL index improved from 258.8 to 245.2 for the right leg, and from 292.5 to 265.5 for the left leg	NR
Hara et al, 2015	62	LE	LVA ($n = 79$) Number of anastomoses (mean): 4.5 (range, 0–9)	NR	NR	LE circumference increased after LVA in patients with an onset age of 1 year or later and before age 11 years, but significantly decreased in patients with an onset age older than 11 years	NR

Table 2 (*Continued*)

Author, year	Patients (n)	Site	Surgical technique	Other procedures	Postoperative treatment	Outcomes	Complications
Ito et al, 2015	2	LE	LVA Number of anastomoses (mean): 2	NR	Compression therapy	The mean circumference reduction rate was 70.4%	NR
Yamamoto et al, 2015	1	LE	Number of drainage pathways/octopus LVA: 14 in 4	NR	NR	Postoperative Campisi stage: II Reduction of the LEL index from 378 to 352	NR
Gennaro et al, 2016	8	LE	LVA Number of anastomoses (mean): 5.75 (range, 5–7)	NR	Lymphatic drainage and compression stocking	Average size reduction was 61% (range 41–87%)	No complications
	1	UE	LVA Number of anastomoses: 5	NR	Lymphatic drainage and compression stocking	41% size reduction	No complications
Yamamoto et al, 2016	1	LE	LT-VLNT + ELLA LVA Number of anastomoses: 2	NR	Compression garment	No episode of cellulitis with reduced degree of compression treatment Lymphedematous volume decreased from 306 to 264 in terms of LEL index	No complications
Chen et al, 2016	4	LE	LVA Number of anastomoses (mean): not specified	NR	NR	12-month postoperative Campisi stage II ($n = 2$) and III ($n = 2$) Significant improvement in QoL scores: decreased 10.5 Overall reduction of 17 point in the LEL index	NR
Mihara et al, 2016	15	LE	Multisite LVA	NR	NR	The average reduction rate was 2.7%	NR
Lee et al, 2017	7	LE	LVA Number of anastomoses (mean): 2.42 (range, 1–3)	NR	Physical therapy	Reduction rate of volume: 39.2 ± 43.9 at 6 months, 20.2 ± 44.2 at 12 months, 38.7 ± 57.4 at 24 months	NR
Cheng et al, 2018	17	LE	LVA ($n = 4$) Number of anastomoses: 1	SM-VLNT ($n = 15$)	NR	Following LVA: Limbs had a mean 1.9 ± 2.9 cm circumference reduction Reduction in body weight 6.6 ± 5.9 kg in VLNT and of 1.7 ± 0.6 kg in LVA LYMQoL improvement for LVA	NR
Giacalone et al, 2019	1	LE	LVA	NR	NR	The difference in volume between the left and right leg was reduced from 1,222 to 224 mL	No complications

(*Continued*)

Table 2 (*Continued*)

Author, year	Patients (*n*)	Site	Surgical technique	Other procedures	Postoperative treatment	Outcomes	Complications
AlJindan et al, 2019	15	LE ($n = 14$) UE ($n = 1$)	LVA Number of anastomoses (mean): 1	NR	NR	Episodes of cellulitis were significantly reduced from 1.7 times/year to 0.7 times/year Circumferential Difference improvement was 3% Patients did not need compression garments postoperatively	No complications
Drobot et al, 2020	22	LE	LVA Number of anastomoses (mean): 3.1 (range, 1–4)	NR	Compression therapy protocol (3 months)	Absolute volume change (in milliliters) at 6 months postoperatively: 372 ± 52 (55%)	No complications
Cheng et al, 2020	2	UE and LE	LVA	NR	None of the patients used compression garments postoperatively	The mean limb circumferential difference was improved by 5.5% (preoperative, 7.7; postoperative 5.5) Episodes of cellulitis decreased by 2.2 times/year	No complications
Onoda et al, 2020	2	LE	LVA Number of anastomoses (mean): 4.5 (range, 4–5)	NR	Inpatient complex decongestive physiotherapy	Percentage reduction from admission to follow-up: 19.4% (range, 8.1–30.7%)	No complications
Scaglioni et al, 2020	1	LE	LVA Number of anastomoses (mean): 1 deep LVA and 5 superficial LVAs	NR	NR	Initial Campisi stage III to Final Campisi stage Ib Overall improvement of symptoms	NR
Hayashi et al, 2022	26	LE	LVA Number of anastomoses (mean): 8.7 total; posterior side 3.5 LVAs and medial–anterior side 4.6 LVAs	Previous LVAs	NR	Mean reduction of the LEL index 5.3–32.9 (18.1) After second procedure: 10.5 ± 4.5 in posterior side LVAs, 5.5 ± 3.6 in medial–anterior side LVAs	NR

Abbreviations: B/L, bilateral; ELLA, efferent lymphaticolymphatic anastomosis; LVA, lymphaticovenous anastomosis; LE, Lower extremity; LEL, lower extremity lymphedema; LYMQoL, Lymphoedema Quality of Life Study; NR, not reported; SEATTLE, side-to-end anastomosis through temporary lymphatic expansion; SM-VLNT, submental-vascularized lymph node transfer; UE, upper extremity; VLNT, vascularized lymph node transfer.

Table 3 Studies reporting surgical outcomes of primary lymphedema using vascularized lymph node transfer

Author, year	Patients (*n*)	Site	Surgical technique	Other procedures	Postoperative treatment	Outcomes	Complications
Fonkalsrud et al, 1969	1	LE	Omentum transposition as described by Goldsmith	NR	NR	Leg swelling subsided during the first 6 months after operation, but gradually returned as the patient became overweight	NR
Gómez Martín et al, 2014	1	LE	G-VLNT (First stage) LT-VLNT (Second stage)	NR	Manual drainage, compressive bandages	Average circumference reduction rate of 59.4% No episodes of cellulitis	No complications
Qiu et al, 2014	1	LE	SM-VLNT	NR	NR	Symptomatic improvement Circumferential reduction rates in the right LE at 15 cm AK, 15 cm BK, and 10 cm AA were 50, 53.3, and 33%, respectively	No complications
Koshima et al, 2015	2	LE	FWS-VLNT ($n=2$)	NR	Compression therapy ($n=1$)	Dramatic improvement without any postoperative complications	NR
Yamamoto et al, 2016	1	LE	LT-VLNT + ELLA	LVA	Compression garment	No episode of cellulitis with reduced degree of compression treatment, and lymphedematous volume decreased from 306 to 264 in terms of lower extremity lymphedema index were reported	No complications
Borz et al, 2018	18	LE and scrotum	Modified enteromesenteric bridging	NR	NR	Decrease of the mid-calf diameters with 5.2 cm on the right and 4.8 cm on the left	No complications
Cheng et al, 2018	17	LE	SM-VLNT ($n=15$)	LVA ($n=4$)	NR	Limbs that underwent VLNT had a mean 3.7 ± 2.9 cm circumference reduction Reduction in body weight 6.6 ± 5.9 kg in VLNT and of 1.7 ± 0.6 kg in LVA LYMQoL in overall score improvement for VLNT and LVA	NR
Sachanandani et al, 2018	3	LE	SM-VLNT ($n=3$)	LVA ($n=1$)	NR	Final circumferential reduction rate of 39.16% above the knee and 34.5% below the knee	Hematoma ($n=1$) Venous thrombosis ($n=2$) Revision surgery ($n=2$)

(*Continued*)

Table 3 (*Continued*)

Author, year	Patients (*n*)	Site	Surgical technique	Other procedures	Postoperative treatment	Outcomes	Complications
Bolleta et al, 2019	15	LE	GE-VLNT ($n=15$)	Brorson's secondary SAL	NR	The average circumference reduction was of 5.9 ± 1.2 cm at mid-thigh, 4.9 ± 2.2 cm at mid-calf, 3.7 ± 0.8 cm at the ankle, and 1.7 ± 0.9 cm at mid-foot Tonicity overall was reduced by 6.8 ± 0.8% No episodes of cellulitis	No complications
Maruccia et al, 2019	1	LE	GE-VLNT—Laparoscopic	CDP—1 week preoperatively	Compression garments	The limb circumference reduction was 62.5% below the knee, and 41.4% above the knee	No complications
Ciudad et al, 2020	11	LE and UE	G-VLNT SC-VLNT GE-VLNT—Open and Laparoscopic A-VLNT IC-VLNT	NR	NR	Circumference reduction rate, % (mean ± SD): 18.9 ± 14.0 The positive circumference reduction was not significantly associated with VLNT	NR
Cheng et al, 2020	9	LE	SM-VLNT ($n=9$) Volt ($n=1$)	NR	NR	The mean limb circumferential difference was improved by 17.2% (preoperative, 26.98; postoperative 22.34) Episodes of cellulitis decreased by 2.67 times/year No use of compression garments postoperatively	Venous congestion with successful salvage (n = 3) Partial skin paddle necrosis (n = 2)
	2	UE	SM-LNT ($n=1$)	NR	NR	The mean limb circumferential difference was improved by 61% (preoperative, 22.7; postoperative, 8.3) Episodes of cellulitis decreased by 3 times/year	No complications

Abbreviations: AA, above the ankle; AK, above the knee; BK, below the knee; A-VLNT, appendicular VLNT; CDP, complex decongestive physiotherapy; ELLA, efferent lymphaticolymphatic anastomosis; FWS-VLNT, first web space VLNT; G-VLNT, groin VLNT; GE-VLNT, gastroepiploic VLNT; LE, lower extremity; IC-VLNT, ileocecal VLNT; LT-VLNT, lateral thoracic; NR, not reported; VLNT; LVA, lymphaticovenous anastomosis; LYMQoL, Lymphoedema Quality of Life Questionnaire; SAL, suction-assisted lipectomy; SC-VLNT, supraclavicular VLNT; SD, standard deviation; SM-VLNT, submental-VLNT; UE, upper extremity; VLNT, vascularized lymph node transfer; VOLNT, vascularized omental lymph node transfer.

[a]Although labeled differently, these flaps correspond to the same procedure.

QoL.[21,22,57,58,73,74,76] Unsatisfactory results were reported in the patient managed with omentum transposition: the leg swelling initially subsided during the first 6 months postoperatively, but the edema gradually returned as the patient became overweight. The overall complication rate was 13%; these included hematoma formation ($n = 1$), venous congestion or thrombosis ($n = 4$), and microsurgical revisions ($n = 4$).[22,73]

Suction-assisted Lipectomy

One hundred and two patients were treated in 8 studies reporting the use of SAL; among them, one specifically used a two-staged SAL technique. An overview of the results is shown in ►**Table 4**. Most of the patients had stage II to III ISL lymphedema or had "end-stage" lymphedema. The mean reduction of original excess volume ranged from 71.9 to 94%.[64,71] Qualitatively, several articles reported a reduction in cellulitis episodes and an improvement of the QoL.[40,46,64] Remarkably, 87.5% of studies highlighted the importance of postoperative compression bandages. The overall complication rate was 11%; these included limited liposuction in certain areas ($n = 1$), skin necrosis ($n = 5$), significant blood loss ($n = 4$), cellulitis ($n = 1$), the requirement of further procedures ($n = 1$), decubitus ulcers ($n = 1$), and temporary peroneal nerve palsy ($n = 2$).[64,65,71]

Excisional Procedures

We found 15 studies reporting outcomes of excisional procedures for primary lymphedema of the extremities in 124 patients. An overview of the results is displayed in ►**Table 4**. Studies reporting the stage of lymphedema included patients with stage III ISL or were referred to as "advanced" disease. Several excisional procedures were reported including a two-stage modified Kondoleon–Sistrunk procedure ($n = 2$); skin-sparing subcutaneous tissue excision ($n = 11$); the Charles' procedure ($n = 16$), the modified Charles ($n = 6$), and delayed modified Charles ($n = 8$); the standard Homan's procedure ($n = 7$); a single-stage ($n = 26$), double-stage ($n = 10$), and triple-stage modified Homan's procedure ($n = 2$); limb disarticulation ($n = 1$); tissue resection or shaving procedures ($n = 28$). Most studies reported a remarkable reduction in the size of the LE, improvement of symptoms, and a reduction in the episodes of lymphangitis and cellulitis over a follow-up period ranging from 1 to 60 months. Remarkably, van der Walt et al used a modified Charles' procedure delaying skin grafting by 5 to 7 days using negative pressure dressings. An average resection of 8.5 kg of lymphedematous tissue was reported without any major complication.[48] Karonidis et al reported a modified Charles procedure with excision of the soft tissue at the dorsum of the toes while preserving the extensor tendon and its paratenon and the skin flaps at the web spaces.[49] Additionally, wedge resection was performed over the lateral and medial aspect thigh as a Homan's procedure, providing a smooth transition between the leg and the thigh.[49] In that series, 18 of 20 patients achieved satisfactory aesthetic and functional results and no recurrent infections had been reported during a 3-year follow-up.[49] Poor cosmetic results were commonly

Table 4 Studies reporting surgical outcomes of primary lymphedema using suction-assisted lipectomy and excisional procedures

Author, year	Patients (*n*)	Site	Surgical technique	Other procedures	Postoperative treatment	Outcomes	Complications
Mainly suction-assisted lipectomy							
Louton et al, 1989	1	LE	SAL	NR	Excision of redundant tissue, 4 days postoperatively	Large amount of redundant skin and subcutaneous tissue draped over an otherwise normal leg	The fibrotic areas over the dorsum of the feet were difficult to debulk
Greene et al, 2006	1	LE	SAL	NR	Pressure bandaging	Lower extremity circumferential measurements corresponded to a 75% reduction from her preoperative volume	NR
Espinosa et al, 2009	1	LE	SAL	NR	40 mm Hg compression bandages	Volume of the legs decreased from 10.7 L and 8.9 L to 6.4 L and 6.1 L, postoperatively Cellulitis has not occurred, and antibiotics have not been required so far	No complications

(*Continued*)

Table 4 (*Continued*)

Author, year	Patients (n)	Site	Surgical technique	Other procedures	Postoperative treatment	Outcomes	Complications
Eryilmaz et al, 2009	1	LE	Two-stage SAL	NR	NR	20% reduction from his first preoperative measurements	No complications
Greene et al, 2016	8	LE	SAL	NR	Compression bandages	The mean reduction in excess extremity volume was 73% (range, 48–94%) Better quality of life; none exhibited recurrence	Skin necrosis ($n=2$) Significant blood loss ($n=2$) Cellulitis ($n=1$) Surgical debridement ($n=1$)
Lamprou et al, 2016	47	LE	SAL	NR	Compression bandages	Average size reduction was 79% and absolute volume reduction of 3,670 mL compared with preoperative affected leg volume A reduction from 8 attacks of cellulitis to 0.2 attacks per year	Decubitus ulcer ($n=1$)
Lee et al, 2016	1	LE	SAL	NR	Continuous compression garment	A stable overall excess volume reduction of 4,227 mL (86%) was achieved at 15 months postoperatively which remained stable thereafter	NR
Stewart et al, 2017	42	LE	SAL	NR	Wrap garments	71.9% reduction of original excess volume at 3 months postoperative 84.3% reduction of original excess volume at 1 year postoperative	Skin necrosis ($n=3$) Temporary peroneal nerve palsy ($n=2$) Significant blood loss ($n=2$)
Mainly excisional procedures							
MacKmull et al, 1950	1	LE	Two-stage modified Kondoleon–Sistrunk Procedure	NR	Elevation 75 degrees	Remarkable reduction in size of the leg No recurrence of lymphangitis	Internal saphenous nerve injury ($n=1$)
Fonkalsrud et al, 1969	3	LE	Skin-sparing subcutaneous tissue excision	NR	Elastic bandages	Adequate cosmesis during postoperative assessment	Transfusion of blood units ($n=$multiple) Delayed wound healing ($n=2$)

Table 4 (*Continued*)

Author, year	Patients (n)	Site	Surgical technique	Other procedures	Postoperative treatment	Outcomes	Complications
Tilley et al, 1974	1	LE	Charles procedure—STSG Staged-tissue excision	NR	NR	Marked improvement in function; the appearance is less than ideal but is vastly improved	Transfusion of blood units ($n=2$) Dermatosis ($n=1$) Skin graft loss ($n=1$)
Dellon et al, 1977	9	LE	Charles procedure	NR	Wrap garments	Excellent functional and cosmetic outcomes Lymphedema in the dorsum of the foot ($n=2$)	Crevices and pits ($n=1$) Chronic ulceration ($n=1$) Scar revision and release ($n=1$)
	1	UE	Charles procedure—FTSG	NR	NR	Excellent functional and cosmetic outcomes	Scar revision and release ($n=1$)
Feins et al, 1977	38	LE (n = 36) UE (n = 2)	Single-stage modified Homan's procedure ($n=26$) Double-stage ($n=10$) Triple-stage ($n=2$)	NR	Compression therapy 3 months	Improvement of symptoms ($n=38$) No episodes of lymphangitis and cellulitis	Wound dehiscence ($n=2$) Revision surgery ($n=1$) Seroma ($n=1$)
Smeltzer et al, 1985	16	NR	Homan's procedure ($n=7$) Charles procedure ($n=3$) Genital procedure ($n=4$)	Thompson buried flap ($n=7$)	NR	Scores: (excellent, good, fair, or poor): - Homan's procedure (fair: 3; poor: 4) - Charles procedure (good: 1; fair: 2)	Recurrent infections in 33% of patients Below-the-knee amputation ($n=1$) Ischemic necrosis (n = 3) Delayed wound healing ($n=4$) Poor cosmetic results ($n=16$)
Mavili et al, 1994	4	LE	Modified Charles procedure	NR	Wrapped with elastic bandages	No progression of disease	Hypertrophic scarring ($n=2$)
Dumanian et al, 1996	1	LE	Charles procedure	NR	Gauze dressing	Near normal contour and appearance No spontaneous cellulitis	Skin graft loss ($n=1$)
Fraga et al, 2004	1	UE	Disarticulation	NR	NR	Limb disarticulation	NR

(*Continued*)

Table 4 (*Continued*)

Author, year	Patients (n)	Site	Surgical technique	Other procedures	Postoperative treatment	Outcomes	Complications
Hosnuter et al, 2006	1	LE	Limited Charles procedure—FTSG Sistrunk procedure 1 year later	NR	Physical therapy	After the second operation, the left calf measurement decreased from 106 to 57 cm	No major complications
van der Walt et al, 2009	8	LE	Delayed modified Charles procedure (negative pressure 90 mm Hg: 7 d)	NR	NR	The mean weight of lymphedematous tissue removed was 8.5 kg (range, 5–14.6 kg). A 45% improvement of the LE Functional Scale	Minor additional grafting ($n = 3$) Transfusion of blood units ($n = 8$) Wound breakdown ($n = 2$)
Karonidis et al, 2010	8	LE	Charles procedure with preservation of toes	Homan's procedure—thigh	Nonadherent dressings and leg elevation	The average size reduction was of 28.75% (range, 22–37%)	NR
Pereira et al, 2010	2	LE	Tissue resection	NR	Manual lymph drainage and mechanical lymph drainage	The size of the limbs can be maintained within the normal range by following the treatment guidelines	NR
Robertson et al, 2020	2	LE	Modified Charles procedure	Preoperative decongestive therapy	Physical therapy	Improved QoL	Focal wound tenderness ($n = 1$) Minor skin graft loss ($n = 1$)
Damstra et al, 2020	28	LE	Shaving procedure	Preoperative short-stretch compression bandaging Circumferential SAL	Analgesic, silicone wound dressings and compression bandages	Decreased episodes of erysipelas: preoperative 17.6, postoperative 0.6	NR

Abbreviations: FTSG, full-thickness skin graft; LE, lower extremity; mm Hg, millimeters of Mercury; NR, not reported; QoL, quality of life; SAL, suction-assisted lipectomy; STSG, split-thickness skin graft; UE, upper extremity.

reported ($n=16$). The overall complication rate was 46%; these included injury of the internal saphenous nerve ($n=1$), blood loss requiring transfusion ($n=13$), delayed wound healing ($n=11$), dermatosis ($n=1$), skin graft loss ($n=6$), presence of crevices and pits ($n=1$), chronic ulceration ($n=1$), the need of scar revision and release ($n=2$), reintervention ($n=1$), seroma ($n=1$), amputation ($n=2$), skin necrosis ($n=3$), hypertrophic scarring ($n=2$), and focal wound tenderness ($n=1$).

Discussion

The present study aimed to report on surgical treatments in the context of primary lymphedema.

Age of onset is undoubtedly relevant to the description and presentation of symptoms as well as the overall prognosis for every patient. The average age in our review was 36 years, seemingly old for most patients with primary lymphedema; this is due to the adulthood onset of the disease, as well as delays in the diagnosis. Ergo, primary lymphedema is not a synonym for childhood lymphedema.

Traditionally, primary lymphedema has been divided into categories based on the age of onset: congenital, praecox, or *tarda*, which failed to separate patients according to developmental age. To avoid miscommunication, a clearer classification has been proposed: infancy (between birth and 1 year of age), childhood (female patients between 1 and 8 years, male patients between 1 and 9 years), adolescence (female patients between 9 and 12 years, male patients between 10 and 21 years), and adulthood lymphedema (21 years or more).[85] The availability of a precise nomenclature may be helpful to successfully detect new and existing cases, with a classification based on a developmental approach.

Some considerations can be highlighted: despite the presence of diseased lymphatic structures, most patients remain at clinical stages I and II due to a probable intrinsic compensatory mechanism that stabilizes the lymphatic anomaly when conservative measures have been implemented.[86] Consequently, patients with an early diagnosis despite an abnormal lymphatic, yet balanced, function may have a better prognosis than those with long-standing untreated lymphedema.[87]

On this matter, treatment for lymphedema seeks to improve symptoms, cellulitis episodes, and QoL. It is known that the mainstay treatment for lymphedema is compression therapy, which promotes mobilization of lymph to proximal areas, reduces capillary filtration, avoids tissue inflammation, and consequently reduces fat deposits and secondary fibrosis.[17] Surgical interventions in this review were synthesized into physiological procedures (LVA and VLNT) and volume reduction or excisional surgeries (SAL and excisional procedures).

Although a clear-cut for determining the required treatment based on the severity stage could be desired, this is not that straightforward. Hence, physiological procedures should be contemplated even if a patient responds well to compression alone: a next-to-normal extremity after a physiological surgery can enable a patient to discontinue the use of a compressive garment, with the accompanying improvement in QoL.[22] Many patients may require more active compression with pneumatic devices, but these were not mentioned explicitly in the reviewed reports.

Despite an absence of uniformity in the reported surgical outcomes, circumferential measurements for volume reduction, episodes of cellulitis, improvement of symptoms, and QoL assessments were somewhat commonly evaluated. Hopefully, lymphedema guidelines should develop a standard method for expressing outcome measures.

LVA was overall the most performed procedure in this review. The size reduction of the affected limbs observed after this procedure in the studies of primary lymphedema patients is remarkable. Of note, isolated reports showed that LVA conditioned an increase in circumference in some patients,[15,53] especially those with an earlier onset of the disease.[15] Higher circumference reduction rates were observed for LVA procedures compared to VLNT, although this should be considered with caution since the sample sizes were heterogeneous. Nevertheless, from our perspective, LVA and VLNT may be considered equivalent in this respect. Finally, both LVA and VLNT improved symptoms and decreased cellulitis episodes. The complication rates appear to be higher in VLNT compared to LVA, owing to the higher complexity of the former. However, for both groups, only some complications were reported.

Since an intrinsic subnormal lymphatic anatomy is present, an essential aspect when selecting the optimal microsurgical treatment for primary lymphedema is the preoperative morphology determination in concordance with the severity of the disease. Cheng and Liu suggest performing LVA in patients with Cheng's Lymphedema Grade 0 to early Grade 2, limb circumferential difference less than 20%, short duration of symptoms, patent lymphatic ducts on indocyanine green lymphography, and partial obstruction on Tc-99 lymphoscintigraphy.[22] For patients with a greater circumferential difference, symptoms over 5 years, and absence of patent ducts or total obstruction by imaging, VLNT should be considered. This rationale indicates that performing LVA on incompetent lymphatic vessels may not only be futile but might aggravate the clinical stage of lymphedema. Similarly, in the presence of competent lymphatic vessels, performing VLNT as a first surgical instance precludes taking advantage of the existing function through the less invasive LVA.

SAL is currently the debulking procedure of choice for lymphedema and is indicated mainly for the advanced stages of the disease. In our review, patients showed a considerable decrease in circumference and improvement in cellulitis episodes and QoL with an approximate complication rate of 14.7%. The role of postoperative compression therapy was emphasized. Additionally, SAL has shown satisfactory results when combined with physiologic procedures, as liposuction addresses the deposits of fibroadipose tissue, while LVA or VLNT corrects the lymphatic flow.[88,89] Recently, a treatment algorithm for the sequence of liposuction with LVA or VLNT for lymphedema stages II to III has been proposed.[90] Nonetheless, the outcomes of this combined treatment have not been exclusively evaluated for primary lymphedema.

Excisional procedures were usually performed in the advanced stages of lymphedema; several complications and poor cosmetic results were described. The earlier the report, the more encouraging perspective was noted, even if results were considered less than ideal.

The challenge that the treatment of primary lymphedema poses is considerable. For instance, the underdeveloped lymphatic system with either abnormal lymph vessels or lymph nodes, or even both, demands an accurate and integral delineation of the lymphatic anatomy and function before considering a physiological procedure; the altered structure and lymphangiogenesis in primary lymphedema may cause inferior surgical outcomes when compared to those obtained in secondary lymphedema. Another defiance is the scenario of bilateral primary lymphedema, where improvements in circumferential measures cannot be assessed concerning a nonaffected contralateral limb. Moreover, as some authors have considered primary lymphedema as an orphan disease, late diagnosis and delayed referral are not uncommon in these patients, which notably influence the course of the disease and treatment indications.[30] This late referral may be because most reconstructive plastic surgeons were traditionally taught that primary lymphedema was not a candidate for physiologic procedures. The reflection of this situation can be seen in the continued use of excisional procedures from its first report in 1950 to the present. Importantly, it was not possible to discern the indications for LVA, neither the preoperative planning, nor the methods of preoperative lymphatic mapping that led to such indications in each study. In this context, detailed information on imaging would be greatly useful.

Similarly, postoperative objective assessments of lymphatic function are uncommon. Furthermore, although follow-up appears to be appropriate, more than 2 years on average, we still ignore the required time of monitoring; for example, some patients may develop LVA failure due to venous reflux after 2 or 3 years.[91]

To our knowledge, there are no previous systematic reviews about the whole treatment spectrum for primary lymphedema. There are two recent systematic reviews partially dealing with our subject. Tang et al focused mainly on QoL and included patients with secondary lymphedema. According to the authors, both ablative and physiologic interventions appear to provide an improvement in both generic and disease-specific quality-of-life domains, these improvements are sustained for at least 6 to 12 months postoperatively, and the choice of treatment for a particular patient is not clear, ideally determined by an experienced team on a case-by-case basis.[92] The review by Fallahian et al included 10 studies in total dealing only with lymphovenous bypass and vascularized lymph node transplant. The number of patients included was considerable ($n = 254$); the authors claimed a statistically significant improvement in the included reports but did not support this conclusion.[93] Half of their included papers (5/10) coincide with those in our review; from our standpoint, and according to the papers we gathered, statistical significance is far from conclusive. A recent meta-analysis dealt with outcomes after microsurgical treatments for lymphedema; the results are very optimistic: patients who underwent microsurgery achieved better outcomes (limb circumference diameter reduction, reduced rates of "skin infections," and enhanced lymphatic transport capacity). It is impossible to discern which patients and which results apply to primary lymphedema.[94]

The main limitation of our study is its dependence on previous and heterogeneous studies which impacts a qualitative synthesis; for example, the scantness of studies focusing only on this pathology reflects the absence of reliable data regarding the prevalence of the disease, which to our knowledge has not been updated after 36 years.[5] Despite this, we made an effort to disaggregate the information from the included articles and analyze only and exclusively cases with primary lymphedema. About the data reviewed, the predominance of case reports, small sample case series, and lack of extensive studies dealing specifically with the surgical treatment of primary lymphedema, obstacle the categorical and unequivocal selection of treatment. In this regard, granular details that would be useful to draw conclusions are missing: number of lymphovenous anastomoses performed in each limb, objective assessment of the long-term outcomes, and number of patients with combined procedures and their outcomes, among others. Unfortunately, most of the papers deal with patient groups, outcomes, and preoperative protocols that are vastly different. Also, because different lymphedema staging methods were used in the studies reviewed, comparisons were difficult to make.

However, although only low-quality data could be drawn from existing reports, an effort was made to further clarify the current management of this condition; in addition, we must consider the ethical and methodological difficulty of designing prospective and comparative studies. Also, it is possible that a selection bias had occurred, considering that those papers with positive findings are more likely to be published, and ineffective results, especially physiologic treatment, might have not been reported and therefore not included in the analysis.

More studies focusing solely on the surgical treatment for primary lymphedema are necessary; these should include detailed preexisting lymphatic morphology through imaging, clinical and surgical specifications, homogenization, and systematization in the reporting of outcomes. In this way, the endeavor of the present work may draw attention to these issues aiding in consensus and adequate communication among different working groups. Consequently, we would recommend the use of the ISL staging system for future reports.

Notwithstanding, our review shows that some treatment can be offered: more complex and sophisticated physiological procedures for earlier presentations with more conserved microstructural anatomy. On the contrary, when the lymphatic vessels' anatomy is severely altered, fibrosis is dire, and the patient is facing the inexorable progression of the disease, excisional treatment provides some relief.

Conclusion

Staging, clinical measurements, symptoms duration, and an accurate objective preoperative description of the lymphatic anatomy and function through imaging techniques, are central in selecting proper surgical treatment, regardless of the age of onset.

Establishing the competence of lymphatic vessels is cardinal to the selection of the ideal supermicrosurgical or microsurgical treatment or a combination of these with an excisional procedure such as suction-assisted lipectomy. To better understand surgical treatment outcomes in the future, comparative studies, hopefully randomized controlled trials, with larger samples and longer follow-ups are required.

Primary lymphedema is amenable to surgical treatment; the currently performed procedures have effectively improved symptoms and QoL in this population.

Authors' Contributions

M.A.G-G. was responsible for conception and design of the work, theoretical framework, analysis and interpretation of data, drafting, and revisions.

J.M.E. was responsible for acquisition and interpretation of data, statistical analysis, drafting and substantial revisions.

O.J.M. was responsible for conception of the work, acquisition and interpretation of data, drafting and substantial revisions.

K.A.S. was responsible for analysis and interpretation of data, drafting and substantial revisions.

B.H.K-C. was the corresponding author, and was responsible for conception and design of the work, analysis and interpretation of data, drafting, and substantial revisions.

Ethical Approval

Anonymity and confidentiality were preserved.

Statement of institutional review board approval or statement of conforming to the Declaration of Helsinki: **The present manuscript did not require IRB approval**.

Patient Consent

Not applicable.

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Conflict of Interest

None declared.

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