A systematic review and meta-analysis of vascularized lymph node transfer for breast cancer-related lymphedema

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ABSTRACT

Background: Vascularized lymph node transfer (VLNT) has become an increasingly popular technique for treating lymphedema. However, although many studies have been performed, its efficacy in increasing patients' quality of life (QoL) and reducing lymphedema in the affected body part has remained controversial. In the present systematic review, we summarized the evidence for VLNT for treating breast cancer-related lymphedema.

Methods: The MEDLINE, Embase, and Cochrane Central databases were searched for studies of patients with breast cancer-related lymphedema who had received VLNT. The study methods were assessed using the MINORS (methodologic index for nonrandomized studies) tool. The primary outcomes were the change in volume difference between the arms and QoL. The secondary outcomes were skin infection, complications, and discontinuation of compression garment use.

Results: A total of 17 studies were included for qualitative synthesis and 8 for meta-analysis. The average reduction rate between the healthy and affected arms in the studies included in the meta-analysis was 40.31%. Five studies had evaluated QoL, and all five studies had reported that QoL was significantly increased. Eight studies had evaluated skin infections, of which three had reported the annual infection rates before and after surgery. In these studies, infection rate had decreased significantly. Three studies had described usage of compression garments. When the patients were pooled, 27 of 60 were able to discontinue use of the compression garment. The donor and recipient complication rates were 12.1% and 7.3%, respectively.

Conclusions: The current evidence indicates that VLNT can improve the volume differences between the arms in patients with unilateral lymphedema by ~40%. In addition, although determined from a few studies, it is likely that VLNT has a positive effect on patients' QoL, the number of skin infections, and compression garment usage and coincided with a low complication rate. (J Vasc Surg Venous Lymphat Disord 2022;10:786-95.)

Keywords: Breast cancer; Lymph node transfer; Lymphedema; Lymphedema surgery

Lymphedema is a common, but serious, condition that can occur after treatment of malignancies. According to the literature, the incidence of breast cancer-related lymphedema (BCRL) varies from 24% to 49% after mastectomy and 4% to 28% after breast-conserving therapy.[1-3] The major risk factors for the development of lymphedema are axillary lymph node dissection, radiation therapy to the axillary region, postoperative seroma in the axilla, and obesity.[4] The mainstay treatment of lymphedema is conservative and consists of an initial and maintenance phase in which compression therapy plays a large role. However, interest in surgical strategies to improve lymphedema has increased.[5-9]

Both excisional and reconstructive approaches have been described in the treatment of BCRL. Excisional approaches have included the infamous Charles procedure, in which a portion of the affected extremity is excised, and liposuction, in which the subcutaneous fat deposits in the affected extremity are removed.[10] These strategies have been most often performed in later stages of the disease, when no functional lymphatic vessels remain.[7,11] In contrast, reconstructive options aim to restore lymphatic flow to aid in lymphatic drainage from the affected extremity. In addition to lymphaticovenular anastomoses (LVAs), promising results have been described for vascularized lymph node transfers (VLNTs) to treat lymphedema.[12-17]

The use of VLNTs was first described by Shesol et al[18] in a rodent animal model in 1979. In 1982, the first application of lymph node transplantation was described by Clodius et al.[19] More recently, Becker,[13] Ciudad et al,[20] and Mardonado et al[21] popularized the use of VLNT among plastic and reconstructive surgeons. Although promising results

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have been described for VLNTs, the mechanisms of action have not been fully elucidated. In addition, multiple variations in the donor site (eg, groin, supraclavicular, submandibular) and acceptor site (eg, wrist, axilla) have been reported. In addition, most reported studies have been quite heterogeneous in patient selection, surgical characteristics, and outcomes reported. Therefore, in the present review, we aimed to summarize the current evidence regarding VLNTs and evaluate the efficacy of VLNTs in the treatment of BCRL regarding the volume of the affected extremity and patient quality of life (QoL).

METHODS

Search method and study identification. The study was performed in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement.[22] A systematic search was performed in the electronic databases, Medline, Embase, and Cochrane Central, to identify relevant studies. The keywords used were "autologous" and "vascularized" combined with "lymph node transfer" and "lymph node transplantation." The titles and abstracts were searched for the terms, and, where applicable, the terms were mapped to medical subject headings. All references were recorded in Endnote, version X8 (Clarivate Analytics, Philadelphia, Pa), after which duplicate reports were removed. Next, the titles and abstracts were screened for eligibility, and the full-text reports were retrieved. To prevent double counts of the data, different studies by the same authors were scanned for uniqueness regarding the included patients. The most recent study with the longest follow-up was chosen in the case of overlap. The full-text reports were screened for other relevant studies. The last search was performed on June 27, 2019. The review and its protocol were not registered.

Inclusion and exclusion criteria. The studies were eligible for inclusion if they had described the use of VLNT in the treatment of BCRL in female patients aged >18 years. Studies were excluded if they had included fewer than five patients, if they were animal studies, or if the full text was not available in English, German, or Dutch.

The methodologic quality and risk of bias for each remaining study was assessed using the MINORS (methodologic index for nonrandomized studies) tool (Supplementary Table, online only). The MINORS tool was constructed and validated for appraisal of nonrandomized trials of surgery.[23] The ideal score for the MINORS assessment is 16 points for noncomparative studies and 24 for comparative studies. All studies selected for inclusion during the search process were scored independently by two of us (H.W. and N.S.), with disagreement resolved by discussion and consensus.

Outcomes and data extraction. The study characteristics were recorded using a predefined form. The primary outcome was a change in the volume difference between the healthy and affected arms and a change in patient QoL. The secondary outcomes were skin infections during follow-up, complication rates, and discontinuation of compression garment use. For compression garment use, only those studies that had also described compression garment use before surgery were included. Data extraction was performed by one of us (H.W.).

Statistical analysis. For the meta-analysis, the data regarding the volumetric and circumference outcomes were extracted and entered into RevMan (Review Manager), version 5.3 (Cochrane Collaboration; The Nordic Cochrane Centre, Copenhagen, Denmark). For the studies describing different treatments, only those patients who had undergone VLNT were included. The patients who had undergone additional liposuction or LVAs during follow-up were excluded. The mean values ± standard errors were recalculated for the VLNT groups to reflect the reduction in volume or the circumference difference between arms, if possible. This could have been a reduction in the volume difference or a reduction in the circumference difference. Heterogeneity was determined using the Cochran Q test and quantified using I^2. In the case of a positive Cochran Q test result ($P < .05$) and a high I^2 (>50%), a random effects model, instead of a fixed effects model, was chosen. To visualize the results, a forest plot was created using RevMan (Cochrane Collaboration).

RESULTS

The systematic search strategy of Medline, Embase, and Cochrane Central yielded 534 reports. After removal of the duplicates, 280 studies remained and underwent title and abstract screening. Of the 280 studies, 240 were excluded because they had not covered the domain or intervention or were the wrong study design (eg, reviews, case reports). The full texts of the remaining 40 reports were assessed for eligibility. Of these 40 reports, 25 were included, 17 for the qualitative synthesis and 8 for the meta-analysis (Figs 1 and 2). The study characteristics and data extracted from included studies are presented in Table I.

Volumetric outcomes

Of the 17 studies, 13 had described the volume outcomes after VLNT. However, only eight of the studies had reported the outcomes for both the healthy and the affected extremities or the decrease in the extremity differences compared with the difference before surgery.[15,25,27-29,34,36,37] These eight studies were analyzed, and the results are demonstrated in a forest plot (Fig 2). The mean reduction in the volume difference between the healthy and affected extremities was 40.31% (95% confidence interval, 31.44%-49.17%). The follow-up between studies varied greatly. However, the mean follow-up of the three studies that had demonstrated a greater reduction (49.2%, 50.6%, and 57.1%) was similar

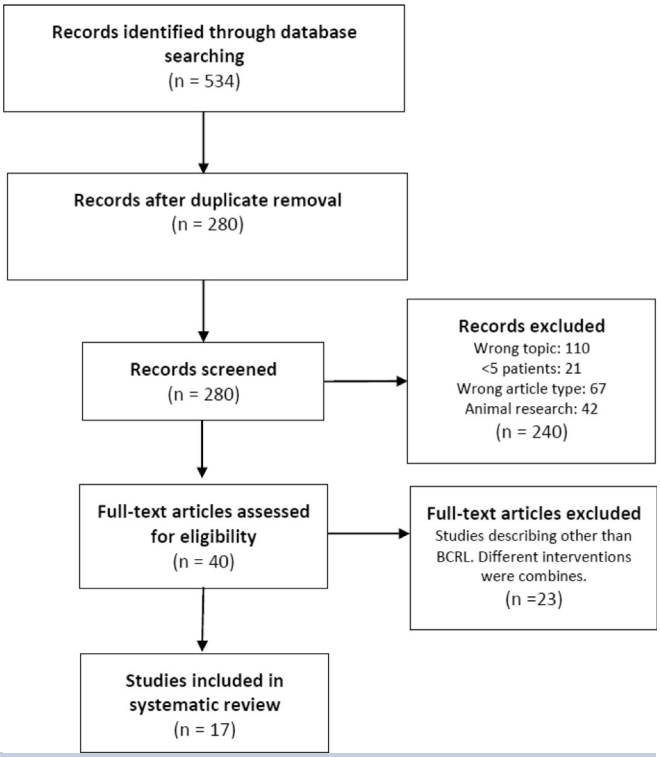

Fig 1. Flowchart demonstrating inclusion process. *BCRL,* Breast cancer-related lymphedema.

to the mean follow-up of the five studies that had reported a more moderate effect (20.1%, 30.3%, 30.5%, 31.8%, and 33.2%). The average follow-up for both groups was 26.8 and 31.13 months.

Of the 17 studies not included in the meta-analysis, Akita et al[24] demonstrated improvement in the upper extremity lymphedema (UEL) index in two groups (deep inferior epigastric artery [DIEP] breast reconstruction plus VLNT and VLNT alone). The score was 13 and 14 points for the DIEP plus VLNT and VLNT group, respectively, with no statistically significant difference between the two groups. Because the baseline UEL index had not been reported, the study by Akita et al[24] could not be included in the meta-analysis.

Becker et al[14] reported the long-term results of VLNT surgery for 24 patients after a mean follow-up of 8.3 years. All the patients had undergone physiotherapy before surgery, with treatment resistance considered present. However, the complete physiotherapy regimen and the use of compression garments were not described. In addition, patients with early edema, no skin infections, and good skin elasticity and patients with long-lasting edema, multiple skin infectious episodes, and no skin elasticity were included. In 10 patients, the perimeter difference between the affected and healthy extremities had returned to normal; in 6 patients, the difference had decreased by >50%; in 6 patients, the volume difference had decreased by <50%; and in 2 patients, the difference between the healthy and affected extremities had remained unchanged.

In 2016, Gratzon et al[31] reported the clinical and psychosocial outcomes after VLNT for 50 patients. They performed circumferential measurements of both arms and calculated the arm volumes and lymphedema reduction rates. However, only 24 of the 50 patients could be included in the statistical analysis of the volume reduction because of missing data or because the patients had not yet reached the 12-month follow-up point. Although the average reduction was comparable to that in the studies included in the forest plot (42.73%), the reduction was not statistically significant ($P = .052$). Because the standard deviation and/or individual patient data were not available, these results could not be included in the meta-analysis.

In 2013, Nguyen et al[35] evaluated the effects of VLNT for 29 consecutive patients. After 12 months of follow-up, the average volume difference between the healthy and affected arms had decreased from 20% to 10%, for a reduction rate of 50%.

Yang et al[38] retrospectively compared the arm circumference reduction between 10 BCRL patients who had undergone VLNT combined with transverse rectus

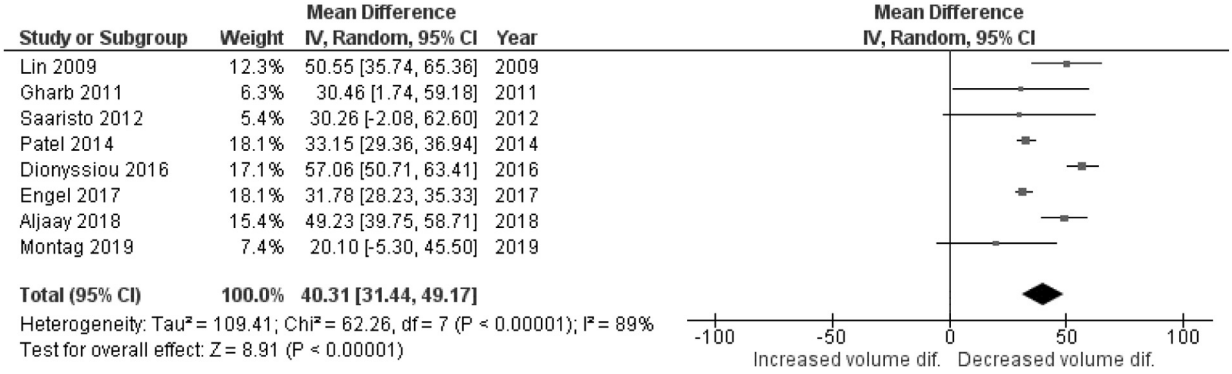

Fig 2. Forest plot demonstrating volume difference changes after vascularized lymph node transfer (VLNT). *CI,* Confidence interval.

abdominis muscle flap or DIEP flap breast reconstruction and 10 BCRL patients who had undergone physiotherapy alone. The circumference measurements were performed at six locations on the affected extremity. A significant reduction from 32.1 cm to 29.1 cm had occurred in the VLNT group after 1 year of follow-up. In the physiotherapy group, a significant increase had occurred in the arm circumference in four of the six measured arm locations after 1 year of follow-up. However, the breast reconstruction plus VLNT group was not compared head-on with the physical therapy group.

More recently, in 2018, Liu et al[32] evaluated the effects on volume and radiologic lymph drainage after VLNT. Of 30 patients, 21 had experienced a volume reduction in the affected arm after surgery. The average reduction for this group was 47.1%. However, the nine patients without volume reduction were not originally included in this proportion. When recalculating the reduction in volume difference, the overall mean reduction rate was 32.9%, assuming no increase in the volume differences. Of all 30 patients, 37% had demonstrated radiologic improvement in the limb. In seven patients, the transport rate was increased, and in four, the transplanted lymph nodes were visible on lymphoscintigraphy.

Maruccia et al[33] explored the added effect of scar release when combined with VLNT to the wrist. They performed VLNT in a group of 21 patients and VLNT with scar release of the axilla in a group of 18 patients. The mean reduction rate between the arms was 42.2% after 24 months for the group receiving VLNT. At 24 months of follow-up, they found no additional volume difference reduction in the group that had undergone axillary scar release in addition to VLNT.

Quality of life

Of the included studies, five had evaluated patients' QoL after VLNT.[25,26,31,33,36] Four studies had used the lymphedema quality of life (LYMQOL) questionnaire. The LYMQOL is a validated questionnaire that rates four specific domains (ie, function, appearance, symptoms, mood) with a score from 1 to 4 and a general QoL rating from 1 to 10. A score of 1 indicates that the specific domain is not affected by the lymphedema at all, and a score of 4 implies the domain is greatly affected by the lymphedema.

Gratzon et al[31] demonstrated an improvement in patient QoL after VNLT in a prospective study. They measured QoL using the LYMQOL before surgery and at 1, 3, 6, 9, and 12 months of follow-up. In addition to the LYMQOL, the patients had also scored the amount of pain and heaviness they had experienced on a scale from 1 to 10, with 10 indicating maximum pain or heaviness and 0, no pain or heaviness. The results for 50 patients were evaluated. The overall QoL score had significantly increased from 5.7 to 7.8 after 12 months of follow-up, and all subdomain scores had significantly decreased. In addition, the amount of pain (from 3.97 to 0.39) and heaviness (from 5.52 to 1.67) had decreased significantly ($P < .01$).

In 2019, Aljaaly et al[25] also reported patient QoL after VLNT. They found that the general QoL score had increased significantly by 5.5 points and that all the subdomain scores had decreased significantly. On subgroup analysis, they found that, after 12 months, the patients who had undergone VLNT to the volar side of the wrist instead of the dorsal side had had a better score for general QoL and the appearance subdomains ($P < .05$).

Patel et al[36] had also used the LYMQOL to evaluate the effect of VLNT on patient QoL. They included 25 patients, of whom 15 had had upper extremity lymphedema. The average follow-up for the upper extremity lymphedema patients was 25.4 ± 8.4 months. In all subdomains, the QoL score had increased significantly after 3 and 6 months. The difference in the functionality domain had reached significance after 12 months. The overall QoL score had increased from 2.1 to 5.8 points. The patient-reported scores were almost maximal before surgery, indicating that only patients with severe complaints on all subdomains had been analyzed in their study.[36]

The final study that had used the LYMQOL as outcome measure for QoL was reported by Maruccia et al.[33] They compared the results of VLNT with scar release, and VLNT alone for 39 patients. They found better scores for all subdomains in the LYMQOL questionnaire ($P < .05$).[33] Furthermore, they reported that the group that had also undergone scar release had had significantly better scores. However, when studying the provided data, the difference between the groups for all subdomains was <1 point.[33] Therefore, one might question the clinical relevance of this difference.

In another study, De Brucker et al[26] had assessed patient QoL before surgery and at an average of 29 months of follow-up using the upper limb lymphedema 27-item (ULL-27) questionnaire. The ULL-27 questionnaire provides an overall QoL score and three different subdomains: physical functioning, psychological dimension, and social dimension. A total of 25 female patients were included, and 22 patients had undergone simultaneous free-flap breast reconstruction. The QoL scores had increased significantly both overall and in the subdomains ($P = .001$). However, most of the patients had undergone breast reconstruction, in addition to the lymphedema treatment, making it difficult to isolate the effects of VLNT. However, the three patients who had undergone VNLT alone had all experienced an increase in overall QoL.

Secondary outcomes

Skin infections. Eight studies had evaluated the results of VLNT on the incidence of skin infections (erysipelas or cellulitis).[14,25-28,31,33,36] In 2006, Becker et al[14] demonstrated that after VLNT, 17 of 24 patients had not

Table I. Study characteristics

Investigator	Patients, No.	Diagnosis confirmation/inclusion criteria	Duration (average)	Site	
				Donor	Recipient
Akita et al,[24] 2017	27	Splash or stardust DBP	NM	Groin	Axilla
Aljaaly et al,[25] 2018	15	Lymphoscintigraphy, ICG	25.9 ± 2.7 months	Submental	Wrist
Becker et al,[14] 2006	24	NM	56.5 months	Groin	Axilla
De Brucker et al,[26] 2016	25	Stage 1 or 2 (system not specified)	42 ± 42 months	Groin	Axilla
Dionyssiou et al,[27] 2016	18	Lymphoscintigraphy, ≥1 infection, ISL stage II	NM	Groin	Axilla
Engel et al,[28] 2017	45	Total obstruction on lymphoscintigraphy; Cheng late grade II, III, and IV	31.3 ± 11.4 months	Groin or submental	Wrist, 41; elbow, 3
Gharb et al,[29,b] 2011	11	ISL stage II/ lymphoscintigraphy	NM	Groin	Wrist,9; forearm, 2
Granzow et al,[30] 2014	8	Lymphoscintigraphy	3.8 years	Groin	Axilla
Gratzon et al,[31] 2017	50[c]	ISL stage I/II or recurrent cellulitis requiring IV antibiotic therapy	4.87 years	Lower abdomen, 42; chest wall, 5; neck, 3	Axilla
Lin et al,[15] 2009	13	Lymphoscintigraphy	33 months	Groin	Wrist
Liu et al,[32] 2018	30	ISL stage I, II, and late II	6 years	Groin	Axilla
Maruccia et al,[33] 2019	39	Lymphoscintigraphy/ISL stage II, III	25 ± 3 months	Groin/gastro epiploic	Wrist
Montag et al,[34] 2019	24	ISL stage II, III	43.6 ± 47.61 months	Groin	Wrist/axilla
Nguyen et al,[35] 2015	29	NM	3.3 years	Groin	Axilla
Patel et al,[36] 2014	15	Lymphocintigraphy, ICG/ Cheng grade 2-4	37.1 ± 30.5 months	Groin and submental	Wrist
Saaristo et al,[37] 2012	9	Symptom duration <10 years	<10 years	Groin	Axilla
Yang et al,[38] 2017	10	>3.1 cm circumference difference; symptomspresent >6 months	NM	Groin	Axilla

DBP, Dermal backflow pattern; *ICG,* indocyanine green; *ISL,* International Society of Lymphology; *IV,* intravenous; *LVA,* lymphaticovenular anastomosis; *MINORS,* Methodologic index for nonrandomized studies; *NM,* not measured; *SSI,* surgical site infection; *UEL,* upper extremity lymphedema.
[a]The total complication rate of the flaps was 8.1% but included breast reconstructions without vascularized lymph node transfer; after vascularized lymph node transfer, one case of donor site lymphedema was reported that was treated with one LVA at the ankle.
[b]For our review, only patients who had not undergone additional liposuction during follow-up were included.
[c]Only 24 patients could be included in their statistical analysis.

Table I. Continued.

Arm difference reduction	Reduction, No.	Complications		Follow-up	MINORS score
		Recipient site	Donor site		
13.5 ± 5.4 point UEL reduction	NM	Seroma, 2	0	19.1 ± 1.7 months	19/24
42.2 ± 32.1	NM	Venous congestion, 2	NM	12 months	16/24
Total reduction, 10; >50% reduction, 6; <50% reduction, 6; no reduction, 2	20/24	0	Lymphorrhea, 8	Average, 8.3 years	10/16
NM	NM	Infection with complete flap loss, 1	Repeated seroma, 3; wound healing problems, 4, 1 of which required surgery	29 ± 14 months	11/16
Average, 57.06% ($P = .000$)	18/18	0	Prolonged lymphorrhea, 2	18 months	19/24
Average, 31.78%	NM	0	Lymphedema managed by LVA,[a] 1	Average, 47.8 months	20/24
Average, 30.46%	8/11	Forearm cellulitis, 1; partial flap necrosis, 1	Inguinal seroma, 1	Average, 39.5 months	9/16
NM	NM	Axillary seroma, 1; delayed healing, 2	0	Average, 25 months	9/16
Average, 58.7% ($P = .052$)	NM	SSI, 3; wound dehiscence, 1; hematoma, 1; bleeding, 1; nonhealing wound, 1	SSI, 6; seroma, 6; wound dehiscence, 3	12 months	10/16
Average, 50.55% ($P < .01$)	12/13	Venous congestion managed by reoperation, 1; SSI, 1	0	Average, 56.1 months	10/16
47.06 ± 27.92	21 (70%)	0	0	22.11 ± 7.83 months	10/16
42.57 ± 9.9	NM	0	0	24.15 ± 5.71 months	16/24
20.1 ± 44.9	NM	NM	NM	18 months	20/24
Average, 50%	23/29	Delayed wound healing, 3; partial flap necrosis, 1; thrombosis requiring surgery, 1	Delayed closure, 1; abdominal bulge, 1; groin seroma, 1; welling managed by compression garment, 1	Average, 11 months	9/16
24.4% ($P = .03$)	NM	No complete or partial flap loss	NM	12 months	20/24
Average, 30.6%	Decrease, 7/9 patients	Axillary seroma, 2	Abdominal seroma, 1; delayed wound closure, 2	6 months	8/16
Average, 3 cm (affected arm only)	NM	Fat necrosis, 1	0	12 months	9/16

Table II. Complications after VLNT

Complication	Recipient site	Donor site
Seroma/lymphorrhea	5 (1.4)	22 (1.7)
Surgical site infection	5 (1.4)	6 (2.1)
Delayed wound healing	6 (1.6)	7 (0.2)
Wound dehiscence	1 (0.3)	3 (0.2)
Partial flap necrosis/fat necrosis	3 (0.8)	0 (0.0)
Lymphedema	0 (0.0)	2 (0.6)
Cellulitis	1 (0.3)	0 (0.0)
Venous congestion	3 (0.8)	0 (0.0)
Thrombosis	1 (0.3)	0 (0.0)
Hematoma	1 (0.3)	0 (0.0)
Bleeding	1 (0.3)	0 (0.0)
Abdominal bulging	0 (0.0)	1 (0.3)
Total	27 (7.3)	41 (12.1)
Total patients	369 (100.0)	338 (100.0)

VLNT, Vascularized lymph node transfer.
Data presented as number (%).

developed any skin infections and 7 patients had experienced one skin infection during 8.4 years of follow-up. Before surgery, the patients had been grouped into two stages using their own staging system.[14] The six patients in stage one had experienced, at most, two skin infection episodes and had preserved skin elasticity. In addition, the perimeter of the affected arm did not exceed 30% more than the contralateral arm. The 18 stage 2 patients had experienced more than two skin infection episodes, had impaired skin elasticity, and had an increased perimeter of the affected arm of 30% to 50% compared with the healthy arm. Although their study was one of the few studies reporting on the incidence of cellulitis after VLNT, it was not possible to compare the incidence of cellulitis before and after the procedure with the data provided.[14]

Patel et al[36] described the results of their prospective study, including the effects of VLNT on the incidence of skin infections. Patients were eligible for VLNT if they had had grade ≥2 using the Cheng lymphedema grading scale, including a circumference difference of >20% and total lymphatic occlusion on lymphoscintigraphy. They included 25 patients, of whom 15 had had edema of the upper limb. For these patients, the incidence had decreased from 3.5 ± 3.3 infections annually to 0.7 ± 0.9 annually ($P = .05$).[36]

Dionyssiou et al[27] had also reported the results of VLNT regarding skin infections. They had randomized their 36 patients into two groups of 18 patients each. In group A, they had performed VLNT, after which the patients had received physiotherapy and compression therapy for 6 months. In group B, the patients had undergone physiotherapy and compression therapy alone for 6 months.[27] All the included patients had had International Society of Lymphology stage II lymphedema and had experienced at least one episode of skin infection during the previous year. In the VLNT group, the incidence of skin infections had decreased from 1.94 to 0.277 episodes annually ($P = .000$). In the physiotherapy group, the incidence had decreased from 1.61 to 1.16 episodes annually ($P = .016$). Although a significant reduction had occurred in both groups, the decrease in the patients treated with VLNT was far greater.[27]

More recently, Engel et al[28] described the effects of VLNT. In their series, the hand and arm were used as recipient sites. The incidence of cellulitis had decreased from 7.4 ± 2.3 to 2.6 ± 2.3 episodes annually for patients who had received VLNT only and from 8.0 ± 1.8 to 2.8 ± 1.8 for the patients who had undergone VLNT, in addition to microvascular breast reconstruction. The difference in the decrease in the episodes was not statistically significant between the patients who had or had not undergone simultaneous breast reconstruction.

In addition, De Brucker et al[26] described the change in the skin infection rate in their study. All the patients included had had lymphedema stage 1 or 2; however, the staging system was not reported. Before surgery, 6 of the 25 patients had experienced recurrent skin infections.[26] After VLNT, the incidence of skin infections in three patients had decreased from two to one episode annually. In the remaining three patients, infections had not occurred during the follow-up period (mean, 29 ± 14 months).

Gratzon et al[31] had also reported on the decrease in the incidence of cellulitis for 10 patients who had experienced skin infections between the onset of edema and VLNT. After VLNT, seven patients had experienced no skin infections, two had developed one infection, and one had developed two infections. Because the number of infections annually was not reported, the reduction rate could not be calculated.

Maruccia et al[33] and Aljaaly et al[25] reported their results with VLNT in 2019. Mariccua et al[33] explored the addition of scar release with lipofilling to VLNT. Although they found no differences between the groups in the incidence of skin infection, the total infection rate had decreased from 3.5 episodes to 0.5 episodes annually, on average. Aljaaly et al[25] compared dorsal vs volar placement of VLNT to the wrist. When both groups were combined, the infection rate had decreased from 3 episodes annually to 0.5 episode annually.

Compression discontinuation. Of the 25 included studies, 3 had described the use of compression therapy during follow-up.[24,26,30] Granzow et al[30] reported a significant decrease in the use of a compression garment for the eight patients who had undergone VLNT ($P = .009$). Before surgery, 87% of the patients had used their compression garment for >8 hours daily and 13% had used their garments for 4 to 8 hours daily. During follow-up, most patients (75%) had been able to discontinue

compression therapy or only used the compression garment when the risk of limb swelling was increased (eg, during exercise). Of the other patients, 12.5% had used the compression garment for 4 to 8 hours daily and another 12.5% had used their garment for >8 hours daily.

In addition to the evaluation of QoL after VLNT, De Brucker et al[26] evaluated the reduction in compression garment use. Before surgery, the patients had had ≥6 months of compression therapy without volume reduction of the limb. Of the 25 patients, 15 (60%) were able to discontinue compression therapy. The criteria for compression garment discontinuation were not provided. The average follow-up was 29 months (range, 8-64 months).

Akita et al[24] evaluated the addition of DIEP flap breast reconstruction to the effects of VLNT. Among the other outcomes, they reported quite thoroughly on the use of the compression garment.[24] In their study, the patients were divided into two groups. One group had undergone VLNT and one had undergone VLNT in addition to DIEP flap breast reconstruction. Compression therapy and manual lymph drainage were stopped during hospital admission and resumed at discharge. At 6 and 12 months of follow-up, indocyanine green lymphography was performed to visualize the dermal backflow patterns. If dermal backflow reduction of 75% was present at 6 months of follow-up, the patients were encouraged to decrease compression garment usage. For 9 of 27 patients, an improved dermal backflow pattern was seen, and they were able to completely stop the use of the compression garment. In four patients, no improvement in the dermal backflow pattern was seen; however, the UEL index and subjective symptoms had improved. These patients were able to discontinue compression garment usage during the day. At 12 months of follow-up, the dermal backflow for all the patients who had reduced or discontinued compression garment usage did not worsen. More patients could reduce compression garment use in the VLNT plus DIEP flap group (10 of 14) than in the VLNT group (3 of 14; $P = .04$).

When these results were pooled, compression garment use could be discontinued by 27 of 60 patients (45%). The proportion of patients who could stop wearing the compression garment was comparable in the studies by Granzow et al[30] and De Brucker et al[26] (75% and 60%, respectively). Akita et al[24] reported a lower discontinuation rate of 35%. Only the study reported by Akita et al[24] had described under which conditions it was decided that patients would discontinue using the compression garment.

Complication rate. Of the 17 studies, 16 had reported on complications (Table II). Of the 16 studies describing complications, 2 had not reported any complications at the donor site. When the complications described in these 16 studies were pooled, the total complication rates at the donor and recipient sites were 12.1% and 7.3%, respectively. Donor site lymphedema occurred in two patients. In one patient, the development of edema of the leg coincided with wound dehiscence. The swelling was controlled with compression garment and had improved after the wound dehiscence had healed.[35] The other patient was successfully treated with LVA at the ankle.[28]

DISCUSSION

Although numerous studies have recently evaluated VLNT, controversy remains regarding the efficacy of such procedures. In addition, a broad range of outcomes across a broad range of patient groups have been reported, making it difficult for clinicians to obtain a complete view of the current evidence regarding VLNT. The aim of the present review was to summarize all the relevant outcomes for a selective patient group—patients with secondary upper extremity lymphedema. We found that although many technical differences must be considered, the reduction in the arm difference in volume or circumference was similar for most studies and the effects on the secondary outcomes were positive.

Volumetric and circumference outcomes were evaluated from eight studies that were included in a meta-analysis. The average reduction in the volume or circumference difference between the healthy and affected arms was 40.31% (95% confidence interval, 31.44%-49.17%). However, just three studies had used a prospective study design. The greatest limitation in the evaluation of the arm difference reduction was the lack of thorough descriptions of compression garment usage before and after VLNT in most studies. It is possible that patients were more compliant with compression therapy after surgery. Therefore, without a standardized protocol, a possible bias caused by compression garment use could not be excluded. The effect of VLNT on QoL was assessed by two prospective studies and three retrospective studies using validated questionnaires. Four studies had used the LYMQOL and one had used the ULL-27 questionnaire. Although all five studies had reported a significant increase in patient QoL after VLNT, the QoL evaluation could have been hampered by the suboptimal conditions in one study. In the study by De Brucker et al,[26] the patients had completed two questionnaires 12 months after surgery. They reported on their QoL before and after surgery at the same moment during follow-up. Therefore, the preoperative QoL analyzed might not have reflected the actual QoL before surgery. In addition, VLNT was combined with breast reconstruction for 22 of 25 patients, which also could have affected the patients' QoL.

One of the most feared complications of VLNT is donor site lymphedema, which can theoretically result from the removal of healthy lymph nodes. However, only two patients who had undergone VLNT had developed lymphedema at the donor site. In one patient, the edema was

controlled with compression garment use and the swelling improved after the wound dehiscence had healed. The other patient had been successfully treated with LVA at the ankle. One of the measures to avoid this complication could be to use reverse lymphatic mapping as described by Dayan et al.[39] For reverse lymphatic mapping, technetium is injected into the first and second web spaces of the foot and indocyanine green is injected into the abdomen. During surgery, the lymph nodes draining the leg can be identified using a gamma probe and the lymph nodes draining the abdomen can be identified using a near infrared camera. The use of the technique allows for safe selection of transplantable lymph nodes.[39] The by far most common complication was seroma formation at the donor site, which, in some cases, had required repeated puncture.

When reviewing the current literature, we identified no trials that had compared conservative treatment directly with VLNT. Only the study by Lin et al[15] had included an adequate control group (VLNT plus microsurgical breast reconstruction vs microsurgical breast reconstruction only).[15] To further evaluate the effect of VLNT, prospective trials are required with a fixed compression therapy protocol to isolate the effects of the transplanted lymph nodes.

CONCLUSIONS

BCRL can be a debilitating condition and can severely affect patients' QoL. Although reconstructive surgical techniques, including VLNT, have been used for >40 years, solid prospective evidence regarding its efficacy is scarce. The current evidence indicates that VLNT can reduce the difference between a patient's healthy and affected arms by ~40%. In addition, although based on a few studies, it is likely that VLNT has a positive effect on patients' QoL, the number of skin infections, and compression garment usage, with a low complication rate. Further trials are required to confirm these findings to compare VLNT and conservative management.

AUTHOR CONTRIBUTIONS

Conception and design: HW, HT, SH, NS, DU
Analysis and interpretation: HW, HT, VP, SH, NS, DU
Data collection: HW, HT, NS, DU
Writing the article: HW, HT
Critical revision of the article: HW, HT, VP, SH, NS, DU
Final approval of the article: HW, HT, VP, SH, NS, DU
Statistical analysis: HW, SH
Obtained funding: Not applicable
Overall responsibility: HW

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Supplementary Table (online only). MINOR Scriteria

Criteria	Possible score
Methodologic items for nonrandomized studies	0-2
A clearly stated aim: the question addressed should be precise and relevant in light of available literature	
Inclusion of consecutive patients: all patients potentially fit for inclusion (satisfying criteria for inclusion) were included in the study during the study period (no exclusion or details reported of reasons for exclusion)	
Prospective collection of data: data collected according to a protocol established before the study began	
Endpoints appropriate to study aim: unambiguous explanation of criteria used to evaluate main outcome, which should be in accordance with the question addressed by the study; also, the endpoints should be assessed on an intention-to-treat basis	
Unbiased assessment of study endpoint: a blind evaluation of objective endpoints and a double-blind evaluation of subjective endpoints; otherwise the reasons for not blinding should be stated	
Follow-up period appropriate to study aim: follow-up should be sufficiently long to allow for assessment of main endpoint and possible adverse events	
Loss to follow-up <5%: all patients should be included in follow-up; otherwise, proportion lost to follow-up should not exceed proportion experiencing major endpoint	
Prospective calculation of study size: information should be provided of size of detectable difference of interest with calculations of 95% confidence intervals, according to expected incidence of the outcome, with information provided about the level of statistical significance and estimates of power when comparing outcomes	
Additional criteria for comparative studies	0-2
An adequate control group: the use of a reference standard diagnostic test or therapeutic intervention recognized as optimal intervention according to available reported data	
Contemporary groups: control and study groups should be managed during same period (no historical comparisons)	
Baseline equivalence of groups: the groups should be similar regarding the criteria other than the studied endpoints; the absence of confounding factors that could bias the interpretation of the results	
Adequate statistical analyses: whether the statistics were in accordance with the study type with calculation of 95% confidence intervals or relative risk	

MINORS, Methodologic index for nonrandomized studies.