Review Article on Lymphedema

Lymphaticovenular anastomosis for breast cancer-related upper extremity lymphedema: a literature review

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Abstract: Breast cancer-related lymphedema is a long-term condition that affects almost half of breast cancer survivors. Clinical studies have looked at the benefits of lymphaticovenular anastomosis (LVA) for the treatment of upper extremities lymphedema after breast cancer, however, there is still controversy if it improves lymphedema. This study aimed to analyze the studies and outcomes related to LVA for breast cancer-related lymphedema. A PubMed/Medline search was performed using "lymphovenous bypass", "upper extremity lymphedema", "arm lymphedema after breast cancer treatment", and "lymphaticovenular anastomosis" as key words. Only English articles reporting outcomes after LVA were included. We found 22 articles that met the inclusion criteria. Positive outcomes were found in 21 studies with an objective volume reduction and subjective symptoms relief after LVA. This literature review concluded that LVA has demonstrated a significant decrease in upper extremity volumes and an improvement in subjectively reporting symptoms in breast cancer-related lymphedema patients.

Keywords: Lymphaticovenular anastomosis (LVA); lymphovenous bypass; lymphovenous anastomosis; breast cancer; lymphedema; upper extremity

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Introduction

Lymphedema after breast cancer treatment affects from 9% to 41% of patients (1). This implies that more than one in five women who survive breast cancer will develop upper extremity lymphedema (2). This condition involves the upper ipsilateral end to the breast affected by cancer.

Associated risk-factors include age, higher body mass index, advanced disease/pathologic stage, axillary lymph node dissection, chemotherapy, radiotherapy, infection, injury, and history of seroma (3-9). Clinically, the protein-rich lymphatic fluid ends up accumulating in the interstitial spaces, producing a progressive swelling of the upper limbs. These symptoms usually appear within the first 2 years after treatment. Moreover, in long-term follow-up, this disease may result in adverse effects, such as pain, skin changes, fibrosis, deformity, functional disability, loss of sensation, heaviness in the arm, distress, and depression (10-13). Therefore, the high costs related to the management of symptoms and adverse effects during outpatient visits and mental health services have an important economic impact in the society.

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Several surgical and nonsurgical treatments have been proposed to treat this condition (9,14-17). Surgical treatments include ablative and physiologic operations, in which new connections are created to increase the drainage capacity of the lymphatic fluid (18-20). Surgical techniques have evolved becoming more effective and less invasive (21-23). The aim of this review is to analyze the clinical studies published to date about lymphaticovenular anastomosis (LVA, also called lymphovenous bypass) for upper extremities lymphedema after breast cancer treatment.

Methods

We performed a search on PubMed/Medline using "lymphovenous bypass", "upper extremity lymphedema", "arm lymphedema after breast cancer treatment", and "lymphaticovenular anastomosis" as key words. We included studies describing clinical experience with lymphovenous bypass surgery for upper extremity lymphedema after breast cancer treatment. Papers included were original studies in which LVA was performed for the treatment of lymphedema secondary to breast cancer treatment. Only clinical studies with reports written in English were considered for data extraction; review articles were excluded. Demographic data, lymphedema duration, surgical technique, follow-up time, and outcomes were collected.

The publications were screened manually to identify reports of surgical treatment of upper extremity lymphedema using LVA. Two investigators (the first and the second authors) independently reviewed and extracted data from the papers according to eligibility criteria.

Results

We found 22 studies from 1977 to 2019 (*Table S1*). Four were prospective studies (24-27) and 18 were retrospective studies (28-45). Number of patients included ranged from 2 (37) to 95 (31). Lymphedema duration ranged from 6 months (28) to 39 years (41). Campisi lymphedema grading system (46-48) was used in 7 studies (25,27,37,38,40,41,44), while MD Anderson system, based on indocyanine green lymphangiography findings, was used in two (24,26). One study (42) used the grading system described by Cheng (49). One study (45) used a personal grading system based on the severity of the edema, another (36) used a specific grading system based on the circumference comparison between the lymphedema limb and the normal limb, and another (39) used a staging system based on the preoperative indocyanine green lymphangiography findings.

LVA with end-to-end or end-to-side anastomoses was the surgical technique used in 17 studies (24-33,35,38,39,41-43, 45), while 3 studies used microsurgical lymphaticovenous implantation technique (34,36,40). The other 2 studies used LVA with the intravascular stenting method (37) and lymphovenous bypass with sleeve-in anastomosis (44). Postoperative follow-up time ranged from 3 months (28) to 84 months (24).

Upper limb circumference and volume change were the most frequently assessed parameters; however, 1 study also considered any scintigraphic uptake as a positive result (25). Outcomes were positive in 21 of 22 studies, with an average objective regression of arm volume around 30%. Subjective clinical improvement was nearly universal, with only 1 study (25) showing no significant improvements in volume or scintigraphic measurements after LVA in long-term follow-up. However, 50% of patients in that study had an initial period of relief of the subjective symptoms (25). One study reported lymphangitis in 3 patients as a surgical adverse effect after LVA (45).

The largest patient populations were reported by Krylov *et al.* (31) (95 patients) and Chang *et al.* (24) (89 patients). Chang *et al.* (24) reported overall mean volume differential reduction rates of 33% at 3 months, 36% at 6 months, and 42% at 12 months in patients who underwent LVA due to lymphedema. Mean volume differential reduction rates were 35% at 2 years and 38% at 3 years after LVA in 10 followed patients (24).

LVA was performed in patients affected by an early stage of lymphedema. When LVA was performed in patients with late stages of lymphedema (i.e., III or IV) , the circumferential reduction rate was not significant, but subjective reporting of the affected extremities as lighter and softer was reported (44).

Discussion

Lymphedema staging was assessed through different classifications over the years (24,45-50). Campisi classification divided patients with lymphedema into 5 stages (46-48). Stage 1a corresponds to absence of edema; stage 1b, to mild swelling that returns to normal after night rest; stage 2, to permanent edema that spontaneously regresses with position; stage 3, to permanent edema that does not regress spontaneously; stage 4, to fibrolymphedema, and stage 5, to elephantiasis with severe extremity deformation (46-48). On the other hand, MD Anderson lymphedema classification

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is based on indocyanine green lymphangiographic findings, dividing the patients into 4 stages: stage 1 refers to many patent lymphatic vessels with minimal patchy dermal backflow; stage 2, to moderate number of patent lymphatic vessels with segmental dermal backflow; stage 3, to few patent lymphatic vessels, with extensive dermal backflow; and stage 4, to no patent lymphatic vessels observed (24). Cheng (49) established their own grading scale, suggesting disease management according to the grade of lymphedema (i.e., 0-IV), which is divided based on the symptoms (ie, reversible, mild, moderate, severe, very severe), circumference differentiation percentage (ie, circumference of the lesioned limb subtracted from the circumference of the healthy limb and divided by the circumference of the healthy limb), and lymphoscintigraphy (i.e., partial or total occlusion). Despite the heterogeneity of classification systems used between studies, most of them reported positive outcomes after LVA [21/22 (95.4%)].

For several decades, a number of preclinical studies have been conducted in an effort to elucidate the impact of LVA intervention in the upper extremity to alleviate lymphedema. In 1962, Jacobson and Suarez (51) described the possibility of performing an anastomosis between lymphatic vessels and veins in a canine model. Further use of this method in the treatment of early secondary lymphedema was mentioned by Gilbert *et al.* in a 1976 study also on dogs (52). With this approach, congestive lymphatic fluid can successfully be drained into the cutaneous veins.

In 1977, O'Brien *et al.* (28) were the first to report a clinical experience using LVA for obstructive lymphedema in humans. In 2000, Koshima *et al.* (35) described the use of LVA for the treatment of lymphedema in the upper extremities. The results of these preliminary analyses were positive, and have driven the field forward for microsurgery-trained plastic surgeons to address this clinical dilemma.

The most frequently performed technique for the surgical treatment of breast cancer-related lymphedema of upper extremity is LVA with either end-to-end or end-to-side anastomosis; however, others have been reported. In 1998, Yamamoto and Sugihara (34) described microsurgical lymphaticovenous implantation, in which multiple collecting lymphatics are implanted into the small vein through modified sleeve anastomotic technique. In 2019, Chung *et al.* (44) described their experience performing lymphovenous anastomosis with the sleeve-in technique, used when there are no venules of similar diameter to other lymphatic vessels. This technique attaches a lymphatic vessel with the surrounding adventitia into the wall of the venule by about 0.2 to 0.3 mm, using the pull-out suture technique. Indeed nowadays, supermicrosurgery techniques allow anastomosis of vessels at the capillary level with a diameter of 0.3 to 0.8 mm (35). Controversy still exists regarding the number of anastomoses that would result in significant reductions. Chen *et al.* (53) proposed their technique by performing between seven to twelve LVA per affected extremity using lymphatic vessels and veins in a range of 0.2 to 0.6 mm.

Krylov *et al.* (31) were the first to raise concern of intralymphatic pressure. In normal physiology, lymphatic pressure should be lower than venous pressure; consequently, the flow through the anastomosis should be directed in the opposite direction to the desired one. Some surgeons have advocated addressing the problem by performing several LVAs on the same vein, but in the patient affected by lymphedema, the flow is directed in the lymphatic-venous direction due to the pressure in extracellular space from the pressing weight of the accumulated lymphedema. Furthermore, Narushima *et al.* (37) found that with a high number of LVAs per limb, the mean percentage reduction in the cross-sectional area increased exponentially, while other authors did not find a significant association in long-term follow-up (27,29,30,45).

Lymphatic microsurgery is ideally indicated in early stages, according to the 5-stage Campisi classification (46-48,54). Importantly, microlymphatic surgery is not recommended in primary lymphedema, since the lymphatics are usually hypoplastic (32). Relative contraindications to lymphatic microsurgery include lymphatic-lymph nodal aplasia, diffuse metastatic disease, advanced stage, and no response to conservative therapies.

On the other hand, it is still not clear if breast reconstruction influences risk of lymphedema. Menezes *et al.* (55) observed that breast reconstruction does not increase the risk of lymphedema in long-term follow-up, while Siotos *et al.* (56) stated that breast reconstruction is associated with lower rates of lymphedema compared to mastectomy only or breast conserving surgery. This association might be due to several factors, such as a self-selecting population and mechanisms that contribute to prevention of lymphedema.

As with all literature reviews, this study has several limitations. First, there is a general lack of large-volume studies addressing LVA in the upper extremity following breast cancer. Moreover, there was an inability to pool data based on different protocols, varying techniques and measurement of the outcomes for statistical analyses.

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Despite this, we feel that our study reports valuable pooled data, particularly pertaining to overall positive outcomes in LVA in the upper extremity across 21 of the 22 studies identified. Furthermore, our review is limited by the heterogeneity of the patient populations and classification systems used in the included studies, as well as the English language inclusion criteria. As such, there is a potential for bias in interpreting the data reported in each study, the comorbidity data and reporting outcomes over a long-period of time. Larger, randomized, multicenter studies are warranted to validate the associations found in this review of the literature.

Conclusions

The results of this review of the literature on LVA for breast cancer-related upper extremity lymphedema demonstrated a significant decrease in upper extremity volumes and improvement in subjective findings of lymphedema in most patients. Importantly, this response was maintained in long-term follow-up. There is evidence to suggest great efficacy in LVA in the upper extremity following breast cancer extirpation.

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Footnote

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Supplementary

Table 1 Clinical studies on lymphaticovenular anastomosis for breast cancer-related upper extremity lymphedema

Author	Year	Type of study	Number of patients, demographic data	Lymphedema duration	Lymphedema grading system	Surgical technique	Follow-up time	Outcomes	Notes
O'Brien BM (28)	1977	Retrospective study	22	6 months–21 years (average: 8.9 years)	NR	LVA, number of anastomoses: 1–7	3–20 months	The excess volume was reduced by an average of 19%. 1–7 cm decrease in the circumference	Incidence of cellulitis dropped from 56% to 13% postoperatively
O'Brien BM (29)	1979	Retrospective study	23	NR	NR	LVA	NR	NR	No correlation was found between the number of LVAs and the final reduction in volume
Gong-Kang H (30)	1981	Retrospective study	2	NR	NR	LVA (end-to-end or end-to-side fashion)	Up to 12 months	Circumference reduction. Decrease of clinical symptoms	The surgeries were performed under epidural anesthesia
Krylov VS (31)	1985	Retrospective study	95	NR	NR	LVA (end-to-end or end-to-side fashion)	NR	NR	Intralymphatic pressure measurements were taken in the course of lymphangiography and intraoperatively
O'Brien BM (32)	1990	Retrospective study	46	NR	NR	LVA	NR	25 patients (54%) had a volume reduction. The average reduction was 34%	Anastomosis at the wrist had a dramatic permanent effect in reduction of hand edema in the vast majority of patients
Filippetti M (45)	1994	Retrospective study	25	NR	Personal classification in 3 grades (45)	LVA	6–18 months	10 patients showed fair or good results at 18 months. Three patients presented with lymphangitis as a surgical adverse effect	A correlation between results and number of anastomoses were found. Two anastomoses caused good results in the short and medium term
Koshima I (33)	1996	Retrospective study	6 female, mean (SD) age: 56.5 (8.7) years, 5 left arm and 1 right arm	Mean (range): 70.8 (11–137) months	Severe-moderate (arbitrary)	LVA	17 months or more (average 25.5 months)	The circumference of the arms decreased maximally by 2–9 cm (average 5.3 cm). The rate of preoperative versus postoperative excess of the arms decreased by 25–94.7% (average 65.7%)	In the postoperative scenario, no correlation was found between the preoperative duration of edema and excess circumference
Yamamoto Y (34)	1998	Retrospective study	5 upper extremities in 5 female patients, 3 right extremities and 2 left extremities; age range: 57–72 years	Mean (range): 9.4 (1–18 years)	NR	Microsurgical lymphaticovenous implantation of the collecting lymphatics into the small vein using the modified sleeve anastomotic technique	Average 1 year and 5 months (9 months–2 years)	The average decrease was 2.7 cm at 3 cm below the wrist, 4.5 cm at 3 cm above the wrist, 4.2 cm at 5cm below the olecranon, and 3.6 cm at 5 cm above the olecranon. A gradual recurrence of edema 9 months postoperatively was found in one patient	A greater reduction in the circumference of the dorsum of hand and forearm than the upper arm was found in all patients
Koshima I (35)	2000	Retrospective study	12, mean age: 57 years	Mean: 8.2 years	Severe-moderate (arbitrary)	LVA. The average number of anastomoses was 4.1 (range: 1–7) in each patient. End-to-end LVAs made with a fine needle holder and 11-nylon under high magnification (×20–×30)	Average: 2.2 years (from 1 month–6 years)	The average decrease in circumference was 4.1 cm (47.3% of the preoperative excess circumference of the forearm)	Supermicrosurgical LVA: lymphatics and subdermal venules were 0.3–0.6 mm in diameter. Use of small venules rather than veins due to the similarity of the caliber to the subdermal lymphatic channels
Yamamoto Y (36)	2003	Retrospective study	18 females; age range: 47–80 years	Mean (range): 7.1 (1–23) years	Average enlargement of edema circumference (AEE), comparing the affected and non-affected limb. Patients were classified into 3 groups (severe, moderate, or mild) according to AEE findings	Microsurgical lymphaticovenous implantation procedure (31) combined with compression therapy. First, the lymphatics were collected, picked up, and drawn inside the vein, 4–6 external interrupted stitches using 11-0 microsutures were placed between the cut end of the vein and the external adventitial and adipose tissue of the collecting lymphatics	Average: 24 months (12–72 months)	77.8% of patients presented excellent or good results. Reduction of more than 50% of the edema circumference at either the distal or proximal site after treatment	Compression therapy with elastic bandage was continued in the postoperative period
Damstra RJ (25)	2009	Prospective study	10 female, mean (range) age: 58.7 (46–68) years	Mean (range): 5.3 (3–14) years	Campisi (46-48)	11 LVA procedures	Mean: 8 years	After 6 months, 5/10 patients showed subjective relief of symptoms. At long-term follow-up, no significant improvements was found after LVA in patients with chronic lymphedema. In addition, there was no effect in volume or scintigraphy measurements	The authors considered any uptake a positive result
Narushima M (37)	2010	Retrospective study	2	NR	Campisi (46-48)	LVA with intravascular stenting method. In each of the 2 upper extremities, 4 and 6 anastomoses were performed. End-to-side LVA at the elbow, and end-to-side and end-to-end LVA at the wrist were performed	NR	Cross-sectional area girth reduction	Increasing the number of LVAs per limb decreased the average percentage in the cross-sectional area
Chang DW (27)	2010	Prospective study	20, mean age: 54 years	Mean (range): 4.8 (1–17) years	Campisi (46-48)	LVA (generally performed end-to-end). The mean (range) number of bypasses performed was 3.5 (2–5)	Mean: 18 months	19 patients (95%) reported improvement immediately after surgery, but not all demonstrated a quantitative measurable difference. In 3 patients, the improvement was only temporary. 13 patients (65%) had quantitative improvement in their lymphedema after surgery. No postoperative adverse effects or worsening of lymphedema were present in any patient. The mean volume differential reduction was 29% at 1 month, 36% at 3 months, 39% at 6 months, and 35% at 12 months	
Auba C (39)	2012	Retrospective study	7	NR	Campisi (46-48)	LVA: First, the lymphatic channels and venules in the subdermal level were identified, then end-to-end anastomosis was performed with 12-0 nylon using a surgical microscope	24 months	The mean (SD) perimeter reduction was 0.85 (1.06) cm	Most patients presented an objective regression of lymphedema
Chang DW (24)	2013	Prospective study	89 (46 left and 43 right upper extremities); mean age: 54 years; mean (range) BMI: 30 (20–51) kg/m^2	Mean (range): 3.5 (1–10) years	MD Anderson (24)	LVA	Mean (range): 30.4 (3–84) months	The mean differential volume reduction was 33% at 3 months, 36% at 6 months, and 42% at 12 months after surgery. In 10 patients, the mean volume differential reduction was 35% at 2 years and 38% at 3 years after surgery	Absence of adverse effects or worsening of lymphedema after surgery during the study
Yamamoto T (38)	2014	Retrospective study	3	NR	Staging based on the preoperative ICG lymphography (56)	LVA using 11-0 or 12-0 nylon sutures	NR	Lymphedema indices decreased in all limbs post-surgery compared with preoperative lymphedema indices. Absence of any postoperative adverse effects	Intraoperative microscopic ICG lymphography enhanced lymphatic vessels
Torrisi JS (26)	2015	Prospective study	6 female	NR	MD Anderson (24)	LVA	6 months	83% of patients with symptomatic improvement 6 months after surgery. 3/6 patients experienced modest decreases in arm volumes at 6 months. 5/6 patients had decreased symptoms	LVA was associated with decreased local tissue inflammation, dermal fibrosis, TGF-β1 expression, hyperkeratosis, epidermal proliferation, and number of capillary lymphatic vessels
Winters H (41)	2017	Retrospective study	29 female (12 left arm, 17 right arm), mean (SD) age: 59 (9) years (range: 41–84 years), mean (SD) BMI: 27 (4) kg/m^2 (range 21–34 kg/m^2)	Mean (SD): 9 (7.3) years (range: 2–39 years)	Campisi (46-48)	LVA: 1–3 anastomoses were created and shunt patency was confirmed using ICG	12 months	29% and 33% volume reduction at 6- and 12-month follow-up was reached, respectively. An improvement of quality of life was identified from 5.8±1.1 to 7.4±0.7. Absence of postoperative adverse effects 30 days after surgery. During follow-up, 2 patients endured 2 episodes of cellulitis	The functionality score decreased from 2.2 to 1.8, the appearance score from 2.6 to 1.9, the symptoms score from 2.8 to 1.8, and the mood score from 2.7 to 1.5
Poumellec MA (40)	2017	Retrospective study	31, mean (SD) age: 64 (11) years (range: 38–65 years)	≥12 months	Campisi (46-48)	LVA: The anastomosis was constructed with separate sutures with 11-0 non-resorbable thread with 5–6 stitches using end-to-end technique or the telescopic method described by Yamamoto (31,33) in the case of differences in vessel diameter	34 months (mean:12.8 months)	Reduction in the circumference was 22.5, 21.32, and 30.2%, respectively, in the wrist, forearm, and arm. Functional improvement was observed in the majority (84%) of patients ranging from moderate to substantial. Two patients had no result. Only patients with a high level of lymphedema experienced recurrence	The procedure was performed under local-regional anesthesia (axillary block), without an arm tourniquet
Engel H (42)	2018	Retrospective study	27 (23 did not receive microsurgical breast reconstruction and 4 underwent microsurgical breast reconstruction)	Mean (SD): 31.3 (11.4) months (range 8.4–120.5 months)	Cheng (49)	LVA in a side-to-end or end-to-end fashion with a 11-0 nylon suture	Mean (SD): 19.1 (5.3) months (range 5.7–62.8 months)	Improved mean (SD) circumferential difference to 4.1% (1.6%) in patients who did not receive microsurgical breast reconstruction and 11.1% (4.9%) in patients who underwent microsurgical breast reconstruction. Mean (SD) circumferential reduction rate was improved to 17.5% (5.5%) in the patients who did not received breast reconstruction and to 11.6% (5.7%) in patients that underwent microsurgical breast reconstruction	The re-exploration rate was 16.9% (n= 21), and the overall adverse effect rate was 8.1% (n=10). Flap losses did not occur
Pereira N (43)	2018	Retrospective study	8/8 in upper extremity, mean (range) age: 48.9 (35–59) years, mean (range) BMI: 23.34 (19.91–29.95) kg/m^2	Mean (range): 4.61 (2–9.25) years	NR	LVA. Mean (range) number of LVA per upper extremity was 3.75 (1–6), mean (range) time per LVA was 96.1 (27.1–261) minutes	Mean (range): 27.4 (3–84) months	Symptoms improved in all patients. Statistically significant quantitative improvement in percentage of excess volume and postoperative mean volume	Preoperative mean (range) number of cellulitis episodes per year was 1.3 (0–3), decreasing to 0 episodes after surgery
Chung JH (44)	2019	Retrospective study	8 patients (5 left and 3 right), Mean age: 51 years, Mean BMI: 23 kg/m^2	4 years	Campisi (46-48)	LVA with the sleeve-in technique	NR	Quantitative improvements in circumferential measurements after surgery were found in all cases. Overall mean circumferential reduction rates of 3.5% at 1 month, 6.4% at 2 months, and 8.3% at 6 months were found in the upper extremities	A subjective perception of lighting and softening in the affected limbs after surgery was found in patients with severe (stage III/IV) lymphedema, although the circumferential reduction rate was not significant

LVA, lymphaticovenular anastomosis; ICG, indocyanine green; NR, not reported.