Comparison of Outcomes between Side-to-End and End-to-End Lymphovenous Anastomoses for Early-Grade Extremity Lymphedema

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Background: Lymphovenous anastomosis is technically challenging and can be successfully performed with an advanced operating microscope, supermicrosurgical instruments, and indocyanine green lymphography. This study compared the outcomes between side-to-end and end-to-end lymphovenous anastomosis configurations for unilateral extremity lymphedema.

Methods: Between April of 2013 and June of 2017, lymphovenous anastomosis was indicated for 58 patients who preoperatively had patent lymphatic ducts by indocyanine green lymphography, including 20 patients with upper limb lymphedema and 38 patients with lower limb lymphedema. Either an end-to-end or a side-to-end lymphovenous anastomosis was used to anastomose the subdermal venule to the lymphatic duct. The circumferential difference and episodes of cellulitis were used as outcome measurements.

Results: Twenty-three patients underwent an end-to-end lymphovenous anastomosis and 35 patients underwent side-to-end lymphovenous anastomosis. All patients had an immediate patency evaluated by indocyanine green lymphography and patent blue assessments. All patients returned to their daily routine without the use of any compression garments. At an average follow-up of 16.5 months (range, 13.4 to 19.6 months), the improvement of circumferential difference (3.2 percent; range, 1.8 to 4.6 percent) in the side-to-end group was statistically greater than that in the end-to-end group (2.2 percent; range, 1 to 3.4 percent; $p = 0.04$). The overall episodes of cellulitis were significantly reduced from 1.7 times/year (range, 1.3 to 2.1 times/year) to 0.7 times/year (range, 0.3 to 1.1 times/year; $p < 0.001$), but no difference was observed between the two groups.

Conclusions: Both side-to-end and end-to-end lymphovenous anastomosis configurations were effective surgical approaches for improving early-grade extremity lymphedema. Side-to-end lymphovenous anastomosis has the advantages of having greater efficacy for lymph drainage, requiring only one anastomosis and eliminating the need to use compression garments. (*Plast. Reconstr. Surg.* 144: 486, 2019.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, III.

Extremity lymphedema is a progressive debilitating disorder that is characterized by proximal failure of the lymphatic transport system. Primary lymphedema results from abnormal lymphatic channels caused by obstruction, malformation, or hypoplasia. When primary lymphedema is present at birth or during infancy, it is known as congenital lymphedema or Milroy disease. However, the presentation of symptoms

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may occur later on, either before the age of 35 years, when it is called lymphedema praecox, or after that age, when it is called lymphedema tarda. Secondary lymphedema is caused by the obstruction of normal lymphatic channels with infection or trauma. Breast cancer treatment with axillary lymph node dissection and radiotherapy is the classic precursor of secondary lymphedema,[1] but it is also observed in patients undergoing treatment for gynecologic cancers with pelvic lymph node dissection and radiation therapy.[2]

Regardless of the causes, obstruction of the lymphatic system results in a specific series of events that leads to extremity lymphedema. Between 29 and 49 percent of breast cancer patients who undergo axillary lymph node dissection will develop upper limb lymphedema, compared with only 5 to 7 percent of those who undergo sentinel lymph node biopsy. On average, these patients develop lymphedema within 8 months of surgery, with 75 percent developing lymphedema within the first 3 years.[3] This secondary lymphedema continues to be a growing burden that can have a significant impact on the quality of life of cancer patients. The result is a limb that is heavy, dysfunctional, painful, and prone to infection and poor quality of life in long-term follow-up. Unfortunately, no definitive cure for extremity lymphedema currently has been reported. Compressive decongestive therapy is the traditional conservative lymphedema management.[4–9] However, the economic and personal burden of compressive decongestive therapy often results in suboptimal patient adherence.[6] Naturally, clinicians have looked for other treatment modalities to improve patient quality of life and decrease the economic burden of lymphedema. Advancements in surgical reconstruction have enabled new avenues to treat chronic lymphedema (e.g., lymphovenous anastomosis and vascularized lymph node transfer) that are less morbid than the traditional operations.[10,11] Lymphovenous anastomosis was first described in 1969 and is a microsurgical technique that involves diverting lymphatic fluid into the venous system within a lymph-flooded bed. Studies have shown that lymphovenous anastomosis is especially effective in those with early-stage lymphedema of the upper extremities.[12] In a prospective analysis of 100 lymphovenous anastomoses performed for lymphedema patients, symptomatic improvement was reported to be 96 percent in the upper extremity and 57 percent in the lower extremity lymphedema. Other benefits from lymphovenous anastomosis include decreased rates of cellulitis, which is a common complication of lymphedema often requiring repeated antibiotic treatment. For patients undergoing oncologic resections, lymphovenous anastomosis has also been shown to have prophylactic results.[13,14] This effect was demonstrated in a group of 14 patients with early-stage lower extremity lymphedema from resection of a variety of gynecologic cancers, and lymphovenous anastomosis effectively prevented symptomatic lymphedema. Lymphovenous anastomosis had successfully prevented upper limb lymphedema in a group of 23 women who underwent axillary lymph node dissection for breast cancer treatment. However, lymphovenous anastomosis is technically challenging. Lymphatic vessels with a diameter of 0.5 to 0.8 mm are anastomosed to subdermal venules 0.6 to 1.0 mm in diameter. Fortunately, advances both in operating microscope optics and in superfine, atraumatic microsurgical instruments, and improvements in imaging modalities of indocyanine green lymphography, have improved the ability to perform this technique. The reported complications with this procedure include a 3.9 percent incidence of infection, a 4.1 percent incidence of lymphorrhea, and a 10 percent incidence of patients requiring a subsequent operation.[15] Despite these variable complications of lymphovenous anastomosis, no reports of the outcomes have previously compared different methods for lymphovenous anastomosis. Several animal studies assessed the long-term anastomosis patency of lymphovenous anastomosis, with 80 percent performed in the end-to-side fashion compared with 47 percent performed in the end-to-end fashion with up to 5 months of follow-up.[16–19] Those studies were conducted in small sample sizes and with different animal models of acute lymphedema but not chronic lymphedema. The purpose of this study was to investigate and compare the long-term outcomes of lymphovenous anastomosis for extremity lymphedema between side-to-end and end-to-end procedures.

PATIENTS AND METHODS

This retrospective study was approved by the institutional review board at Chang Gung Memorial Hospital, and written informed consent was obtained from the participants. Cheng's Lymphedema Grading system was used to select the patients for whom lymphovenous anastomosis was indicated based on symptom severity, circumferential differentiation, and partial obstruction on lymphoscintigraphy.[20] Briefly, lymphovenous anastomosis was indicated for Cheng's Lymphedema grade I and II patients who had patent

lymphatic ducts evaluated by preoperative indocyanine green lymphography, without episodes of cellulitis within 1 month, at our center. An individualized treatment plan is determined based on each patient's clinical symptoms and signs and Cheng's Lymphedema Grading, with subsequent imaging studies of lymphoscintigraphy and indocyanine green lymphography. Grade I and II patients are provided with the options of complex decongestive therapy or lymphovenous anastomosis. Patients with Cheng's Lymphedema grade I and II are advised to undergo lymphovenous anastomosis with patent lymphatic ducts using indocyanine green lymphography.[20] All patients who underwent lymphovenous anastomosis for symptomatic extremity lymphedema between April of 2013 and June of 2017 were included (Table 1). Only one anastomosis, either end-to-end or side-to-end, was performed in each group. Cases of more than one anastomosis in a single lymphedematous limb were excluded in this study. All of the procedures were performed by the same senior surgeon (M.H.C.), with the same supermicrosurgical technique under a Mitaka 42× microscope (Mitaka Kohoki Co., Tokyo, Japan), and with the same postoperative care. The patients who had bilateral extremity lymphedema who underwent both end-to-end and side-to-end lymphovenous anastomoses or underwent more than two end-to-end lymphovenous anastomoses in a single limb were excluded. The circumferential difference was calculated as follows: the circumference of the affected extremity subtracted from the circumference of the healthy extremity and subsequently divided by the circumference of the healthy extremity. These circumference measurements were taken preoperatively and every month postoperatively by the same senior coordinator (C.Y.L.) at certain anatomical locations (i.e., 15 cm above and below the knee, 10 cm above the ankle in patients with lower extremity lymphedema, and 10 cm above and below the elbow in those with upper extremity lymphedema).[21]

Table 1. Demographics of 58 Consecutive Early Lymphedema Patients Who Underwent Lymphovenous Anastomosis

Part of Lymphedema	No. of Cases (%)	Median Age (IQR) (yr)	Median Body Mass Index (IQR) (kg/m^2)	Median Symptom Duration (IQR) (mo)	Chemotherapy (%)	Radiation Therapy (%)	Median Preoperative Period of Compression Garment (IQR) (mo)	Reason for Lymphedema	
								Primary (%)	Secondary (%)
ETE									
ULL	8 (34.8)	42.1 (38.1–46.2)	21.1 (19.1–23.1)	54.1 (12–96.2)	8 (100)	8 (100)	12.1 (10–14.2)	0 (0)	8 (100)
LLL	15 (65.2)	55.6 (43–68.2)	25.1 (21.4–28.8)	49.1 (15.4–83.2)	12 (80)	12 (80)	26.8 (3–50.6)	3 (20)	12 (80)
Subtotal	23 (39.7)	51.7 (38.1–65.4)	23.5 (19–28)	50.7 (12–95.4)	20 (86.9)	20 (86.9)	25.6 (3–48.2)	3 (13)	20 (87)
STE									
ULL	12 (34.3)	38.4 (5–71.8)	24.2 (18.6–29.8)	25.1 (6–44.2)	11 (91.7)	11 (91.7)	19.4 (3–35.8)	1 (8.3)	11 (91.7)
LLL	23 (65.7)	48.7 (12.4–85.4)	25.9 (20.5–31.3)	49.9 (6–93.8)	12 (52.2)	12 (52.2)	30.2 (5–55.4)	11 (47.8)	12 (52.2)
Subtotal	35 (60.3)	46.8 (5–88.6)	24.8 (18.6–31)	40.4 (6–74.8)	23 (65.7)	23 (65.7)	25.8 (3–48.6)	12 (34.3)	23 (65.7)
Total	58 (100)	49.3 (5–93.6)	24.4 (18.6–29)	42.8 (4–81.6)	43(74.1)	43(74.1)	25.7(3–48.4)	15 (25.9)	43 (74.1)
p									
ETE vs. STE		0.5	0.6	0.3	0.04*	0.04*	0.7	0.04*	
ETE-ULL vs. STE-ULL		0.06	0.07	0.02*	0.04*	0.04*	0.06	0.04*	
ETE-LLL vs. STE-LLL		0.04*	0.8	0.9	0.04*	0.04*	0.06	0.9	

IQR, interquartile range; ETE, end-to-end; STE, side-to-end; ULL, upper limb lymphedema; LLL, lower limb lymphedema.
*Statistical difference between end-to-end and side-to-end groups.

Indocyanine Green Lymphography

Indocyanine green lymphography was performed preoperatively (Fig. 1). Indocyanine green (0.5%, 0.5 ml; Diagnogreen; Daiichi Pharmaceutical, Tokyo, Japan) was injected subdermally into the dorsal aspect of the affected extremity (first and fourth web spaces). The fluorescence was observed with the assistance of a custom-made device with a near-infrared camcorder (Sony HD Handycam CM05; Sony Corp., Tokyo, Japan) at 5 minutes and 20 hours after injection

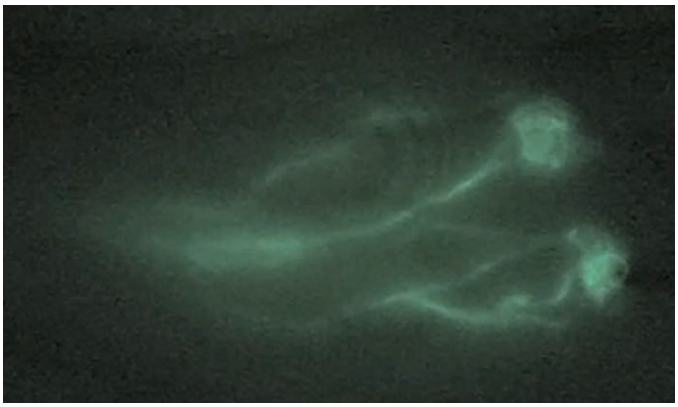

Fig. 1. Lymphography with indocyanine green was performed preoperatively.

of indocyanine green. Lymphodynamic images were recorded using a high-definition digital video format. The fluorescence was highlighted on the skin of the involved extremity. Repeated lymphodynamic images were recorded intraoperatively after anastomosis for real-time evaluation of patency of anastomosis and lymphatic flow into the subdermal venule.

Surgical Technique

All procedures were performed under general anesthesia by the senior author (M.H.C.). A 3-cm-long skin incision was made in the dorsal aspect of the affected extremity distally; this site is where functional lymphatics could be clearly visualized by the indocyanine green lymphography preoperatively. Injection of 0.1 cc of patent blue dye 5 cm distal to the incision site was carried out. After the skin incision was made, careful dissection was performed to identify the small subdermal veins (0.6 to 1.0 mm in diameter) and the collecting lymphatic vessels (Fig. 2), of which the diameters were 0.5 to 0.8 mm, under 20× to 40× high-power magnification (Mitaka MM50 Surgical Microscope). After identifying a suitable subdermal vein and a collecting lymphatic vessel, end-to-end or side-to-end anastomosis was performed using 11-0 nylon sutures to bypass the lymph into the anastomosed subdermal venule (Fig. 3). The selection of methods of anastomosis (end-to-side or side-to-end) was made depending on the length of the subdermal venule, quality of the lymphatic ducts, and location of both lymphatic ducts and subdermal venule. End-to-end anastomosis was performed using a technique published previously by Koshima et al.[22] The side-to-end anastomosis was started after the dissection of an adequate length of the subdermal venule, which was divided at the far distal side and brought to reach the lymphatic duct with a smooth curve. Next, the lymphatic duct was cut to make a hole approximately 0.8 mm in diameter. A 6-0 nylon suture 2 cm in length was inserted into the hole as a stent, usually to the left side. The 11-0 nylon suture was used to suture the venule first and then the lymphatic duct at the 9-o'clock position, followed by the 11-o'clock and 1-o'clock positions. Next, the 7-, 5-, and 3-o'clock stitches were sewn and cut individually to avoid suturing

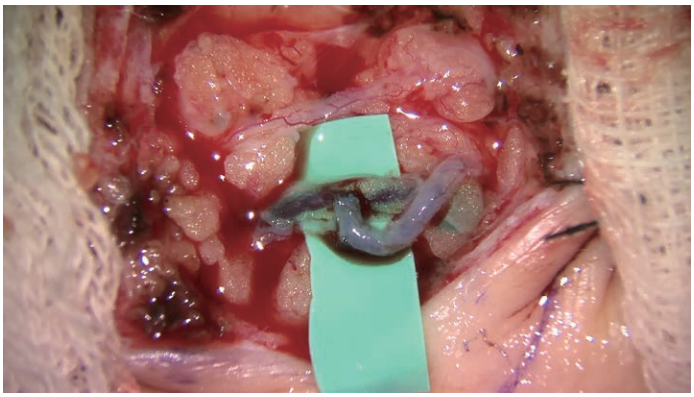

Fig. 2. Patent blue dye traversing the anastomosis, ensuring patency.

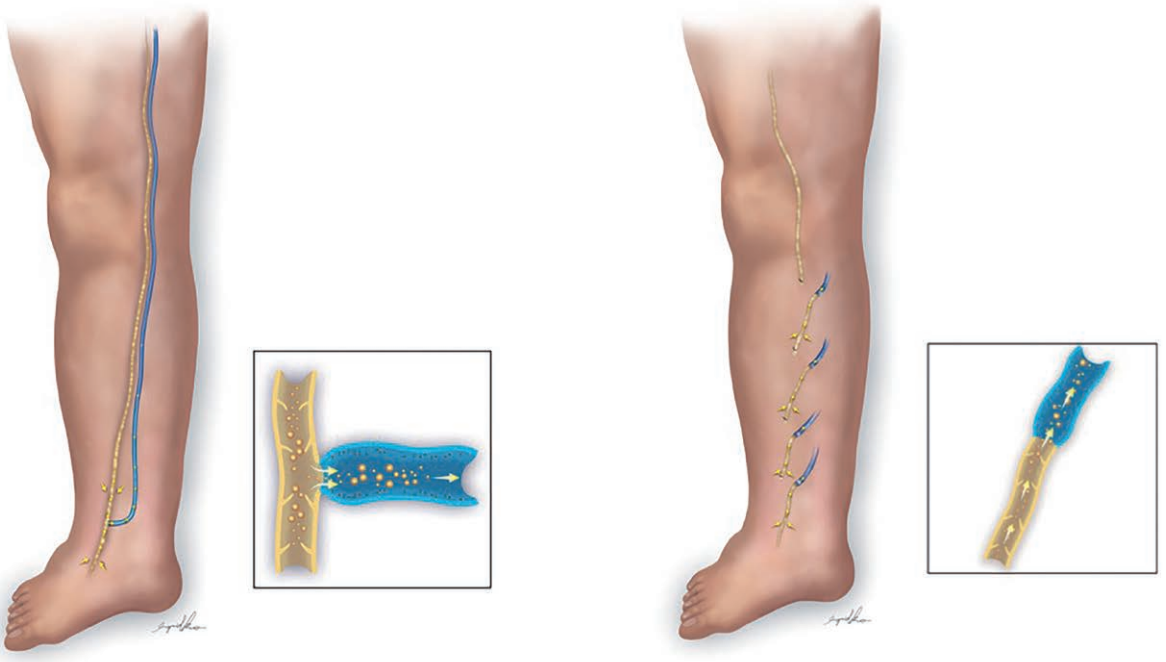

Fig. 3. Comparisons of lymphatic drainage directions and patterns between side-to-end and end-to-end lymphovenous anastomoses. Side-to-end lymphovenous anastomosis drains both proximal and distal lymph into the venous system. End-to-end lymphovenous anastomosis drains only distal lymph into the venule and requires more lymphovenous anastomoses in the more proximal sites.

the back wall, and they were tied one by one after removing the 6-0 nylon stitch. (**See Video, Supplemental Digital Content 1**, which demonstrates lymphovenous anastomosis in a side-to-end fashion, available in the "Related Videos" section of the full-text article on PRSJournal.com or, for Ovid users, at ***http://links.lww.com/PRS/D613***.) Immediately after the anastomosis was completed, a patency test was carried out using patent blue to determine whether the blue die moved through the lymphatic vessel into the venule. Next, the near-infrared camcorder or the Mitaka microscope was used with the room lights turned off to check if the indocyanine green fluorescence moved from the lymphatic duct to the subdermal vein in order to confirm anastomotic patency. (**See**

Video 1. Supplemental Digital Content 1, which demonstrates lymphovenous anastomosis in a side-to-end fashion, is available in the "Related Videos" section of the full-text article on PRSJournal.com or, for Ovid users, at ***http://links.lww.com/PRS/D613***.

Video, Supplemental Digital Content 2, which demonstrates the patency test of the side-to-end lymphovenous anastomosis using indocyanine green lymphography and patent blue, available in the "Related Videos" section of the full-text article on PRSJournal.com or, for Ovid users, at ***http://links.lww.com/PRS/D614***.)

Postoperative Protocol

Patients were hospitalized in the ward while limiting their activity level to allow better endothelial healing of anastomosis for 3 days. Compression garments were discontinued from postoperative day 1. Patients were then started on a 2-week rehabilitation program that included manual drainage using massage from the proximal to the distal end of the affected limb. In addition, patients were instructed to avoid having any direct pressure on the operation site, and to avoid high intensity use of the arm or leg for at least 1 month postoperatively. No heparin or anticoagulant was needed.

Outcome Measurement

The circumferences of the bilateral extremities were measured at three sites as mentioned above, preoperatively and every month postoperatively. The circumferential differences and the episodes of preoperative and postoperative cellulitis were compared between the end-to-end and side-to-end groups. Further analyses were performed between upper and lower limb lymphedema subgroups and between primary and secondary lymphedema subgroups.

Statistical Analysis

All data are expressed as the median and interquartile range. The data were analyzed using SPSS Version 17.0 software (SPSS, Inc., Chicago, Ill.). The Kolmogorov-Smirnov test was used to examine the skewness of the data for a normal distribution. The Mann-Whitney U test was used to analyze the age, body mass index, lymphedema symptom duration, period of wear compression garment, Cheng Lymphedema Grading, postoperative circumferential difference, episode of cellulitis, and follow-up duration in two groups. Chi-square or Fisher's exact test was used to assess categorical variables on chemotherapy, radiation therapy, and reason for lymphedema. All statistical tests were two-sided, and a value of $p < 0.05$ was considered to be statistically significant.

RESULTS

A total of 58 patients with extremity lymphedema who underwent lymphovenous anastomosis were included; 38 of them had lower extremity lymphedema and 20 had upper extremity lymphedema. The patients of both the end-to-end and the side-to-end groups had similar severity of extremity lymphedema, including symptom duration, preoperative period of compression garments, and Cheng's Lymphedema Grading (Tables 1 and 2). Fifteen of those patients had primary lymphedema, and 43 had secondary lymphedema. Thirty-three patients were categorized as having grade I lymphedema, and 25 patients were categorized as having grade II lymphedema.

Video 2. Supplemental Digital Content 2, which demonstrates the patency test of the side-to-end lymphovenous anastomosis using indocyanine green lymphography and patent blue, is available in the "Related Videos" section of the full-text article on PRSJournal.com or, for Ovid users, at ***http://links.lww.com/PRS/D614***.

There were no statistical differences in the median age, body mass index, symptom duration, or preoperative compression garments use between the end-to-end group and the side-to-end group ($p = 0.5$, $p = 0.6$, $p = 0.3$, and $p = 0.7$, respectively) (Table 1). The incidences of chemotherapy and radiation therapy were statistically greater in the end-to-end group than in the side-to-end group ($p = 0.04$ and $p = 0.04$, respectively) (Table 1). Twenty-three patients underwent an end-to-end lymphovenous anastomosis, and 35 patients had a side-to-end lymphovenous anastomosis. All cases had an immediate patency test with indocyanine green lymphography and patent blue before wound closure. In all cases, the affected extremities became softer and lighter immediately after lymphovenous anastomosis, and none of them reported worsening of their lymphedema symptoms postoperatively. At an average follow-up of 16.5 months (range, 13.4 to 19.6 months), the improvement in circumferential difference was statistically significant in the side-to-end group, with a mean of 3.2 percent (range, 1.8 to 4.6 percent), compared with the end-to-end group, with a mean of 2.2 percent (range, 1 to 3.4 percent; $p = 0.04$). The overall number of cellulitis episodes was significantly reduced from 1.7 times/year (range, 1.3 to 2.1 times/year) to 0.7 times/year (range, 0.3 to 1.1 times/year; $p < 0.01$) (Table 2). All 58 patients were completely recovered and returned to their daily routine without the use of compression garments. Complete recovery was defined as no need for compression garments postoperatively with follow-up greater than 12 months. The rate of complete recovery was 100 percent for both groups (Table 2).

Response to Upper and Lower Lymphedema

In upper limb lymphedema, the median symptom duration of 54.1 months (range, 12 to 96.2 months), incidence of chemotherapy of 100 percent, and incidence of radiation therapy of 100 percent in the end-to-end group were statistically greater than 25.1 months (range, 6 to 44.2 months), 91.7 percent, and 91.7 percent, respectively, in the side-to-end group ($p = 0.02$, $p = 0.04$, and $p = 0.04$, respectively) (Table 1). The average improvement in circumferential difference of 3.4 percent (range, 2.3 to 4.5 percent), and the reduction of episodes of cellulitis from 2.4 times/year (range, 1.1 to 3.7 times/year) to 1.8 times/year (range, 1.1 to 2.5 times/year) in the side-to-end group, were statistically greater than 2.5 percent (range, 1.4 to 3.6 percent), and from 2.1 times/year (range, 0.8 to 3.4 times/year) to 0.9 times/year (range, 0.3 to 1.5 times/year) in the end-to-end group ($p = 0.04$ and $p < 0.01$, respectively) (Table 2).

In patients with lower limb lymphedema, besides the median symptom duration of 49.1 months (range, 15.4 to 83.2 months) versus 49.9 months (range, 6 to 93.8 months) ($p = 0.9$), average incidence of chemotherapy of 80 percent, and incidence of radiation therapy of 80 percent in the end-to-end group were statistically greater than 52.2 percent, and 52.2 percent, respectively, in the side-to-end group ($p = 0.04$, and $p = 0.04$, respectively) (Table 1). The average improvement in circumferential difference of 2.9 percent (range, 1.7 to 4.1 percent), and the reduction of episodes of cellulitis from 2.1 times/year (range, 1.3 to 2.9 times/year) to 0.4 times/year (range, 0.3 to 0.5 times/year), in the side-to-end group were statistically greater than the 1.8 percent (range, 1 to 2.6 percent), and from 1.4 times/year (range, 0.7 to 2.1 times/year) to 0.6 times/year (range, 0.4 to 0.8 times/year), in the end-to-end group ($p = 0.04$ and $p < 0.01$, respectively) (Table 2).

Response to Primary and Secondary Lymphedema

In total, 15 patients with primary lymphedema and 43 patients with secondary lymphedema underwent a single lymphovenous anastomosis. Mean improvement in the circumferential difference did not differ statistically between the primary and secondary lymphedema subgroups ($p = 0.9$). The episodes of cellulitis were reduced in both groups ($p = 0.6$). The secondary lymphedema subgroup had a significantly longer follow-up period compared with the primary lymphedema subgroup ($p = 0.04$) (Table 3).

DISCUSSION

Koshima et al. performed six to 10 lymphovenous anastomoses in an end-to-end fashion in a single limb under local anesthesia.[22] Lymphovenous anastomosis is a very delicate procedure and, in our opinion, should be performed in a tension-free environment with the patient under general anesthesia. To ensure proper healing after lymphovenous anastomosis, it is suggested that the patient should limit activity for at least 3 days for endothelial healing. Lymphovenous anastomosis alleviates the lymphedema symptoms, bypassing proximal obstruction by draining the congested lymph directly into the venous circulation.[23] As retrograde lymph flow always exists in obstructive lymphedema, it is important

Table 2. Comparisons of Cheng's Lymphedema Grading, Postoperative Improvement of Circumferential Difference, Episodes of Cellulitis, and Follow-Up between the End-to-End and Side-to-End Groups

Part of Lymphedema	No. of Cases (%)	Cheng's Lymphedema Grading				Postoperative Improvement of Circumferential Difference (%)			Median Cellulitis (IQR) (times/yr)		Complete Recovery (Non compression Garment) (%)	Median Follow-Up (IQR) (mo)
		Preoperative		Postoperative		Above Knee 15 cm/Above Elbow 10 cm	Below Knee 15 cm/Below Elbow 10 cm	Mean				
		Grade	Median (IQR)	Grade	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Pre-operative	Post-operative		
ETE												
ULL	8 (34.8)	I: 2 II: 6	1.5 (1–2)	I: 4 II: 4	1.2 (1–1.4)	2.9 (1.1–4.8)	2.1 (1.8–2.4)	2.5 (1.4–3.6)	2.1 (0.8–3.4)	0.9 (0.3–1.5)	8 (34.8)	12.7 (10.15.4)
LLL	15 (65.2)	I: 6 II: 9	1.8 (1–2.6)	I: 15 II: 0	1.3 (1–1.6)	2.1 (0.9–3.3)	1.7 (1.1–2.2)	1.8 (1–2.6)	1.4 (0.7–2.1)	0.6 (0.4–0.8)	15 (65.2)	22.1 (18–26.2)
Subtotal	23 (39.7)	I: 8 II: 15	1.4 (1–1.8)	I: 19 II: 4	1.2 (1–1.6)	2.5 (0.9–4.1)	1.8 (1.2–2.4)	2.2 (1–3.4)	1.7 (0.6–2.8)	0.9 (0.3–1.5)	23 (39.7)	14.1 (9.2–28.2)
STE												
ULL	12 (34.3)	I: 8 II: 4	1.4 (1–1.8)	I: 9 II: 3	1.1 (1–1.2)	3.8 (2.2–5.4)	3.1 (2.4–3.8)	3.4 (2.3–4.5)	2.4 (1.1–3.7)	1.8 (1.1–2.5)	12 (34.3)	12.6 (10.3–14.9)
LLL	23 (65.7)	I: 17 II: 6	1.6 (1–2.2)	I: 20 II: 3	1.1 (1–1.2)	3.3 (1.5–5.1)	2.4 (1.8–3.0)	2.9 (1.7–4.1)	2.1 (1.3–2.9)	0.4 (0.3–0.5)	23 (65.7)	23.1 (14.9–31.3)
Subtotal	35 (60.3)	I: 25 II: 10	1.4 (1–1.8)	I: 29 II: 6	1.1 (1–1.2)	3.5 ± 0.3 (1.5–5.6)	2.9 (2.1–3.7)	3.2 (1.8–4.6)	2.2 (1.2–3.2)	1 (0.5–1.5)	35 (60.3)	18.3 (12.7–23.9)
Total	58 (100)	I: 33 II: 25	1.4 (1–1.8)	I: 48 II: 10	1.2 (1–1.6)	3.0 ± 1.1 (0.9–6.1)	2.9 (1.1–4.7)	3.0 (1.1–4.9)	1.7 (1.3–2.1)	0.7 (0.3–1.1)	58 (100)	16.5 (13.4–19.6)
Preoperative vs. postoperative p												
ETE vs. STE				0.4				0.04*	<0.01*			0.2
ETE-ULL vs. STE-ULL				0.5				0.04*	<0.01*			0.9
ETE-LLL vs. STE-LLL				0.6				0.04*	<0.01*			0.9

IQR, interquartile range; ETE, end-to-end; STE, side-to-end; ULL, upper limb lymphedema; LLL, lower limb lymphedema.
*Statistical difference between the ETE and STE groups.

Table 3. Comparisons of Cheng's Lymphedema Grading, Postoperative Improvement of Circumferential Difference, Episodes of Cellulitis, and Follow-Up between Primary and Secondary Lymphedema Subgroups

Group	No. of Cases (%)	Part of Lymphedema (%)	Cheng's Lymphedema Grading				Postoperative Improvement of Circumferential Difference (%)			Median Cellulitis (IQR) (times/yr)		Complete Recovery (Non compression Garment) (%)	Median Follow-Up (IQR) (mo)
			Preoperative		Postoperative		Above Knee 15 cm/ Above Elbow 10 cm	Below Knee 15 cm/ Below Elbow 10 cm	Mean	Pre-operative	Post operative		
			Grade	Median (IQR)	Grade	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)				
Primary	15 (25.9)	ULL:1 (1.7)	I: 9	1.2 (1–1.14	I: 12	1.1	3.3	2.7	3.0	2.1	1.1	15	14.2
		LLL:14 (24.1)	II: 6		II: 3	(1–1.2)	(1.3–5.3)	(2.1–3.3)	(1.8–4.2)	(1.6–2.6)	(0.3–1.9)	(100)	(12.3–16.1)
Secondary	43 (74.1)	ULL:19 (32.8)	I: 24	1.9 (1–2.8)	I:36	1.2	2.9	3.0	3.0	1.8	0.8	43	23.2
		LLL:24 (41.4)	II: 19		II: 7	(0.9–1.4)	(2.1–3.7)	(2.3–3.7)	(2.3–3.7)	(1.5–2.1)	(0.6–1.0)	(100)	(18.1–28.3)
Total	58 (100)	58 (100)	I: 33	1.3 (1–1.8)	I: 48	1.2	3.0	2.9	3.0	1.7	0.7	58	16.5
			II: 25		II: 10	(1–1.4)	(1.4–4.6)	(2.4–3.4)	(2.2–3.8)	(1.5–1.9)	(0.5–0.9)	(100)	(13.4–19.6)
p			0.4						0.9		0.6		0.04*

IQR, interquartile range; ETE, end-to-end; STE, side-to-end; ULL, upper limb lymphedema; LLL, lower limb lymphedema.
*Statistical difference between ETE and STE groups.

to bypass not only the antegrade lymph flow but also the retrograde lymph flow.[24,25] Among the different lymphovenous anastomosis anastomotic configurations, side-to-end and side-to-side lymphovenous anastomoses having bidirectional drainage without the need to ligate the proximal lymphatic vessel are theoretically superior to end-to-end lymphovenous anastomoses, with only one direction of lymph flow (Fig. 3). However, side-to-side anastomosis is frequently anatomically unfeasible because it requires a suitable subdermal venule with an adequate length in close proximity to a sufficiently healthy lymphatic vessel.[26,27] Therefore, side-to-end anastomosis is more consistently feasible and is recommended in most cases (Fig. 3). Compression garments were not needed for any patients because of gravity enhancing lymph drainage from the proximal direction down to the distal end, then shunting into the venous system when the patient is in a standing position.[25] The main disadvantage of the side-to-end anastomosis is its technical difficulty. This issue was overcome with the advancement in microsurgical instruments and microscopes and by practice with supermicrosurgery.

One of the concerns in this study was that we used tape measurement to compare the progress of the lymphedematous limb. Volumetric measurement is much more accurate than circumferential measurement. Volumetric measurement can be performed by means of water replacement, computed tomography, or magnetic resonance imaging. Water replacement is not popular because of several concerns (i.e., it is time consuming, there is a hygiene issue, and it is difficult to apply to severe lower extremity lymphedema). Although computed tomography is not a practical method of measurement because of many radiation exposures, especially when it needs to be repeated in tracking the outcome of lymphedema. Tape measurement is easy to perform, it is less invasive, it is reproducible with no radiation exposure, and it is more cost-effective than computed tomographic volumetric measurement. We had submitted one article to compare the correlations between tape measurement and volumetric measurement by computed tomography and found that both measurements are statistically correlated. Our results showed that patients in early stages of lymphedema, Cheng Lymphedema Grade I and II patients, had a positive outcome regardless of the lymphovenous anastomosis configuration used. Based on our selection criteria in accordance with Cheng Lymphedema Grading, lymphovenous anastomosis was indicated for patients exhibiting partial obstruction on

lymphoscintigraphy and grade I and early grade II lymphedema with patent lymphatic ducts that presented on indocyanine green lymphography. The patients with late grade II, III, and IV lymphedema without patent lymphatic ducts on indocyanine green lymphography were advised to undergo vascularized lymph node transfer. The effectiveness of lymphovenous anastomosis—either end-to-end or side-to-end for—late grade II, III, and IV lymphedema requires further investigation.

The postoperative improvement in circumferential limb circumference was statistically greater in the side-to-end group than in the end-to-end group. The episodes of cellulitis were significantly decreased by the lymphovenous anastomosis in both groups, which is consistent with previously published reports.[24] To our knowledge, this study is the first report to compare the outcomes of different configurations of lymphovenous anastomosis and to confirm the superiority of side-to-end anastomosis over end-to-end anastomosis at a 16-month follow-up. The limitations of this study were its retrospective nature, the small number of patients, and the relatively short postoperative follow-up period. Therefore, larger prospective studies with longer follow-up are needed to confirm the long-term efficacy of the technique.

Side-to-end lymphovenous anastomosis has the advantages of more effective lymph drainage for early-grade extremity lymphedema compared with end-to-end lymphovenous anastomosis, requiring only one anastomosis for drainage of both proximal and distal sites into the venous system, and no compression garment is required because of gravity.

CONCLUSIONS

Both side-to-end and end-to-end lymphovenous anastomoses were effective surgical approaches for early extremity lymphedema. Side-to-end lymphovenous anastomosis has the advantages of more effective lymph drainage and requiring only one anastomosis without the use of compression garments.

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