Original Article

Lymphaticovenular Anastomosis for Patients with Lymphedema of the Upper Extremity at Siriraj Hospital: A Quantitative Analysis Study

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Background: Lymphedema occurrence in patients that underwent breast cancer-related lymphedema (BCRL) treatment can become a major problem. Over the past decade, lymphaticovenular anastomosis (LVA) has become widely utilized. This surgery replicates the body's system by creating a connection between the lymphatic tracts and the venous system and replaces a damaged lymphatic system caused by the consequences from BCRL.

Objective: To analyze the results of LVA surgery targeting particularly the upper extremity areas from BCRL patients at Siriraj Hospital, Thailand.

Materials and Methods: This retrospective study was based on the medical records of patients that underwent LVA surgery between January 2010 and August 2018. Lymphoscintigraphy examination (^{99m}Tc-dextran lymphoscintigraphy) or ICG lymphography was performed to confirm the physician's diagnosis. The present study aimed to compare the arm circumference size and the rate of infection of patients between the pre-surgery and post-surgery of LVA.

Results: One hundred eighteen patients underwent the LVA operation and were included in the study. They had an average of 3.2±1.3 anastomoses. The average duration for the follow-up after surgery was 32 weeks. The different sizes in both arms were 5.8±1.6 cm and 5.5±1.4 cm, which were measured from 10 centimeters above and below the elbows, respectively. Comparing the sizes of the arms based on pre-surgery and post-surgery measurements, the arm circumference decreased by 0.9±0.6 centimeters (15.5%) and 0.9±0.4 centimeters (16.4%) post-surgery for the position above and below the elbow, respectively. The number of infections decreased from 1.9±0.8 times per year to 0.8±0.1 times per year. However, it was found that the rate of applying skin-care treatments in patients was relatively low at 3.4%.

Conclusion: The authors' revealed that LVA surgery of the upper extremity is one of the most effective treatments for lymphedema patients. According to the authors experience in Siriraj Hospital, this treatment is not only decreasing the size of the limb, but it can also minimize the infection rate. However, most patients note that other additional treatments, such as elastic bandage, elastic stocking, or skin-care treatment, are still necessary.

Keywords: Lymphedema, Lymphatic obstruction, Breast Cancer Related Lymphedema (BCRL), Lymphaticovenular anastomosis (LVA)

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Lymphedema is a widespread problem in clinical practice and has become an important global issue affecting approximately 140 to 300 million patients worldwide[1,2]. Its emergent variability can be either primary, involving maldevelopment of the lymphatic system, or secondary lymphedema, which is more common and usually results from injury to the lymphatic system. Unfortunately, at the present time, successful cancer treatment is the major cause of lymphedema occurrence in developed countries[3-6]. In Thailand, its incidence is still not clearly known; however, it is believed that the prevalence and incidence of lymphedema have been surging in Thailand due to the exponential increase in cancer patient survival. Cancer survivors, particularly in breast cancer, can experience chronic disability, often derived from development of a lymphedema condition as well as its associated complications, such as lymphangitis. This referred condition decreases the quality of life of patients a great deal[7,8]. The incidence rate of lymphedema is approximately 3% to 42.2% of patients who have undergone sentinel biopsy or axillary lymph node dissection[9-11]. The most recent

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prospective study in this field revealed a cumulative incidence of lymphedema of 41.5% over a 10-year duration of time[12]. Further, the incidence tends to increase in patients who have received additional adjuvant therapy[13-16].

The treatment of lymphedema, regardless of the cause, consists of non-surgical therapy as the mainstay and surgical treatment[17]. Lymphaticovenular anastomosis (LVA), a physiological treatment replicating surgical procedure, was introduced earlier in general practice[18,19] and later became widely accepted, such as in Koshima's supermicrosurgery technique in particular[20]. In LVA, multiple connections between subdermal lymphatic vessels and adjacent venules have been created and their success rates have been well documented in the medical literature[21,22].

LVA has been performed in Thailand at Siriraj Hospital since 2010, with the Siriraj medical teams dealing with approximately 40 to 50 cases per year. Consequently, the present study aimed to investigate the characteristics of the upper extremity lymphedema patients who had been treated by LVA at Siriraj Hospital as well as to assess the surgical treatment outcomes in these patients.

Materials and Methods

In terms of ethical and legal issues, the present study was approved by the Institutional Review Board (SiRB) of Siriraj Hospital, under protocol number 912/2561. The medical records of patients diagnosed with lymphedema and that underwent LVA at the Department of Surgery, Siriraj Hospital, Mahidol University, between January 2010 and August 2018 were retrospectively reviewed. One hundred eighteen patients were included in the present study. To note, 31 patients were excluded as four missed follow-up processes and another 27 patients because their follow-up treatment was less than three months later.

Pre-operative evaluation

Lymphoscintigraphy examination (^{99m}Tc-dextran lymphoscintigraphy) was performed for each patient to confirm the physician's diagnosis. Even though in certain cases the lymphoscintigraphy results might have been negative, the physicians suspected that those patients might still have lymphedema conditions, and consequently, they still underwent indocyanine green (ICG) lymphography analyses. Note, this analysis is highly sensitive to lymphedema occurrence, even more than other measures. All the patients with lymphedema developed from cancer treatment were assessed, regardless of whether they had already recovered or were in a dormant state as these could still mean possible recurrent cases.

Surgical technique

At the beginning of the operationalization of LVA at Siriraj Hospital, which was initially performed under general anesthesia, the surgery was later adjusted to be performed under local anesthesia. The major approach taken to find the lymphatic vessel location was either determined using an anatomical approach, a lymphoscintigraphy approach, or by the indocyanine lymphography approach. Patients were injected with 1% isosulfan blue or ICG (Diagnogreen, DAIICHI SANKYO CO., Tokyo, Japan) at the first and second webspace or just proximal to the incision with 0.1 mL per area in the areas of the intradermal or the subcutaneous layers to assist in identifying the lymphatic vessels. Besides, ICG was utilized to seek out the lymphatic vessel location with a handheld ICG camera (FLUOBEAM®, Fluoptics Co., Grenoble, France). Once the physicians had designated the incision area, lidocaine with epinephrine was injected. After that, the incision, ranging from 2.5 to 4.0 cm, was performed. Surgeons searched for the lymphatic vessels under an operative microscope (OPMI Pentaro 900 and OPMI Vario S88 system, Carl Zeiss Co., Jena, Germany) and sought nearby venules. Afterward, the referred lymphatic vessels and the venules were connected, accordingly with 11-0 nylon. This procedure was considered by utilizing an end-to-end, end-to-side, or side-to-side technique. Other forms of connecting the vessels could be assigned in accordance with the number and attributes of the vessels found.

Initially, Dr. Isao Koshima was kind enough to pass on his knowledge and techniques in LVA to Siriraj Hospital. His technique involved connecting the subdermal lymphatic, which was the lymphatic pathway that resulted from regurgitation from the normal pathway that had obstructions, with the subdermal or the subcutaneous venules. These procedures were operated by employing a supermicrosurgery technique (0.3 to 0.8 mm).

Later, the operation was made less intricate. Here, there was an attempt to seek out and connect the lymphatic vessels in the subcutaneous layer and the suprafascial layer. This discovery contributed to getting larger lymphatic vessels. Then by using the referred connection, the surgeon can confirm the patency of the anastomosis by observing the washout of the bleeding found in the lymphatic vessel. These

procedures can be assessed by the Acland test or the dynamic ICG lymphography test.

Postoperative care

During the postoperative care period, especially in the first or second week after the LVA operation, patients are advised to refrain from wearing pressure garments or other conservative treatments that might have a negative effect on the anastomosis result.

Outcome measurement

Patient's demographic information, medical history, physical examination, intraoperative findings, and an objective assessment of edema were recorded and analyzed. The circumferences of the affected and contralateral normal arms were measured at the referent point at 10 cm, at the above and the below positions of the olecranon at the elbow. The team measured these circumference sizes at least three times, namely before the LVA operation, six months after the operation, and finally, at the last follow-up period.

Statistical analysis

The present study employed descriptive statistical measurements. Qualitative demographic data were presented as the frequency and percentage. Quantitative data were presented as the mean and standard deviation, or median and minimum and maximum values. Data analyses were conducted using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA). A paired t-test was applied to evaluate statistics differences in the number of episodes of cellulitis before and after LVA treatment, statistical significance was determined at p-value less than 0.05.

Results

The preoperative demographic data of 118 patients that underwent LVA are shown in Table 1. The average postoperative follow-up time was approximately eight months. Interestingly, it was found that most patients were female (99.2%). The mean age of the patients was 56.9±10.2 years old, ranging from 7 to 82 years old. The average time at which the patients had been suffering from lymphedema was 7.3 years, ranging from 1 to 20 years, before visiting the present study clinic.

The common diseases and related complications comprised of hypertension, diabetes mellitus, and heart disease. In general, most patients had secondary iatrogenic lymphedema due to breast cancer treatment (97.5%). The most common operation was modified radical mastectomy. Most patients received adjuvant therapy, with 66.1% receiving radiation as an adjuvant therapy, while 44.9% of patients received chemotherapy. Of the 118 cases, only two cases (1.6%) were primary lymphedema patients.

Table 1. Demographic data (n=118)

	n (%)
Age (years); mean±SD	56.9±10.2
Sex	
Male	1 (0.8)
Female	117 (99.2)
BMI (kg/m^2); mean±SD	24.6±4.3
Follow-up (weeks); mean±SD	31.9±20.1
Onset after cancer therapy (years); mean±SD	8.0±1.7
Duration of lymphedema (years); mean±SD	7.3±2.8
Side	
Right	52 (44.1)
Left	66 (55.9)
Underlying disease	
DM	11 (9.3)
Hypertension	25 (21.2)
Dyslipidemia	6 (5.1)
Heart disease	4 (3.4)
Renal disease	0 (0.0)
Liver disease	1 (0.8)
Cause of lymphedema	
Breast cancer	115 (97.5)
Amniotic band syndrome	1 (0.8)
Primary lymphedema	2 (1.6)
Other diagnosis	0 (0.0)
Cancer treatment	
MRM	104 (88.1)
TM with SLNB	5 (4.2)
ALND	7 (5.9)
Other surgery	1 (0.8)
Chemotherapy	53 (44.9)
Radiation therapy	78 (66.1)

BMI=body mass index; DM=diabetes mellitus; MRM=modified radical mastectomy; TM=total mastectomy; SLNB=sentinel lymph node biopsy; ALND=axillary lymph node dissection; SD=standard deviation

The characteristics of lymphedema in both groups are shown in Table 2. The number of patients who underwent LVA in the early Campisi stage (stages I, II) was relatively similar to that of the late stages (stages III, IV). There were 39 patients (33.1%) who had a history of cellulitis before receiving the LVA

Table 2. Characteristic of lymphedema (n=118)

	n (%)
Campisi's lymphedema stage	
Early stage (I to II)	62 (52.5)
Late stage (III to IV)*	56 (47.5)
Previous cellulitis	39 (33.1)
Non-surgical treatment	
Pressure garment	82 (69.5)
Compression bandage	5 (4.2)
Manual lymphatic drainage	2 (1.7)
Skin care	4 (3.4)
Twisting tourniquet decongestive therapy	6 (5.1)
Pneumatic pump	3 (2.5)

* No stage V

Table 3. Intraoperative findings (n=118)

	Mean±SD
Type of anesthesia; n (%)	
General	34 (28.8)
Local	84 (71.2)
Operative time: general (minutes)	232.3±58.8
Operative time: local (minutes)	230.4±82.1
Number of anastomoses (range)	3.2±1.3 (1 to 7)
Lymphatic vessel diameter	0.7±0.2

SD=standard deviation

operation.

In terms of the non-surgical treatment modality techniques, it was found that patients prevalently used a pressure garment (69%). Six persons (5.1%) used the twisting tourniquet decongestive therapy technique. Other types of treatments included the pneumatic pump and manual lymphatic drainage. The number of patients using daily skin care treatments was minimal (3.4%). This care varied and depended on the patient's lifestyle.

LVA was performed under local anesthesia in 84 cases and under general anesthesia in 34 cases (Table 3). The average operative time was relatively similar in both the local and the general anesthesia cases (232.3±58.8 and 230.4±82.1 minutes). The average number of anastomoses was 3.2±1.3. The average diameter of lymphatic vessels was 0.7±0.2 mm.

In the present study, it was found that the LVA operation had a satisfactory success rate. The circumferential reduction rates were 15.5% for the above-elbow area and 16.4% for the below-elbow area (Table 4). The number of episodes of cellulitis decreased from 1.9±0.8 to 0.8±0.1 times per year ($p<0.05$) (Table 5). No surgical complications were reported.

Table 4. Circumferential reduction

	Above elbow 10 cm; mean±SD	Below elbow 10 cm; mean±SD
Pre-operative circumferential difference (cm)	5.8±1.6	5.5±1.4
Circumferential reduction (cm)	0.9±0.6	0.9±0.4
Reduction rate (%)	15.5	16.4

SD=standard deviation

Table 5. Episodes of cellulitis

	Episodes of cellulitis (times/year); mean±SD		p-value
	Pre-LVA	Post-LVA	
Upper extremity (n=39)	1.9±0.8	0.8±0.1	<0.05*

SD=standard deviation

* Statistical significance was determined at $p<0.05$

Discussion

Most upper extremity lymphedema patients at Siriraj Hospital whose symptom were caused by treatment for cancer, particularly breast cancer, are female. These statistical results are in line with studies from various countries worldwide[20,23].

Although the incidence of lymphedema derived from post-cancer treatment in Thailand is still unknown, the number of lymphedema patients positively correlates with the proportion of effective cancer treatment, which results in an increase in the survival rate and life expectancy. In addition, patients are nowadays likely to have better access to more information about lymphedema from various media and channels.

There were only two patients with primary lymphedema in the present study population, which showed it is an uncommon symptom with a rare prevalence of only 1 to 1.15 per 100,000 population. The symptom is commonly found in women and more often appears in the leg than the arm[24,25]. Despite being believed to be a contraindication for primary lymphedema, recent research findings confirmed that LVA can be performed in well-chosen patients[26]. In addition, a diagnosis of lymphedema in the arm tends to be less differential than in the leg and is usually free of venous disease.

In terms of the presence of co-morbidity disease, diabetes and hypertension are common comorbid diseases due to patients' average age of 56.9 years old, which is an intermediate stage between middle-aged and elderly. These referred patients are required to assess whether they can cooperate in the need to lie down for about three hours and undergo an operation under local anesthesia as an outpatient case. Therefore, they need to undertake an appropriate preoperative evaluation and preparation and need to give information about any medication or herbal medicines they usually consume.

According to the demographic data, most patients undergo LVA after having been suffering from lymphedema for seven years on the average, which is relatively similar to the figure reported in other studies[20,26,27]. It should be noted that the most recent research found that the duration of lymphedema bears no relation to the LVA treatment, and the disease and disease progression are different depending on each patient's condition[26].

The fact that the proportion of lymphedema patients with a high clinical stage at Siriraj Hospital is similar to those with early stage is in accordance with other studies[20,28]. However, this data contradicts the original idea that LVA must be performed only in early-stage lymphedema patients who are resistant to non-operative treatment[28-30]. In the present study, it is believed that even patients in a high clinical stage can be improved since their lymphatic loading is less than in the lower extremity.

It was also found that various lymphedema staging, namely Campisi and ISL staging, mainly based on findings from the skin and subcutaneous tissue. This notion contradicts previous studies suggested that the transformation of the skin and soft tissue has no direct relation to the pathological changes of the lymphatic vessels. In addition, recent studies confirmed that LVA in sclerotic lymphatic vessels can lead to effective treatment if using an appropriate technique[31]. The reason that most patients' conditions had developed into the high clinical stage as chronic ones was because the LVA operation had not been available in Thailand until 2010.

In terms of the success rate in LVA, most studies did not report their criteria for the selection parameters of patients. It was found that some used a variety of protocols for patient selection. For instance, some studies employed the different timescales that patients had failed conservative treatment from three to six months[20,23,28]. Other studies used staging or grading as the criteria to determine the types of operation[28,32]. Consequently, the broad variety of criteria leads to selection bias from the onset stage.

There is also a variation in the follow-up protocols and the wide-ranging criteria used to evaluate the efficiency of the treatment by focusing on different factors, such as objective and subjective assessments, a decline in the size of the arm, or the evaluation of the quality of life.

Additionally, some studies did not report whether elastic stockings were applied along with other therapies after LVA. This treatment can be a crucial factor affecting the treatment of lymphedema[33].

Even though volumetric analysis measurement is widely regarded as the gold standard to measure arm volume reduction, the general clinical practice, including at the lymphedema clinic at Siriraj Hospital, the preference is to use circumference measurement instead. This is because of its convenience, affordability, and the fact that patients are not required to be exposed to radiation. Furthermore, some studies used various formulas for calculating the volume of the arm from the circumference measurement.

In the present study, the average decline in the size of the circumference was 15% within eight months. Compared to other similar studies that also employed LVA and a non-operative treatment using elastic bandages and stockings and that used circumference measurement to assess the treatment efficiency, it could be seen that the result of the treatment was at a good level.

Koshima et al (2000) studied 12 lymphedema patients without classifying stages from moderate to severe lymphedema, and found that the maximum circumference decreased by 47.3%[20]. This indicated a major success, but one which is radically different from other studies' results.

In 2009, Damstra et al conducted a prospective study on 10 lymphedema patients with Campisi stage III and found that the average reduction in the size of circumference was 4.8% within one-year period[28]. Recently, AlJindan et al (2019) carried out a study on 20 patients within a 16.5-month time frame. The study revealed the size of the circumference decreased by 2.5% to 3.4%[32].

Most studies generally suggested the number of anastomoses per patient ranged from 1.7 to 10 anastomoses in the arm and up to 15 anastomoses in the leg.

Koshima et al (2004)[34] revealed a positive relation between the number of anastomoses and the efficiency of the treatment. This research suggested applying six to ten anastomoses per patient by

adopting the multiple team approach and employing two to four operative microscopes. Nevertheless, they also noted that only two to three anastomoses were sufficient for most patients to observe the change in the referred volume[34,35]. A study carried out by Seki et al (2015) revealed that the key success predictors of LVA not only depended on the number of anastomoses but rather on the lymphatic flow of each lymphatic vessels and a diameter over 0.65 mm[36]. Later, in the study by Hayashi et al (2018), they introduced the use of frequency ultrasound to find lymphatic vessels[37]. Seki et al[31] subsequently adopted this ultrasound technique to help determine the surgical position that could promote the best lymphatic flow and a draining vein that could create negative pressure in the diastolic phase and receive lymphatic fluid without reflux. These are the important principles of the "functional LVA" or "dynamic LVA"[31].

In terms of postoperative care, there are slightly different procedures. Some institutes omit to apply pressure therapy, including pressure garments for one to four weeks to wait until a micro anastomosis becomes adequately strong and stable enough[37-39]. However, other institutes recommend immediately continuing to apply pressure garments to increase lymphatic flow without adequate explanation or evidential support[40].

LVA can successfully reduce the incidence of lymphangitis and cellulitis. According to their medical history, 33% of the patients in the present study had developed lymphangitis. Moreover, lymphedema is also considered a contributing factor in lymphangitis[41,42].

Meanwhile, lymphangitis can result in fibrosis in both lymphatic vessels and subcutaneous tissue and can aggravate lymphedema into a vicious cycle[43]. It should be noted that even in the general population without lymphedema, they can also develop cellulitis in limbs. Shih et al (2009)[42] reported a comparison between the incidence of cellulitis in breast cancer patients and in a control population. The research showed that 15.9% of breast cancer patients and 8% of the control population developed cellulitis, respectively[42]. Likewise, other studies have indicated the prevalence of lymphangitis, which emerges following lymphedema, at 5% to 35%[20,44-46].

Teerachaisakul et al (2011) reported the prevalence of lymphangitis in a Thai population with lymphedema and discovered a prevalence of 47.6%[47]. Lymphangitis is more likely to occur in the leg rather than the arm.

The present study found that the occurrence of cellulitis was reduced from 1.9 to 0.8 times per year after LVA. Comparing to the study conducted by AlJindan et al (2019)[32] thus showed that the outcomes of both studies were relatively similar.

One of the interesting observations is that the rate of the use of skin care is relatively low even though it was found to be simpler and more inexpensive than applying pressure garments and elastic stockings. Skin care can help lessen the infectious likelihood and might decrease the incidence of lymphangitis, which is commonly found in Thai patients. Hence, this issue should be the healthcare providers' responsibility in terms of ensuring better communication and encouraging patients to recognize the importance of skin care and other non-operative treatments.

There is constant curiosity regarding the patency rate of LVA. The pioneering research by Winters et al (2019)[48] reported a patency rate of LVA with an average anastomosis of 1.8 when examining patency by using ICG lymphography. The study indicated that 56.5% of anastomoses (15/22) remained patent and 66.7% of patients had at least 1 anastomosis that remained patent[48].

However, the relation between the patency rate and clinical outcome remains unclear. Wolfs et al (2019) studied the tendency of the relation among the patency rate of LVA, the improvement in the quality of life, and the circumference of the upper extremity, and concluded that there was no statistically significant difference[49].

Moreover, there is a relation between the patency rate and body parts. A study on lower extremity lymphedema patients by Suzuki et al (2019)[50,51] found that the patency rate of anastomosis near a joint tended to be higher than at other positions, due to the muscle around the joint pumping allowing better lymphatic flow and reducing the venous pressure. When veins travel near thick and strong structures, such as tendons, there is usually a valve to prevent lymphatic reflux, which is believed to be the cause of anastomosis occlusion[50]. They also reported that there was no difference in the patency rate, regardless of a side-to-end or end-to-end anastomosis operation[51].

Among the major difficulties with the evaluation of the patency rate is that most research uses ICG in the evaluation process, which can reportedly cause false-negative results, due to the maximum depth of the injection being limited to 1.5 cm from the epidermis[31] and the optimal injection point[52,53]. Last, the evaluation process must be considered along with surgical techniques and other post-operative

treatments.

To educate patients and cancer specialists on the importance of lymphedema, treatment options are essential for the prevention and diagnosis of lymphedema.

An early treatment can speed up the improvement of patients' quality of life. A study by Fahradyan et al (2018)[54] showed a positive correlation between high patients' expectations and the duration of lymphedema. Unfortunately, a high expectation in treatment is considered unrealistic. Apart from this, it was observed that lymphedema patients are apt to assume that the first doctors who treat them usually lack sufficient experience and expertise in the disease[54]. Consequently, it is necessary to train specialists in related fields in the knowledge of lymphedema and to develop a clinical practice guideline to solve this problem at the national level.

Conclusion

Based on the experience from the present study at Siriraj Hospital, the LVA operation provides effective results in lymphedema cases and can reduce the size of the arm to a satisfactory level and can decrease the occurrence of lymphangitis. Its highly effective outcomes are similar to surgical outcomes from many international world-class institutes. In addition, since this treatment is a less invasive procedure and can be done under local anesthesia in an outpatient department, the treatment is worthwhile and suitable for all patients with no contraindications.

Finally, it should be noted that it is the medical personnel's primary responsibility to provide patients with sufficient knowledge of the disease. They should also encourage them to undergo the relevant medical procedures to enhance lymphedema patients' quality of life.

What is already known about this topic?

As previous studies have shown, LVA must be performed only in early-stage lymphedema who are resistant to non-operative treatment[28-30].

What this study adds?

Referring to this study, the LVA operation is still highly effective when performed on lymphedema patients, especially in the areas of the upper extremity. These patients belong to the high clinical stage. It is hypothesized that the arms have a lower lymphatic load than the legs. Furthermore, the clinical stage does not reflect the underneath lymphatic nodes' quality due to the various clinical stages represent a quality assessment based on the quality of skin and subcutaneous tissues.

Conflicts of interest

The authors declare no conflict of interest.

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