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Lymphatic ultrasound (D-CUPS) and multi-point ICG lymphography for successful LVA

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Abstract

Securing dilated lymphatic vessels with good function is challenging when performing lymphaticovenous anastomosis (LVA). To achieve this, we propose multi-point indocyanine green (ICG) lymphography and lymphatic ultrasound (D-CUPS; Doppler, Cross, Uncollapsible, Parallel, and Superficial fascia). With multi-point ICG lymphography, more lymphatic vessels can be found than with conventional ICG lymphography, which leads to better surgical results. Lymphatic ultrasound is more useful because it allows the observation of cross-sections of lymphatic vessels. It is known that lymphatic degeneration occurs in the lymphatic vessels in lymphedematous limbs, and LVA is most effective when dilated lymphatic vessels are anastomosed. The degree of lymphatic degeneration can be diagnosed with lymphatic ultrasound, and the proximity of dilated lymphatic vessels and veins suitable for anastomosis can be reliably identified and selected as the skin incision site for LVA. Lymphatic ultrasound is a safe, versatile and useful imaging technique that does not require a contrast agent and can be performed by anyone. By mastering multi-point ICG lymphography and lymphatic ultrasound (D-CUPS), the operation time can be shortened, and more effective LVA can be performed. In this Technical Note article, we comprehensively describe lymphatic function examinations that we have developed so far.

Keywords: Lymphedema, indocyanine green, ICG, lymphatic ultrasound, ultrasound, lymphosome, D-CUPS

INTRODUCTION

Surgical treatments for lymphedema include lymphaticovenous anastomosis (LVA)[1-3], lymph node transfer[4,5], liposuction[6], and excisional surgery[7]. Among these, LVA is a minimally invasive surgery that can be performed under local anesthesia[8]. Anastomosing a lymph vessel with accumulated lymph fluid into a vein is a bypass surgery that allows the lymph to flow back to the heart via the vein. LVA reduces the circumference of the affected limb, softens the skin of the affected limb, and reduces the frequency of cellulitis[9,10]. Lymphangiosclerosis is known to occur in limbs with lymphedema, and LVA has traditionally been indicated for early-stage lymphedema in which well-functioning lymphatic vessels remain[11-14]. However, in recent years, lymphatic function examinations have developed rapidly, and multi-point indocyanine green (ICG) lymphography (originally reported as multi-lymphosome ICG lymphography)[15-19], photoacoustic ICG lymphography[20-22], lymphatic ultrasound[23-30], and ultra-high frequency ultrasound[31-33], have been developed, in addition to conventional ICG lymphography or lymphoscintigraphy[32-38].

We are actively performing multi-point ICG lymphography and lymphatic ultrasound as a preoperative examination for LVA, which has improved surgical outcomes and made it possible to perform LVA even for advanced lymphedema[2], which was not indicated before. Lymphatic ultrasound is particularly useful and can be widely used for preoperative examination[23-25], diagnosis of lymphedema[28-30], and evaluation of physiological and pathological changes in lymphatic vessels[27]. After LVA, the patients resume the same compression therapy as before from postoperative day 1. The same compression therapy is continued for six months postoperatively to accurately evaluate the effect of LVA. Hamada and Kaciulyte reported that LVA can reduce or discontinue compression therapy[39,40].

In this Technical Note article, we comprehensively describe lymphatic function examinations that we have developed so far. The institutional ethics committee approved the study and written informed consent was obtained from each patient (approval number: R03-04).

MULTI- POINT ICG LYMPHOGRAPHY

Multi-point ICG lymphography is usually performed as a preoperative examination for LVA. The concept of “lymphosome” was proposed by Suami to explain the lymphatic territory of the whole body[41]. We slightly revised the territories and injected ICG at three points: the first web space, the proximal point of the lateral malleolus, and the lateral midline point at the level of the superior border of the patella [Figure 1]. Each injection point was located in the saphenous lymphatic area, lateral calf lymphatic area, and lateral thigh lymphatic area.

In conventional ICG lymphography, we injected ICG only at the distal end of the limbs, first web space, and around the Achilles tendon. In this method, only lymphatic vessels passing through the distal injection point are enhanced. Moreover, when the lymphatic vessels around the injection point were severely damaged, no lymphatic vessels were found.

With multi-point ICG lymphography, we can find a greater number of lymphatic vessels than with conventional ICG lymphography or lymphoscintigraphy, and the surgical result improves[15,16]. In addition, multi-point ICG lymphography sometimes detects lymphatic dysfunction, which cannot be observed on lymphoscintigraphy[30].

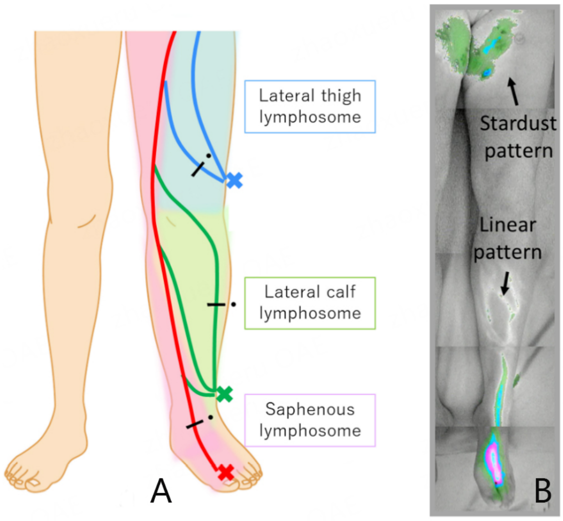

Figure 1. Multi-point indocyanine green (ICG) lymphography (originally reported as multi-lymphosome lymphography). (A) Schematic illustration of multi-point ICG lymphography. The crosses indicate the injection points of ICG (the first web space, the proximal point of the lateral malleolus, and the lateral midline point at the level of the superior border of the patella). The red line indicates the lymphatic vessel in the Saphenous lymphatic area, the green line indicates the lymphatic vessel in the Lateral calf lymphatic area, and the blue line indicates the lymphatic vessel in the Lateral thigh lymphatic area. When performing lymphatic ultrasound, we apply the probe so that the lymphatic vessel and the probe are at right angles, imagining the running of these lymphatic vessels (-●); (B) Clinical pictures of multi-point ICG lymphography.

Shinaoka *et al.* reported on the lymphatic map with injecting ICG "below the medial malleolus, below the lateral malleolus, in the first interdigital space, fourth interdigital space, and at the midpoint of the straight line that connects the head of the fifth metatarsal bone and the lateral malleolus"[42]. We agree with their theory, although additional injections in the proximal part (the calf and thigh) are necessary to evaluate the lymphatic vessels in the whole leg. While each theory has its merits, further research is required to determine the best injection point for ICG.

Considering the effectiveness of multi-point ICG lymphography as a preoperative examination for LVA, we strongly feel that the lymphatic ultrasound, which will be described below, is more useful. We previously reported that LVA is most effective when dilated lymphatic vessels are anastomosed[3]. Even if some lines are found on multi-point ICG lymphography, lymphatic vessels are often not dilated. Dilated lymphatic vessels are often present 1-2 cm lateral or medial to the line observed on ICG lymphography. We used the results of ICG lymphography as a reference and finally determined the skin incision site using lymphatic ultrasound.

LYMPHATIC ULTRASOUND

Ultrasonography has three purposes.

1. Evaluate the location, thickness, and degree of degeneration of lymphatic vessels.

2. Evaluate the location and thickness of veins suitable for anastomosis[43].

3. Evaluate the presence and degree of edema.

We performed ultrasonography when designing the incision site for the LVA. With the patient in a supine or long-sitting position, imagining the position of the lymphatic vessels in [Figure 1], we applied the probe to the skin, perpendicular to the long axis of the lymphatic vessels. For lower extremity venous ultrasound, the probe is placed parallel to the long axis of the vein, but lymphatic vessels are very thin (0.11 mm) and often tortuous in lymphedematous limbs; therefore, long-axis images are often difficult to observe. Therefore, we observed a short-axis view of the lymphatic vessels.

After placing a probe on the skin and finding a vessel (a circle with a black interior and white circumference) beneath the superficial fascia, we moved the probe proximally and distally, tracing the vessel. If the circle has a long continuous structure, it is considered a type of vessel. If it disappears quickly when the probe is moved, it may be fibrous tissue between the subcutaneous fat. Specifically, we identified lymphatic vessels using D-CUPS as a clue in the next chapter.

In lymphatic ultrasound, the short-axis image of lymphatic vessels is observed; therefore, the degree of lymphatic sclerosis can be morphologically diagnosed[28,29]. We previously reported the process of lymphatic degeneration (NECST classification: normal, ectasis, contraction, and sclerosis types), and LVA was most effective when dilated lymphatic vessels were anastomosed[3,12,13]; however, conventional ICG lymphography and lymphoscintigraphy did not reveal whether the lymphatic vessels were dilated or sclerosed. We previously reported that normal lymphatic vessels, dilated lymphatic vessels, and sclerotic lymphatic vessels coexist in linear lymphatic vessels on ICG lymphography[12]. By performing lymphatic ultrasound, dilated lymphatic vessels can be reliably identified and effective LVA can be performed[23-25]. Lymphoedema may also be diagnosed using lymphatic ultrasound by evaluating the morphology of lymphatic vessels[28,30].

Another advantage of lymphatic ultrasound is that it does not require a contrast agent. There is no concern about allergies and it does not cause pain in the patient. In lymphoscintigraphy and ICG lymphography, which enhance lymphatic vessels with medicines, the visualized lymphatic vessels are limited depending on where the medicine is injected. Not all lymphatic vessels can be visualized, even with multi-point ICG lymphography. As Yang *et al*. reported previously, some lymphatic vessels are flow-positive, but ICG enhance-negative[44]. They reported that LVA was also effective when the lymphatic vessels were anastomosed. Lymphatic ultrasound is useful as a preoperative examination for LVA because it is contrast-independent and can identify all dilated lymphatic vessels, that is, all lymphatic vessels suitable for LVA.

D-CUPS IN LYMPHATIC ULTRASOUND

When performing lymphatic ultrasound, it is essential to distinguish lymphatic vessels from the veins. To achieve this, we established an index, D-CUPS[23,28].

D (Doppler): Veins are colored in Doppler mode, but lymphatic vessels are not [Figure 2A and B]. However, thin veins may not be colored in the Doppler mode.

C (Cross): Veins merge with nearby veins, but lymph vessels cross past veins [Figure 3].

U (Uncollapsible): Lymphatic vessels in lymphedema-affected limbs, in particular, have high internal pressure, so they are less likely to collapse than veins when compressed with a probe.

P (parallel): Two or three lymphatic vessels may run side by side without merging [Figure 4]. The frequency of this phenomenon is approximately 20%.

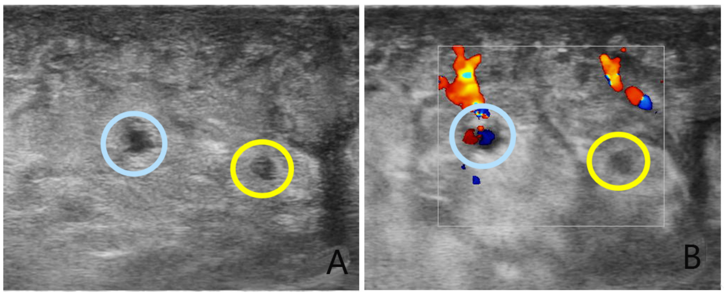

Figure 2. Lymphatic ultrasonogram. Of the D-CUPS (Doppler, Cross, Uncollapsible, Parallel, Superficial fascia) indices, D is explained. Blue circles indicate veins and yellow circles indicate lymph vessels. (A) B-mode image; (B) Doppler mode image. Vein is colored blue, but lymphatic vessel is not colored. (Link to YouTube video of lymphatic ultrasound: https://www.youtube.com/watch?v=lYrxIgB9c-Q).

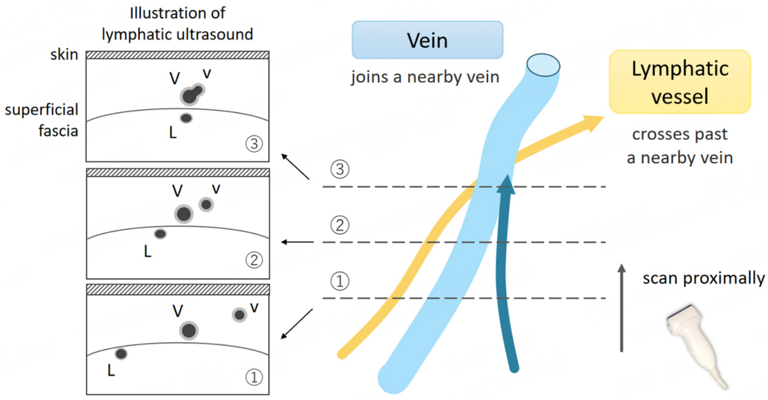

Figure 3. Illustration of lymphatic ultrasound. Of the D-CUPS (Doppler, Cross, Uncollapsible, Parallel, Superficial fascia) indices, C is explained. When we find a vessel in the subcutaneous fat layer and trace it proximally, if it merges with a nearby vein, it is a vein. On the other hand, if it crosses past a vein without joining, it is a lymphatic vessel. V: large vein; v: small vein; L: lymphatic vessel.

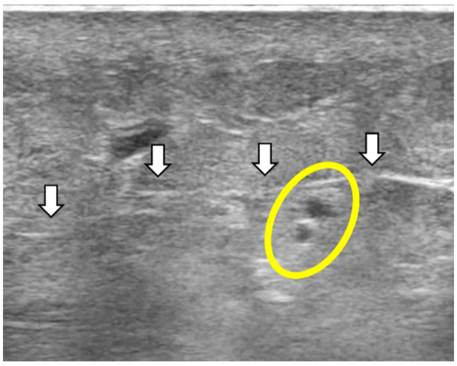

Figure 4. B-mode image of lymphatic ultrasonography. Of the D-CUPS (Doppler, Cross, Uncollapsible, Parallel, Superficial fascia) indices, P, and S are explained. A yellow circle indicates lymph vessels and white arrows indicate the superficial fascia. Two lymphatic vessels run parallel to each other just below the superficial fascia.

S (Superficial fascia): Lymphatic vessels run parallel to and beneath the superficial fascia. In contrast, veins run obliquely from just under the skin to thick veins just above the deep fascia.

Among these indicators, C was the most reliable. Caution should be exercised in the presence of lymphatic malformations, as lymphatic-venous communication may be observed; however, C is approximately 100% sensitive. A video of lymphatic ultrasound can be seen on YouTube (https://www.youtube.com/watch?v=IYrxIgB9c-Q).

SELECTION OF PROBE

Hayashi *et al*. reported the usefulness of ultra-high-frequency ultrasonography (70 MHz) for observing lymphatic vessels[31]. We usually use a linear probe of 18 MHz (Noblus EUP-L65; Hitachi Medical Corp., Tokyo, Japan), which is similar to that used for general lower-extremity veinous ultrasound. Lymphatic vessels are usually about 1 cm deep from the skin surface in lymphedema of the lower extremities, and this probe is suitable for observing the depth around it. However, when observing the lymphatic vessels in the upper extremities, dorsum of the feet, lower legs of lean individuals, and extremities of healthy individuals, the subcutaneous fat layer is thin; therefore, lymphatic vessels often exist at a depth of approximately 5 mm from the skin surface, and it is difficult to observe them with an 18 MHz linear probe. In such cases, we used a higher frequency 33-MHz linear probe (Aplio i900, Canon Medical Systems Corp., Tokyo, Japan) to observe the superficial layers [Figure 5][33]. Furthermore, as the resolution generally increases with higher probe frequencies, it is considered that observing small lymphatic vessels is more feasible at higher frequencies. A disadvantage of using ultrahigh-frequency probes such as 33 MHz and 70 MHz is that the penetration is insufficient, making it difficult to observe deep layers of 1 cm or more. However, recent advances in ultrasound equipment have led to the development of ultrahigh-frequency equipment that can observe objects as deep as 1-2 cm. Especially in infant patients, the subcutaneous tissue is very thin; therefore, an ultrahigh-frequency probe would be useful[45,46]. It is expected that even better equipment will be developed in the future.

EVALUATION OF ADIPOSE TISSUE FOR LIPOSUCTION

Ultrasonography can also diagnose the presence or absence of edema[47,48]. Lymphoedema-affected limbs become stiff, but it is sometimes difficult to ascertain by palpation alone whether the stiffness is due to the accumulation of tissue fluid or fibrosis. In addition, when the affected limb is thick, it may not be possible to determine only by palpation whether the limb is thick due to the accumulation of tissue fluid or fat. If tissue fluid is retained, lymphatic drainage treatment, such as compression therapy[49-51], LVA, and lymph node transplantation, is required, but liposuction is indicated if there is fat accumulation. Accurate diagnosis is also important when choosing appropriate treatment, including lymphatic reconstructive surgery, liposuction, or conservative treatment. Ultrasonography is useful for selecting treatment methods because the differences between both causes can be observed at a glance.

Case 1

A 52-year-old woman underwent hysterectomy and bilateral ovarian resection for ovarian cancer when she was 32 years of age. Thirteen years later, lymphedema developed in the left leg. Although she wore elastic stockings, lymphedema gradually worsened, and she consulted our hospital [Figure 6A].

Lymphoscintigraphy revealed dermal backflow in the left thigh and slightly around the right inguinal lymph node [Figure 6B]. In addition, we found line patterns that indicated the presence of functional lymphatic vessels, and we decided to apply LVA. In multi-point ICG lymphography, we found a greater number of lymphatic vessels than in lymphoscintigraphy [Figure 6A]. We then performed ultrasonography to detect the dilated lymphatic vessels and a suitable vein. We designed incision sites at 4 points with dilated lymphatic vessels and well-sized veins [Figure 6C]. At each site, lymphatic vessels and veins consistent with ultrasonographic findings were observed intraoperatively and successfully anastomosed. The time taken to

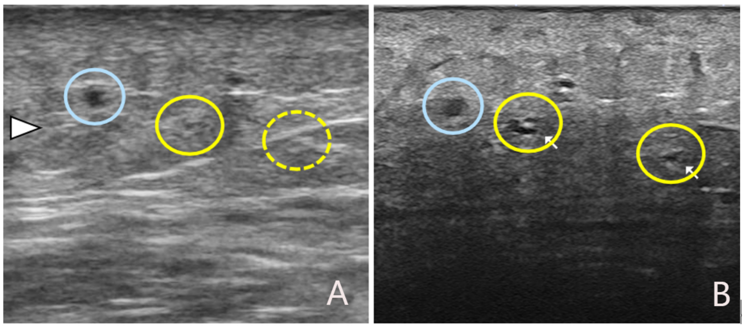

Figure 5. Example of lymphatic ultrasound at the lymphedematous medial calf using different kinds of probes. Blue circles indicate veins and yellow circles indicate lymphatic vessels. White arrowhead indicates a depth of 5 mm. (A) Ultrasonogram with an 18 MHz linear probe (Noblus EUP-L65; Hitachi Medical Corp., Tokyo, Japan). One vein and one lymphatic vessel can be observed. The dashed circle indicates the lymphatic vessel, which we found only after observing it with a 33MHz probe; (B) Ultrasonogram with a 33 MHz linear probe (Aplio i900, Canon Medical Systems Corp., Tokyo, Japan). One vein and three lymphatic vessels are recognized. There are two lymphatic vessels in the central yellow circle. Compared to A, it can be seen that ultrasound is attenuated in areas deeper than 5 mm, making it difficult to observe.

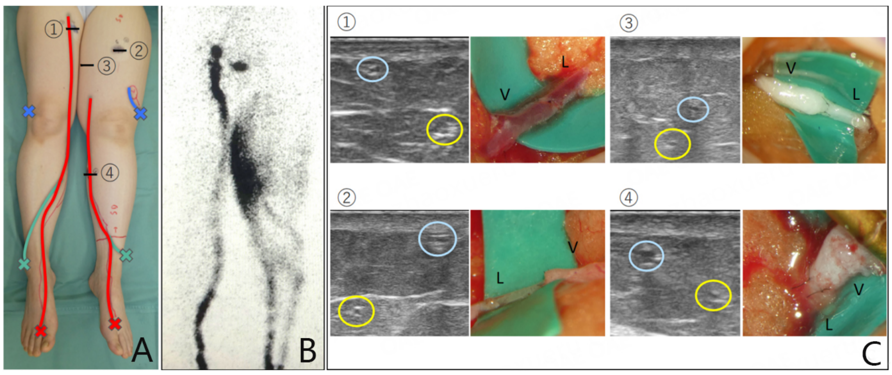

Figure 6. Case 1. A 52-year-old woman with secondary lymphedema in the legs. Black lines and numbers indicate skin incisions in lymphaticovenous anastomosis (LVA). (A) Clinical pictures and results of multi-point indocyanine green (ICG) lymphography. Cross marks indicate ICG injection sites; (B) Image of lymphoscintigraphy. Dermal backflow is observed in the left thigh. Additionally, slight dermal backflow is observed around the right inguinal lymph node; (C) Ultrasound findings and corresponding intraoperative findings during LVA. Blue circles indicate veins and yellow circles indicate lymph vessels. At each site, lymphatic vessels and veins consistent with ultrasonographic findings are observed. V: vein; L: lymphatic vessel.

perform LVA at a single site was 25-35 min.

Case 2

A 92-year-old woman. She had had primary lower extremity lymphedema since birth. At the age of 90, she developed idiopathic chylous pleural effusion, which resolved spontaneously. At the age of 91, she had a recurrence of idiopathic chylous pleural effusion and visited our hospital for the treatment of lower extremity lymphedema and chylous pleural effusion. Lymphoscintigraphy showed isotope retention in the left lower extremity and left thoracic cavity [Figure 7][52].

Considering that the isotope injected into the feet leaked into the thoracic cavity, it was possible that leg compression therapy would increase pleural effusion. As a result of the multidisciplinary discussion about treatment methods, we decided to perform LVA in the leg first, create an escape route for the lymph, and then perform leg compression therapy [Figure 7]. Lymphatic ultrasound revealed many dilated lymphatic vessels. When a skin incision was made on the proximal thigh, cloudy chyle flowed out vigorously, making

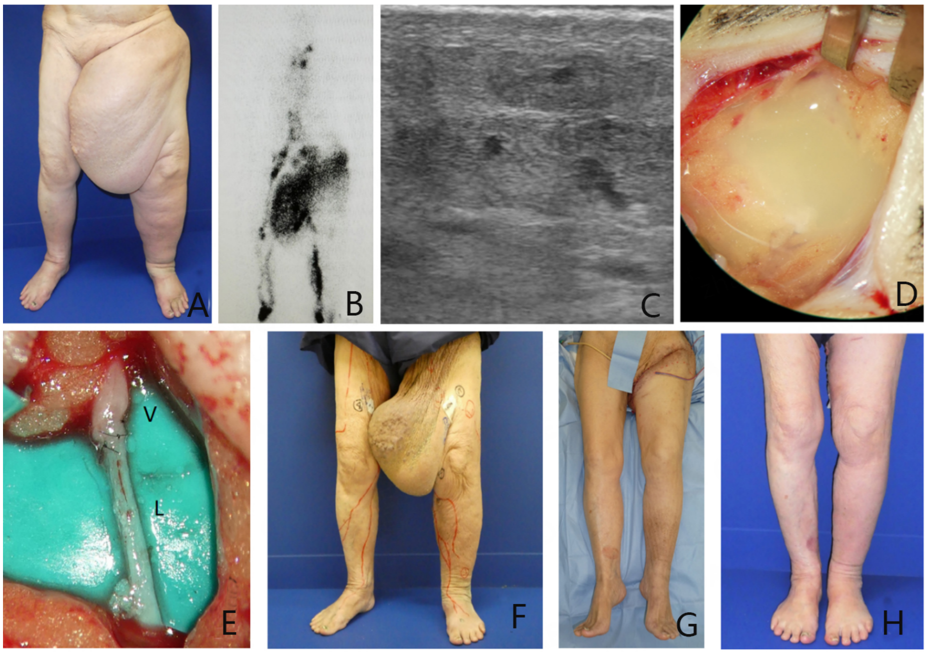

Figure 7. Case 2. A 92-year-old woman with primary lymphedema in the left leg and chylous pleural effusion. (A) Clinical picture at the first consultation. Severe edema can be observed in the left leg, especially in the thigh; (B) Lymphoscintigram; (C) Lymphatic ultrasonographic finding in the left thigh; (D) Intraoperative finding during lymphaticovenous anastomosis (LVA) in the left thigh. Milky discharge, which seems to be a reflux from the intestinal lymph, is observed; (E) Intraoperative finding during LVA. V indicates a vein and L indicates a lymphatic vessel; (F) Clinical picture after LVA and compression therapy. Edema in the left lower extremity has improved; (G) Findings immediately after excision of excess skin and adipose tissue in the left thigh; (H) Clinical picture a few months after the surgery. (A,F,G[52]).

surgical operation difficult. Both retrograde and antegrade anastomosis were performed in order to allow both proximal and distal lymph to flow into the vein.

After that, compression therapy was performed, and the edema of the lower extremities improved without exacerbation of pleural effusion. At the strong request of the patient, we performed a simple excision of the excess skin and fatty tissue on the left thigh and sutured the wound in one stage (lumbar anesthesia, 2 h).

There were no problems during the perioperative period, and the patient remains well 2 years after the operation.

CONCLUSION

When performing LVA, the most important aspect is the super-microsurgery technique for reliably anastomosing a lymphatic vessel of 1 mm or less to a vein. However, even with this technique, finding a thin transparent lymphatic vessel in a thick fat layer is a problem. To perform a successful LVA, it is necessary to reliably identify dilated lymphatic vessels with good function, and multi-point ICG lymphography and lymphatic ultrasound are useful for this purpose. By mastering lymphatic ultrasound (D-CUPS), the operation time can be shortened, and a more effective LVA can be performed. Compression therapy and weight control are also important keys for successful LVA; therefore, it is important to cooperate with the lymphedema therapists and provide appropriate guidance to the patients.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Hara H, Mihara M

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The institutional ethics committee approved the study (approval number: R03-04) and consent to participate was obtained from each patient.

Consent for publication

Written informed consent was obtained from each patient.

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