Lymphology 44 (2011) 155-167

CLASSIFICATION OF LYMPHOSCINTIGRAPHY AND RELEVANCE TO SURGICAL INDICATION FOR LYMPHATICOVENOUS ANASTOMOSIS IN UPPER LIMB LYMPHEDEMA

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ABSTRACT

Upper limb lymphedema that develops after breast cancer surgery causes physical discomfort and psychological distress, and it can require both conservative and surgical treatment. Lymphaticovenous anastomosis has been reported to be an effective treatment; however the disease severity criteria that define indications for this treatment remain unclear. Here, we examined lymphoscintigraphic findings in 78 patients with secondary upper limb lymphedema and classified them into 5 major types (Type I-V) and 3 subtypes (Subtype E, L, and 0). Results revealed that this classification is related to the clinical stage scale of the International Society of Lymphology. Based on intraoperative examination findings in 20 of the 78 patients, lymphatic pressure is likely to be further elevated in Type II-V cases which are characterized by the presence of dermal back flow. Therefore, lymphaticovenous anastomosis should be considered as a treatment option for lymphedema in Type II-V cases. Furthermore, there are only limited lymph vessel sites usable for lymphaticovenous anastomosis in more severe lymphedema types [Types IV and Type V (which is characterized by dermal back flow only in the hand)]. The findings in Type IV-V cases suggest that therapeutic strategies for severe upper limb lymphedema need further consideration.

Keywords: lymphoscintigraphy, upper limb lymphedema, surgical treatment, lymphaticovenous anastomosis

Regarding malignant tumors, the prevalence rate of breast cancer is relatively high for women in Japan, Europe, and North America (1). Currently, less invasive treatments with limited resection is becoming a preferred surgical option for primary lesions along with advances in chemotherapy and radiotherapy (2-6). Additionally, the use of sentinel lymph node biopsy (SNB) is providing a reduction in axillary lymph node dissection (7-9). Despite these advances, lymphedema is still seen as a common morbidity following breast cancer treatment. According to recent studies, the incidence of lymphedema after breast cancer treatment is in a range of 6-60%, and this appears to increase to 45-60% when patients receive chemotherapy combined with axillary lymph node dissection (1,10,11). In addition, upper limb lymphedema leads to decreases in activities of daily living (ADL) and is often complicated by cellulitis and lymphorrhea (12,13), causing significant distress to patients (14-16).

Treatment options for upper limb lymphedema are similar to those for lower limb lymphedema and include conservative therapy and/or surgical therapy. Conservative therapy includes physical treatment, such as massage and mechanical methods that use elastic compression stockings and bandages (17-19), while the primary surgical options are lymphaticovenous anastomosis (20,21), lymph vessel transplantation (22), and lymph node transplantation (23). In particular, the efficacy of lymphaticovenous anastomosis, which reduces the high pressure of the lymphatics to assist conservative therapy in patients with upper limb lymphedema, has already been demonstrated (24). Few studies, however, have clearly examined the disease severity criteria that define indications for lymphaticovenous anastomosis. In this study, we classified findings from lymphoscintigraphy performed in patients with secondary upper limb lymphedema with their clinical staging and investigated relevance of the classification for use as an indicator for surgical therapy.

PATIENTS AND METHODS

Subjects

Seventy-eight cases of upper limb lymphedema in patients (n=78; 1 male and 77 female; mean age at initial consultation, 55.5 ± 13.2 years; range 22-84 years) who were examined by lymphoscintigraphy at our department between January 2004 and June 2010 were investigated. All patients had a history of previous surgical treatment for breast cancer and had been diagnosed with secondary upper limb lymphedema on the basis of their clinical history and physical findings (edema in the arm on the same side as previous surgery) at initial consultation. Seventy-seven patients previously underwent axillary lymph node dissection, and the remaining one underwent SNB. None of the patients had suspected venous obstruction (e.g., no clinical signs of venous dilation, varicosities, or thrombophlebitis), and they did not undergo an ultrasound examination. None of the patients had a history of previous surgery on the healthy side.

Lymphoscintigraphy

Technetium-99m-labeled human serum albumin was subcutaneously injected (0.2 ml, 40 MBq) between the first and second fingers and between the third and fourth fingers of both hands. Anterior and posterior images were obtained with a gamma camera 30 and 120 min after injection.

The images were first classified into type (Type I-V) on the basis of the sites where dermal back flow (DBF) was observed, in a similar manner to the classification of lymphoscintigraphic findings in patients with lower limb lymphedema (25), and then classified further into subtype (Subtype E, L, or 0) according to the time when supraclavicular or infraclavicular lymph nodes were visualized (Subtype E, detectable on early images taken 30 min after injection; Subtype L, detectable on late images taken 120 min after injection; Subtype 0, not detectable on any images). The clinical stage of each patient was determined according to the clinical stage scale proposed by the International Society of Lymphology (ISL) (26). The criteria for type classification we used were as follows:

Type I–lymphatic flow from the hand to the lymph nodes around the clavicle is depicted as a line. Mild lymphatic obstruction and additional collateral vessels are observed, but signs of DBF are absent in the forearm and upper arm. A typical image of Type I-Subtype E lymphedema is shown in *Fig. 1.*

Type II–mild lymphatic obstruction is observed, and signs of DBF appear in the upper arm on images taken 30 min and/or 120 min after injection. A typical image of Type II-Subtype L is shown in *Fig. 2.*

Type III—significant lymphatic obstruction is observed, and signs of DBF appear in the upper arm and forearm on images taken 30 min and/or 120 min after injection. A typical image of Type III-Subtype L is shown in *Fig. 3.*

Type IV–lymphatic flow from the hand to the lymph nodes around the clavicle

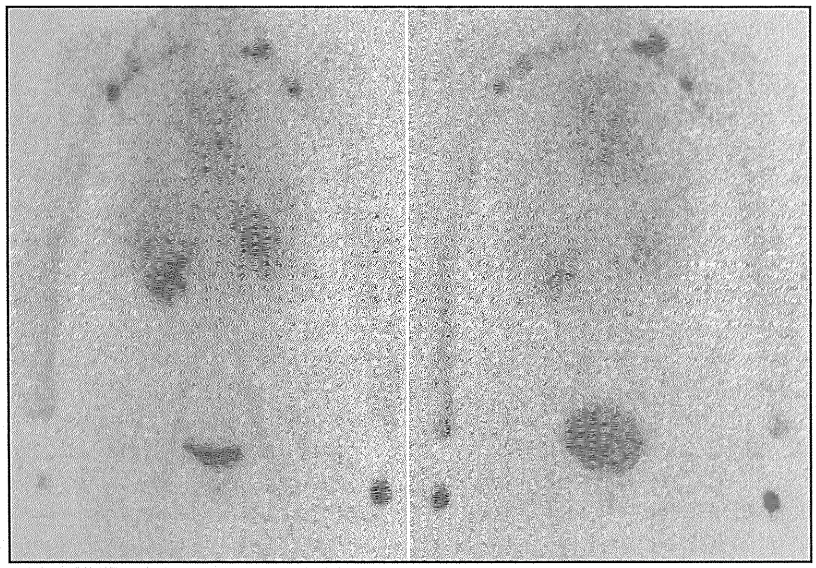

Fig. 1. Lymphoscintigraphy images of a case of Type I-Subtype E lymphedema in the left arm. The left and right panels show images taken 30 and 120 min, respectively, after injection of a contrast medium. Lymph nodes around the clavicle, but not axillary lymph nodes, were observed in the affected left arm. Dermal back flow (DBF) was confirmed to be absent in both arms.

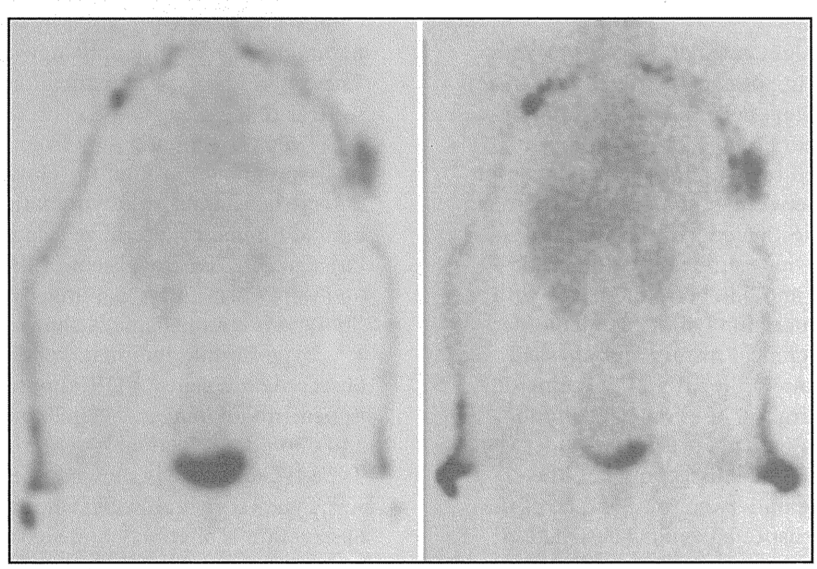

Fig. 2. Lymphoscintigraphy images of a case of Type II-Subtype L lymphedema in the left arm. The left and right panels show images taken 30 and 120 min, respectively, after injection of a contrast medium. Lymph nodes around the clavicle were observed only on the image taken at the later time point. DBF was found only in the left upper arm.

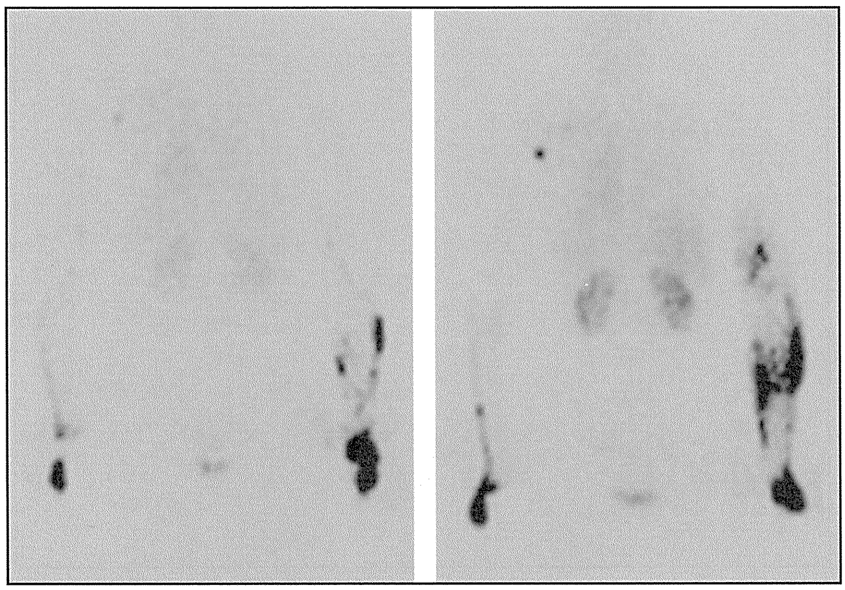

Fig. 3. Lymphoscintigraphy images of a case of Type III-Subtype 0 lymphedema in the left arm. The left and right panels show images taken 30 and 120 min, respectively, after injection of a contrast medium. Lymph nodes around the clavicle were not observed even on the image taken at the later time point. DBF was found in the upper arm and forearm of the affected side on the image taken 120 min after injection.

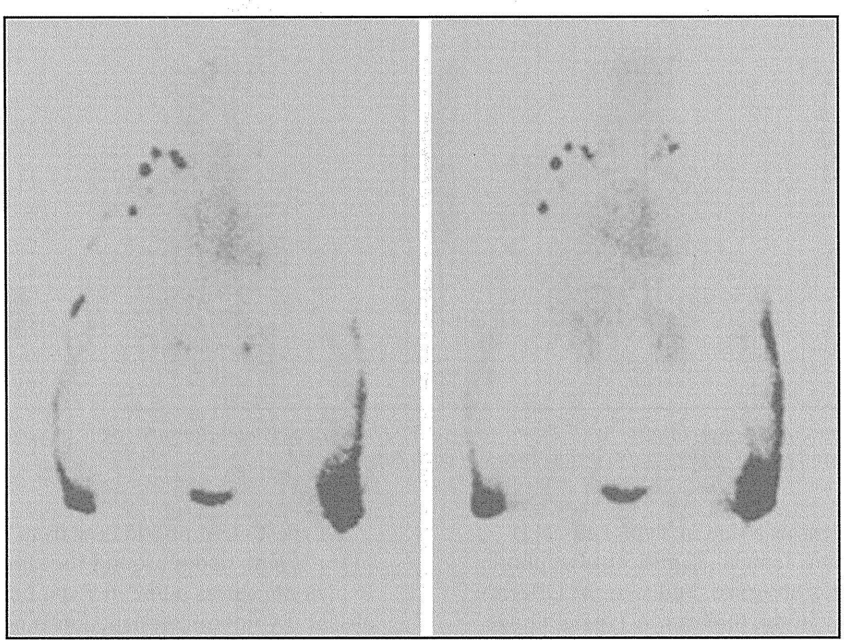

Fig. 4. Lymphoscintigraphy images of a case of Type IV-Subtype L lymphedema in the left arm. The left and right panels show images taken 30 and 120 min, respectively, after injection of a contrast medium. Lymph nodes around the clavicle were observed only on the image taken at the later time point. DBF was found only in the left forearm.

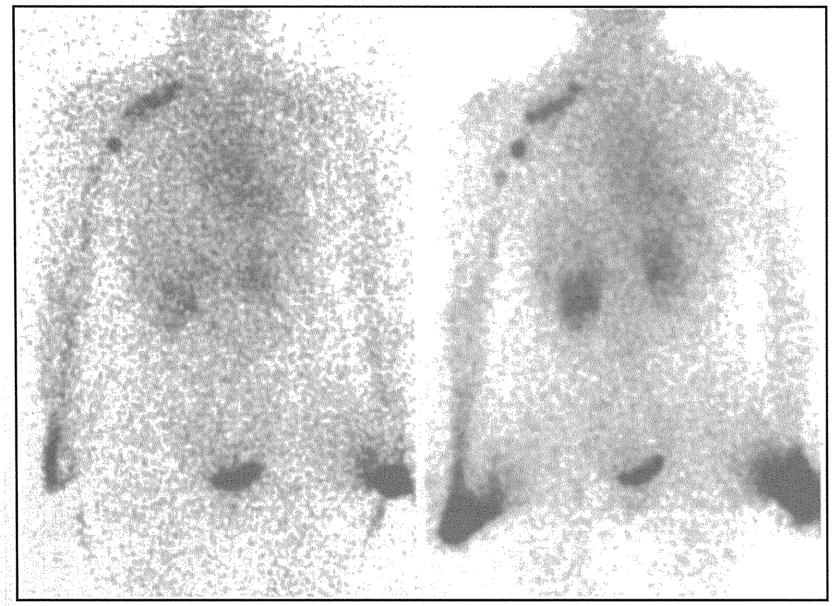

Fig. 5. Lymphoscintigraphy images of a case of Type V-Subtype 0 lymphedema in the left arm. The left and right panels show images taken 30 and 120 min, respectively, after injection of a contrast medium. Lymph nodes around the clavicle were not observed even on the image taken at the later time point. DBF was found only in the hand.

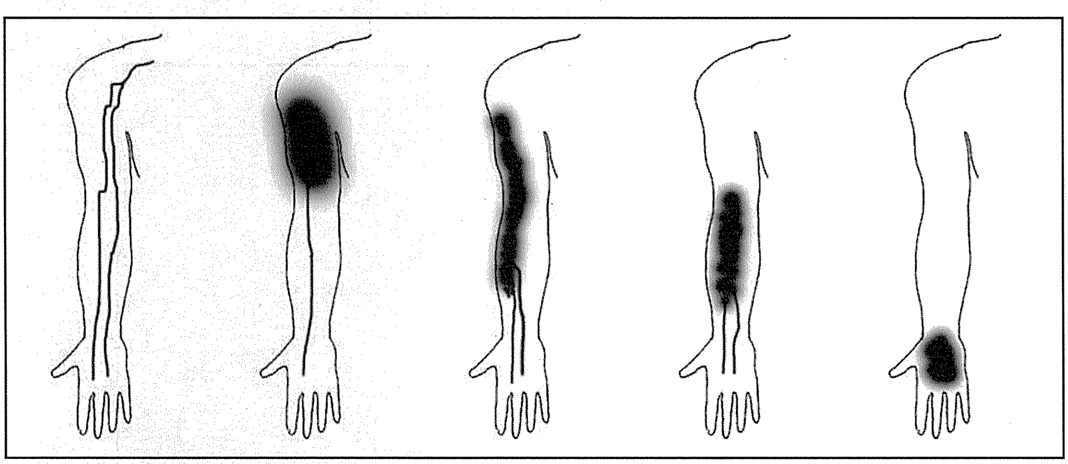

Fig. 6. Schemes of lymphoscintigraphy of Type I to Type V. The lines of lymph-flow are vague in some cases while the location and extent of dermal back flow varies in each case.

(which appear as a line in Type I cases) is almost absent. Instead, significant lymphatic obstruction is observed, and signs of DBF are present only in the forearm. A typical image of Type IV-Subtype L is shown in *Fig. 4*.

Type V–Lymphatic flow from the hand to the lymph nodes around the clavicle (which appear as a line in Type I cases) is absent. Lymphatic obstruction is not observed, and signs of DBF are present only

TABLE 1
Cases of Lymphaticovenous Anastomosis by Type

	Subtype E	Subtype L	Subtype 0	TOTAL
Type I	1	1	0	2
Type II	2	1	2	5
Type III	0	1	2	3
Type IV	0	2	3	5
Type V	0	0	5	5

Subtype E, detectable on early images taken 30 min after injection; Subtype L, detectable on late images taken 120 min after injection; Subtype 0, not detectable on any images

in the hand. A typical image of Type V-Subtype 0 is shown in *Fig. 5*.

Fig. 6 shows schematic illustrations of the images in *Figs. 1-5*.

Surgical Procedures

Lymphaticovenous anastomosis was performed in 20 patients under general or local anesthesia depending on age and underlying diseases (status of cancer and bronchial asthma) (*Table 1*). Prior to making skin incisions, we performed two-color spectral fluorescence lymphangiography using a 5% patent blue dye and indocyanine green (ICG) to identify the anastomosis sites (27,28). ICG infrared fluorescence lymphangiography was performed during surgery to map lymph flow and patent blue was used to indicate the functional superficial lymphatics without the need for special devices. The DBF sites (hand, forearm, and upper arm) were recorded for each classification type.

Several skin incisions were made to reach the superficial lymphatic vessels in the hand, forearm, and upper arm according to the map of lymph flow based on ICG infrared fluorescence lymphangiography. We then identified macroscopically functional lymphatics stained by patent blue. When vessel identification was difficult, skin incisions were made at positions slightly distal from the DBF, and side-to-end (lymphatic-to-vein) anastomosis was performed. This was done in order to preserve the original flow of lymphatics should the anastomosis become obstructed, which is a possibility that should not be ignored in patients with a limited number of functional lymphatic vessels. In addition, further surgery remains possible to other parts of the same lymphatic vessels used for anastomosis if the anastomosis becomes occluded in the future. Usually, the veins were anastomosed just proximal to the venous valve in order to prevent blood reflux into the lymphatics. Venous transplantations were needed in a few sites when a suitable vein was absent. The same surgeon (JM) performed the surgical procedures in all patients.

The circumferences of three points in the arm (point A, wrist; point B, 10 cm distal to the cubital fossa in the forearm; and point C, 10 cm proximal to the cubital fossa in the upper arm) and the distance between points A and B were measured before and after surgery. Arm volume was calculated using a previously reported formula (29) to examine changes in arm volume after surgery. The rates of change in arm volume after surgery were calculated using the following formula:

TABLE 2
Clinical stage scale of the International Society of Lymphology (see Ref. 26)

Stage 0:	Subclinical condition
Stage 1:	Early accumulation of fluid relatively high in protein content; subsides with limb elevation. Pitting may occur.
Stage 2:	Limb elevation alone rarely reduces tissue swelling and pitting. The limb may or may not pit as tissue fibrosis supervenes.
Stage 3:	Lymphostatic elephantiasis where pitting is absent, trophic skin changes such as acanthosis, fat deposits, and warty overgrowths develop.

TABLE 3
Results of Type Classification

Subtype	Type I	Type II	Type III	Type IV	Type V	TOTAL
E	12	5	5	0	0	22
L	2	2	4	6	0	14
0	1	6	13	16	6	42
TOTAL	15	13	22	22	6	78

Subtype E, detectable on early images taken 30 min after injection; Subtype L, detectable on late images taken 120 min after injection; Subtype 0, not detectable on any images.

rate of change in arm volume (%) = (postoperative arm volume x preoperative arm volume)/(preoperative arm volume) x 100. An additional calculation of "edema volume" based on a comparison with the non-affected arm was made in each case before and after surgery and the rate of change was calculated.

Statistical Analyses

The type classification results were examined in relation to the clinical stage by ISL (*Table 2*) using Dunn's multiple comparison test. Statistical significance was set at $p<0.05$. The total number of limbs presenting DBF in each site in Group A (Type I-III) and those in Group B (Type IV-V) were compared using the Kruskal Wallis H-test as previously (25). Statistical significance was set at $p<0.05$. STAT MATE III (ATMS Co. Ltd., Tokyo, Japan) was used for all statistical analysis.

The mean rate of change of arm volume and edema volume before and after lymphaticovenous anastomosis (LVA) in Group A was compared to that in Group B using the Student t-test.

RESULTS

Type Classification on the Basis of Lymphoscintigraphy Findings

Abnormal lymphoscintigraphy findings include lymphatic obstruction, appearance of additional collateral vessels and DBF, and poor or no visualization of the supraclavicular

TABLE 4
Type and Clinical Stage Scale

Clinical stage scale	n	1	2	3
Type I	15	14	1	0
Type II	13	6	7	0
Type III	22	5	16	1*
Type IV	22	8	13	1**
Type V	6	1	5	0**
TOTAL	78	34	42	2

n, number of limbs; Type I vs. Types III, IV, and V, *p < 0.01, **p < 0.05 (Dunn's multiple comparison test)

TABLE 5
Number of Patients Presenting Dermal Back Flow on Intraoperative Indocyanine Green Lymphangiography Images

	n	Hand	Forearm	Upper arm
Type I	2	0	1	0
Type II	5	2	3	4
Type III	3	0	3	3
Type IV	5	2	3	0
Type V	5	4	4	2

n, number of limbs

or infraclavicular lymph nodes. All 78 cases were successfully classified (*Table 3*). There were 15 Type I cases (12 Subtype E, 2 Subtype L, and 1 Subtype 0), 13 Type II cases (5 Subtype E, 2 Subtype L, and 6 Subtype 0), 22 Type III cases (5 Subtype E, 4 Subtype L, and 13 Subtype 0), 22 Type IV cases (6 Subtype L, and 16 Subtype 0), and 6 Type V cases (6 Subtype 0). Lymphoscintigraphy findings of the healthy arm were similarly classified. There were 77 Type I cases (68 Subtype E, 8 Subtype L, and 1 Subtype 0), and 1 Type II-Subtype E case. The clinical stage scale proposed by ISL is shown in *Table 2*. Statistical analysis of the relationship between the type classification and the clinical stage of the ISL revealed significant differences between Type I and III (p<0.01), Type I and IV (p<0.01), and Type I and V (p<0.05) cases (*Table 4*).

Intraoperative Findings

The sites of DBF were identified by two-color lymphangiography. In Group A, DBF was found in 2 sites in the hand, 7 in the forearm, and 7 in the upper arm. In Group B, DBF was found in 6 sites in the hand, 7 in

TABLE 6
Total and Mean Number of Anastomoses per Limb in Each Type

	n	Hand	Forearm	Upper arm	Total
Type I	2	2 (1)	4 (2)	2 (1)	8 (4)
Type II	5	5 (1)	13 (2.6)	5 (1)	23 (4.6)
Type III	3	4 (1.3)	9 (3)	1 (0.3)	14 (4.7)
Type IV	5	5 (1)	14 (2.8)	2 (0.4)	20 (4)
Type V	5	6 (1.2)	12 (2.4)	0 (0)	18 (3.6)

Values are show as total (mean) number

TABLE 7
Volume Change of Limbs

	n	Increased	Decreased	Average percent of change (%)	Average percent of change (%)
Type I	2	1	1	0.67	15.05
Type II	5	0	5	-9.65	-4.18
Type III	3	1	2	-11.5	-2.4
Type IV	5	2	3	-2.47	-10.96
Type V	5	3	2	0.47	1.68
TOTAL	20	7	13	-4.57	-2.22

n, number of limb

the forearm, and 2 in the upper arm. There were no significant differences between the 2 groups (*Table 5*).

Relationship Between Type and Number of Anastomosis Sites

Table 6 shows the total number of anastomosis sites and its mean (per limb) value for each type as determined from the lymphoscintigraphy findings. The mean value was largest for Type III (4.7). There were no significant differences in the mean values of anastomosis sites between Group A (4.30 ±1.16) and Group B (4.00 ± 1.15).

Rates of Changes in Arm Volume after Surgery

Arm volume was decreased after surgery in 13 of 20 patients, but increased in the remaining 7 patients (*Table 7*). The mean rate in 20 patients was −4.57 ± 9.6%, while those in Group A and Group B were −8.15% and −1.0%, respectively. The difference between the two groups was not statistically significant (p=0.067). Arm volume increase was observed in 1 case of Type I (Subtype E), 1 case of Type III (Subtype L), 2 cases of Type IV (Subtype L and Subtype 0), and 3 cases of Type V (Subtype 0). The average change in edema volume in Group A was 0.2% (±12.8) while that in Group B was −4.64% (±16.5). The difference between the two groups was not statistically significant (p=0.483).

DISCUSSION

Type classification of lymphoscintigraphy findings was partially related to the ISL clinical stage (*Table 4*). We presumed that the lymphoscintigraphy images of healthy arms would be classified as Type I-Subtype E, provided the patients had no history of previous surgery, external injury, or exposure to radiation (29). Indeed, our results were generally in agreement with this presumption. However, there were 10 (of 78) exceptional cases in this study, and asymptomatic primary lymphedema or tracer entry into collateral routes is considered a possible reason for these cases.

According to Koshima et al, occlusions of the lymphatic vessels and degeneration of smooth muscle cells start from the proximal ends of the extremities in cases of secondary extremity lymphedema (30), and this is supported by a study reported by Suami et al (31). These findings suggest that DBF may also appear from the proximal ends of the arm on lymphoscintigraphy images of upper limb lymphedema and thus be confirmed only in the hand in the most severe cases.

On the basis of the above assumption, we previously reported the classification of lymphoscintigraphy findings, with an emphasis on the sites of DBF, in patients with lower limb lymphedema (25). In addition, in the present study, we considered the report by Szuba et al (29) and examined the timing of when lymph nodes around the clavicle were visualized on images. As shown in *Table 3*, approximately 54% and 41% of patients in Type II and Type III groups, respectively, were classified as Subtype E or L. These results suggest that collateral routes form more frequently in the upper limbs than in the lower limbs (31). On the other hand, the prevalence of Subtype 0 was higher in Type IV and Type V, suggesting that disruption of the lymph system worsens in proximal sites (30,31). Taken together, we believe that the type classification proposed in this study reflects the severity of secondary lymphedema, despite the fact that the Kruskal Wallis H-test did not indicate statistical significance, which may be due to the small sample size examined.

One of the patients examined in the present study developed lymphedema after SNB but not axillary lymph node dissection. This patient was a clinical stage 1 patient, and the upper arm volume was changed by 3.49% after surgery. However, a lymphoscintigraphy image of the same patient was judged as Type 2-Subtype L and intraoperative ICG lymphangiography indicated DBF in the hand, forearm, and upper arm, presenting many similarities to the case reported by Suami et al (31). Considering that approximately 5% of patients who undergo SNB reportedly develop lymphedema (32), this patient may fall into this subpopulation that develops lymphedema after SNB.

Szuba et al reported a lymphedema severity scoring system based on the findings from lymphoscintigraphy performed in 19 patients who developed upper limb lymphedema after breast cancer surgery (29). Similarly, Pecking et al reported a lymphedema severity staging system based on the findings of 4,328 patients with lower limb lymphedema (33). We have also previously reported a classification of lymphoscintigraphy findings with an emphasis on the relation to indications for microsurgery for lower limb lymphedema using a simpler classification method than the previous two lymphoscintigraphy-based systems (25). This system's usefulness as an indicator for microsurgery in lower limb lymphedema has already been confirmed (25). High-resolution magnetic resonance (MR) lymphangiography is another static image-based approach that has been shown to be effective for diagnosing lymphatic flow disturbances (34). Although MR lymphangiography clearly depicts functional lymphatic vessels, the timing of scanning is difficult to control among patients. Thus, it is not suitable for comparative studies requiring identical examination conditions or for severity classification.

TABLE 8
Comparison Between Pre and Postoperative Scintigraphy

Affected side	Preoperative type	Post-operative type	Duration from surgery to postoperative scintigraphy
L	2-E	2-L	12 months
L	4-L	4-L	21months

Subtype E, detectable on early images taken 30 min after injection; Subtype L, detectable on late images taken 120 min after injection

We performed surgery for secondary lymphedema in 20 patients in this study. Based on our experience with patients with secondary lower limb lymphedema, we performed surgery in two Type I patients, regardless of their subtype: one with a high swelling rate (affected arm versus healthy arm) determined by measurement of arm circumference and volume; and another who strongly requested withdrawing from treatment that used a compression stocking. Swelling continued in the former patient after surgery, but use of an elastic compression stocking was successfully withdrawn approximately 1 year after surgery in the latter patient. Furthermore, the number of anastomosis sites in Type I patients was not markedly different from that in the other types, albeit on the basis of comparisons of a limited number of cases (*Table 6*). Taking these findings together, unlike Type I secondary lower limb lymphedema (25), surgical therapy might be indicated in a few cases of Type I secondary upper limb lymphedema, as in our two cases.

Lymphaticovenous anastomosis is our preferred surgical procedure for the treatment of secondary lymphedema. Prior to making skin incisions, we perform two-color lymphangiography using a 5% patent blue dye and ICG to identify the anastomosis sites (27,28). In this procedure, we can identify only superficial lymphatic drainage that is suitable for microscopic LVA. The sites of DBF identified by ICG lymphangiography shifted from the proximal to distal end of the arm as lymphedema progressed from Type I to Type V. The number of anastomosis sites in each part of the arm showed similar trends (*Table 6*). The number of cases of each type was insufficient for statistical analysis, so the differences among the types were not statistically tested. Nevertheless, our results suggested that possible sites for anastomosis can be found throughout the arm – from the hand to the upper arm – in patients with Type I-II, while such sites are mainly in the hand (the dorsum) and not in the upper arm in patients with Type V secondary lymphedema. Patients with lymphedema of the dorsum of the hand must wear an elastic glove in everyday life, and this sometimes leads to decreased ADL. Thus, the effects of anastomosis will be significant for patients when lymphedema is alleviated by this surgical treatment.

On the basis of the reduction in arm volume, Type II and Type III lymphedema are the most likely indications for microscope-assisted lymphaticovenous anastomosis. On the other hand, we routinely initiate complex physical therapy approximately 1 week after surgery. Therefore, the results shown in *Table 7* were not solely attributed to surgery, and the effects of complex physical therapy should be taken into consideration. In addition, surgery was performed in only 20 of the 78 patients in this study, and like our previous study on secondary lower limb lymphedema (25), the type classification did not reflect several factors such as elapsed time after breast cancer surgery, exposure to radiation, history of previous chemotherapy, occupation, and lifestyle. Indeed, postoperative lymphoscintigraphy was performed in two of our cases, which showed little change from the preoperative images (*Table 8*). In the protocol of this study, postoperative lymphoscintigraphy was not included because the late patency of every anastomosed site would not have been indicated clearly, although decreased DBF could have indirectly shown the effectiveness of LVA (35). Given the results of this study, postoperative lymphoscintigraphy should be included in future research protocols. In addition, prospective studies that give consideration to the timing and procedures of physical therapy are necessary in order to closely examine the usefulness of the proposed type classification as an indicator for surgery and to determine the significance of the subtypes.

CONCLUSION

Here we established a simple classification method, employing a commonly used diagnostic method, for classifying type of lymphoscintigraphic findings in secondary upper limb lymphedema, with an emphasis on the sites of DBF and visualization of lymph nodes around the clavicle. We believe that lymphoscintigraphy is effective for assessing patients with secondary upper limb lymphedema before lymphaticovenous anastomosis. Patients meeting the criteria for Type I secondary upper limb lymphedema, unlike previously reported criteria for Type I secondary lower limb lymphedema, might have indication for lymphaticovenous anastomosis. Our results suggest that lymphaticovenous anastomosis can be performed throughout the arm, from the hand to the upper arm, and its outcome is likely to be good in Type II and Type III patients, regardless of subtype. On the other hand, the sites and numbers of lymphatic vessels suited for anastomosis appear limited in Type IV patients with more severe lymphedema and Type V patients with DBF only in the hand.

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European Journal of Vascular and Endovascular Surgery 43 (2012) 602–608

Contents lists available at SciVerse ScienceDirect

European Journal of Vascular and Endovascular Surgery

journal homepage: www.ejves.com

Net Effect of Lymphaticovenous Anastomosis on Volume Reduction of Peripheral Lymphoedema after Complex Decongestive Physiotherapy

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WHAT THIS PAPER ADDS

- This study disclosed each effect of volume reduction in peripheral lymphoedema by microlymphatic surgery and conservative therapy, respectively, for the first time because both effects were not separated in previous studies.
- A number of patients who desire to have microlymphatic surgery have recently been increasing world over. The patients want to know net and true effect of the operation; therefore, this study can contribute the patients' decision whether or not they undergo the operation. This study also gives some good information to co-medical and therapists who wonder if the operation is effective.

ARTICLE INFO

Article history:
Received 30 September 2011
Accepted 24 December 2011
Available online 24 January 2012

Keywords:
Bandage
Compressive stocking
Microsurgery
Lower limb lymphoedema
Statistical evaluation

ABSTRACT

Objective: The results of reported lymphaticovenous anastomoses include some effects of complex decongestive physiotherapy (CDP). The present study aimed to determine the net effect of lymphaticovenous side-to-end anastomosis (LVSEA) in patients with lower limb lymphoedema treated by preoperative CDP.
Design: Retrospective observational study.
Materials: 37 LVSEAs in 31 patients.
Methods: Volumes of the thigh and leg with oedema were compared between the time of initial examination, and before (application of CDP) and after LVSEA. The patients were divided into two groups based on the number of anastomoses and lymphoscintigraphic findings.
Results: Preoperative CDP resulted in a reduction of 593 ml (both leg and thigh; $p < 0.001$). After CDP, LVSEA (1–8 anastomoses; average of 5) reduced the volume by 109 ml (52 ml for the thigh ($p = 0.01$) and 57 ml for the leg ($p = 0.002$)). There was no significant difference in volume reduction on lymphoscintigraphy. Volume was significantly reduced (by 55 ml in the thigh, $p = 0.049$; 96 ml in the leg, $p = 0.006$) in the group that underwent 6–8, but not 1–5 LVSEAs.
Conclusions: The net effect of LVSEA on volume reduction was confirmed, but was not particularly large. The need for CDP decreased in some patients postoperatively, and these patients should be considered for evaluation.

Although several reports[1–8] have described the effect of microlymphatic surgery on peripheral lymphoedema, details of treatment protocols and the individual effects of the surgery and of complex decongestive physiotherapy (CDP) are limited. Several facilities have recently been established to provide lymphaticovenous anastomosis (LVA), which is a physiological and relatively noninvasive surgery,[1–3,5,6] but the net effect of surgery on oedema has not been statistically analysed. Such surgical approaches are thought to require the accompaniment of CDP and thus reported results have included some effects of CDP performed by therapists at various facilities using different procedures. Moreover, the effect of separate CDP and LVA on oedema has not been analysed and evaluated after microlymphatic surgery. Here we statistically evaluated the net effect of surgery after CDP reduction on peripheral lymphoedema before applying a combination of pre- and

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doi:10.1016/j.ejvs.2011.12.032

postoperative CDP and unique lymphaticovenous side-to-end anastomosis[9] (LVSEA) for patients with chronic lower limb lymphoedema. We also compared the effect of treating patients based on the number of LVSEA per surgical procedure and type classifications derived from preoperative lymphoscintigraphic findings that we believe can indicate the severity of lymphatic dysfunction.[10]

Methods

From among 107 patients diagnosed with chronic lower limb lymphoedema at our department from a medical history and preoperative lymphoscintigraphy between June 2006 and June 2010, we selected 31 patients who had undergone 37 operations and for whom the same therapist (A.T.) qualified in manual lymph drainage had performed CDP and the same surgeon (J.M.) had performed one to eight (average of 5) LVSEAs. Thirty-one female patients (age range: 34–74 years; mean, 60 years with a standard deviation (SD) of 11 years) with cancer-related secondary lymphoedema were included. The ethics committee of Yokohama City University Hospital approved this study (Approval no. 027) and all 31 patients provided written, informed consent to participate in the study. The clinical stages of the 31 patients as proposed by the International Society of Lymphology[11] were I, II, late stage II and stage III in 1, 3, 21 and 6 patients, respectively. One, four and 26 patients underwent three, two and one operation, respectively. The patients were examined by lymphoscintigraphy before each operation and classified as type I ($n = 1$), II ($n = 3$), III ($n = 7$), IV ($n = 22$) and V ($n = 4$) according to type classifications based on preoperative lymphoscintigraphy.[10] The types are defined as follows: type I, visible inguinal lymph nodes with lymphatics along the saphenous vein and/or collateral lymphatics; type II, dermal backflow in the thigh and stasis of an isotopic material in the lymphatics; type III, dermal backflow in the thigh and leg; type IV, dermal backflow in the leg; and type V, radiolabeled colloid remaining in the foot and ankle. We assigned the patients to group TA ($n = 11$) comprising types I, II and III or group TB ($n = 26$) comprising types IV and V because the oedema was considered to be more severe in types IV and V than in types I to III.

We improved the original technique of end-to-end anastomosis[1–3,5,6] by performing LVSEA between the sidewall of the lymphatics and the proximal stump of the vein.[9] Patients with types II, III, IV and V were indicated for LVSEA because they had an obstruction, stenosis or lymph flow stasis. One patient with type I in this series underwent LVSEA because of a personal preference for surgery to minimise the need for conservative therapy. Thus, LVSEA with an average of 5 (range, 1–8) anastomoses was applied to the affected limb during one operation and comprised an average of four for the foot and leg, and one for the thigh. We also divided the patients according to the numbers of LVSEA per surgical procedure: group NA ($n = 24$), 1–5 anastomoses, and group NB ($n = 13$), 6–8 anastomoses. The median value of the number of anastomoses was 5 in this series. Whether patients with five anastomoses should be included in group NA or NB remains controversial. Our previous findings[9] revealed that the patency rate of anastomosis gradually decreases, which means more anastomoses are required to obtain favourable results. Therefore, we excluded patients with five anastomoses from group NB to evaluate the surgical effects.

The therapist (A.T.) measured the circumference of the affected limbs at the ankle, knee and 20 cm above the knee. The measurement frequency is shown in Table 1. When patients underwent multiple procedures, the first measurement after each was taken as the initial measurement. We calculated the approximate volumes of the leg and thigh using the circumferences measured in the affected limbs and compared the volume at the initial examination ($n = 37$) with mean volumes during Preop 100 ($n = 37$), between Preop 100 and Postop 100 ($n = 37$), Preop 100 and Postop 101–200 ($n = 34$), Preop 100 and Postop 301–400 ($n = 30$), Preop 100 and Postop 501–600 ($n = 14$) and Preop 100 and Postop 701–800 ($n = 8$).

Table 1
Frequency of measurement at each time.

Time	Frequency of measurement (average), times
Preop 100	2–15 (7)
Postop 100	1–13 (6)
Postop 101–200	1–14 (5)
Postop 301–400	1–14 (4)
Postop 501–600	1–13 (4)
Postop 701–800	1–9 (3)

Preop 100, preoperative day 3–100; Postop 100, postoperative day 8–100; Postop 101–200, postoperative day101–200; Postop 301–400, postoperative day 301–400; Postop 501–600, postoperative day 501–600; Postop 701–800, postoperative day 701–800.

Our protocol for treating chronic lower limb lymphoedema was as follows. We initially performed CDP as preoperative manual lymph massage to reduce the volume on an outpatient basis by having the patients wear mainly flat-knit and short-stretch single- or double-layered compressive stockings on the affected limb in the daytime and wrapping the limb with soft materials at night. We performed LVSEA when these procedures had almost maximally reduced the volume of the affected limb. The decision regarding the optimal time to undergo the operation was based on a change in the charted volume of the affected limb. Preoperative reduction of the affected limb by CDP can be estimated from a volume curve that reaches a plateau. The same CDP was repeated at 1–2 weeks postoperatively from a few days after discharge from the hospital for about 5 months on an outpatient basis. We attempted to reduce the number applications and classes of the layered stockings, the frequency and duration of manual lymph massage and the amount of time that the patients had to wear the stockings at around 6 months after surgery if the volume of the affected limb did not change. The period of CDP from the start of therapy until anastomosis was a maximum of 1024 (minimum, 37; mean, 387; SD, 272) days. Patients underwent LVSEA over a hospitalisation period of about 1 week using fluorescent near-infrared lymphangiography with indocyanine green[12,13] under general anaesthesia. Between one and eight anastomoses were performed between the foot region and the thigh. The average follow-up period after surgery was 527(265) days.

Statistical analysis

Assuming that fluctuations were neutralised by measurement tolerances, physical condition and minimal changes in physical condition, the lower limb circumference was regularly measured for around 100 days. Thus, we analysed mean values for 100 days at several times after surgery. When the period before surgery was <100 days, we used the measured values for the period. The effects of the CDP were judged based on differences between mean values for the 100 days before surgery and the start of CDP (initial examination) for all groups. In addition, the differences between means for 100 days before and for 100 days at each period after surgery were used to judge the effectiveness of the operations, which was considered to be the net effect. Data were analysed using IBM SPSS Statistics 18 software (SPSS Japan Inc., Tokyo, Japan). Significance was set at 0.05 (5%).

Results

The Shapiro–Wilk test of the normality of the data showed that the distribution was normal. Differences in the volumes of the leg and thigh were examined using a paired *t*-test. Mean differences between the volumes at initial examination (2969 and 2569 ml in the thigh and leg, respectively) and mean volumes during Preop 100 (312 and 281 ml in the thigh and leg (593 ml per limb), respectively) were statistically significant ($p < 0.001$). The ratio of the reduction in volume to the initial volume (reduction ratio) was 0.11 (11%) per limb. Mean volume was reduced by 52 ml ($p = 0.01$) in the thigh and 57 ml ($p = 0.002$) in the leg between Preop 100 and Postop 100. The reduction rate was 0.02 (2%), and the net volume reduction (109 ml) achieved by surgery was equivalent to 16% of the total volume reduction (702 ml; 109 + 593 ml) including that by preoperative CDP between the initial volume and the mean volume at 100 days after surgery. Mean volume reductions did not significantly differ between Preop 100 and Postop 101–200, 301–400, 501–600 and 701–800 (Fig. 1).

Mean volumes were reduced by 56 ml in the thighs ($p = 0.036$) and 71 ml in the legs ($p = 0.038$) of group TA ($n = 11$; Fig. 2), and by 51 ml in the legs ($p = 0.02$) of group TB ($n = 26$; Fig. 3) between Preop 100 and Postop 100.

Reductions in mean volumes did not significantly differ between Preop 100 and any other time frame in group NA (Fig. 4). In group NB with six to eight LVSEAs, mean volumes were significantly reduced by 55 ml in the thigh ($p = 0.049$) and 96 ml in the leg ($p = 0.006$) between Preop 100 and Postop 100 ($n = 13$), by 124 ml in the leg ($p = 0.004$) between Preop 100 and Postop 101–200 ($n = 12$) and by 85 ml in the leg between Preop 100 and Postop 301–400 ($n = 12$; Fig. 5).

Case report

Lymphoedema developed in the left lower limb of a 67-year-old woman 5 years after undergoing treatment for uterine cancer. She had received CDP for around 8 months (Fig. 6A) and lymphoscintigraphy indicated type II, which classified her into group TA (Fig. 6B). Preoperative CDP with compression stockings improved the oedema (Fig. 6A and C). She underwent LVSEA with eight anastomoses between the foot and the thigh. Oedema in the left lower limb improved after surgery with continued CDP (Fig. 6D). When she removed the stockings at about 6 months after surgery (Fig. 6E), oedema of the affected limb temporarily deteriorated. The oedema improved later without further treatment and the patient has remained free of compression stockings and bandaging for about 1 year. The overall reduction including the effect of CDP and surgery was 879 ml in the left lower limb at 18 months after surgery (Fig. 6F).

Discussion

The individual effect of LVA cannot be evaluated because it is always combined with various complex physiological therapies. We considered that oedema can be reduced using CDP with elastic stockings and/or bandaging before surgery, the net effect should be evaluated and then the net effect of subsequent LVA should be evaluated. The same examiner measured the circumference of affected limbs in patients who had undergone repeated LVSEA by the same surgeons and repeated CDP by the same therapists. Thus, the statistical reliability of the data was high. The circumference of the affected limb was influenced by factors such as weight, daily load and daily fluctuations. We suppressed variation in measured values by taking more measurements before and after surgery to generate data suitable for statistical processing. The patients included in this study differed in terms of place of residence, occupation, severity of oedema, and other factors. Therefore, the duration and frequency of CDP differed and standardising the conditions for the study was almost impossible. However, we could determine that the effects of preoperative CDP were maximal for each because we could determine when individualised reduction volume curves reached a plateau in each patient. Our experience has shown that patients with peripheral lymphoedema do not remain motivated to continue with long-term CDP. Therefore, a randomised comparative study of patients who have undergone only long-term CDP with those treated by CDP plus surgery might be a more appropriate way to separately evaluate the net effects of CDP and surgery in the future.

The numbers of lymphaticovenous anastomoses affected the mid-term volume reduction after surgery. Oedema in group NB with six to eight LVSEAs was reduced particularly in the leg between Preop 100 and at several time points after surgery because

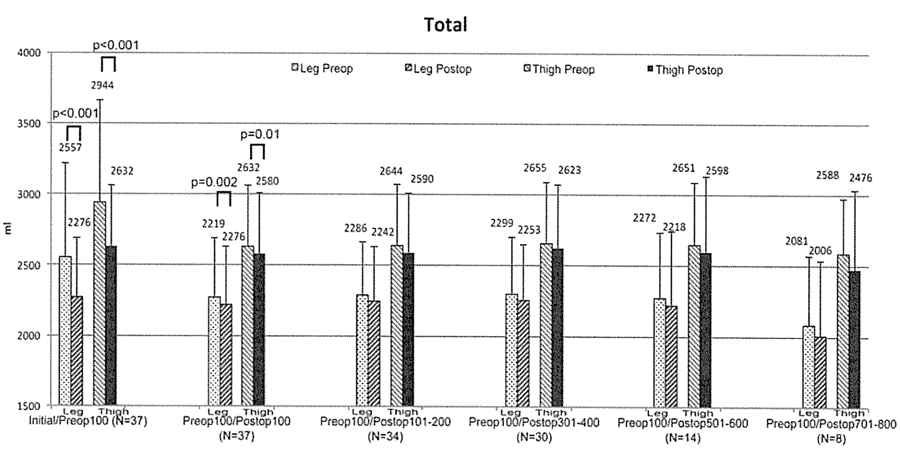

Figure 1. Comparisons of values obtained at initial examination (Initial) and mean values during 100 days before surgery (Preop 100) (Left 4 bars) and between mean values obtained during Preop 100 and by postoperative day (POD) 100 (Postop 100), POD 101 to 200 (Postop 101–200), POD 300 to 400 (Postop 301–400), POD 501 to 600 (Postop 501–600), and POD 701 to 800 (Postop 701–800) in all patients. Volumes and mean volumes of leg and thigh in each comparison are indicated above each standard error bar. *P* values indicate statistical differences ($p < 0.05$).

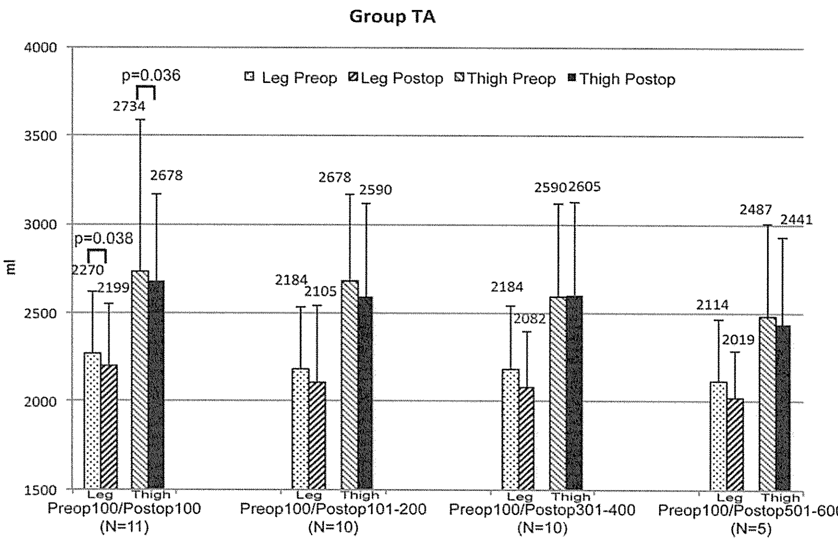

Figure 2. Comparisons between mean values obtained during Preop 100 and POD 100 (Postop 100), POD 101 to 200 (Postop 101–200), 301 to 400 (Postop 301–400) and 501 to 600 (Postop 501–600) in Group TA. Mean volumes of legs and thighs are indicated above standard error bars. *P* values indicate statistical differences ($p < 0.05$).

more anastomoses were performed in the feet and legs than in the thigh. Although a relationship between the numbers of anastomoses and volume reduction has been suggested by Hung et al.,[2] we did not find such a relationship. Furthermore, the ideal number of anastomoses required to achieve a reduction in volume reduction remains unclear. We found that over six anastomoses were required for volume reduction, which does not necessarily indicate a minimal number, but several anastomoses should be considered necessary to improve outcomes. The patency rate of LVA decreased over time as we previously reported,[9] and thus we consider that many anastomoses are needed to achieve good long-term outcomes.

We did not uncover obvious evidence that surgery reduced the volume any better in patients with mildly dysfunctional lymph flow

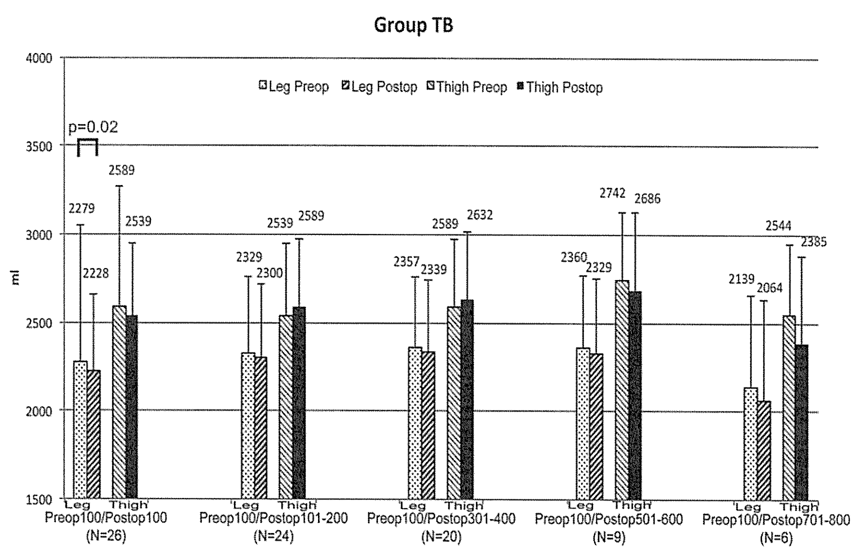

Figure 3. Comparisons of mean values between Preop 100 and POD 100 (Postop 100), 101 and 200 (Postop 101–200), 301 and 400 (Postop 301–400), 501 and 600 (Postop 501–600) and 701 and 800 (Postop 701–800) in Group TB. Mean volumes of legs and thighs are indicated above standard error bars. *P* values indicate statistical differences ($p < 0.05$).

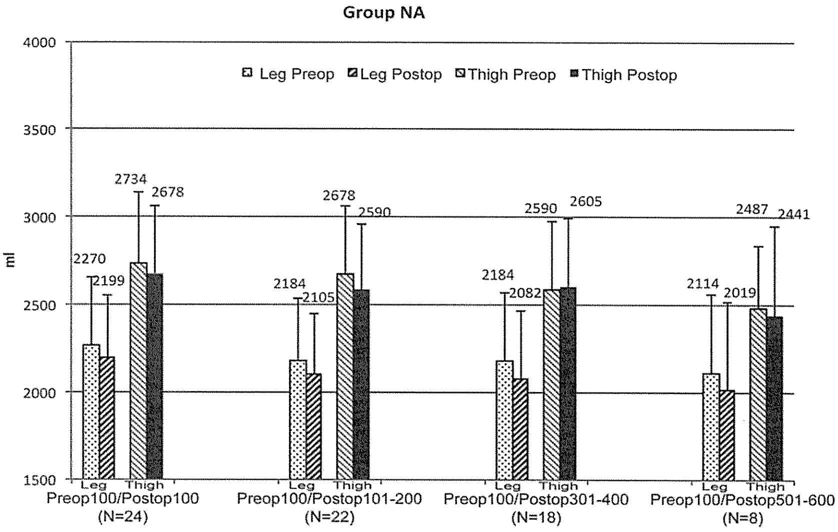

Figure 4. Comparisons of mean values between Preop 100 and POD 100 (Postop 100), POD 101 and 200 (Postop 101–200), 301 and 400 (Postop 301–400) and 501 and 600 (Postop 501–600) in Group NA. Mean volumes of legs and thighs are indicated above standard error bars. Values did not significantly differ in any comparison.

than in those with more severe lymphoscintigraphic findings. The former and latter types of patients were classified into groups TA and TB, respectively. Secondary lower limb lymphoedema has been classified using lymphoscintigraphy[14,15] and oedema tends to worsen with progressive types.[10] These types of classifications correlate to some extent with the clinical severity proposed by the International Society of Lymphology,[11] and are considered to reflect lymphatic function in patients with secondary lymphoedema. More LVSEAs are also being performed in different locations (such as the thigh) in patients with mild to moderate lymphoedema compared with patients with a more severe condition.[10] According to these results, the patients in group TA, whose lymphatic functions were relatively well maintained and reflected in the ease of surgery, should have had better volume reductions, but they did not. By

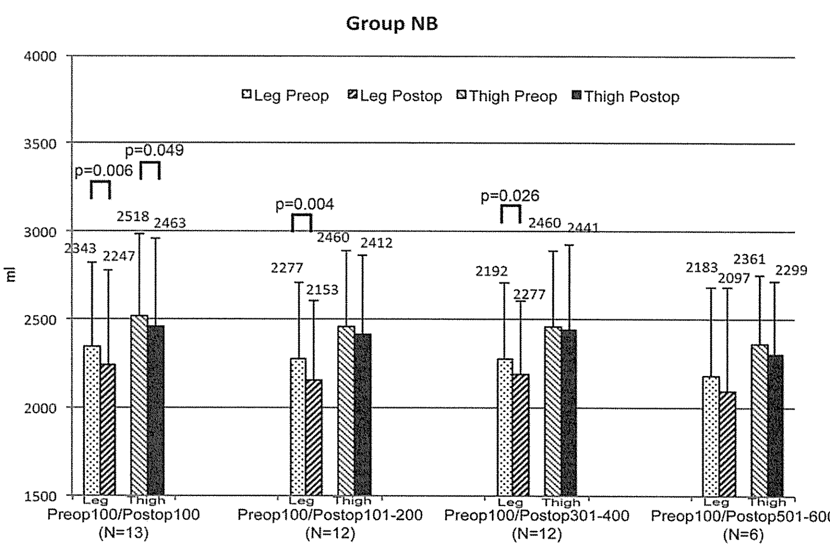

Figure 5. Comparisons of mean values between Preop 100 and POD 100 (Postop 100), POD 101 and 200 (Postop 101–200), 301 and 400 (Postop 301–400) and 501 and 600 (Postop 501–600) in Group NB. Mean volumes of legs and thighs are indicated above standard error bars. *P* values indicate statistical differences ($p < 0.05$).

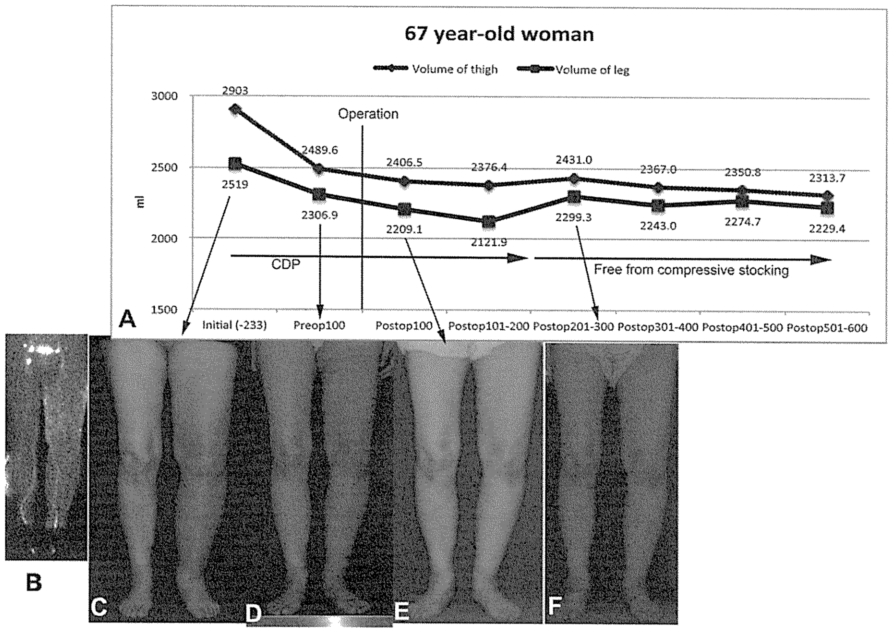

Figure 6. Line chart of volume change in leg and thigh of 68-year-old woman with left lower limb lymphoedema during CDP and lymphaticovenous anastomosis (A). Preoperative lymphoscintigraphy shows dermal backflow of contrast medium in left thigh area indicating Type II according to our classification (B). Frontal view of lower limb at initial examination shows extreme swelling with skin redness (C). Remarkable improvement in left lower limb oedema after preoperative CDP (D). Oedema has continued to improve by 3 months after surgery (E). Slight relapse of left limb oedema at 8 months after surgery when compressive garments were removed (F). Oedema has continued to improve for about 2 years (F).

contrast, functioning lymph ducts were difficult to identify during surgery in group TB with more severely affected lymphatic functions. Furthermore, fibrosis of the subcutaneous tissue was already complete in many such patients, and improving volume in the affected limb through surgery was considered difficult. Further studies are needed to conclude whether lymphoscintigraphy can be a predictor of the outcomes of strategies aimed at volume reduction in patients with a dysfunctional lymphatic system.

Experienced therapists or physiologists thoroughly reduced oedema before surgery by applying CDP. Some patients had already been treated at other facilities by the time of the initial examination. The period from initial examination to surgery was short for such patients. To accurately determine the limits of CDP was difficult, but experienced therapists or physiotherapists consider that they can be comparatively determined by measuring the extent to which the oedema has been reduced or the oedematous skin of the affected limb. Charts of volume changes in affected limbs might help to raise awareness of the limitation of CDP and define the optimal timing for microlymphatic surgery.

The overall findings from all of the patients indicated that CDP reduced oedema more effectively than surgery. The approximate 600 ml (11%) reduction achieved by preoperative CDP in affected limbs was significantly better than that achieved by surgery (about 100 ml; 2%). Compressive bandaging reduces volume more effectively than compression stockings.[16,17] Badger et al. reported a mean overall reduction rate of lower limb lymphoedema of 31% after bandaging followed by compression stockings compared with 15.8% using compression stockings alone.[17] However, stockings are more convenient and allow easier continuation of routine activities.[18] Layered stockings can also produce almost as much interface pressure as compression bandaging.[19] Therefore, we preferred to reduce volume by CDP mainly with stiff compressive stockings on an outpatient basis considering the medical circumstances in Japan.[20] We do not believe that surgical intervention is inferior to CDP because volume reduction is only one factor that is evaluated when considering treatment for lymphoedema. Surgical intervention such as LVA plays an important role in treating peripheral lymphoedema because lymph drainage from dysfunctional lymph vessels to a vein is essential and physiological in treating obstructive lymphoedema. From this perspective, surgical intervention seems superior to CDP. We also believe that drainage due to anastomosis does not always correlate with volume reduction.

Our experience indicated that the surgical effect should include not only the amount of oedema reduction such as lower limb volume but also changes in skin stiffness, subjective symptoms and the frequency of cellulitis. The frequency of outpatient treatment in this series sequentially decreased after surgery. The primary goals for patients with peripheral lymphoedema are, for example, oedema reduction and cellulitis control. On the other hand, the final outcomes for these patients are freedom from compressive garments or a reduction in the need for conservative therapies, which seems difficult to achieve by conservative therapy. The present series included some patients (one of whom was presented in the case report) who became free of CDP after the anastomosis and many for whom the class of pressure in the elastic stockings could be decreased. Both of these outcomes should be evaluated as effects of anastomosis. Therefore, how to perform such evaluations will require further discussion.

Acknowledgements

We thank Mr. Koukichi Hashimoto for analysing the data, and Ms. Nanae Matsuda for data collection.

Conflict of Interest

None declared.

Funding

None declared.

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