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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

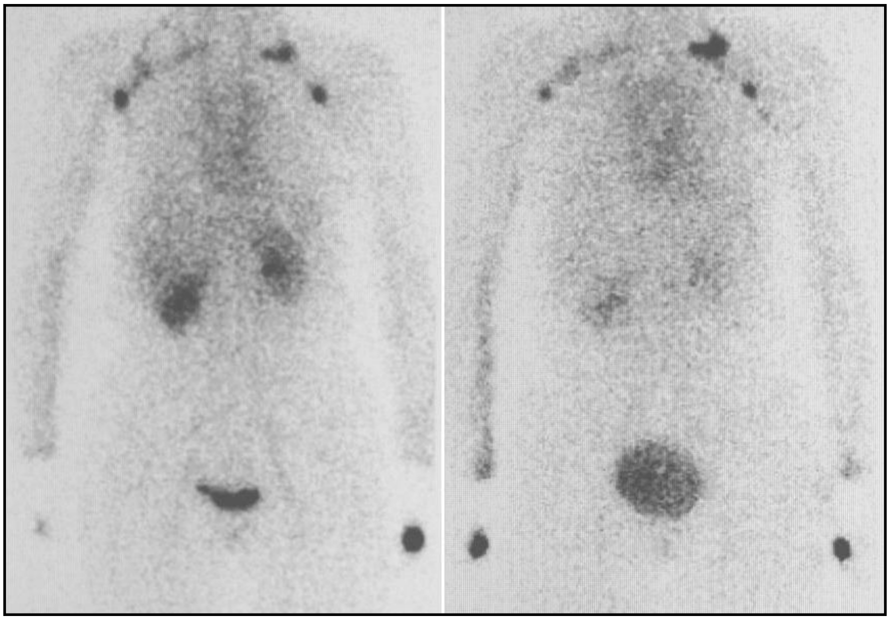

Fig. 1. Lymphoscintigraphy images of a case of Type I-Subtype E lymphedema in the left arm. The left and right panels show images taken 30 and 120 min, respectively, after injection of a contrast medium. Lymph nodes around the clavicle, but not axillary lymph nodes, were observed in the affected left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

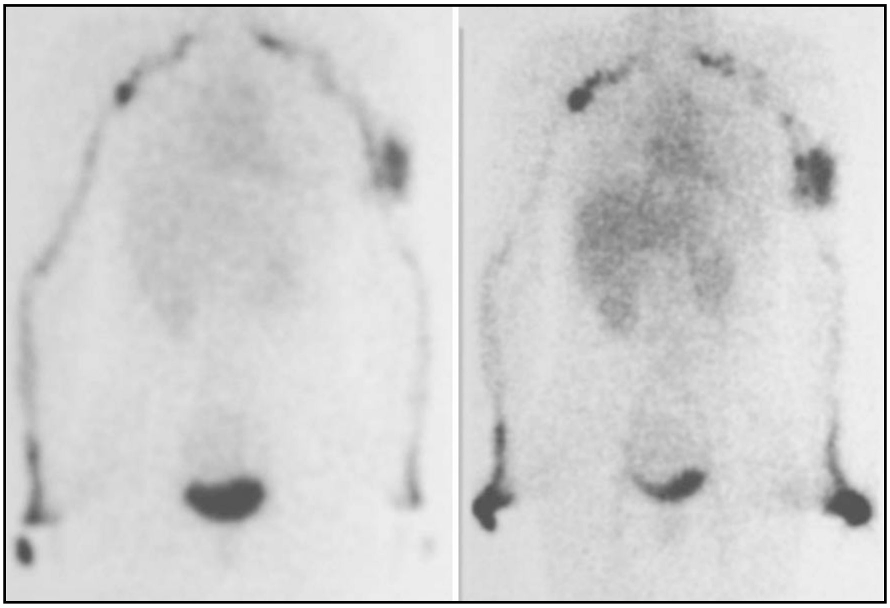

Fig. 2. Lymphoscintigraphy images of a case of Type II-Subtype L lymphedema in the left arm. The left and right panels show images taken 30 and 120 min, respectively, after injection of a contrast medium. Lymph nodes around the clavicle were observed only on the image taken at the later time point. DBF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

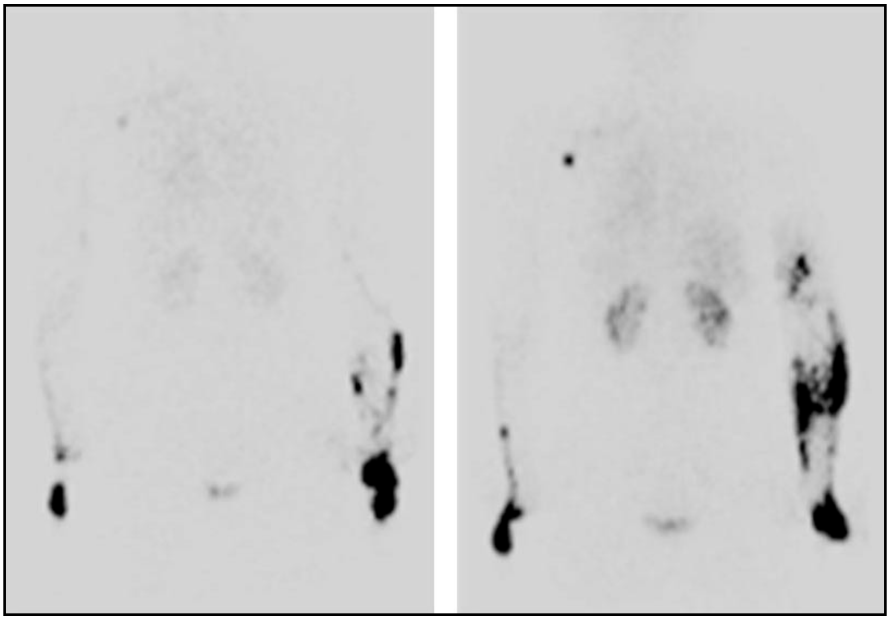

Fig. 3. Lymphoscintigraphy images of a case of Type III-Subtype 0 lymphedema in the left arm. The left and right panels show images taken 30 and 120 min, respectively, after injection of a contrast medium. Lymph nodes around the clavicle were not observed even on the image taken at the later time point.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

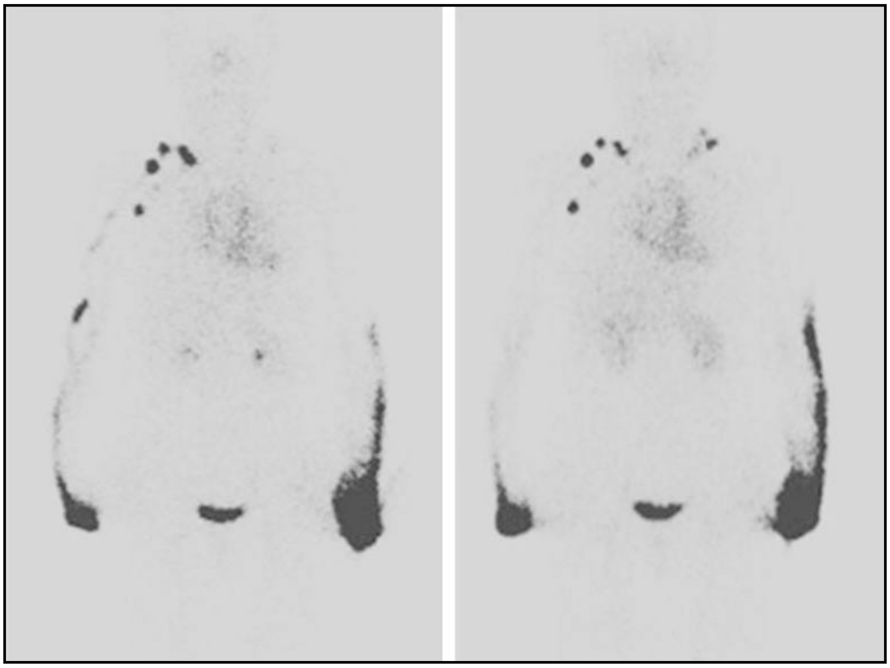

Fig. 4. Lymphoscintigraphy images of a case of Type IV-Subtype L lymphedema in the left arm. The left and right panels show images taken 30 and 120 min, respectively, after injection of a contrast medium. Lymph nodes around the clavicle were observed only on the image taken at the later time point. DBF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

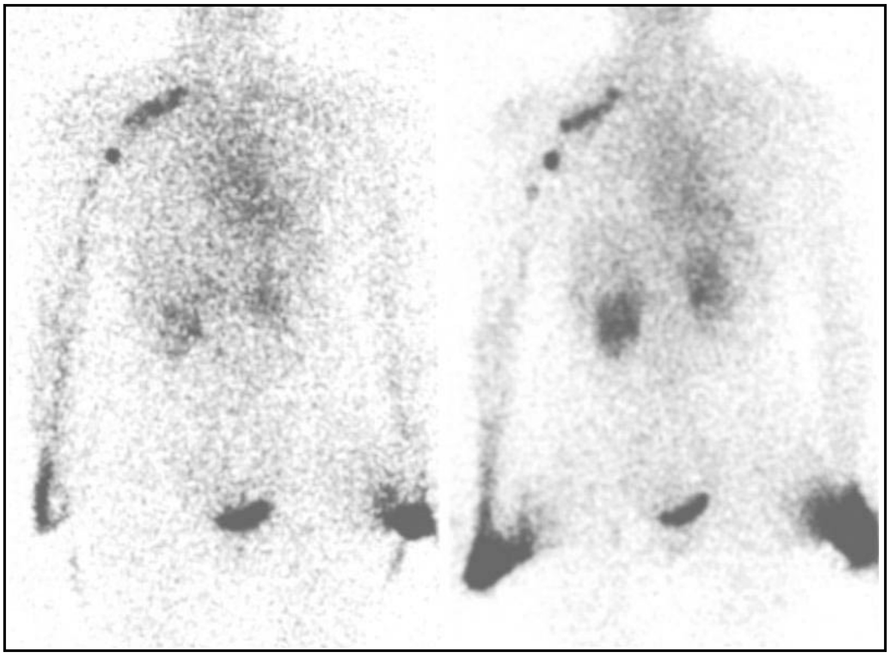

Fig. 5. Lymphoscintigraphy images of a case of Type V-Subtype 0 lymphedema in the left arm. The left and right panels show images taken 30 and 120 min, respectively, after injection of a contrast medium. Lymph nodes around the clavicle were not observed even on the image taken at the later time point.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

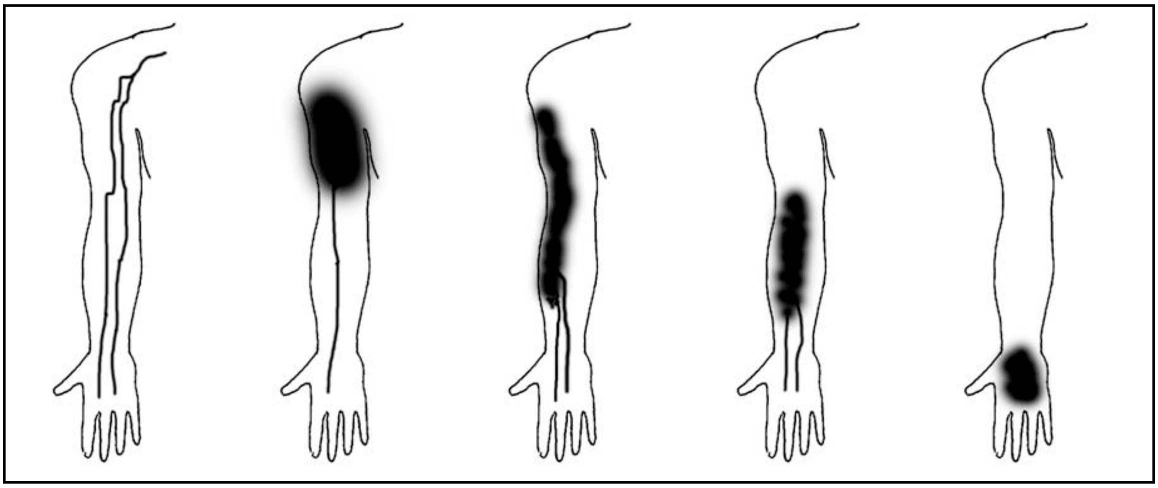

Fig. 6. Schemes of lymphoscintigraphy of Type I to Type V. The lines of lymph-flow are vague in some cases while the location and extent of dermal back flow varies in each case.

(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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