Lymphedema is a chronic and progressive disease mainly caused by cancer and its treatments. Lymphaticovenular anastomosis (LVA) is a generally effective, minimally invasive surgical treatment for lymphedema. However, LVA is still challenging procedure for microsurgeons especially for upper extremity lymphedema (UEL), because very small (mostly less than 0.50 mm in diameter in the upper extremity) and thin-walled lymphatic vessels are difficult to detect and anastomose even under an operating microscope. 

Indocyanine green (ICG) lymphography is a minimally invasive imaging modality that is useful for the preoperative detection of lymphatic vessels by mapping linear patterns on the patient’s limb. However, ICG lymphography still has difficulty in assisting intraoperative detection of lymphatic vessels in performing LVA, because strong light from the operating microscope usually disturbs ICG fluorescence imaging. Only some built-in ICG camera systems with specific operating microscopes make real-time ICG lymphography possible in lymphaticovenular anastomosis (LVA). We applied a new high-resolution ICG videolymphography system, which is separated from the operating microscope. Because the system can divide near-infrared fluorescence light of ICG from visible light of the operating microscope, real-time ICG videolymphography-navigated LVA under operating microscope illumination is possible regardless types of operating microscopes. The study involved 10 patients with upper extremity lymphedema characterized by International Society of Lymphology stage 2 and treated by 3 lymphaticovenular anastomoses at the forearm (30 lymphaticovenular anastomoses incorporating 30 lymphatic vessels) under real-time ICG videolymphography. The rate of intraoperative detection of lymphatic vessels using real-time ICG videolymphography was 86.7% (0.25–0.85 mm in diameter), and that of lymph flow through the lymphaticovenular anastomoses was 76.7%. None of lymphatic vessels and no flow were detected under the microscope light by means of another non-built-in ICG lymphography camera. Real-time ICG videolymphography in LVA is beneficial, because the surgeon could find lymphatic vessels easily by checking dual images of original view and ICG fluorescent view and ensure accuracy of the LVA in a suture by a suture without any pauses of the surgical procedures. (Plast Reconstr Surg Glob Open 2019;7:e2253; doi: 10.1097/GOX.0000000000002253; Published online 24 May 2019.)

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PATIENTS AND METHODS
The study included 10 patients with International
Society of Lymphology (ISL) stage 2 breast cancer treat-
ment-related UEL in whom, between March 2018 and July
2018, 3 LVAs had been created at the forearm. Three
1.5-cm-long incisions for LVA were decided using preop-
erative dynamic ultrasonography and preoperative lymph
mapping using ICG lymphography device currently in use
(PDE-Neo; Hamamatsu Photonics, Hamamatsu, Japan)
to analyze effective muscle pumping areas at the arm; we
previously reported this LVA method as the dynamic-LVA
method. All 30 LVAs in the study patients were created
by the same surgeon (YS). A new ICG videolymphography
device and current ICG lymphography device were used in
evaluating LVA procedures intraoperatively.

Real-time ICG Videolymphography
Two hours before the surgery, 0.1 mL of ICG (Diag-
nogreen 0.25%; Daiichi Pharmaceutical, Tokyo, Japan)
was injected intradermally at the second web space of the
hand, at the anterior border of the styloid process of ra-
dius, and at the anterior border of the styloid process of
ulna. A new device of ICG videolymphography (LIGHTVI-
SION; Shimazu Corporation, Kyoto, Japan) was set to visu-
alyze each incision site under magnification with specific
configuration of the system (intensity of ICG fluorescent
ranged from 8 to 22 and intensity of visible light ranged
from 0 to 8) (Fig. 1). All LVAs were created using a Carl
Zeiss surgical microscope OPMI Pentero under 5–20%
power of the microscope illumination of the xenon light.

RESULTS
LVA was performed under local anesthesia in all
10 patients. Patients’ age ranged from 31 to 73 (mean
55.8 ± 13.1) and body mass index (BMI) ranged from 23.6
to 30.5 (mean 25.9 ± 2.2). Five patients revealed ISL stage
2a UEL and other 5 patients revealed ISL stage 2b UEL.
Each 3 LVAs were successfully created in 10 study patients
(30 lymphaticovenular anastomoses incorporating 30
lymphatic vessels at the forearm). In all 30 anastomoses,
intraoperative real-time ICG fluorescent detection of lym-
phatic vessels and flow through the anastomoses were ac-
cessed per ICG fluorescent features (linear, stardust, and
diffuse) (Table 1). Under the new ICG videolymphogra-
phy, the rate of real-time detection of lymphatic vessels
was 86.7% (0.25–0.85 mm in diameter) (Fig. 2) and that
of lymph flow through the lymphaticovenular anastomo-
ses was 76.7% (Fig. 3). None of lymphatic vessels and no
flow were detected under the microscope light by means
of another ICG lymphography modality currently in use.

Table 1. Intraoperative Findings of Lymphatic Vessels in Real-time ICG Videolymphography

|                          | Sclerosis of Lymphatic Vessels (n = 30 Vessels) | Detection Rate of Lymphatic Vessels (n = 30 Vessels) | Lymph-to-venous Flow (n = 30 Vessels) |
|--------------------------|-----------------------------------------------|---------------------------------------------------|-------------------------------------|
|                          |                                              | 26/30 (86.7%)                                      | 23/30 (76.7%)                       |
| Total                    |                                              | 25/30 (76.7%)                                      |                                     |
| In “linear pattern” incisions (n = 6 vessels) | 2/6 (33.3%)                                   | 6/6 (100%)                                        | 5/6 (83.3%)                         |
| In “stardust pattern” incisions (n = 21 vessels) | 18/21 (85.7%)                                  | 17/21 (81.0%)                                     | 16/21 (76.2%)                       |
| In “diffuse pattern” incisions (n = 3 vessels)  | 3/3 (100%)                                    | 3/3 (100%)                                        | 2/3 (66.7%)                         |

Number (and percentage) of lymphatic vessels are shown.
“linear pattern” incisions, incisions made at sites where the ICG lymphography pattern was linear; “stardust pattern” incisions, incisions made at sites where a star-
dust ICG lymphography pattern was seen; “diffuse pattern” incisions, incisions made at sites where a diffuse ICG lymphography pattern was seen.
Figure 2. Detection of the lymphatic vessel in stardust patterns using real-time ICG videolymphography imaging. ICG fluorescence images are clearly visualized by an ICG videolymphography under the microscope illumination of the xenon light. The system monitors the operation field real-timely by 3 different simultaneous images: original view with visible light, which include no ICG fluorescence images, ICG view with near-infrared fluorescence light images, and ICG plus original view, which combines original view and ICG view with enhancing ICG fluorescence as green color in the image.

Figure 3. Real-time ICG videolymphography imaging in lymphaticovenular anastomosis. The lymphatic vessel with a diameter of 0.50 mm under fat tissue is easily detected and anastomosed to a subcutaneous vein with a diameter of 0.40 mm. Lymph-to-venous flow of lymph is observed real-timely in performing the anastomosis.
DISCUSSION

ICG lymphography is useful as a minimally invasive imaging modality for evaluating the severity of lymphedema and for detecting the lymphatic vessels preoperatively.4,7,11-24

In conventional ICG-navigated LVA, regions in which preoperative ICG lymphography reveals linear patterns are recommended for LVA because lymphatic vessels in these areas are typically nonsclerotic, especially in patients with early-stage UEL.20,27-29 However, preoperative detection of lymphatic vessels using ICG lymphography was difficult in most of late-stage UEL patients, because linear patterns were usually concealed by stardust patterns or diffuse patterns in progressive lymphedema.22-24,26,29-32 Furthermore, ICG lymphography has limitations in detecting lymphatic vessels real-time, because strong light of an operating microscope and stardust patterns around the incision sites usually influences delicate ICG fluorescent imaging. In this study, real-time ICG videolymphography under operating microscope light could detect 20 lymphatic vessels for LVAs from 24 stardust or diffuse pattern incision sites intraoperatively (83.3% detection rate).

Lymphatic vessels at the arm in UEL patients are relatively small in diameter than that of lower extremity lymphedema patients.6,14,20,26,32 When lymphatic vessels are under 0.30 mm in diameter, it is not easy to detect lymphatic vessels from connective tissue fibers or nerves in lymphedematous fibrotic subcutaneous tissues even for experts. With our real-time ICG videolymphography, lymphatic vessels were easily detected from these structures.

ICG lymphography has limitation in detecting lymphatic vessels intraoperatively.26,31,32 Yang et al53 reported that 36.1% of lymphatic vessels were not enhanced intraoperatively by ICG fluorescence. Detection rate of lymphatic vessels in real-time ICG videolymphography in this study was 86.7%. This result suggests that our videolymphography could detect most of lymphatic vessels, which can be enhanced by ICG fluorescence. Further study is needed to ascertain whether technical improvements in ICG lymphography could increase the intraoperative detection rate of lymphatic vessels.

In real-time ICG videolymphography, the surgical procedure of LVA could be evaluated in a suture by a suture, because flow of lymph enhanced by ICG fluorescence was visible in the anastomosis of lymphatic vessel and vein real-time (see video, Supplemental Digital Content 1, which shows the real-time intraoperative ICG videolymphography in lymphaticovenular anastomosis. By real-time ICG fluorescence imaging, lymphatic vessels are easily detected and flow of lymph in the anastomosis is visible in a suture by a suture. This video is available in the “Related Videos” section of the Full-Text article on PRSGlobalOpen.com or at http://links.lww.com/PRSGO/B68). Real-time assessment of lymphatic flow at the anastomosis could improve the accuracy of surgical procedures.

CONCLUSION

Real-time ICG videolymphography is beneficial, because the surgeon could find lymphatic vessels easily by checking dual-imaging of original and ICG fluorescent views and ensure accuracy of the LVA intraoperatively.

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REFERENCES

1. Langer I, Guller U, Berclaz G, et al. Morbidity of sentinel lymph node biopsy (SLN) alone versus SLN and completion axillary lymph node dissection after breast cancer surgery: a prospective Swiss multicenter study on 659 patients. Ann Surg. 2007;245:452-461.
2. Sakorafas GH, Peros G, Cataliotti L, et al. Lymphedema following axillary lymph node dissection for breast cancer. Surg Oncol. 2006;15:153–165.
3. DiSipio T, Rye S, Newman B, et al. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol. 2013;14:500–515.
4. Akita S, Mitsukawa N, Rikihisa N, et al. Early diagnosis and risk factors for lymphedema following lymph node dissection for gynecologic cancer. Plast Reconstr Surg. 2013;131:283–290.
5. Ferrandina G, Mantegna P, Petrillo M, et al. Quality of life and emotional distress in early stage and locally advanced cervical cancer patients: a prospective, longitudinal study. Gynecol Oncol. 2012;124:389–394.
6. Biglia N, Librino A, Ottino MC, et al. Lower limb lymphedema and neurological complications after lymphadenectomy for gynecologic cancer. Int J Gynecol Cancer. 2015;25:521–525.
7. Akita S, Nakamura R, Yamamoto N, et al. Early detection of lymphatic disorder and treatment for lymphedema following breast cancer. Plast Reconstr Surg. 2016;138:192e–202e.
8. Yamada Y. Studies on lymphatic venous anastomosis in lymphedema. Nagoya J Med Sci. 1969;32:1–21.

9. O’Brien BM, Sykes P, Threlfall GN, et al. Microlymphaticovenous anastomoses for obstructive lymphedema. Plast Reconstr Surg. 1977;60:197–211.

10. Koshima I, Inagawa K, Urushihara K, et al. Supermicrosurgical lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. J Reconstr Microsurg. 2000;16:437–442.

11. Granzow JW, Soderberg JM, Kaji AH, et al. Review of current surgical treatments for lymphedema. Ann Surg Oncol. 2014;21:1195–1201.

12. Garza R 3rd, Skoracki R, Hock K, et al. A comprehensive overview on the surgical management of secondary lymphedema of the upper and lower extremities related to prior oncologic therapies. BMC Cancer. 2017;17:468.

13. Garza RM, Chang DW. Lymphovenous bypass for the treatment of lymphedema. J Surg Oncol. 2018;118:743–749.

14. Yamamoto T, Narushima M, Yoshimatsu H, et al. Minimally invasive lymphatic supermicrosurgery (MILS): indocyanine green lymphography-guided simultaneous multisite lymphaticovenular anastomoses via millimeter skin incisions. Ann Plast Surg. 2014;72:67–70.

15. Seki Y, Yamamoto T, Yoshimatsu H, et al. The superior-edge-of-the-knee incision method in lymphaticovenular anastomosis for lower extremity lymphedema. Plast Reconstr Surg. 2015;136:665e–675e.

16. Seki Y, Kajikawa A, Yamamoto T, et al. Single lymphaticovenular anastomosis for early-stage lower extremity lymphedema treated by the superior-edge-of-the-knee incision method. Plast Reconstr Surg Glob Open. 2018;6:e1679.

17. Yang JC, Wu SC, Chiang MH, et al. Targeting reflux-free veins with a vein visualizer to identify the ideal recipient vein preoperatively for optimal lymphaticovenous anastomosis in treating lymphedema. Plast Reconstr Surg. 2018;141:793–797.

18. Hayashi A, Hayashi N, Yoshimatsu H, et al. Effective and efficient lymphaticovenular anastomosis using preoperative ultrasound detection technique of lymphatic vessels in lower extremity lymphedema. J Surg Oncol. 2018;117:290–298.

19. Chang DW, Masia J, Garza R 3rd, et al. Lymphedema: surgical and medical therapy. Plast Reconstr Surg. 2016;138(suppl 3): 209S–218S.

20. Yamamoto T, Yamamoto N, Yoshimatsu H, et al. Factors associated with lymphosclerosis; an analysis on 902 lymphatic vessels. Plast Reconstr Surg. 2017;140:734–741.

21. Ogata F, Narushima M, Mihara M, et al. Intraoperative lymphography using indocyanine green dye for near-infrared fluorescence labeling in lymphedema. Ann Plast Surg. 2007;59:180–184.

22. Yamamoto T, Narushima M, Doi K, et al. Characteristic indocyanine green lymphography findings in lower extremity lymphedema: the generation of a novel lymphedema severity staging system using dermal backflow patterns. Plast Reconstr Surg. 2011;127:1979–1986.

23. Yamamoto T, Matsuda N, Doi K, et al. The earliest finding of indocyanine green lymphography in asymptomatic limbs of lower extremity lymphedema patients secondary to cancer treatment: the modified dermal backflow stage and concept of subclinical lymphedema. Plast Reconstr Surg. 2011;128:941–947.

24. Yamamoto T, Yamamoto N, Doi K, et al. Indocyanine green-enhanced lymphography for upper extremity lymphedema: a novel severity staging system using dermal backflow patterns. Plast Reconstr Surg. 2011;128:941–947.

25. International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema. 2009 consensus document of the International Society of Lymphology. Lymphology. 2009;42:51–60.

26. Seki Y, Kajikawa A, Yamamoto T, et al. The dynamic-lymphaticovenular anastomosis method for breast cancer treatment-related lymphedema: creation of functional lymphaticovenular anastomoses with use of preoperative dynamic ultrasonography. J Plast Reconstr Aesthet Surg. 2019;72:62–70.

27. Koshima I, Kawada S, Moriguchi T, et al. Ultrastructural observations of lymphatic vessels in lymphedema in human extremities. Plast Reconstr Surg. 1996;97:397–405; discussion 406.

28. Mihara M, Hara H, Hayashi Y, et al. Pathological steps of cancer-related lymphedema: histological changes in the collecting lymphatic vessels after lymphadenectomy. PLoS One. 2012;7:e11126.

29. Hara H, Mihara M, Seki Y, et al. Comparison of indocyanine green lymphographic findings with the conditions of collecting lymphatic vessels of limbs in patients with lymphedema. Plast Reconstr Surg. 2013;132:1612–1618.

30. Seki Y, Yamamoto T, Kajikawa A. Lymphaticovenular anastomosis for breast cancer treatment-related lymphedema: three-line strategy for an optimal outcome. J Plast Reconstr Aesthet Surg. 2018;71:e13–e14.

31. Mihara M, Seki Y, Hara H, et al. Predictive lymphatic mapping: a method for mapping lymphatic channels in patients with advanced unilateral lymphedema using indocyanine green lymphography. Ann Plast Surg. 2014;72:706–710.

32. Gentileschi S, Servillo M, Albanese R, et al. Lymphatic mapping of the upper limb with lymphedema before lymphatic supermicrosurgery by mirroring of the healthy limb. Microsurgery. 2017;37:881–889.

33. Yang JC, Wu SC, Chiang MH, et al. Intraoperative identification and definition of “functional” lymphatic collecting vessels for supermicrosurgical lymphatico-venous anastomosis in treating lymphedema patients. J Surg Oncol. 2018;117:994–1000.