Outcomes of lymphaticovenous side-to-end anastomosis in peripheral lymphedema

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Objective: Lymphaticovenous anastomosis has been used for patients with peripheral lymphedema. However, the efficacy of this procedure is controversial due to a lack of evidence regarding postoperative patency. We sought to determine midterm postoperative patency of lymphaticovenous side-to-end anastomoses (LVSEAs) using indocyanine green fluorescence lymphography.

Methods: This was a retrospective observational study set in a teaching hospital. Of 107 patients with chronic lymphedema who underwent 472 LVSEAs, 57 (223 anastomoses) consented to fluorescence lymphography and comprised the study cohort. The intervention consisted of a microsurgical LVSEA performed with a suture-stent method. Patients also had preoperative and postoperative complex decongestive physiotherapy. Anastomosis patency was assessed using indocyanine green fluorescence lymphography ≥ 6 months after surgery. Patency rates were calculated using Kaplan-Meier analysis. We assessed volume reduction on the operated-on limb and compared this between patients in whom anastomoses were patent and those in whom anastomoses were not obviously patent.

Results: Patency could be evaluated only at the dorsum of the foot, ankle, and lower leg because the near-infrared rays emitted by the special camera used could not penetrate the deep subcutaneous layer containing collective lymphatics in areas such as the thigh. Several patterns were observed on fluorescence lymphography: straight, radial, and L-shaped. Cumulative patency rates of LVSEAs were 75% at 12 months and 36% at 24 months after surgery. No significant difference in volume change of the affected limb was seen between the 34 patients with patent anastomosis (600 \pm 969 mL) and the 24 patients without obvious evidence of patency (420 \pm 874 mL).

Conclusions: Although further study is required to determine factors leading to anastomotic obstruction and to optimize the results of microlymphatic surgery, the present LVSEA technique appears promising. (J Vasc Surg 2012;55:753-60.)

Lymphaticovenous anastomosis (LVA) has been performed for patients with peripheral lymphedema since 1977.¹ Several authors have since applied LVA in several variations of end-to-end or end-to-side,¹⁻⁴ or both, and have described long-term results of LVA in circumferential and volume reduction, or both, of the affected limbs.⁵⁻⁷ However, few reports have used lymphoscintigraphy to address the postoperative patency of LVA.^{6,8,9} In addition, patency of anastomoses can be difficult to evaluate on real-time lymphoscintigraphic images.

As an improvement over the original technique of end-to-end anastomosis, we have been performing lymphaticovenous side-to-end anastomosis (LVSEA) between the sidewall of the lymphatics and the proximal stump of the vein (Fig 1) for patients with chronic peripheral lymphedema since 1998. From the perspective of lymph flow in the anastomosed lymphatics, LV-SEA can divert the obstructed lymph flow and decompress lymphatic hypertension to the same extent as

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conventional LVA, in addition to theoretically preserving the original flow even if the anastomosis becomes obstructed, a possibility that should not be ignored in patients with a limited number of functional lymphatic vessels. In addition, further operations remain applicable to other parts of the same lymphatic vessels used for anastomoses if those anastomoses become occluded in the future.

The recent development of the Photo Dynamic Eye near-infrared camera system (Hamamatsu Photonics, Hamamatsu, Japan) has enabled the detection of lymph flow in real-time through the skin as fluorescent lymphangiography using indocyanine green (ICG).^{10,11} The camera activates ICG with emitted light at a wavelength of 760 nm and filters out light with wavelengths below 820 nm. ICG is injected intradermally at the web spaces of the affected limb, and lymph streams and stasis can be observed a few minutes after massage on a monitor applying the camera at 5 to 40 cm from the skin surface.

Our procedures for LVSEA have changed since May 2006, because ICG florescence lymphography and the stent method,¹² by which anastomoses can be performed more precisely, were introduced to our department at that time. The present study assessed midterm postoperative patency in LVSEA using ICG fluorescence lymphography in patients with peripheral lymphedema.

METHODS

Patients. Between May 2006 and August 2010, we performed LVSEA in 114 limbs of 107 patients with peripheral lymphedema. A total of 472 procedures were per-



Fig 1. Operative photographs (*upper row*) and illustrations (*lower row*) show the lymphaticovenous side-to-end anastomosis technique. A, The side wall of the lymphatic vessel (L) is incised with a microknife. V, Subcutaneous vein. B, A nylon suture-stent (*) is inserted into the lumen of the lymphatic vessel and a stitch is inserted at the edge. C, Another nylon suture-stent is inserted and stitches are inserted from edge-to-edge. D, After completion of the anastomosis, stents are removed through the anastomosis.

formed, at a mean \pm standard deviation of 4 ± 1.6 procedures per limb. In 10 of these patients, 13 LVAs were performed in an end-to-end manner because of difficulties applying LVSEA.

Of the 107 patients, 85 had lymphedema of the lower extremity and the remaining 22 had lymphedema of the upper extremity. Among the 85 patients with lymphedema of the lower extremity, 57 (52 women, 5 men), who were a mean age of 55 ± 15 years (range, 13-80 years), consented to postoperative fluorescence lymphography using ICG.

All patients underwent LVSEA. The total number of anastomoses in this series was 223. The 57 patients comprised 51 with secondary lymphedema after treatment for cancer and 16 with primary lymphedema. Clinical stage for the 57 patients, as proposed by the International Society of Lymphology,¹³ was stage I in 2, stage II in 17, late stage II in 29, and stage III in 9.

All patients underwent complex decongestive physiotherapy (CDP) for 3 to 12 months preoperatively, and reduction of the affected limb was obtained in most patients. However, reductions were insufficient in some patients who had undergone CDP at other facilities for a long time. Postoperative CDP with the same contents as preoperative CDP was started 10 to 14 days after surgery and was performed for ≥ 6 months. Postoperative CDP lasted or decreased according to physiologic changes and complaints of the patients thereafter.

Before and at ~ 6 months after surgery, circumferential measurements of the affected limbs were performed at the following sites: 10 cm above the proximal margin of the patella, 10 cm beneath the distal margin of the patella, and

at the level of the lateral and medial malleoli of the ankle. Approximate volumes of the affected limbs were calculated using those measurements. Volume reductions were compared between patients with and without midterm postoperative patency of anastomoses at the foot and around the ankle.

We performed lymphoscintigraphy before surgery to select candidates for LVSEA.14 Patients with obvious obstruction of the lymphatic pathway with no regional lymph nodes or showing stasis of contrast medium with decrease of regional lymph nodes on lymphoscintigraphy were indicated for surgery. The operation was planned after completion of CDP for acute reduction of the affected limbs. At the beginning of surgery, a small amount of ICG ($\sim 0.1 \text{ mL}$ each injection) for fluorescence lymphography was injected at four interdigital spaces in the affected limb and 5% patent blue dye (~ 0.1 mL each injection) was then injected intradermally at the same sites for detection of functional lymphatic vessels. ICG near-infrared fluorescent lymphography was then performed using the Photo Dynamic Eye. At ≥ 6 months after surgery, ICG fluorescence lymphography was repeated in consenting patients to determine patency of the anastomoses.

Operative technique. LVSEA was performed by one of the authors (M.J.) with the patient under general anesthesia because multiple anastomoses were required at a time. After injection of the two contrast agents, sites of anastomosis were determined between the dorsum of the foot to the thigh according to lymph stream or stasis observed by ICG fluorescence lymphography. If several lymphatic vessels were suitable for anastomoses, the one

with the most contrast agent was selected. Even if we could detect lymphatic vessels with no fluorescence and no contrast agent in the lumen, these were not selected for anastomosis because we considered that the vessels would not work well after anastomoses were performed.

Side-to-end anastomosis was performed using a suturestent technique and 11-0 sutures. The sidewall of the lymphatic vessel was incised using a microknife according to the size of the anastomosed vein (Fig 1, A). The incision is one of the most difficult procedures in this technique, because the lumen of the lymphatic vessel can be narrow due to degeneration of the lymphatic wall in some severe cases we have encountered. In addition, care should be taken not to incise too much, otherwise adaptation of both stumps becomes difficult. Exposure of the lumen of the lymphatic vessel led to the extrusion of dyed lymph. Two 6-0 or 7-0 nylon suture stents, 3 mm in length, were inserted, one into the proximal side of the lumen and the other into the distal side (Fig 1, B and C).

If several veins were present in the incision, a vein with an appropriate size for anastomosis was selected. In our experience, a vein with a diameter of 0.5 to 1.0 mm is technically easy for anastomosis. A vein diameter <0.3 mm required insertion of a stent into the vein.

The side-to-end anastomosis began with the first stitch of the distal end of the incision on the lymphatic wall if possible, because the distal side of the lymphatics is expected to contribute a greater volume of lymph flow than the proximal side. The first stitch can be made more precisely than subsequent stitches. Clamps were used for veins with a backflow of blood from the stump, but never for lymph vessels. Side-to-end anastomoses were then completed using 11-0 nylon sutures with a tapered needle (80 μ m in diameter, 4 mm in length), followed by removal of any stents (Fig 1, *D*).

Every anastomosis was performed using the OPMI Pentero operative microscope (Carl Zeiss Meditec AG, Oberkochen, Germany) with magnifications of $\times 10$ to $\times 15$. Patency of anastomoses during or at the end of surgery was always confirmed by Photo Dynamic Eye or by a patency test under microscopy (Fig 2). The number of anastomoses was decided according to the number of functional lymphatic vessels remaining and the operative time allocated for the patient. During and after the operation, no heparin or anticoagulant was used.

Statistical analysis. We calculated postoperative patency rates of LVSEA and analyzed data using the Kaplan-Meier method in the follow-up period. Differences between means of preoperative and postoperative volume were analyzed using the Student *t* test. Values of P < .05were considered statistically significant. StatMate III software (ATMS, Tokyo, Japan) was used for statistical analysis. A Kaplan-Meier survival curve was generated in Graph-Pad Prism 5 software (GraphPad Software, La Jolla, Calif).

RESULTS

We performed 223 anastomoses in the 57 patients. Of these, 79 anastomoses in the ankle and dorsum of the foot

Fig 2. Patency of a lymphaticovenous anastomosis is confirmed through the surgical wound by indocyanine green fluorescence lymphography during surgery. The *star* and *triangle* indicate a cutaneous vein and a lymphatic vessel, respectively.



Fig 3. Kaplan-Meier survival curve is shown for patency of lymphaticovenous side-to-end anastomosis. The *error bars* show the standard error.

could be evaluated. The remaining 144 anastomoses in other areas could not be evaluated because the subcutaneous layer was too thick to allow the detection of lymph vessels by ICG fluorescence lymphography.^{10,11} Outer diameters were within the ranges of 0.2 to 0.6 mm for lymph vessels and 0.2 to 1.2 mm for veins. Mean duration of follow-up after surgery was 14 ± 9 months (range, 6-34 months).

Postoperative patency could be observed in 48 anastomoses in the dorsum of the foot and ankle areas. Of the 57 patients, 34 had at least one patent anastomosis (group A); in the remaining 23 no anastomoses appeared patent (group B). Cumulative patency rates of LVSEAs were \sim 75% ± 7.1% at 12 months and 36% ± 9.4% at 24 months after surgery (Fig 3).





Fig 4. A, A 64-year-old patient with secondary lymphedema of the left lower extremity. The *star* indicates the site of a lymphaticovenous side-to-end anastomosis at the dorsum of the right foot. **B,** Indocyanine green fluorescence lymphographic images at the same site in the same patient (*star*, anastomosis site; *triangles*, lymphatic vessel; and *arrows*, subcutaneous vein). At this time, the image shows a straight pattern. **C** and **D**, When the vein is compressed, indocyanine green flows proximally through its branches, and the image shows a tree pattern.

Several ICG fluorescence lymphography patterns of the anastomosed vein could be observed at the patent anastomosis sites: straight and tree (Fig 4), radial (Fig 5), straight, and L-shaped (Fig 6).

The mean volume reductions in the leg and in the lower extremity on the affected side did not differ significantly between groups A (600 ± 969 mL) and B (420 ± 874 mL) at 14 ± 8.8 months after LVSEAs. No significant differences in volume reduction and number of anastomotic sites were seen between primary and secondary lymphedema.

As postoperative complications, ecchymoses expanding proximally along dermal backflow areas in the affected limb were observed on intraoperative ICG fluorescence lymphography in four patients. In all cases, this finding disappeared ≤ 2 weeks after surgery.

Report of a typical case. A 72-year-old woman who had undergone an extended hysterectomy with regional lymph node dissection because of uterine cancer 15 years previously developed edema of the left leg 10 years postoperatively. The patient consulted our department for surgical treatment of this edema (Fig 7, *A*). Lymphoscintigraphy was performed to assess whether surgery was indicated, resulting in a classification of type 4 lymphedema with a lymphoscintigraphic image of dermal backflow at the lower leg and foot and no regional lymph nodes, according to our previously described system for classifying the severity of lymphedema,¹³ in both the right and left lower extremities. Lymphedema was severe in the left lower extremity (volume, 5413 mL) and mild in the right (volume, 3668 mL).

LVSEA was indicated and performed in the left lower leg because obstruction of the lymphatic pathway in the affected limb was obvious and few lymphatic vessels seemed to be able to be detected from a clinical perspective and this patient desired a reduction in CDP. We performed two LVSEAs in the dorsum of the foot, three in the leg, and one in the thigh (Fig 7, B). At 6 months, ICG fluorescence lymphography showed patency of the LVSEA on the medial side of the dorsum of the foot, whereas a tree pattern (Fig 7, C) and nonpatency were observed for the other LVSEA of the foot. The volume of the left leg was 4326 mL and that of the right was 4328 mL (Fig 7, D). Patency of the LVSEAs in the leg and thigh could not be confirmed by lymphography due to the thickness of the skin and subcutaneous tissue. Preoperative CDP with class III compression stockings was reduced to class I knee-high socks in this patient.

DISCUSSION

An animal experiment demonstrated that the end pressure of lymphatics was higher than the venous pressure.¹⁵ This suggested that LVA might be effective in peripheral lymphedema. However, postoperative patency of LVA has remained unknown in the clinical setting because of the lack of appropriate and reliable methods for postoperative detection of lymph vessels.

Several experiments assessing patency have been performed using animal models of lymphedema. Gloviczki et al¹⁶ reported that four of six anastomoses were patent at 3



Fig 5. A 64-year-old patient with secondary lymphedema of the left lower extremity. **A**, Five lymphaticovenous side-to-end anastomoses were performed from the foot to the thigh on the affected limb. **B**, Enlargement of the anastomosis at the ankle. **C**, A radial pattern is seen in the indocyanine green fluorescence lymphographic imaging. The *star* indicates the site of anastomosis at the ankle, and the *triangles* indicate the lymphatic vessels. **B** and **C**, The *white arrows* indicate subcutaneous veins that resemble a tree with several branches.

months after LVA and that two remained patent at 8 months. In contrast, Puckett et al^{17} reported that all LVAs were occluded ≤ 3 weeks after surgery and confirmed this by re-exposure of the wound. However, al Assal et al^{18} showed long patency of a new technique of microlymphovenous anastomosis in dogs.

In clinical studies, Campisi et al⁸ reported various changes in lymphoscintigraphy images after LVA, providing indirect proof of postoperative patency. In a study of grafting of lymph vessels, Baumeister et al⁹ showed patency using lymphoscintigraphy, but that method differed physiologically from LVA. Anastomoses between lymphatics and veins may become obstructed more often than those between lymphatics.

Until recently, no reliable method has been available to determine the patency of LVAs.⁸ However, ICG fluorescence lymphography evaluated using a Photo Dynamic Eye camera has recently been introduced, and this equipment has been used for detection of lymphatic vessels through the skin.^{10,11}

The present study used ICG fluorescence lymphography to determine the competency of LVSEAs. However, because of optical limitations (the Photo Dynamic Eye camera can detect ICG no deeper than 1 cm below the skin), the areas we could evaluate were confined to the foot, ankle, and lower leg of the affected limb. In addition, the reproducibility of ICG fluorescence lymphography needs to be validated regarding the visualization of lymphatic vessels during surgery and post-operatively. Kinetics of the lymph vessels during surgery appear to differ from those at ≥ 6 months after surgery. In the future, we anticipate improvements in equipment for evaluating dynamic lymph flow.

Despite these limitations, this appears to represent the first clinical report of midterm postoperative patency for LVA in patients with peripheral lymphedema assessed by ICG fluorescence lymphography. Cumulative patency rates of LVSEA were 75% at 12 months and 36% at 24 months after anastomoses, meaning that patients with anastomoses show a possibility of deterioration in lymphedema in the future. Furthermore, periodic examinations may be necessary to clarify whether additional operations are needed for patients who have received a lymphaticovenous shunt.



Fig 6. An L-pattern in a 32-year-old patient with primary lymphedema of the left lower extremity. The *star*, *triangles*, and *arrows* indicate the anastomosis site, lymphatic vessel, and subcutaneous vein, respectively, at the extensor side of the left lower leg.

We found no significant difference in volume change of the affected limb between patients with patent anastomoses and those without obvious evidence of patency. It is possible that the anastomoses could possibly have been patent in the areas where we could not detect by ICG fluorescence lymphography; therefore, we cannot evaluate efficacy of the patency precisely.

ICG fluorescence lymphography revealed several patterns at the patent anastomosis sites, and these patterns seemed to depend on the anastomosed vein. The radial pattern demonstrates the proximal parts of the superficial subcutaneous veins radiating like the spokes of a wheel. In the straight or straight and tree patterns, ICG seems to flow into the vein for some length and may then flow into its branches. If the proximal side of the anastomosed lymph vessel is closed, an S-shaped lymphographic pattern may be obtained. A correlation of these patterns and efficacy in edema reduction is unknown at the moment and a further examination on this issue will be performed.

Regarding the technique of LVA, the end-to-end technique joining the distal stump of the lymph vessel and the proximal stump of the vein is probably the most common worldwide.¹⁻⁴ If end-to-end anastomoses do not work well due to stenosis or obstruction of the anastomotic sites, edema may become worse because most patients with chronic and obstructive lymphedema are likely to have few lymphatic vessels that cannot be expected to compensate for anastomotic failure. Several reports have described good results on physiologic examination in long-term follow-up of conventional LVA, but the patency rate of conventional LVA remains unclear.⁵⁻⁷ Further investigation is thus required to clarify optimal procedures for LVA anastomosis.

One advantage of the side-to-end technique is the potential for preservation of lymph flow if the proximal side of the anastomosis of the lymphatics remains patent. However, incision of the sidewall of the lymphatic vessel is difficult with this technique compared with the endto-end method in some advanced cases where the lumen of the lymphatic vessel is narrow. Selection of lymph vessels is thus required and in such cases, the end-to-end method may be indicated. As a postoperative complication, ecchymosis was observed at areas proximal to the anastomotic sites. The area corresponded to the areas of dermal backflow observed on perioperative ICG fluorescence lymphography. We found no obvious leakage or breakage at the anastomotic sites during surgery; therefore, we believe that blood leaked into the interstitial space through the lymph vessels via the lymph capillary, in a similar manner to dermal backflow.^{19,20} Looking back at the operative video in which we could confirm the vein selected for anastomoses, patency of the anastomotic sites tended to be observed in cases with no or little back flow from the stump of the selected vein.

In the present study, the stent method appeared useful in achieving accurate anastomosis between lymphatic vessels and small veins. Shaper et al⁶ reported that LVAs using Teflon stents were of better quality than conventional sutured LVAs, although all anastomoses were occluded after 4 weeks. To obtain good results in microlymphatic surgery, we consider 100% patency at the time of completing the anastomosis as a requirement; otherwise, postoperative patency of the anastomosis will deteriorate. Several factors may predict postoperative anastomotic failures. One such factor may be high venous pressure due to venous disorders such as valve incompetence. Campisi et al⁸ stressed the importance of treating venous problems before application of LVAs. Another factor may be lymph flow and pressure, because continuous inflow of lymph from the lymphatics into the vein can be expected if lymphatic pressure always overcomes venous pressure. Conversely, lymph flow is decreased in lymph vessels with very thickened walls,²¹ which may result in lower success rates for LVA.

In severe chronic lymphedema, lymphatic vessels lose the ability to automatically contract because of a lack of normal smooth muscle.²¹ Even though LVA is technically successful, lymph drainage from the lymphatics to the vein tends to cease at some point after the operation, when a back flow of blood occurs once the intraluminal pressure of lymph decreases. At rest, the pressure of lymph is lower than that in the vein.⁸ Early manual massage or CDP may thus be helpful to prevent early occlusion by fibrin or clots and to maintain long-term patency.

CONCLUSIONS

We demonstrated midterm postoperative patency of a LVSEA between the lymphatics and subcutaneous veins at 12 months after surgery in >70% of the present patients with peripheral lymphedema. Postoperative volume reduction in patients with anastomotic patency did not differ from that in patients without obvious patency. On the basis of these findings, development of equipment or methods to evaluate lymph flow more precisely and clearly would appear useful.



Fig 7. **A**, A 72-year-old woman presented with lymphedema of the left lower extremity after an extended hysterectomy with regional lymph node dissection performed 15 years previously because of uterine cancer. Severe lymphedema was evident (volume, 5413 mL). **B**, Two lymphaticovenous side-to-end anastomoses (LVSEAs) were performed for the dorsum of the foot, three were performed for the leg, and one for the thigh. **C**, Postoperative indocyanine green fluorescence lymphography shows patency of the LVSEA at the medial side of the dorsum of the foot, where a tree pattern was observed, and nonpatency at the other LVSEA of the foot (*star*, anastomosis site; *triangles*, lymphatic vessel; *arrow*, subcutaneous vein). **D**, At 6 months after LVSEA, lymphedema of the left lower extremity has improved (volume, 4326 mL).

AUTHOR CONTRIBUTIONS

Conception and design: JM Analysis and interpretation: JM Data collection: YY, HT, MH, KY Writing the article: JM Critical revision of the article: JM Final approval of the article: JM Statistical analysis: JM and YY Obtained funding: Not applicable Overall responsibility: JM

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INVITED COMMENTARY

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Chronic lymphedema continues to be an incurable and disabling condition. Microsurgical reconstructions of lymph vessels have been possible because of the pioneer work done by Julius H. Jacobson in the early 1960s; variations of techniques have been used by few microsurgical groups around the world during the past 5 decades with mixed results. Recent progress in imaging of the lymphatic system and in microsurgical techniques sparked renewed interest in microsocic lymphatic reconstructions and the article by Maegawa and colleagues (in this issue) of the *Journal of Vascular Surgery* is an example of what dedicated lymphatic microsurgeons can achieve in this challenging and frequently frustrating field.

One major problem of lymphatic microsurgery has been the proper patient selection for the operation. These authors have used the technique of indocyanine green fluorescence lymphography to identify patent lymph vessels during surgery. The indocyanine green dye was injected subcutaneously in the foot of the patient and the lymphatics were imaged within a few minutes through the skin using a near-infrared camera system. This imaging technique, introduced previously by Ogata et al and by Unno et al (^{10,11} in the article) is a new and useful tool to help during surgery and to document late patency of the anastomoses.

Supermicroscopic surgical techniques have progressed in recent years¹⁻⁵ and better operating microscopes with high-power magnifications (\times 15-20), better instruments and fine (11-0) monofilament sutures with an 80-µm needle have permitted to perform anastomosis with lymph vessels with a diameter of 0.2 to 0.6 mm. Two technical improvements these authors applied deserve to be mentioned. One is the use of 6-0 or 7-0 monofilament sutures to stent the lymph vessel or a small vein for easier and better anastomosis. The other is the side-to-end lymphovenous anastomosis technique that, in theory, may keep the lymph vessel patent even if the vein occludes after surgery. This may avoid progression of the lymphedema as a complication of surgical treatment. Both of these technical improvements were reported previously by Narushima et al.³

One of many critiques of the lymphovenous operations has been the lack of objective documentation of late patency in humans. The main value of this publication, therefore, is the attempt to confirm patency of lymphovenous anastomoses. While patency

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of several of the anastomoses at the level of the ankle or foot beyond 6 months could be documented using indocyanine green lymphoscintigraphy, the cumulative patency rates (75% at 12 months and 36% at 24 months) as reported by the authors, cannot be accepted without major criticism. This study originally included 472 anastomoses in 107 patients. Attempts to assess function at 6 months or later were done in only 57 patients who underwent 223 anastomoses, but only 48 of these were close to the skin and were suitable for lymphoscintigraphic evaluation. Finally, patency rates in this limited group were not reported by the number of anastomoses but by the number of patients with any patent anastomosis.

Shortcomings notwithstanding, this work by Maegawa and colleagues is an important contribution to the literature, with demonstration of exceptional microsurgical technique and a welcome documentation of late patency of lymphovenous anastomoses to improve lymphatic drainage in patients with chronic lymphedema.

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