A Prospective Analysis of 100 Consecutive Lymphovenous Bypass Cases for Treatment of Extremity Lymphedema

David W. Chang, M.D.
Hiroo Suami, M.D., Ph.D.
Roman Skoracki, M.D.

Houston, Texas

Background: The authors prospectively evaluated the efficacy of lymphovenous bypass in patients with lymphedema secondary to cancer treatment.
Methods: The authors prospectively enrolled 100 consecutive patients with extremity lymphedema secondary to cancer treatment. Sixty-five patients underwent lymphovenous bypass with indocyanine green fluorescent lymphangiography. Evaluation included qualitative assessment and quantitative volumetric analysis before and 3, 6, and 12 months after bypass.
Results: Lymphovenous bypass was performed in 89 upper extremities and 11 lower extremities. For upper extremity lymphedemas, the mean preoperative volume differential was 32 percent. Symptom improvement was reported by 96 percent of patients and quantitative improvement was noted by 74 percent. The overall mean volume differential reduction was 33 percent at 3 months, 36 percent at 6 months, and 42 percent at 12 months after surgery. The mean volume differential reductions at 3, 6, and 12 months after lymphovenous bypass in patients with stage 1 or 2 lymphedema (58, 52, and 61 percent, respectively) were significantly larger than those in the patients with stage 3 or 4 lymphedema (12, 16, and 17 percent, respectively). Eleven bypasses were performed in seven patients with lower extremity lymphedema, with a mean preoperative volume differential of 38 percent. Only four (57 percent) of these patients reported symptom improvement; postoperative volume measurements were available for only two of these four.
Conclusions: Lymphovenous bypass can be effective in reducing lymphedema severity, particularly in patients with early-stage upper extremity lymphedema. Indocyanine green lymphangiography accurately identified functional lymphatic vessels and may have a role in objectively assessing lymphedema severity and patient selection. (*Plast. Reconstr. Surg.* 132: 1305, 2013.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, IV.

Lymphedema is a chronic, debilitating condition that causes physical and psychological morbidity, affecting up to 250 million people worldwide. In the United States and other developed countries, cancer and its treatments are the most common causes of lymphedema.[1–28]

Unfortunately, no definitive treatment for lymphedema currently exists. However, microsurgical procedures, such as lymphovenous bypass (also known as lymphaticovenular bypass), has recently gained popularity to help reduce the severity of lymphedema.[29–46] Lymphovenous bypass, in which surgeons use a supermicrosurgical technique to anastomose subdermal lymphatic vessels and adjacent venules less than 0.8 mm in diameter, creates new channels to drain excess fluid trapped in lymphedematous areas into the venous circulation to increase the region's capacity to transport lymph.[29–46]

One recent technological advance in lymphovenous bypass procedures is the use of indocyanine green fluorescence lymphangiography to map lymphatic vessels.[32–36] After indocyanine

From the Department of Plastic Surgery, The University of Texas M. D. Anderson Cancer Center.
Received for publication January 25, 2013; accepted May 21, 2013.
Presented at the 92nd Annual Meeting of the American Association of Plastic Surgeons, in New Orleans, Louisiana, April 20 through 23, 2013.

DOI: 10.1097/PRS.0b013e3182a4d626

Disclosure: *The authors have no financial interest to declare in relation to the content of this article.*

green dye has been absorbed by the lymphatic vessels, fluorescence lymphangiography detects the near-infrared light emitted by indocyanine green dye, thereby demonstrating the path of the lymphatic vessels. Thus, indocyanine green fluorescence lymphangiography enables surgeons to locate and make incisions precisely over functional lymphatic vessels for the lymphovenous bypass, substantially reducing operating time, and may significantly improve the outcomes of lymphovenous bypass operations.

Although the microsurgical approach to lymphedema surgery (e.g., lymphovenous bypass) has gained in popularity, for most, it is still a novel concept and there is much that we do not yet understand. For example, there is no objective and universally supported assessment of the quality or severity of lymphedema that accurately correlates with clinical findings. Another challenge is uncertainty in understanding optimal patient selection for lymphovenous bypass procedures. In the present study, we prospectively evaluated our experience with lymphovenous bypass in 100 consecutive patients with extremity lymphedema secondary to cancer treatment to assess its efficacy and to better understand the lymphedema evaluation process and the optimal patient selection for lymphovenous bypass.

PATIENTS AND METHODS

This prospective study was approved by The University of Texas M. D. Anderson Cancer Center's Institutional Review Board. Between December of 2005 and December of 2012, 100 patients with extremity lymphedema after treatment for cancer were enrolled in the study and underwent lymphovenous bypass at our institution.

A lymphedema therapist performed qualitative assessment and quantitative volumetric analysis before lymphovenous bypass and 3, 6, and 12 months after lymphovenous bypass. Volumetric analyses of patients' lymphedematous and unaffected limbs were performed using an optoelectronic limb volumeter (Perometer model and software; Pero-System, Wuppertal, Germany), which uses infrared light to scan the limb and then performs a circumference measurement every 0.5 cm to calculate the total volume of the limb. Volume measurements were performed three times and were averaged to ensure more consistent analysis.

The volume differential (the excess volume of the lymphedematous limb compared to the unaffected contralateral limb) was defined as follows: (volume of the lymphedematous limb – volume of the unaffected contralateral limb)/volume of the unaffected contralateral limb. The volume differential reduction (the reduction in the excess volume of the limb following the procedure) was defined as follows: (preoperative volume differential – postoperative volume differential)/preoperative volume differential.

The first 35 patients underwent lymphovenous bypass without indocyanine green fluorescent lymphangiography, which was not yet available at our institution. The remaining 65 patients underwent lymphovenous bypass with an indocyanine green fluorescent lymphangiography system (Photodynamic Eye; Hamamatsu Photonics K.K., Hamamatsu, Japan) composed of near-infrared–emitting diodes, a charge-coupled device camera, and a camera controller. The charge-coupled device camera has a fixed focus ranging from 15 to 25 cm, which allows investigation of a 10-cm field with one image.[32] The system can detect anatomical structures by detecting near-infrared radiation in the tissue at a depth up to 12 mm from the surface. The patients' lymphedema severity was classified according to indocyanine green lymphangiographic findings (Fig. 1).

Surgical Approach

All patients were under general anesthesia during the procedures. Indocyanine green lymphangiography was performed by intradermally injecting 0.01 to 0.02 ml of indocyanine green (Akorn, Inc., Lake Forest, Ill.) into each finger/toe web of the lymphedematous limb. Soon after the injections, a Hamamatsu Photodynamic Eye was used to visualize fluorescent images of lymphatic vessels, and fluorescent stains were identified proximal to the injection sites (Fig. 2). Using the images as a guide, we used a pen to mark the visible lymphatic pathways and the sites for incisions for lymphovenous bypasses. The patient's limb was then prepared for surgery.

Before making each incision, we injected local anesthetic with epinephrine at the incision site to achieve optimal hemostasis. To help visually identify lymphatic vessels during the operation, we used a 30-gauge needle to intradermally inject 0.1 to 0.2 ml of isosulfan blue dye (Lymphazurin; United States Surgical Corp., Norwalk, Conn.) into each finger/toe web space and/or 1 to 2 cm distal to each incision.

The entire operation was performed under a surgical microscope. Using the microscope, 2- to 3-cm incisions were made at the predetermined

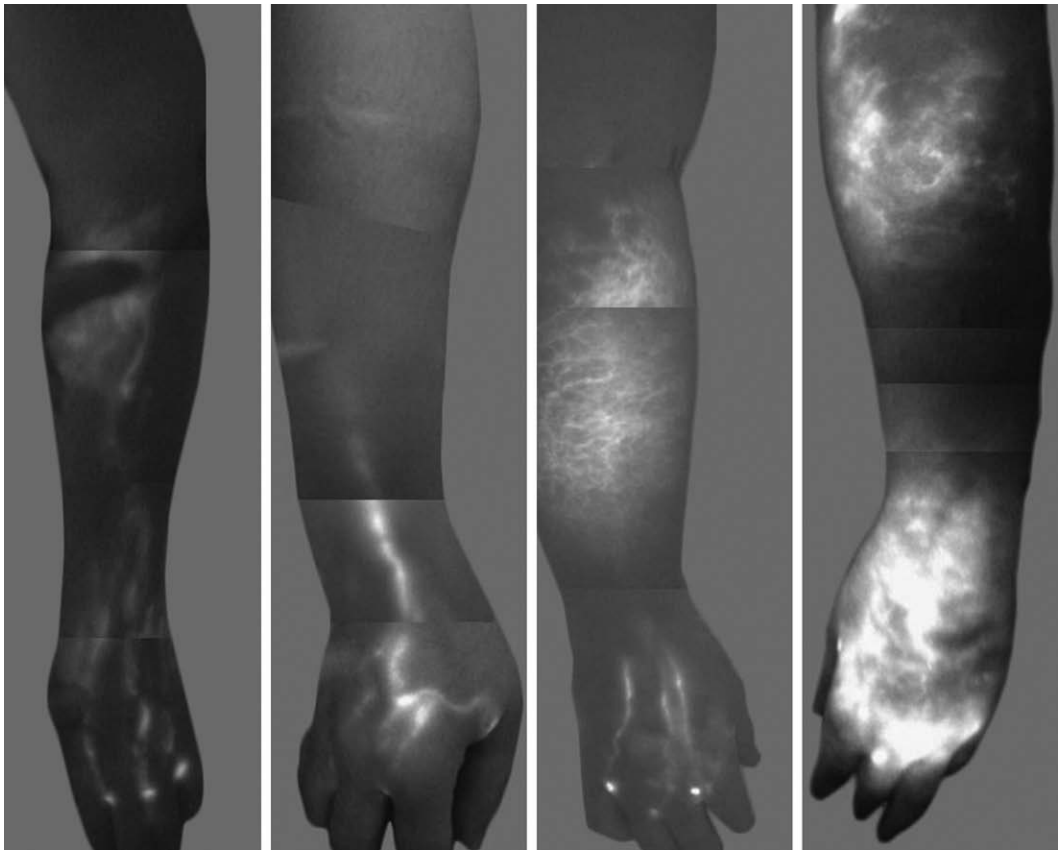

Fig. 1. M. D. Anderson lymphedema classification based on indocyanine green lymphangiographic findings. (*Left*) Stage 1: many patent lymphatic vessels, with minimal, patchy dermal backflow. (*Second from left*) Stage 2: moderate number of patent lymphatic vessels, with segmental dermal backflow. (*Second from right*) Stage 3: few patent lymphatic vessels, with extensive dermal backflow involving the entire arm. (*Right*) Stage 4: no patent lymphatic vessels seen, with severe dermal backflow involving the entire arm and extending to the dorsum of the hand.

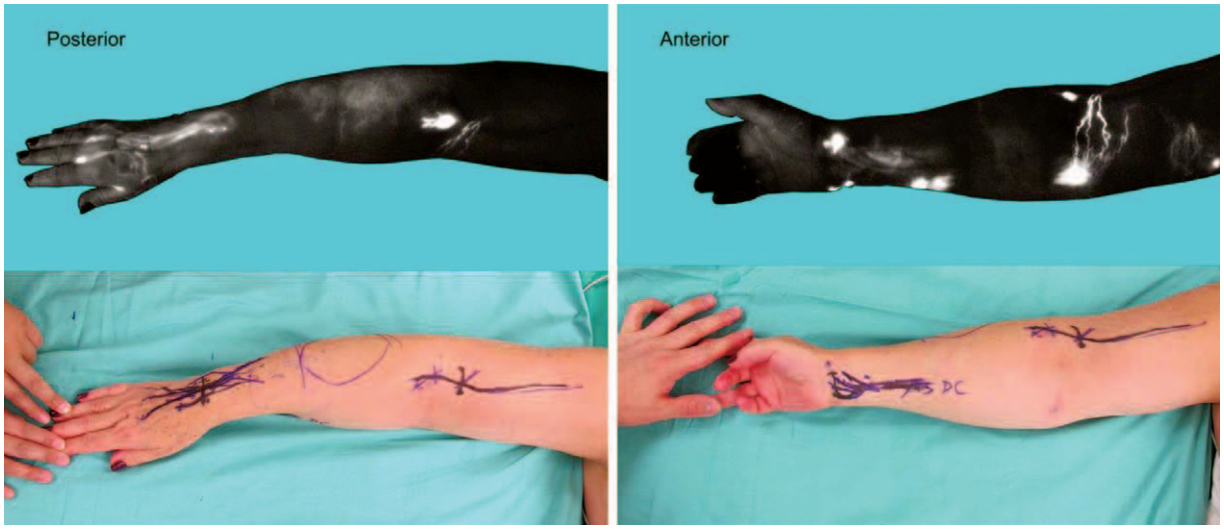

Fig. 2. Indocyanine green lymphangiography is performed by intradermally injecting 0.01 to 0.02 ml of indocyanine green into each finger/toe web of the lymphedematous limb. A Hamamatsu Photodynamic Eye is used to visualize and mark the visible lymphatic pathways.

sites based on the indocyanine green lymphangiographic mapping. The subdermal region was dissected to identify lymphatic vessels. Lymphatic vessels appeared either blue with Lymphazurin dye or clear if no dye was taken up. Once we identified a viable lymphatic vessel, we anastomosed it to a similarly sized adjacent recipient venule to create the bypass. End-to-end anastomoses were performed unless the recipient vein was substantially larger than the lymphatic vessel, in which case end-to-side anastomoses were performed. We used superfine microsurgical instruments (S&T Surgical, Neuhausen, Switzerland) for dissection and for creating end-to-end or end-to-side anastomoses with 11-0 nylon sutures with 50-μm needles. We confirmed the patency of the bypasses by observing the isosulfan blue dye pass from the lymphatic vessel through the anastomosis and into the venule (Fig. 3).

Following surgery, the affected limb was wrapped loosely with compression bandages and elevated on a pillow, and the patient was given prophylactic intravenous antibiotics. All patients were discharged within 24 hours. Patients were encouraged to continue previous compression therapy and wear compression garments beginning 4 weeks after surgery.

Statistical Analysis

Means and standard deviations were used to summarize continuous variables. Frequencies and proportions were used to summarize categorical variables. We used the Pearson chi-square test and Fisher's exact test to compare the percentages of quantitative improvement between different groups of patients. A two-sample t test was used to compare the bypass numbers, lymphedema durations, and volume differential reductions between patients with early- or late-stage lymphedema, and a paired t test was applied to assess the changes of volume over time. All tests were two-sided. Values of $p < 0.05$ were considered significant. The analyses were performed using the SAS 9.2 statistical software program (SAS Institute, Inc., Cary, N.C.).

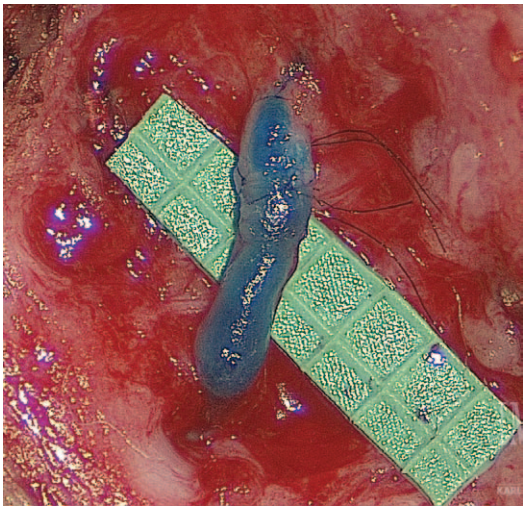

Fig. 3. The patency of the bypasses is confirmed by observing the isosulfan blue dye pass from the lymphatic vessel through the anastomosis and into the venule.

RESULTS

Lymphovenous bypass was performed in 89 upper extremities (46 left and 43 right) and 11 lower extremities (six left and five right). All upper extremity lymphedemas were secondary to breast cancer treatment, and the lower leg extremities were caused by treatment of sarcoma ($n = 3$), melanoma ($n = 2$), or gynecologic cancer ($n = 6$).

Upper Extremity

The mean age of the patients was 54 years. The mean lymphedema duration was 3.5 years (range, 1 to 10 years). The mean body mass index was 30 (range, 20 to 51). The mean preoperative volume differential for patients' lymphedematous arms compared with their unaffected arms was 32 percent (range, 1 to 112 percent). Patients' mean follow-up time was 30.4 months (range, 3 to 84 months). The diameter of the lymphatic vessels used for bypass ranged from 0.2 to 1.0 mm. The mean operative time was 4 hours (range, 3 to 5 hours). The mean preoperative volume differential between the lymphedematous limb and unaffected limb was 32 percent.

Symptom improvement was reported by 96 percent of patients. These patients reported that their lymphedematous arms felt lighter, softer, and less painful than they did before surgery. Not all patients with symptom improvement demonstrated measurable differences in arm volume. Quantitative improvement based on postoperative volume measurements was noted in 74 percent of the patients. The overall mean volume differential reductions of the lymphedematous limbs of the patients who underwent lymphovenous bypass were 33 percent at 3 months, 36 percent at 6 months, and 42 percent at 12 months (Fig. 4).

Patients who underwent lymphovenous bypass with indocyanine green lymphangiography who were followed for at least 1 year were further analyzed based on their indocyanine green lymphangiographic classifications of lymphedema severity.

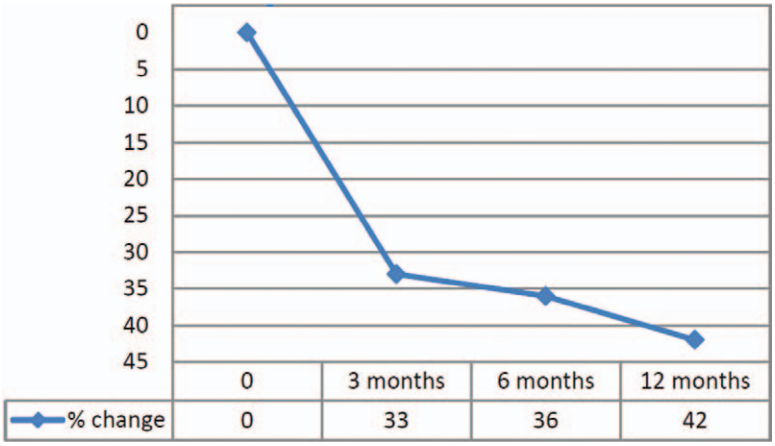

Fig. 4. Quantitative volumetric analysis at 3, 6, and 12 months after bypass.

Compared with preoperative volumes, the volumes were significantly reduced at 3, 6, and 12 months after lymphovenous bypass ($p = 0.001$, $p = 0.017$, and $p = 0.032$, respectively) (Table 1). Patients with stage 1 or 2 lymphedema received a higher mean number of bypasses and had significantly better results than patients with stage 3 lymphedema. The mean volume differential reductions at 3, 6, and 12 months after lymphovenous bypass in the lymphedematous limbs of patients with stage 1 or 2 lymphedema (58, 52, and 61 percent, respectively) were larger than those in the lymphedematous limbs of patients with stage 3 lymphedema (12, 16, and 17 percent, respectively) (Table 2).

In 10 patients who were followed for at least 2 years, the mean volume differential reduction was 35 percent at 2 years and 38 percent at 3 years after lymphovenous bypass. No patients experienced postoperative complications or worsening of lymphedema during the study period.

Lower Extremity

Eleven lower extremity lymphovenous bypasses (six left and five right) were performed in seven patients; two patients underwent lymphovenous bypass in both legs, and one patient underwent lymphovenous bypass twice, the first time without indocyanine green lymphangiography and the second time with indocyanine green lymphangiography. Eight lower extremity lymphovenous bypasses were performed with indocyanine green lymphangiography.

The mean age of the patients was 54 years. The mean lymphedema duration was 6.6 years (range, 1 to 25 years). The mean body mass index was 31 (range, 22 to 42). The mean preoperative volume differential for patients' lymphedematous legs compared with their unaffected legs was 37.6 percent (range, 17 to 85 percent). Patients' mean follow-up time was 18.2 months (range, 1 to 36 months).

Of the seven patients who underwent lower extremity lymphovenous bypass, only four (57 percent) noted symptom improvement. Postoperative volume measurements were available for only two of these four patients, and both of these patients underwent bilateral lymphovenous bypasses. One of these patients had a 42 percent volume reduction at 1 year and a 33 percent reduction at 3 years in her right leg; in her left leg, in which the lymphedema was more severe, a reduction of only 7 percent was noted at 3 years. The second patient noted a significant improvement and stopped wearing her compression garments; however, her volumetric measurements did not demonstrate significant improvement. Of the three patients who did not notice any significant symptom improvement after lymphovenous bypass, one ultimately underwent vascularized lymph node transfer, which did result in a significant improvement in symptoms.

Table 1. Results of Paired *t* Test Applied to Assess the Changes of Volume over Time

Changes in Volumes	Difference (%)	SD (%)	*p*
Preoperatively to 3 mo postoperatively	−9.6	9.1	0.001
Preoperatively to 6 mo postoperatively	−8.5	11.2	0.017
Preoperatively to 12 mo postoperatively	−7.7	8.2	0.032

Table 2. Results Based on Indocyanine Green Lymphangiographic Classification

Characteristic	Patients with Stage 1 or 2 Lymphedema ($n = 16$)	Patients with Stage 3 or 4 Lymphedema ($n = 14$)	p
Mean lymphedema duration, yr	3.3	3.7	0.684
Mean BMI	28	32	0.399
Mean preoperative volume excess, %	31	34.9	0.689
No. of bypasses			
Mean	6.5	4.8	
Range	4–12	2–7	0.044
Symptom improvement, no. of patients (%)	16 (100)	12 (86)	0.480
Mean reduction in volume differential, %			
At 3 mo	58	12	0.033
At 6 mo	52	16	0.006
At 12 mo	61	17	0.008

BMI, body mass index.

DISCUSSION

In this study, we prospectively evaluated our experience with lymphovenous bypass in 100 consecutive patients with extremity lymphedema secondary to cancer treatment to better understand its efficacy, and to assess and share what we have learned as the procedure continues to evolve with introduction of better technology and increase in our experience. We found that lymphovenous bypass can be effective in reducing severity of lymphedema, particularly in patients with early-stage lymphedema involving the upper extremity. For lower extremity lymphedema, although our experience is still limited, we did not find that lymphovenous bypass was as effective compared with the upper extremity. We also found that indocyanine green lymphangiography, which facilitates lymphovenous bypass by accurately identifying functional lymphatic vessels, may also be useful in objectively assessing lymphedema severity and in selecting patients for lymphovenous bypass.

One recent technological advance in lymphovenous bypass is the use of indocyanine green fluorescence lymphangiography to map lymphatic vessels intraoperatively.[32–36] Indocyanine green is a water-soluble compound that has been widely used to assess cardiac output, hepatic function, and ophthalmic angiography. When it binds to protein in the tissue, indocyanine green emits energy in the near-infrared region between 750 and 810 nm. After indocyanine green dye has been absorbed by the lymphatic vessels, fluorescence lymphangiography detects the near-infrared light emitted by indocyanine green dye, thereby demonstrating the path of the lymphatic vessels. Using this technique, we were able to rapidly and objectively evaluate lymphedema severity and identify functional lymphatic vessels and optimal anatomical locations for lymphaticovenular shunts before making incisions.

One of the main challenges of performing lymphovenous bypass in patients before indocyanine green fluorescence lymphangiography was available was accurately identifying functioning lymphatic vessels for bypasses. In these patients, we made incisions arbitrarily and conducted random exploration under the microscope to identify the vessels. The benefit of indocyanine green fluorescence lymphangiography was evident: in a previous study, the mean number of bypasses performed in patients who underwent lymphovenous bypass without indocyanine green fluorescence lymphangiography was 3.5; in contrast, the mean number of bypasses performed in patients who underwent lymphovenous bypass with indocyanine green lymphangiography in the present study was 5.6.[31]

Although we observed subjectively that the patients who underwent lymphovenous bypass with indocyanine green lymphangiography had better outcomes than patients who underwent lymphovenous bypass alone, volumetric analysis did not reveal that this difference was significant, as we had expected. There are several possible explanations for this discrepancy. First, the two groups of patients may have had different characteristics that influenced the outcomes of lymphovenous bypass regardless of whether indocyanine green lymphangiography was used. For our earlier study, patient selection may have been more stringent and the patients who appeared to have severe lymphedema based on clinical findings may not have been offered the procedure because of a concern that viable lymphatic vessels for bypasses would be difficult to identify. However, after the introduction of indocyanine green lymphangiography, which enabled us to more easily identify lymphatic vessels, we may have become less restrictive in selecting patients for the procedure and offered lymphovenous bypass to patients who would not have been offered lymphovenous bypass before indocyanine green lymphangiography was available.

We also found that patients with stage 1 or 2 lymphedema identified with indocyanine green fluorescence lymphangiography had significantly better results than patients with stage 3 or 4 lymphedema (Figs. 5 through 8). The mean volume differential reductions in the lymphedematous limbs of patients with stage 1 or 2 lymphedema at 3, 6, and 12 months after surgery (58, 52, and 61 percent, respectively) were significantly greater than those of patients with stage 3 or 4 lymphedema (12, 16, and 17 percent, respectively). These findings suggest that lymphovenous bypass is more effective in reducing the severity of early-stage lymphedema than that of late-stage lymphedema. The amount of quantitative improvement or the changes that can be achieved in lymphedematous tissues with chronic irreversible fibrosis and lymphatic vessels that have smooth muscle dysfunction or are occluded may be limited. Furthermore, the mean volume differential reductions in the lymphedematous limbs of 10 patients for whom more than 2 years of follow-up volumetric measurements were available were 35 percent at 2 years and 38 percent at 3 years after lymphovenous bypass, indicating that quantitative improvement eventually seems to plateau after 1 year. This finding suggests that lymphovenous bypass is best indicated for patients with intact functional lymphatic vessels and minimal irreversible tissue fibrosis. In patients with stage 3 or 4 lymphedema, few functioning lymphatic vessels are available for lymphovenous bypass and they already have significant irreversible tissue fibrosis, and expected outcomes are poor; in these patients, vascularized lymph node transfer might be considered instead. Thus, based on our findings, we feel that the best indication for lymphovenous bypass to treat lymphedema is for early and mild lymphedema, thus preventing progression of lymphedema to severe lymphedema, which becomes very difficult to treat.

The outcomes achieved in patients who underwent lymphovenous bypass for lower extremity lymphedema were not as impressive as those in patients who underwent lymphovenous bypass for upper extremity lymphedema. Of the seven patients who underwent lower extremity lymphovenous bypass, only four noted symptom improvement, and postoperative volume measurements were available for only two of these patients, making it difficult to accurately assess symptom improvement in this group. The fact that the lower extremities are much larger than the upper extremities and are almost always dependent, with higher venous pressure, may partially explain why the results of the lower extremity lymphovenous bypass group were worse than those of the upper extremity lymphovenous bypass group. Of the

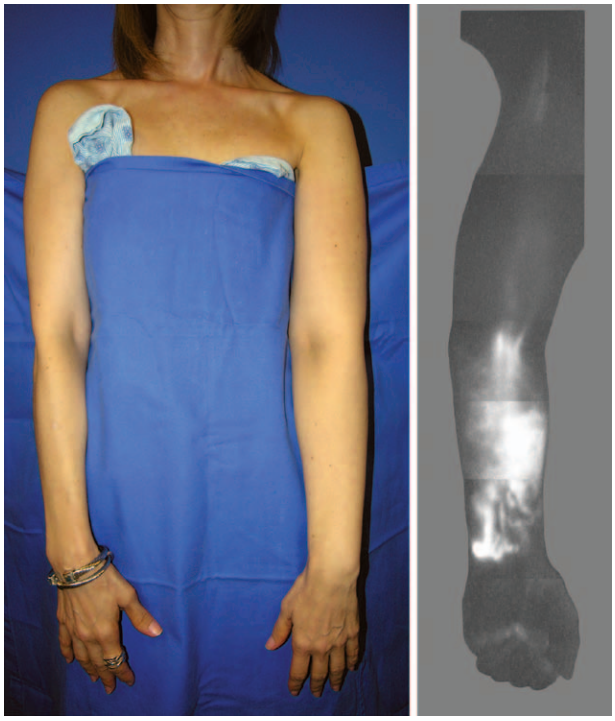

Fig. 5. (*Left*) A 54-year-old woman with a 5-year duration of lymphedema in her left arm following left mastectomy and radiotherapy. Her left arm is 32 percent larger than her right arm. (*Right*) Preoperative indocyanine green lymphangiography (stage 2).

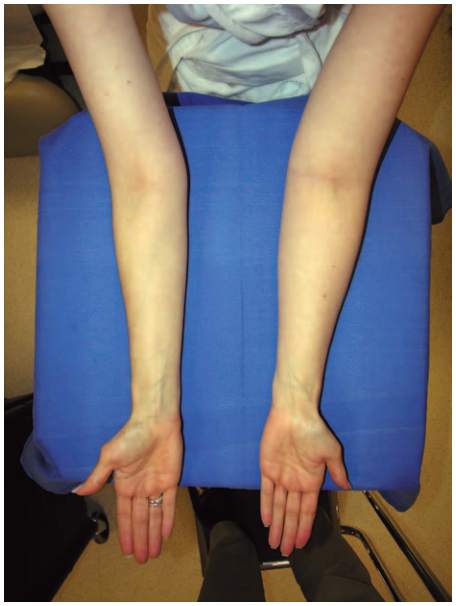

Fig. 6. Five bypasses (anastomosis range, 0.2–1.0 mm) were performed in this patient. At 15 months, the patient's left arm is 12.6 percent larger than her right arm (a 61 percent reduction in volume differential).

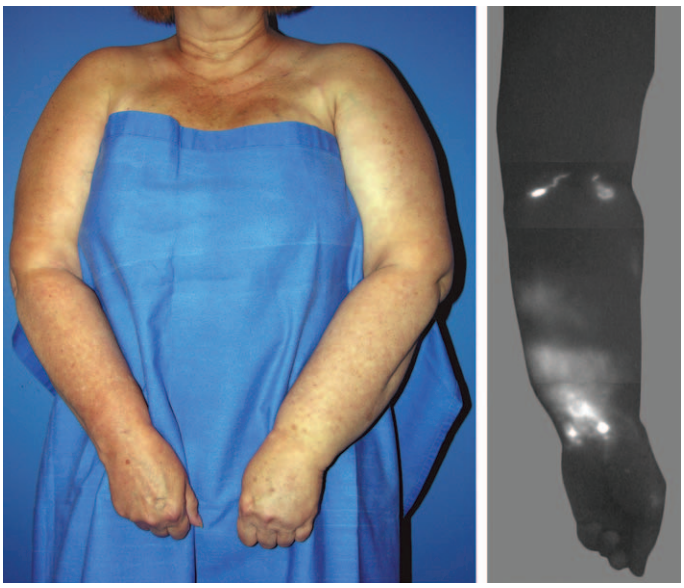

Fig. 7. (*Left*) A 58-year-old woman with lymphedema in her left arm for 1.5 years. Her left arm is 18 percent larger than her right arm. (*Right*) Preoperative indocyanine green lymphangiography (stage 3).

three patients who did not notice any significant symptom improvement, one ultimately underwent vascularized lymph node transfer that significantly improved the patient's lymphedematous leg. However, our experience with lower extremity lymphovenous bypass is limited; thus, drawing any definite conclusions is difficult.

Another observation in our experience, as mentioned in our previous article, is that the duration of the lymphedema does not necessarily correlate with the severity of the lymphedema or the outcome following surgery.[15] There are patients who have had lymphedema for many years but, because their lymphatic obstruction is minimal and because of their diligence in taking care of the limb, the lymphedema is not severe. In contrast, there are patients who have had lymphedema for only few months but, because their lymphatic damage is extensive, present with severe lymphedema and do not respond well to the lymphovenous bypass. This observation supports the belief that the severity of lymphedema depends mostly on the extent of the damage to the lymphatic system.

A major challenge of lymphatic surgery is that there is no accurate and universally supported assessment of the quality or severity of lymphedema that correlates with clinical findings. Currently, there is no validated lymphedema instrument available specifically for evaluation of outcomes following surgery for treatment of lymphedema. Even for this study, our subjective evaluation was simply based on the patient's responses to our verbal questions. Most lymphedema staging systems are based on clinical findings; other evaluations, including circumferential measurements, water displacement volume measurements, volumetric analysis using computerized perometry, and bioimpedance, have limitations and do not always correlate with clinical findings. The findings of the present study suggest

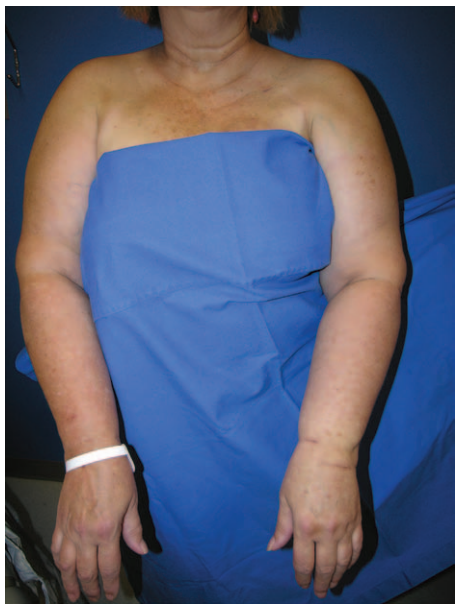

Fig. 8. Seven bypasses (anastomosis range, 0.3 to 0.8 mm) were performed in this patient. At 3 months, the patient said the arm was softer and lighter than it was before lymphovenous bypass, but there has been no measurable reduction in volume.

that indocyanine green fluorescence lymphangiography is useful for accurately assessing lymphedema severity and predicting lymphovenous bypass surgery outcomes. Indeed, Yamamoto et al. recently reported using an indocyanine green lymphangiography–based system to stage lymphedema.[36] Although that system is useful, we found it to be complicated and not user-friendly. On the basis of our own experience, we developed a simple, user-friendly, clinically relevant staging system of lymphedema using indocyanine green fluorescence lymphangiography (M. D. Anderson classification). Based on this staging system, we were able to see the significant difference in the outcomes following lymphovenous bypass for patients in different stages of lymphedema as already discussed above. This staging system could be useful in helping us to develop a better patient selection process for lymphovenous bypass.

In summary, based on our experience, we have learned the following:

- Lymphovenous bypass can be effective in reducing the severity of lymphedema.
- Lymphovenous bypass appears to be more effective in patients with early-stage lymphedema with intact functioning lymphatic vessels and minimal tissue fibrosis.
- Lymphovenous bypass may be more effective for managing upper extremity lymphedema than for managing lower extremity lymphedema.
- Indocyanine green fluorescence lymphangiography can be useful in identifying functioning lymphatic vessels and optimal anatomical locations to perform lymphovenous bypass.
- Indocyanine green fluorescence lymphangiography can be used to assess the functional severity of lymphedema and can enable surgeons to preoperatively stage and select patients who are best suited for lymphovenous bypass.
- Indocyanine green fluorescence lymphangiography may be a tool with which to objectively assess the change in the lymphedema status of patients following lymphedema surgery.

CONCLUSIONS

Lymphovenous bypass can effectively reduce the severity of lymphedema, particularly in patients with early-stage lymphedema affecting the upper extremities. Indocyanine green lymphangiography, which we found facilitates lymphovenous bypass by accurately identifying functional lymphatic vessels, may also be useful in objectively assessing lymphedema severity and selecting patients for lymphovenous bypass.

David W. Chang, M.D.
Department of Plastic Surgery
The University of Texas M. D. Anderson Cancer Center
1515 Holcombe Boulevard
Houston, Texas 77030-4009
dchang@mdanderson.org

ACKNOWLEDGMENTS

This study was supported in part by the Kyte Research and Education Fund and by the National Institutes of Health through M. D. Anderson's Cancer Center Support Grant CA016672. The authors thank Hamamatsu Photonics, Japan, for allowing them to use the Photodynamic Eye, and Jun Liu, M.D., M.S., for assisting with statistical analysis.

REFERENCES

1. Kissin MW, Querci della Rovere G, Easton D, Westbury G. Risk of lymphoedema following the treatment of breast cancer. *Br J Surg.* 1986;73:580–584.
2. Mazeron JJ, Otmezguine Y, Huart J, Pierquin B. Conservative treatment of breast cancer: Results of management of axillary lymph node area in 3353 patients. *Lancet* 1985;1:1387.
3. Erickson VS, Pearson ML, Ganz PA, Adams J, Kahn KL. Arm edema in breast cancer patients. *J Natl Cancer Inst.* 2001;93:96–111.
4. Fleissig A, Fallowfield LJ, Langridge CI, et al. Post-operative arm morbidity and quality of life: Results of the ALMANAC randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. *Breast Cancer Res Treat.* 2006;95:279–293.
5. 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.
6. Lucci A, McCall LM, Beitsch PD, et al.; American College of Surgeons Oncology Group. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. *J Clin Oncol.* 2007;25:3657–3663.
7. Fisher B, Redmond C, Fisher ER, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. *N Engl J Med.* 1985;312:674–681.
8. Krag DN, Weaver DL, Alex JC, Fairbank JT. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. *Surg Oncol.* 1993;2:335–339; discussion 340.
9. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg.* 1994;220:391–398; discussion 398.
10. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med.* 2003;349:546–553.

11. Wilke LG, McCall LM, Posther KE, et al. Surgical complications associated with sentinel lymph node biopsy: Results from a prospective international cooperative group trial. *Ann Surg Oncol.* 2006;13:491–500.
12. Sakorafas GH, Peros G, Cataliotti L, Vlastos G. Lymphedema following axillary lymph node dissection for breast cancer. *Surg Oncol.* 2006;15:153–165.
13. Ahmed RL, Prizment A, Lazovich D, Schmitz KH, Folsom AR. Lymphedema and quality of life in breast cancer survivors: The Iowa Women's Health Study. *J Clin Oncol.* 2008;26:5689–5696.
14. Pyszel A, Malyszczak K, Pyszel K, Andrzejak R, Szuba A. Disability, psychological distress and quality of life in breast cancer survivors with arm lymphedema. *Lymphology* 2006;39:185–192.
15. Franks PJ, Moffatt CJ, Doherty DC, Williams AF, Jeffs E, Mortimer PS. Assessment of health-related quality of life in patients with lymphedema of the lower limb. *Wound Repair Regen.* 2006;14:110–118.
16. Beaulac SM, McNair LA, Scott TE, LaMorte WW, Kavanah MT. Lymphedema and quality of life in survivors of early-stage breast cancer. *Arch Surg.* 2002;137:1253–1257.
17. Pereira de Godoy JM, Braile DM, de Fatima Godoy M, Longo O Jr. Quality of life and peripheral lymphedema. *Lymphology* 2002;35:72–75.
18. Ganz PA. The quality of life after breast cancer–solving the problem of lymphedema. *N Engl J Med.* 1999;340:383–385.
19. Brady MS, Garfein CF, Petrek JA, Brennan MF. Post-treatment sarcoma in breast cancer patients. *Ann Surg Oncol.* 1994;1:66–72.
20. Shih YC, Xu Y, Cormier JN, et al. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: A 2-year follow-up study. *J Clin Oncol.* 2009;27:2007–2014.
21. O'Brien BM, Chait LA, Hurwitz PJ. Microlymphatic surgery. *Orthop Clin North Am.* 1977;8:405–424.
22. O'Brien BM, Mellow CG, Khazanchi RK, Dvir E, Kumar V, Pederson WC. Long-term results after microlymphaticovenous anastomoses for the treatment of obstructive lymphedema. *Plast Reconstr Surg.* 1990;85:562–572.
23. Campisi C, Davini D, Bellini C, et al. Lymphatic microsurgery for the treatment of lymphedema. *Microsurgery* 2006;26:65–69.
24. Huang GK, Hu RQ, Liu ZZ, Shen YL, Lan TD, Pan GP. Microlymphaticovenous anastomosis in the treatment of lower limb obstructive lymphedema: Analysis of 91 cases. *Plast Reconstr Surg.* 1985;76:671–685.
25. Campisi C, Bellini C, Campisi C, Accogli S, Bonioli E, Boccardo F. Microsurgery for lymphedema: Clinical research and long-term results. *Microsurgery* 2010;30:256–260.
26. Mehrara BJ, Zampell JC, Suami H, Chang DW. Surgical management of lymphedema: Past, present, and future. *Lymphat Res Biol.* 2011;9:159–167.
27. Suami H, Chang DW. Overview of surgical treatments for breast cancer-related lymphedema. *Plast Reconstr Surg.* 2010;126:1853–1863.
28. Cormier JN, Rourke L, Crosby M, Chang D. The surgical treatment of lymphedema: A systematic review of the contemporary literature (2004–2010). *Ann Surg Oncol.* 2012;19:642–651.
29. Koshima I, Kawada S, Moriguchi T, Kajiwara Y. Ultrastructural observations of lymphatic vessels in lymphedema in human extremities. *Plast Reconstr Surg.* 1996;97:397–405; discussion 406.
30. Koshima I, Inagawa K, Urushibara K, Moriguchi T. Supermicrosurgical lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. *J Reconstr Microsurg.* 2000;16:437–442.
31. Chang DW. Lymphaticovenular bypass for lymphedema management in breast cancer patients: A prospective study. *Plast Reconstr Surg.* 2010;126:752–758.
32. Suami H, Chang DW, Yamada K, Kimata Y. Use of indocyanine green fluorescent lymphography for evaluating dynamic lymphatic status. *Plast Reconstr Surg.* 2011;127:74e–76e.
33. Kitai T, Inomoto T, Miwa M, Shikayama T. Fluorescence navigation with indocyanine green for detecting sentinel lymph nodes in breast cancer. *Breast Cancer* 2005;12:211–215.
34. Unno N, Inuzuka K, Suzuki M, et al. Preliminary experience with a novel fluorescence lymphography using indocyanine green in patients with secondary lymphedema. *J Vasc Surg.* 2007;45:1016–1021.
35. Ogata F, Narushima M, Mihara M, Azuma R, Morimoto Y, Koshima I. Intraoperative lymphography using indocyanine green dye for near-infrared fluorescence labeling in lymphedema. *Ann Plast Surg.* 2007;59:180–184.
36. 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;128:314e–321e.
37. Yamamoto Y, Horiuchi K, Sasaki S, et al. Follow-up study of upper limb lymphedema patients treated by microsurgical lymphaticovenous implantation (MLVI) combined with compression therapy. *Microsurgery* 2003;23:21–26.
38. Yamamoto T, Koshima I, Yoshimatsu H, Narushima M, Miahara M, Iida T. Simultaneous multi-site lymphaticovenular anastomoses for primary lower extremity and genital lymphoedema complicated with severe lymphorrhea. *J Plast Reconstr Aesthet Surg.* 2011;64:812–815.
39. Damstra RJ, Voesten HG, van Schelven WD, van der Lei B. Lymphatic venous anastomosis (LVA) for treatment of secondary arm lymphedema: A prospective study of 11 LVA procedures in 10 patients with breast cancer related lymphedema and a critical review of the literature. *Breast Cancer Res Treat.* 2009;113:199–206.
40. Demirtas Y, Ozturk N, Yapici O, Topalan M. Supermicrosurgical lymphaticovenular anastomosis and lymphaticovenous implantation for treatment of unilateral lower extremity lymphedema. *Microsurgery* 2009;29:609–618.
41. Campisi C, Boccardo F. Lymphedema and microsurgery. *Microsurgery* 2002;22:74–80.
42. Demirtas Y, Ozturk N, Yapici O, Topalan M. Comparison of primary and secondary lower-extremity lymphedema treated with supermicrosurgical lymphaticovenous anastomosis and lymphaticovenous implantation. *J Reconstr Microsurg.* 2010;26:137–143.
43. Gloviczki P, Fisher J, Hollier LH, Pairolero PC, Schirger A, Wahner HW. Microsurgical lymphovenous anastomosis for treatment of lymphedema: A critical review. *J Vasc Surg.* 1988;7:647–652.
44. Maegawa J, Mikami T, Yamamoto Y, Satake T, Kobayashi S. Types of lymphoscintigraphy and indications for lymphaticovenous anastomosis. *Microsurgery* 2010;30:437–442.
45. Mukenge SM, Catena M, Negrini D, et al. Assessment and follow-up of patency after lymphovenous microsurgery for treatment of secondary lymphedema in external male genital organs. *Eur Urol.* 2011;60:1114–1119.
46. Nagase T, Gonda K, Inoue K, et al. Treatment of lymphedema with lymphaticovenular anastomoses. *Int J Clin Oncol.* 2005;10:304–310.