REVIEW ARTICLE

Current Status of Lymphatic Reconstructive Surgery for Chronic Lymphedema: It Is Still an Uphill Battle!

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ABSTRACT

The goal of reconstructive lymphatic surgery is to restore normal lymphatic function to "cure" permanently the lymphedematous limb in patients with lymphedema. In reality, reconstructive surgery remains an adjunctive treatment at best, with its current indication being refractory lymphedema in patients treated with complex decongestive therapy (CDT) alone. The role of reconstructive lymphatic surgery remains controversial and is far from being accepted as standard independent therapy because of multiple reasons. However, reconstructive surgery appears to be most effective in controlling the progression of lymphedema during the early stages when the paralyzed lymph vessels are still able to function and recover. Our experience in reconstructive surgery has shown that improved long-term results are dependent on prolonged patient compliance with maintenance CDT and the prevention and treatment of infection. To better understand the role of reconstructive surgery in the management of chronic lymphedema, well-constructed clinical trials based on well-organized multicenter studies with similar protocols are mandated. For the future, it remains the only possible treatment method capable of providing a cure.

KEYWORDS: Chronic lymphedema, reconstructive lymphatic surgery, compliance, maintenance CDT

Chronic lymphedema is a clinical manifestation of disrupted lymph transport.[1–4] The majority of patients are managed satisfactorily with manual lymphatic drainage (MLD)-based complex decongestive therapy (CDT).[5–8] However, CDT is effective in controlling the edema only during the treatment program period, and its long-term control requires lifelong commitment.[9,10]

Therefore, a new approach to restore normal lymphatic flow with direct surgical correction of disabled lymph transport has been a dream among lymphatic/vascular surgeons since Olszewski et al made a landmark report on direct anastomosis between lymphatic and venous system using microscopic surgical technique a half century ago. This breakthrough gave new hope to the management of chronic lymphedema.[11–14]

This new approach became popular throughout the past century because of its potential to restore normal lymphatic flow when performed properly, providing a

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chance of a "cure" in theory. However, over the past several decades, an often cavalier approach with limited knowledge of lymphatic anatomy and physiology, adopted by many surgeons, resulted in disastrous outcomes and added more confusion with erroneous prejudice. Many surgeons condemned the procedure due to the poor outcomes, which were believed to be a result of the surgery itself rather than an ill-planned treatment strategy and lack of proper knowledge regarding lymphatic anatomy and physiology.

I (B.B.L.) was no exception, being among the first group of surgeons who began performing lymphovenous anastomosis ($n = 15$, patients operated) in early 1980s. Interim follow-up results were embarrassingly poor despite technical success in performing flawless surgery without a clear explanation. It took almost a decade to figure out why and what went wrong to make ourselves better prepared before resuming lymphatic reconstructive surgery.

In our second group of patients treated with lymphatic reconstructive surgery, we learned another lesson as to why this second group ($n = 32$) of patients also had poor results and failed to meet our expectations.[15,16]

Based on our limited experience over three decades, we attempted to answer several key questions related to this delicate surgery together with an appropriate review of the current medical literature.

GENERAL OVERVIEW

Reconstructive surgery[17–26] is one of two surgical treatments available to lymphedema patients, the other being ablative, excisional surgery.[27–36] Unlike ablative surgery, reconstructive surgery is the only approach aimed at relieving lymphatic hypertension with the possibility of a "cure" when performed under ideal conditions. In reality, however, it barely met its minimum goal to "improve" the condition, especially as an independent treatment with variable and often disappointing long-term results. Reconstructive lymphatic surgery was further recognized for its dependency on postoperative maintenance MLD-based CDT.

After careful review of data accumulated over several decades, the observed poor outcomes turned out to be directly linked to the "timing" of the surgical intervention.[15,16]

Reconstructive surgery has been known to be best performed during the "early" clinical stage, where the residual lymph transporting system remains in salvageable condition and surgical restoration and relief of lymphatic obstruction and stasis can result in revitalization of transiently paralyzed lymphatic vessels to resume normal function.[37–39]

Long-term results of reconstructive lymphatic surgery are dependent on timing of the surgical procedure.[40,41] In addition to surgical timing, proper selection of best-suited surgical technique among many different modalities is also very important. An exhaustive investigation to define precisely the status of lymphedema, including its clinical as well as laboratory stage, also provides critical information.

There are two different reconstructive surgical approaches available with different indications: Direct reconstruction to restore the lymphatic flow by various anastomotic surgery, and indirect reconstruction to restore the lymphatic flow.[13,14]

We selected lymphatic-venous anastomotic surgery (LVAS)[42,43] as a direct method and free lymph-node transplant surgery (FLTS)[26,44–46] as an indirect method.

There are several direct methods to restore lymphatic function using microsurgical technique: direct lymphatic-venous anastomosis, lymphatic-lymphatic bypass, lymphatic-venous-lymphatic bypass, and lympho-lymphatic segmental reconstruction.[17–26,40–43] Interposition of an autologous vein graft (lymphatic-venous-lymphatic anastomosis) is one way to treat a lymphatic obstruction in situations where the more common lymphatic-venous anastomosis is not possible.[47,48]

These lymphatic bypasses eliminate occluded lymph-collecting vessels by connecting normal distal lymph vessels to proximal lymph vessels (lymphatic-lymphatic anastomoses) or to a defunctionalized adjacent vein segment with normal valvular function to prevent lymphatic reflux (lymphatic-venous anastomoses).

LVAS is one of the most popular methods of relieving lymphatic obstruction and restoring normal lymphatic function. It is now fully accepted and has been established as one of the leading direct lymphatic reconstructive methods.

Regardless of the type of reconstructive surgery, it is ideal to intervene at an earlier stage of lymphedema, at a time before lymph-collecting vessels are permanently damaged by lymphatic stasis. Normal lymphatic vessels with normal peristaltic function are required for successful surgical intervention.[38,39]

FLTS reconstruction of a damaged lymph-transport system after radical mastectomy with axillary lymph node dissection has been reported with excellent results.[26,44–46] However, compared with LVAS, FLTS lacks sufficient clinical data regarding efficacy.

FLTS reports by other groups, including our own experience, failed to reproduce similar results. Additional studies are required to obtain conclusive efficacy data before it is fully accepted as an indirect reconstructive surgical procedure.[15,16]

Ideal candidates for lymphatic reconstruction, either LVAS or FLTS, are less frequently found among patients with primary lymphedema due to variations in

lymphatics and lymph nodes. This is because the majority of patients with primary lymphedema often present with the clinical manifestation of a developmental defect along the lymphatic trunk formation period (the truncular stage of lymphangiogenesis) as a lymphatic malformation.[15,16]

These truncular, lymphatic malformations often present with various anatomical deformities with varying degrees: aplasia, hypoplasia, and hyperplasia.[49–53]

Surgery outcomes are also variable among patients with primary lymphedema due to the underlying cause where the procedures are generally not as effective as is seen in patients with secondary lymphedema.[54,55]

In contrast, patients with secondary lymphedema often have a surgically correctable lesion along the major lymphatics so that the immediate as well as long-term results are often better than those seen in patients with primary lymphedema. Our data support this contention.[15,16] However, some centers claim similar results in both primary and secondary lymphedema patients.[41–43]

There are several reasons why reconstructive lymphatic surgery has failed to gain popularity. It is technically demanding, time consuming, and requires a dedicated team with experience in microsurgical techniques. Limited surgical expertise has prevented widespread adoption of lymphatic reconstruction. Furthermore, indiscriminate use of this delicate and time-consuming procedure has likely resulted in variable results among different institutions.

Because of the complexity of reconstructive lymphatic surgery, it has never been fully understood by most surgeons. These procedures subsequently gained a bad reputation with poorly reproducible outcomes in the majority of cases.

Reconstructive lymphatic surgery, therefore, failed to be recognized as the sole, primary treatment of lymphedema. In the majority of cases, it is only considered when CDT-based therapy[56–58] has failed to control the progression of lymphedema.[9,10] Currently, these procedures are routinely performed as an independent therapy in only a few centers worldwide and remain controversial.

EVALUATION OF SURGICAL CANDIDATES

Candidates for reconstructive lymphatic surgery require a detailed history and complete physical examination, which is most important for accurate clinical staging. Based on the clinical assessment findings, appropriate combinations of various noninvasive imaging and physiologic studies[59–68] will be able to confirm the diagnosis and allow precise lymphedema staging.

In general, infrared optometric volumetry for measurement of limb volume and radionuclide lymphoscintigraphy (LSG) have become the standard baseline studies to determine lymphatic function, and duplex ultrasonography and air-plethysmography remain the standard baseline studies for venous disease assessment. Occasionally, computed tomography or standard magnetic resonance imaging is required to assess patients with primary lymphedema due to truncular lymphatic malformation.[49–52]

However, LSG remains the gold standard among the various laboratory studies aimed at lymphatic function assessment and will remain the most important laboratory test to assist with clinical staging.

For clinical staging, we prefer to use the modified clinical staging system[69,70] rather than the International Society of Lymphology (ISL) staging system.[71,72]

The ISL staging system is a three-stage system that is too simple/too crude for evaluation of lymphedema patients to determine suitability for surgical reconstruction. The newer four-stage system we proposed[69,70] better delineates the level of lymphatic involvement and therefore improves selection of the appropriate surgical procedure.[9,10]

We learned the first lesson of the critical role of staging for the selection of surgical candidates through the first group of 15 patients who underwent reconstructive surgery during a 5-year period (1980–1985). Among $n = 15$ (primary = 6, secondary = 9, male = 3, female = 11, average age of 32 years) patients, $n = 4$ with secondary lymphedema in particular belonged to ISL stage II despite all other clinical and laboratory findings suggesting much more advanced disease. All those findings confirmed our suspicions in that these cases were more advanced with irreversible damage of the lymph vessels. Successful lymphatic anastomoses require functioning lymph vessels. All four patients failed to improve despite technically successful anastomosis made on half-paralyzed vessels.

Our second group of 32 patients (1995–2008) selected based on the new, improved staging system[69,70] has shown better outcomes with reconstructive surgery performed on patients with earlier clinical and laboratory stage (both LVAS and FLTS groups) throughout a 4-year follow-up period. Therefore, we strongly believe that a reliable lymphedema staging system is extremely important to the multidisciplinary team in order to assess for critical timing of the surgery with no further delay. Lymphatic surgery is indicated in patients who meet two criteria, discussed below.

The first criterion is a commitment to lifelong maintenance CDT after surgery. Because the majority of lymphedema patients often present with significant damage to the lymphatic system already with little chance for recovery, most patients would require lifelong maintenance CDT. Therefore, postoperative maintenance CDT is absolutely required.

The second criterion is documented "failure to obtain satisfactory control of the lymphedema progression

or to prevent disease progression despite vigorous nonsurgical treatment" for at least 1 year.

Although a 2-year observation period is often recommended, the 2-year observation period before declaring a patient a "treatment failure" is generally considered to be too conservative. There is significant controversy regarding this "waiting" period before performing reconstructive surgery, as a delay of more than 1 year may increase the risk of failure due to irreparable damage to the lymphatic system.

Therefore, we recommend that reconstructive lymphatic surgery be offered at the earliest possible time whenever lymphedema patients meet the following conditions:

1. Clinical evidence of substantial progression of lymphedema, from clinical stage I to stage II, or from stage II to stage III, despite an adequate CDT-based treatment program over a minimum 12-month period.
2. Progressive lymph fluid accumulation, preferably by lymphoscintigraphy to document dermal backflow, especially below the knee level.
3. Increasing difficulty of relieving edema by MLD-based CDT, particularly at the below-knee level.
4. Documented treatment failure at least twice during a minimum period of a year with 6-month interval assessments.

To restore normal lymphatic function, lymphatic-venous anastomosis is ideal for treating secondary lymphedema that develops after cancer surgery or radiation therapy. In this setting, there is selective damage to the lymph nodes, and the distal lymph-collecting vessels remain intact. Primary lymphedema due to the dysplasia of lymph nodes alone can also be treated by FLTS if a bypass is not feasible. However, primary lymphedema involving the lymphatic vessels (e.g. aplasia, hypoplasia) is often difficult to manage with either LVAS or FLTS.

Our results of the second group of patients (1995–2008) has shown similar results with better long-term outcome among secondary lymphedema patients in both LVAS and FLTS groups. Among $n = 19$ (female = 18, male = 1; mean age 49.0 years; primary lymphedema = 4, secondary lymphedema = 15) patients who underwent LVAS, the last 3 patients in excellent condition through 48 months follow-up were all secondary lymphedema in clinical stage II. Also, among $n = 13$ FLTS patients (female = 10, male = 3; mean age 34.0 years; primary lymphedema = 6, secondary lymphedema = 7), the only patients that were in excellent condition at 48 months, $n = 3$ patients, were secondary lymphedema patients in clinical stage II.

An early report by Gloviczki et al on 14 patients with lymphovenous anastomosis[19] also showed only 5 patients were able to maintain initial improvement at an average of 46 months after surgery, which is similar to our experience.

SURGICAL MANAGEMENT

Reconstructive surgery with LVAS or lymphatic-lymphatic anastomotic surgery requires assessment of the anatomic and functional status of the proximal lymph nodes and lymph-collecting vessels. The determination of function is necessary to identify normal (unparalyzed) lymphatic vessels. The response to MLD can be an indirect indication of their functional status. To confirm these observations, lymphoscintigraphy should be included in the preoperative evaluation. Both qualitative and semiquantitative assessment are sufficient to provide necessary information based on the response to the MLD (e.g., percentage reduction of the dermal backflow and/or improved clearance ratio, etc.).

To improve our overall assessment of the candidates, we attempted to incorporate magnetic resonance lymphography and ultrasonographic lymphography findings as well. However, the imaging quality was rather disappointing, of limited value, and unable to provide sufficient information to plan appropriately the lymphatic surgery. In addition to lymphatic functional assessment, assessment of venous function from duplex ultrasonography is also required for LVAS to evaluate for risk of venous insufficiency or reflux within the venous system.

In FLTS, the selection of appropriate donor lymph-node groups for harvesting is equally important as is the selection of the recipient site. Lymphoscintigraphic evaluation of donor sites (e.g., inguinal, cervical, or axillary groups) and duplex ultrasonographic evaluation of the lymph nodes is required. Computed tomography can also be useful in the evaluation. The patency of the venous system at the recipient site should also be confirmed with ultrasonography.

LVAS involves microscopic end-to-end or end-to-side anastomoses between healthy, well-functioning lymphatic vessels and healthy vein segments free of reflux. Lymph-collecting vessels are anastomosed to "defunctionalized" branches of the saphenous or adjacent superficial veins in the lower limb. A minimum of three to four sets of the anastomosis is often required.

The operation is performed at the inguinal or popliteal level depending on the status of local lymphatics. The classical approach at the inguinal level is preferred during the earlier stages of lymphedema where the majority of the collecting vessels at the inguinal region are competent. Good long-term results can be expected if LVAS is performed before the collecting vessels become irreversibly paralyzed, for example, in clinical stage I[21,41–43] as is advocated by Campisi, Boccardo, and others.

In reality, however, ideal candidates are scarce so that anastomosis at the popliteal level may be necessary in situations where the lymphedema has progressed to clinical stage II or early stage III. Evidence of progressive damage and paralysis of lymph-collecting vessels at the inguinal level is an indication for performing LVAS anastomosis at the popliteal level[9,10,22] where it is likely to have better lymph vessels for surgical reconstruction as is advocated by Krylov and others.

In our series of patients, there was significant progression of lymphedema in the majority of patients, advancing from clinical stage II to III. Deterioration of the lymphedema was more prominent in the lower leg and foot in general, which was confirmed with lymphoscintigraphy. In addition, preoperative CDT was only effective above the knee. Because of this, we performed the LVAS in half of the patients ($n = 10$ of 19) at the popliteal level to decompress the distal leg and foot. All 10 patients were found to have well-functioning, unparalyzed lymph vessels at the popliteal level, which allowed LVAS between the lymphatics and the defunctionalized vein branches with no reflux.[9,10]

The FLTS technique is based on the principle of free flap tissue grafting technique.[26,44–46] The lymph node-bearing tissue is harvested from the donor site (e.g., axillary lymph node group) with its feeding artery and veins intact. The subsequent anastomoses are constructed between the donor artery and recipient artery and between the donor veins and recipient veins using microsurgical techniques. An anastomosis between multiple sets of donor and recipient arteries and veins is preferred over a single set, especially for the venous anastomosis.

Harvesting an adequate number of lymph nodes with intact vessels from the donor site is an important prerequisite for successful decompression after node grafting. But at the same time, an adequate number of normal nodes must be left behind after removal of the donor lymph nodes to maintain normal lymphatic function of the donor limb after harvest. Special attention should be given to the number of remaining lymph nodes at the donor site to minimize the risk of developing lymphedema in the donor limb.[9,10] Iatrogenic lymphedema may be the result of an unnecessarily aggressive lymph node harvest. To minimize lymphatic congestion, aggressive perioperative MLD-based CDT to the donor sites should be performed for a minimum of 2 weeks before and after surgery.

LONG-TERM MANAGEMENT

Lifelong maintenance CDT therapy after surgical reconstruction is the single most important factor that determines the long-term outcome of a successful lymphatic reconstruction when done in a less than ideal setting with delayed surgery. The second most important issue regarding postoperative care is the prevention and treatment of infection, especially when the clinical stage is relatively advanced. The majority of lymphatic surgery failures observed in our series of patients was due to recurrent infection.[9,10]

We support an aggressive surveillance and prevention program in addition to prompt diagnosis and treatment of systemic and local infection such as cellulitis and erysipelas to prevent further injury to an already compromised lymphatic system. Lifelong antibiotic prophylaxis should be considered in patients with a high risk of recurrent cellulitis.[73,74]

COMMENTS

Current maintenance CDT can provide satisfactory management of lymphedema, particularly in its early stage, in the majority of cases. Therefore, it is very difficult to recommend early reconstructive surgery before a failure of CDT is confirmed, though it can hardly be justified. In the early stage of lymphedema, the lymphatic dysfunction is often still reversible. Because of the inherent risk of further damage by delaying reconstructive surgery to an already jeopardized lymphatic system, the surgical outcome is often doomed because of the loss of critical lymph vessels.

Unfortunately, all candidates for lymphatic reconstruction are offered reconstruction only when CDT-based therapy fails to prevent the progression of lymphedema over a specific period of time and when there is clear evidence of further damage to the lymphatic system during this waiting period. The majority of patients offered reconstruction often have significant damage to lymph-transporting vessels caused by long-term lymphatic hypertension.

Therefore, postoperative maintenance CDT after successful reconstructive surgery is essential for good long-term outcomes. Without appropriate maintenance CDT after surgery, a flawless, technically successful reconstruction alone is unable to completely correct damaged lymph vessels due to delayed surgery.

Postoperative maintenance CDT is completely dependent on patient compliance. Unfortunately, the majority of patients with chronic lymphedema have poor compliance. Therefore, patient compliance is absolutely necessary before offering reconstructive surgical treatment. Lifelong maintenance CDT after lymphatic surgery is required to maintain satisfactory long-term results.

CONCLUSION

Reconstructive lymphatic surgery at best remains an adjunctive treatment that is effective in some patients with refractory lymphedema treated with CDT alone.

Reconstructive surgery appears to be successful in controlling the progression of lymphedema during the early stages. Our experience supports the contention that improved long-term results is dependent on patient compliance with maintenance CDT and the prevention and treatment of infection.

To better understand the role of reconstructive surgery in the management of chronic lymphedema, well-constructed clinical trials are required. They must consist of well-organized multicenter studies that use similar protocols and incorporate peer-reviewed outcome results. For the future, it remains the only possible method capable of providing a cure.

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