MICROSURGERY FOR LYMPHEDEMA: CLINICAL RESEARCH AND LONG-TERM RESULTS

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Objectives: To report the wide clinical experience and the research studies in the microsurgical treatment of peripheral lymphedema. *Methods:* More than 1800 patients with peripheral lymphedema have been treated with microsurgical techniques. Derivative lymphatic microvascular procedures recognize today its most exemplary application in multiple lymphatic-venous anastomoses (LVA). In case of associated venous disease reconstructive lymphatic microsurgery techniques have been developed. Objective assessment was undertaken by water volumetry and lymphoscintigraphy. *Results:* Subjective improvement was noted in 87% of patients. Objectively, volume changes showed a significant improvement in 83%, with an average reduction of 67% of the excess volume. Of those patients followed-up, 85% have been able to discontinue the use of conservative measures, with an average follow-up of more than 10 years and average reduction in excess volume of 69%. There was a 87% reduction in the incidence of cellulitis after microsurgery. *Conclusions:* Microsurgical LVA have a place in the treatment of peripheral lymphedema, and should be the therapy of choice in patients who are not sufficiently responsive to nonsurgical treatment. © 2010 Wiley-Liss, Inc. Microsurgery 30:256–260, 2010.

Lymphedema, refractory to nonoperative methods, may be managed by surgical treatment. Indications include insufficient lymphedema reduction by well performed medical and physical therapy (less than 50%), recurrent episodes of lymphangitis, intractable pain, worsening limb function, patient unsatisfied of the result obtained by nonoperative methods and willing to proceed with surgical options.

The first microsurgical derivative operations were those using lymphnodal-venous shunts. These have been largely abandoned, except in endemic areas of lymphatic filariasis such as India where thousands of these procedures have been performed. Lymphatic channels in lymphnodal-venous anastomoses are often widely dilated due to the high rate of anastomotic closures caused by the thrombogenic effect of lymph nodal pulp on the venous blood and the frequent re-endothelization of the lymph nodal surface.[1] Because of the difficulties encountered with lymphnodal-venous shunts by surgeons worldwide, the next approach was to use lymphatic vessels directly anastomosed to veins.[2]

The technique consists in anastomosing lymphatic vessels to a collateral branch of the main vein, checking the perfect function of the valvular apparatus, to be sure of the correct continence of the vein segment used for the anastomosis. This way, inside the venous tract there flows only lymph and not blood, avoiding any risk of thrombosis of anastomosis.[3]

The retrospective evaluation of our wide clinical experience in the microsurgical treatment of peripheral lymphedema is reported, underlying long term outcome and analyzing which are the correct indications and technical details that allow us to obtain successful results long term after operation.

MATERIALS AND METHODS

More than 1,800 patients affected by peripheral primary and secondary lymphedema have been treated over the past 30 years mostly using lymphatic-venous derivative techniques.

The operations consisted in performing microsurgical multiple lymphatic-venous anastomoses (LVA). Healthy appearing lymphatics found at the site of surgical operation were directly introduced together into the vein by a U-shaped stitch and then fixed to the vein cut-end by means of additional stitches between the vein border and the perilymphatic adipose tissue. With the use of Patent Blue dye, properly functioning lymphatics appear blue, and the passage of blue lymph into the vein branch verifies the patency of the lymphatic-venous anastomosis under the operating microscope when the anastomosis is completed (Fig. 1).

For patients with lower limb lymphedema, anastomoses are performed at the subinguinal region. Lymphatic-lymph nodal superficial structures are isolated, and all afferent lymphatics are used for the operation. Lymph nodes are subjected to histopathologic examination. The usual finding in primary lower limb lymphedemas is a varying grade of nodal fibrosclerosis and thickening of the nodal capsule but with normal afferent lymphatic vessels.

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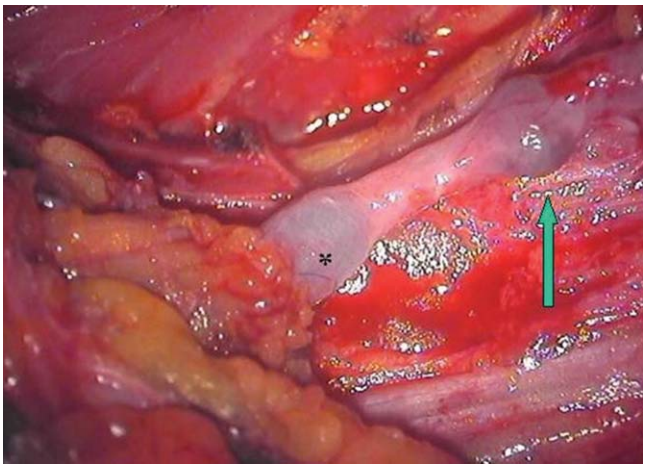

Figure 1. Microsurgical multiple lymphatic-venous anastomosis. The passage of blue lymph into the vein branch (*) verifies the patency of the anastomosis under the operating microscope when the anastomosis is completed. The vein has a well functioning valve (arrow). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

For upper limb lymphedema, LVA are performed at the medium third of the volar surface of the arm, using both superficial and deep lymphatic collectors, evidenced by the blue dye. Deep lymphatics are found in between humeral artery, vein and the median nerve. The vein used for anastomoses is a patent branch of one of the humeral veins, and the technique most performed is the microsurgical one.

Primary lymphedemas largely included lymph nodal dysplasias (LAD II, according to Papendieck's classification[4]) consisting of hyperplastic lymph nodes with sinus histiocytosis and a thick and fibrous capsule with microlymphangioadenomyomatosis. In these cases, lymph flow obstruction was apparent as seen by alterations of the afferent lymphatics which appeared dilated and swollen with thickened walls and where smooth muscle cells are reduced in number and appear fragmented by associated fibrous elements. In our experience, secondary lymphedemas were largely due to lymphadenectomy and radiotherapy performed for oncological reasons (carcinoma of the breast, uterus, penis, bladder, prostatic gland, rectum, and seminoma of epididymis), as well as for complications of minor operations for varicose veins, crural and inguinal hernias, lipomas, tendinous cysts, or axillary and inguinal lymph node biopsies. Most of the lymphedemas treated by microsurgery were at stages II (39%) and III (52%), while 3% of the patients were stage Ib and 6% were stages IV and V.

Lymphoscintigraphy, performed with either 99mTc-labeled antimony sulfur colloid or 99mTc-nanocolloid Human Serum Albumin (90% of the particles >80 nm in size), was employed in the diagnostic work-up of patients with lymphedema and as a test for selecting patients for derivative microsurgical operations. Lymphoscintigraphy clearly discriminated whether or not edema was of lymphatic origin and also provided important data about the etiologic and pathophysiologic aspects of the Lymphedema.

Echo Doppler was performed in all patients to identify any venous disorders possibly associated with lymphedema. In most patients, venous dysfunctions were corrected at the same time of microlymphatico-venous anastomoses (i.e., valvular plasty in case of venous insufficiency). In other cases, finding venous dysfunction contraindicated derivative lympho-venous shunts but at the same time facilitated referral of the patient for reconstructive microsurgical operations.

In those cases involving the lower limbs, where surgically uncorrectable venous disease exists, it is not advisable to use derivative lymphatic-venous techniques, and accordingly, reconstructive methods are used. The most commonly used technique is the interposition of an autologous vein graft between lymphatics above and below the obstacle to lymph flow. The venous segment can be obtained from the same operative site or from the forearm (mostly the cephalic vein). The length of the graft is variable from 7 to 15 cm, and it is important to collect several lymphatics at the distal cut end of the vein so as to maintain the segment filled with lymph and avoid closure due to fibrosis (Figs. 2A and 2B). The valves of the veins are useful for the correct direction of the lymphatic flow and to avoid gravitational backflow. The technique of anastomosis is the microsurgical one with introduction of lymphatics inside the vein cut ends by a U-shaped stitch, which is then fixed by some peripheral stitches.

RESULTS

Clinical outcome improves the earlier microsurgery is performed owing to absent or minimal fibrosclerotic alterations of the lymphatic walls and surrounding tissues. Subjective improvement was noted in 87% of patients. Objectively, volume changes showed a significant improvement in 83%, with an average reduction of 67% of the excess volume. Of those patients followed-up, 85% have been able to discontinue the use of conservative measures, with an average follow-up of more than 10 years and average reduction in excess volume of 69%. There was a 87% reduction in the incidence of cellulitis after microsurgery.

Lymphoscintigraphy helped in verifying the patency of microanastomoses long term after operation by direct and indirect findings: reduction of dermal backflow together with the appearance of preferential lymphatic pathways not visible before microsurgery; disappearance of the tracer at the site of LVA due to direct tracer passage

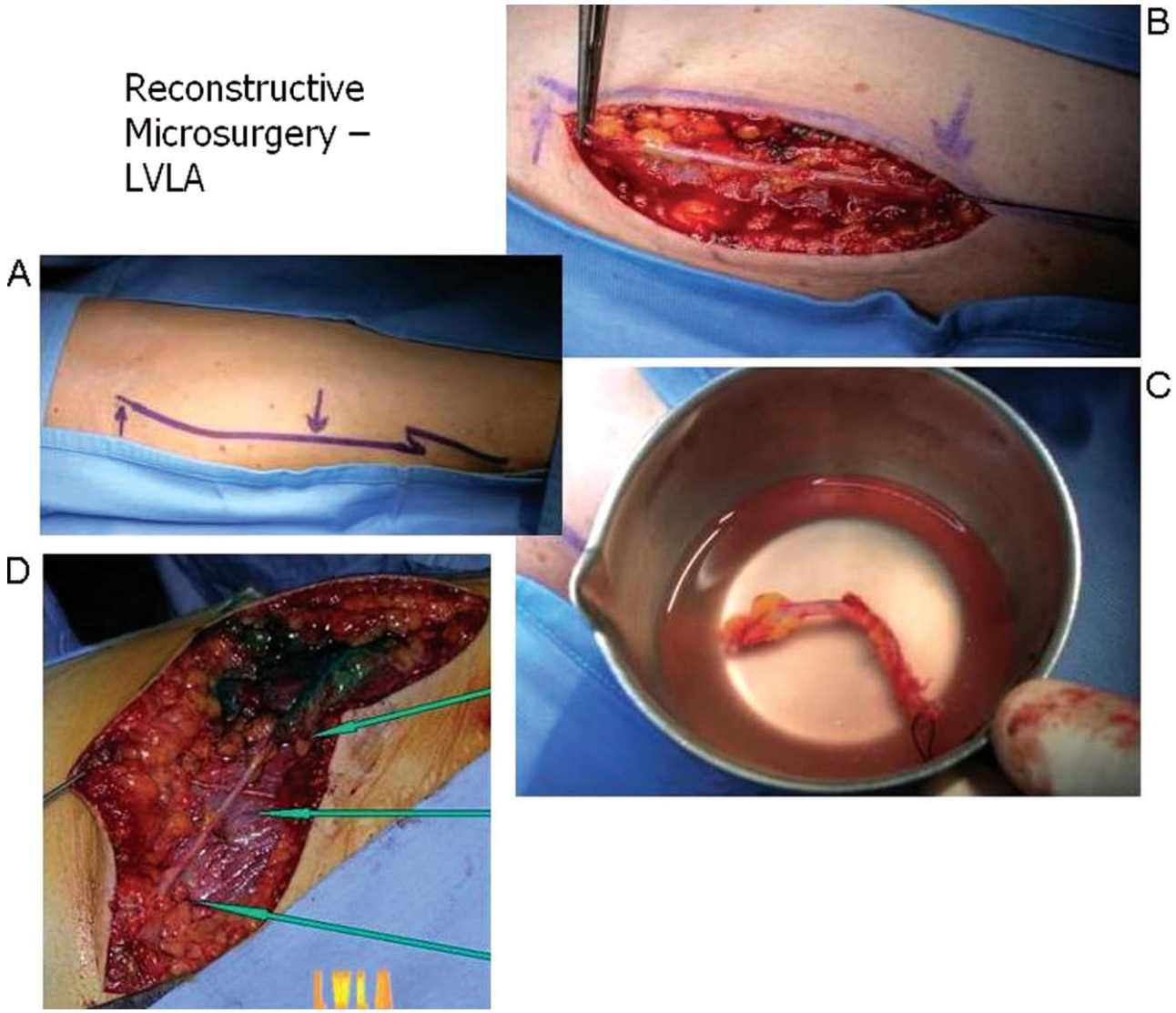

*Figure 2. Reconstructive technique with the interposition of an autologous vein graft between lymphatics above and below the obstacle to lymph flow: the venous segment is obtained from the the forearm (the cephalic vein) (**A**, **B**);Venous segment harvested (**C**); several lymphatics are anastomosed at the distal cut end of the vein so as to maintain the segment filled with lymph and avoid closure due to fibrosis (arrows) (**D**). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]*

into the blood stream; and earlier liver uptake compared to preoperative parameters (indirect patency test) (Figs. 3A and 3B).

DISCUSSION

Lymphatic microsurgery represents a means to bypass the obstacle to lymph flow through lymphatic-venous drainage (LVA) or by using venous grafts between lymphatic collectors below and above the obstruction (lymphatic-venous-lymphatic plasty). Combined physical therapy nonetheless represents the initial treatment of patients affected by peripheral lymphedema and it is best performed in specialized centers. The surgical timing follows completion of conservative treatment when further clinical improvement can no longer be achieved and/or recurrent lymphangitic attacks are not further reduced.[5] Microsurgical operations can then be performed and provide further improvement in the condition.[6,7]

The optimal indications for lymphatic microsurgery are represented by: early stages (Ib, II, early III); lymphoscintigraphy showing a low inguinal or axillary lymph nodal uptake and minimal or absent passage of the tracer beyond this proximal nodal area; excellent patient compliance; and a lymphological center where the patient can easily refer for any needs in addition to a Center of

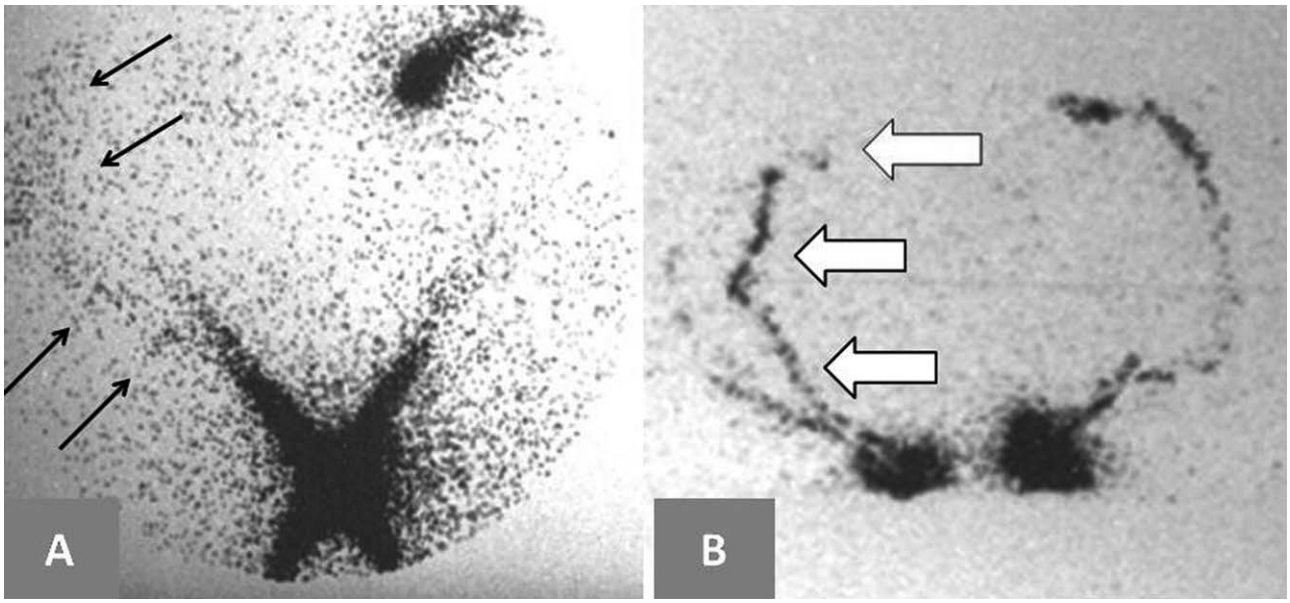

*Figure 3. (**A**) Lymphoscintigraphy in a patient affected from right arm lymphedema secondary to breast cancer treatment. Poor lymphatic transport along the arm with dermal back flow (arrows). (**B**) Postoperative lymphoscintigrapy showing the appearance of preferential lymphatic pathways and disappearance of dermal back flow (arrows).*

Lymphatic Surgery where the patient undergoes this specialized surgery.

At later stages (advanced III, IV, and V), with absent visualization of lymphatic channels and regional lymph nodes, it is necessary to reduce the stage of the lymphedema by nonoperative methods before microsurgery. After operation, it is particualrly important for these patients to be followed closely to improve the clinical outcome and maintain the short-term operative results for the long term [so called Complete Lymphedema Functional Therapy (CLyFT)[8]]. In case of poor patient compliance, the results may be unsatisfactory. Relative contraindications to lymphatic microsurgery are represented by cases of lymphatic-lymph nodal aplasia (extremely rare), diffuse metastatic disease, and advanced stage (V) not responsive to conservative therapy. Traditional debulking operations are presently less utilized to treat lymphedema except in cases of late stage lymphedema to reduce skin folds after marked edema reduction obtained by conservative physical and microsurgical methods; in body regions relatively inaccessible to effective compression such as the genitalia; in advanced lymphatic filariasis at times combined with lymphatic-venous or nodal-venous anastomosis in the setting of widely dilated lymphatic channels; and in localized lipolymphedema associated with massive obesity and forced immobility.

In recent years, both primary and secondary peripheral lymphedemas are becoming better understood and more manageable problems with increased awareness and early detection.[9–13] Nonetheless, apparent nonoperative measures are aimed at minimizing morbidity without removing the cause of the underlying disturbance.[14,15] Microsurgical derivative and reconstructive operations can restore lymphatic drainage, both in the short and long term, and the best results are obtained when these surgical procedures are combined with physical rehabilitative methods.

REFERENCES

1. Dellachà A, Boccardo F, Zilli A, Napoli F, Fulcheri E, Campisi C. Unexpected histopathological findings in peripheral lymphedema. Lymphology 2000;33:62–64.
2. Campisi C, Boccardo F. Lymphedema and microsurgery (Invited Review). Microsurgery 2002;22:74–80.
3. Campisi C, Boccardo F. Microsurgical techniques for lymphedema treatment: Derivative lymphatic-venous microsurgery. World J Surg 2004;28:609–613.
4. Papendieck CM. The big angiodysplastic syndromes in pediatrics with the participation of the lymphatic system. Lymphology 1998;31:390–392.
5. Dellachà A, Fulcheri E, Boccardo F, Campisi C. Post-surgical lymphedema: Latrogenic or pre-existing disease? Lymphology 1998;31:562.
6. Erickson VS, Pearson ML, Ganz PA. Arm edema in breast cancer patients. J Natl Cancer Inst 2001;93:96–111.
7. Ferrandez JC, Serin D, Bouges S. Frequency of lymphedema of the upper limb after treatment of breast cancer. Risk factors. A propos of 683 cases. Bull Cancer 1996;83:989–995.
8. Campisi C, Boccardo F. Terapia funzionale completa del linfedema (CLyFT: complete lymphedema functional therapy): Efficace strategia terapeutica in 3 fasi. Linfologia 2008;1:20–23.
9. Bellini C, Boccardo F, Taddei G, Mazzella M, Arioni C, Villa G, Hennekam RC, Serra G, Campisi C. Diagnostic protocol for lymphoscintigraphy in newborns. Lymphology 2005;38:9–15.

10. Bourgeois P, Leduc O, Leduc A. Imaging techniques in the management and prevention of posttherapeutic upper limb edemas. Cancer 1998;83 (12 Suppl American): 2805–2813.
11. Mariani G, Campisi C, Taddei G, Boccardo F. The current role of lymphoscintigraphy in the diagnostic evaluation of patients with peripheral lymphedema. Lymphology 1998;31:316.
12. Pecking AP, Gougeon-Bertrand FJ, Floiras JL. Lymphoscintigraphy. Overview of its use in the lymphatic system. Lymphology 1998; 31:343.
13. Witte C, Mcneill G, Witte M. Whole-body lymphangioscintigraphy: Making the invisible easily visible. In: Mitsumas N, Uchino S, Yabuki S, editors. Progress in Lymphology, XII: Amsterdam: Elsevier; 1989. 123.
14. Campisi C. Use of autologous interposition vein graft in management of lymphedema: Preliminary experimental and clinical observations. Lymphology 1991;24:71–76.
15. Campisi C, Boccardo F, Tacchella M. Reconstructive microsurgery of lymph vessels: The personal method of lymphatic-venous-lymphatic (LVL) interpositioned grafted shunt. Microsurgery 1995;16:161–166.