Lymphatic Truncular Malformations of the Limbs: Surgical Treatment

51

Corradino Campisi, Melissa Ryan, Caterina Sara Campisi, Francesco Boccardo, and Corrado Cesare Campisi

Introduction

While the international scientific community, through its institutional components, most representative of the major societies involved (International Society of Lymphology, ISL; International Union of Phlebology, UIP; International Society for the Study of Vascular Anomalies, ISSVA; and the newly formed Italian Society for the Study of Vascular Anomalies, SISAV) is fully committed to defining common guidelines for diagnostic-therapeutic considerations based on the official consensus documents, we offer for publication the contributions on the "surgical treatment of lymphatic truncular malformations of the limbs" and "thoracic duct dysplasias with chylous reflux," which we wish to be understood as an attempt to systematically classify a complex pathology of vascular malformation that is still under the "strong influence of subject area," which is often in contrast to a clinical reality, and where there is not a clear and constant academic distinction between diseases and syndromes exclusively attributable to predominantly lymphatic malformations. The contributions will consider lymphatic truncular malformations consisting of primary lymphedema and also the thoracic duct dysplasias and associated syndromes of chylous reflux.

C. Campisi, MD, PhD, FACS (✉)
Department of Surgery (DISC), Operative Unit of General and Lymphatic Surgery, Section & Research Center of Lymphatic Surgery, Lymphology, and Microsurgery, IRCCS University Hospital San Martino – IST National Institute for Cancer Research, Genoa, Italy

Postgraduate School of Alimentary Tract Surgery, Siena, Italy
e-mail: campisi@unige.it

M. Ryan, PhD • F. Boccardo, MD, PhD
Operative Unit of General and Lymphatic Surgery, Section & Research Center of Lymphatic Surgery, Lymphology, and Microsurgery, Department of Surgery (DISC), IRCCS University Hospital San Martino – IST National Institute for Cancer Research, Genoa, Italy
e-mail: ryame269@hotmail.com

C. Sara Campisi, MD
Operative Unit of Dermatology, Department of Health Sciences (DISSAL), IRCCS University Hospital San Martino – IST National Institute for Cancer Research, Genoa, Italy

C. Cesare Campisi, MD, RAS-ACS
Operative Unit of Plastic, Reconstructive and Aesthetic Surgery, Department of Surgery (DISC), IRCCS University Hospital San Martino – IST National Institute for Cancer Research, Genoa, Italy

Truncular Lymphatic Malformations

There remains significant confusion about the relationship between primary lymphedema and lymphatic malformations, which is further complicated by disagreements surrounding the definition of primary lymphedema. However, primary lymphedema is regarded as a clinical

R. Mattassi et al. (eds.), *Hemangiomas and Vascular Malformations: An Atlas of Diagnosis and Treatment*,
DOI 10.1007/978-88-470-5673-2_51, © Springer-Verlag Italia 2009, 2015

manifestation of a lymphatic malformation that developed during the later stage of lymphangiogenesis [1, 2]. Lymphatic malformations are low-flow vascular malformations and can be divided into extra-truncular and truncular forms. The truncular lymphatic malformations are further divided into primary lymphedema and visceral forms (those which include lymphangiectasis and lymphangiomatosis). Some truncular and visceral lymphatic malformations have proliferative potential (lymphangiomatosis). Truncular and extra-truncular lymphatic malformations can coexist (ISSVA Classification International Consensus, 11 Workshop, Rome, 1996).

The majority of the clinical conditions that are considered to be primary lymphedema are due to truncular lymphatic malformation that arises during the final stages of the lymphangiogenesis [3, 4], when there is formation of the lymphatic trunks, vessels, and nodes [5, 6]. These malformations result in hypoplasia, hyperplasia, or aplasia of the lymphatic vessels and/or the lymph nodes and may clinically manifest as obstruction or dilatation. When the malformations result in the absence or defectiveness of the endoluminal valves, reflux of the lymph is the primary clinical manifestation. In contrast, the extra-truncular lymphatic malformations develop at an earlier stage of the embryogenesis and are associated with immature embryonic tissue that fails to involute, remaining in the earlier embryonic stages [5, 6].

Some primary or congenital lymphedemas are not true congenital defects but occur due to postnatal destruction of the lymphatic collectors or nodes. These mimic the congenital condition in terms of clinical presentation and are classified as congenital lymphedema because the symptoms are present at birth [7, 8]. Other primary lymphedemas do not have anatomically evident truncular malformations of the lymphatic system but represent a functional defect that is molecular in origin [9, 10].

Primary lymphedemas have typically been classified into three groups, depending on the age of the onset of clinical manifestations: congenital (before age 2 years), praecox (between age 2 and 35 years), and tarda (after age 35 years). However, there is significant criticism of this arbitrary categorization as it is not clinically useful [9]. In addition, the category of primary lymphedema often includes other types of lymphedema of an idiopathic nature without an identifiable etiology (i.e., radiation, surgery, or infection) [11]. Some experts also believe that all lymphedema and lymphatic malformations are genetically derived and have proposed that lymphedema should be considered as an abnormality of lymph drainage and classified only by the tissue territory drained [10]. We prefer to classify the lymphedemas using an etiological basis, as can be seen in Fig. 51.1.

In order to provide a comprehensive classification system of lymphedema that encompasses immunohistopathological criteria, level of clinically evident edema, lymphoscintigraphic findings, and level of physical disability, we developed a three-stage model (Fig. 51.2) [9, 12, 13]. In clinical practice, stages IA, IB, IIA, and early IIB can be considered as early manifestations of disease and late IIB, IIIA, and IIIB stages to be chronic and advanced. It should be noted that lymphedema is a progressive disease and can move rapidly between the stages without adequate treatment [14–17].

General Considerations of the Surgical Treatment of Lymphedema

Refractory lymphedema unresponsive to conservative treatment measures may be appropriately managed by surgical means. Indications for surgery include insufficient volume reduction by appropriate conservative methods (less than 50 % reduction), recurrent lymphangitis or erysipelas episodes, intractable pain or discomfort usually associated with excess swelling and inflammation, loss of limb function and increasing disability, and patient dissatisfaction with previous treatment outcomes and willingness to proceed with surgery.

The initial derivative microsurgical approaches involved lymph node-venous shunts, but, aside from India where these have been used frequently in the treatment of lymphatic filariasis, these approaches have been largely superceded by more refined and effective techniques.

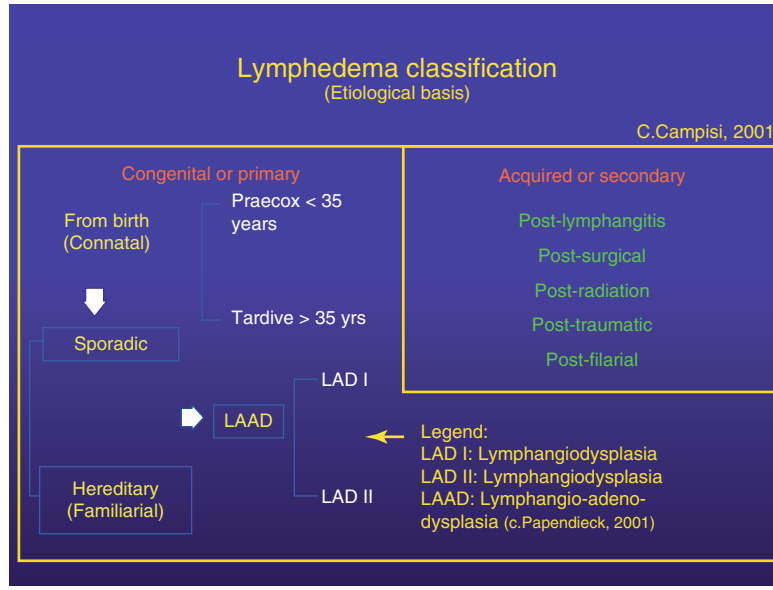

Fig. 51.1 Classification of lymphedema (C. Campisi, 2001)

Staging of Lymphedema	
Stage I	A. Latent lymphedema, without clinical evidence of edema, but with impaired lymph transport capacity (provable by lymphoscintigraphy) and with initial immunohistochemical alterations of lymph nodes, lymph vessels and extracellular matrix.
	B. Initial lymphedema, totally or partially decreasing by rest and draining position, with worsening impairment of lymph transport capacity and of immunohistochemical alterations of lymph collectors, nodes and extracellular matrix.
Stage II	A. Increasing lymphedema, with vanishing lymph transport capacity, relapsing lymphangitic attacks, fibroindurative skin changes, and developing disability.
	B. Column shaped limb fibrolymphedema, with lymphostatic skin changes, suppressed lymph transport capacity and worsening disability.
Stage III	A. Properly called elephantiasis, with scleroindurative pachydermitis, papillomatous lymphostatic verrucosis, no lymph transport capacity and life-threatening disability.
	B. Extreme elephantiasis with total disability.

Fig. 51.2 Staging of lymphedema, based on immunohistological criteria, lymphoscintigraphic findings, clinical symptoms, and grade of physical disability (C. Campisi, August 2009)

Lymph node-venous shunts had a high rate of anastomotic closure due to the thrombogenic effect of the lymph nodal pulp on the blood and the frequent re-endothelialization of the lymph node surface [18]. Worldwide, surgeons moved to anastomosing lymphatic vessels directly into the veins in order to increase the long-term efficacy of the procedures [19].

The lymphatic-venous anastomosis technique involves joining an appropriate lymphatic vessel to a collateral branch of a main vein, ensuring that the vein has competent valvular function and continence. This is essential to prevent reflux of the blood into the lymphatic vessel and thereby thrombosis of the anastomosis [12].

Clinical Experience and Surgical Techniques

The microsurgical interventions involved multiple lymphatic-venous anastomoses (LVA). Blue patent violet dye (BPV; a sodium or calcium salt of diethylammonium hydroxide) is used intraoperatively to identify properly functioning lymphatic vessels at the surgical incision. Healthy-appearing lymphatic vessels at this site are selected and introduced directly into the vein segment with a U-shaped stitch (using 8/0–10/0 Prolene sutures depending on the caliber of the vessels). These are then secured by additional stitches between the perilymphatic adipose tissue and the vein border. The passage of the blue-stained lymphatic fluid into the vein, evident under the operating microscope, verifies the patency of the anastomosis (Fig. 51.3).

For patients with lower-limb lymphedema, multiple LVAs are applied in the subinguinal region. Superficial lymphatic-lymph nodal structures are identified and isolated, and all available and healthy afferent lymphatic collectors are used for the anastomoses. Samples of lymph nodes, vessels, vein segments, and adjacent tissues are subjected to histopathological analyses. Common findings in primary lower-limb lymphedema are significant thickening of the nodal capsule and varying levels of nodal fibrosclerosis. Afferent lymphatic vessels are usually normal, indicating a proximal obstruction in lymphatic flow.

For patients with upper-limb lymphedema, multiple LVAs are performed at the middle third of the volar surface of the arm. Both superficial and deep lymphatic collectors identified by BPV are used. Deep lymphatics are typically found in the vicinity of the humeral artery, vein, and median nerve. A patent branch of one of the humeral veins is used in the application of microsurgical anastomoses.

Lymphoscintigraphy is performed in all cases as part of the diagnostic workup to select appropriate candidates for surgery based on evidence of proximal obstruction of lymphatic flow. Lymphoscintigraphy is performed with either ^{99m}Tc-labeled antimony sulfur colloid or ^{99m}Tc-nanocolloid human serum albumin (90 % of the particles of >80 nm in size) injected into the interdigital space of the toes or fingers of both limbs in the affected region. It is essential to ensure that the edema is of lymphatic origin. Lymphoscintigraphy also provides important etiological and pathophysiological information about the nature of the disease. In the last 2 years of our experience, evaluation of the superficial lymphatic pathways distal to the surgical site in the affected limb has also been performed using the photodynamic eye (PDE) method with injection of indocyanine green fluorescence. The simultaneous use of PDE with BPV gives two methods of visualizing the lymphatic flow and confirmation of patency of the anastomoses intraoperatively [20, 21]. PDE can also be used postoperatively, in addition to lymphoscintigraphy, to verify the long-term stability of the surgical outcomes.

Primary lymphedemas typically involve lymph node dysplasias (LAD II according to Papendieck's classifications [22]) with hypoplastic lymph nodes associated with sinus histiocytosis and a thick fibrous capsule and microlymphangioadenomyomatosis. In these cases, obstruction to lymphatic flow is evident in the changes in the afferent lymphatic collectors: these are dilated, swollen, and tortuous with thickened walls and reduced numbers

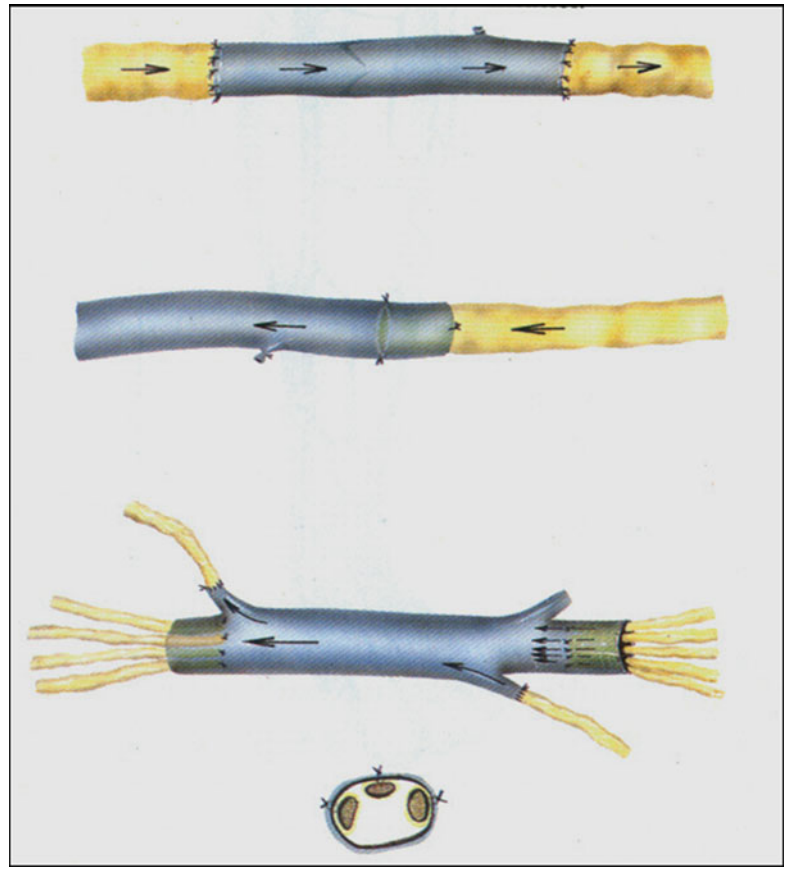

Fig. 51.3 LVA: the passage of blue lymph into the vein branch can be seen under the operating microscope, verifying the patency of the anastomosis

of smooth muscle cells, which are fragmented by numerous fibrotic elements. In our clinical experience, the majority of the peripheral lymphedemas treated by microsurgical means were at stages IIA (39 %) and IIB (52 %), where a minority were at other stages (3 % at stage IB and 6 % at stages IIIA and B; according to the Campisi staging system for lymphedema [9, 12, 13]).

Echo Doppler is performed in all cases to exclude venous-only causes of edema and also to identify any venous anomalies associated with the lymphedema, such as phlebolymphedema. In most cases, the venous anomalies can be corrected contemporaneously, such as valvuloplasty for venous insufficiency. In other cases, venous disease is an indication for performing a venous graft between the lymphatic collectors above and below the site of lymphatic obstruction, as the valvular incompetency of the diseased veins would compromise the efficacy of the anastomoses if LVA was performed instead. This venous bridge type of graft is called a lymphatic-venous-lymphatic anastomosis (LVLA). Competent venous segments are harvested from the same operative site or can be taken from the forearm (usually the cephalic vein). The length of the grafted vein section varies from 7 to 15 cm as required. It is essential to collect several lymphatic collectors to join to the distal end of the vein to ensure that the vein segment is filled with sufficient lymph and to avoid closure due to subsequent fibrosis development. The competent valves of the vein segment are vital for directing the flow of lymph in the correct direction and to avoid gravitational backflow or reflux. As with the LVA, the lymphatic collectors are directly introduced into the vein cut ends by means of a U-shaped stitch, which is then stabilized with additional peripheral stitches (Fig. 51.4).

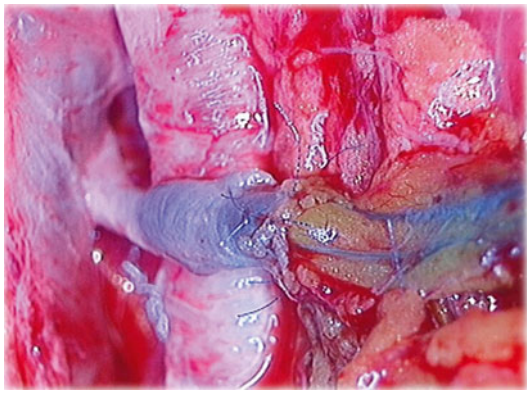

Fig. 51.4 A schematic drawing of the derivative multiple LVA and the reconstructive multiple LVLA technique with the interposition of an autologous vein graft between lymphatics above and below the obstacle to the lymph flow (C. Campisi, 1982)

Results

Clinical outcomes improved earlier that microsurgical techniques are applied in the treatment of peripheral lymphedema, due to the absence of, or minimal, fibrosclerotic tissue changes in the lymph vessel walls and surrounding tissues. Compared to preoperative conditions, patients obtained significant reductions in excess limb volume of over 84 %, with an average of 69 % as measured by limb water volumetry and circumference. These results were stable over an average of 10 years of follow-up. Over 86 % of patients with stages I and IIA gradually stopped using conservative therapies over the length of the follow-up period. In patients with more advanced lymphedema (stages IIB, IIIA, and IIIB), 42 % could decrease the frequency of physical therapies in the long term. In all patients, the frequency of DLA attacks considerably reduced by over 91 %, compared to preoperative conditions.

There were no immediate postoperative complications, such as postoperative infections, postoperative lymphorrhea, or worsening of edema. Most recently, patency verification was also performed postoperatively using the PDE method with indocyanine green fluorescence. This method allows visualization of the superficial lymphatic pathways and is valuable to confirm the significant reduction in dermal backflow of lymph after microsurgery. When PDE is used immediately after surgery, it is possible to verify the anastomosis patency and provide evidence that no thrombosis has occurred.

Lymphoscintigraphy was used to verify the patency of the microanastomoses in the long term by direct and indirect methods (Fig. 51.5). These included the following:

- Reduced dermal backflow of the tracer and the appearance of preferential lymphatic pathways not evident preoperatively
- The disappearance of the tracer at the site of the lymphatic-venous anastomoses, indicating the passage of lymph into the bloodstream
- Earlier liver uptake of tracer, compared to preoperative parameters, taken as indirect evidence of the passage of lymph in the bloodstream

Additional Considerations

Combined physical therapy should be the initial treatment for peripheral lymphedema and is best conducted in specialized treatment centers. The timing of the surgical intervention is important. In the case of established lymphedema (stages IB and onwards), surgical treatment should be implemented as soon as there is no further reduction in limb volume obtained by conservative methods or earlier if there are recurrent lymphangitic attacks that act to worsen the lymph transport [23]. Microsurgery applied at this point provides further amelioration in the condition [24, 25]. Early application of microsurgery techniques is efficacious in preventing the development of lymphedema in certain cases and is discussed further in a later section.

The ideal indications for microsurgical intervention, in our experience, include relatively early stages of disease (stages IB, IIA, and early IIB); lymphoscintigraphy patterns showing low inguinal or axillary nodal uptake of the tracer and minimal or absent passage of the tracer beyond this proximal area; excellent patient compliance with all treatment aspects; and access to a well-organized lymphedema treatment center where the patient can be referred to a center of lymphatic surgery when a specialized surgery is required.

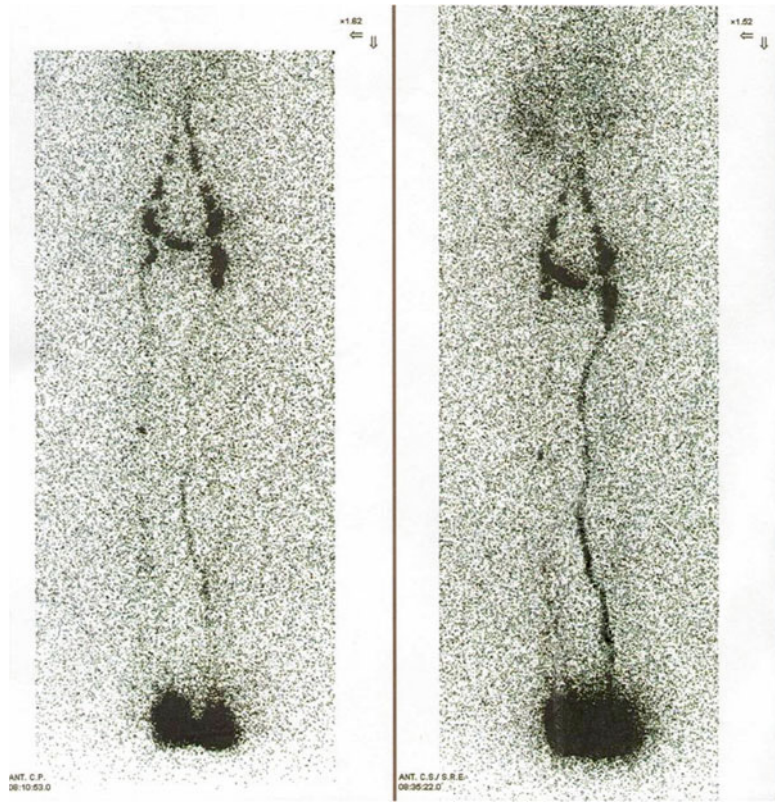

Fig. 51.5 Preoperative lymphoscintigraphy in a patient affected by primary lymphedema of the left leg (*left*). Postoperative lymphoscintigraphy shows the appearance of preferential lymphatic pathways into the inguinal region (*right*)

In more advanced cases (late IIB, IIIA, IIIB), where lymphoscintigraphy shows no visualization of lymphatic channels and regional lymph nodes, it is necessary to reduce the stage of lymphedema by intensive conservative methods prior to surgery, in order to reduce the clinical stage of the disease and best prepare the limb for surgery. Lymphatic microsurgery has an important role in the treatment of advanced lymphedema where addressing the chronic lymph stasis helps with edema reduction but also is likely to improve the immune function in the affected limb [15], as recent research indicates that chronic lymph stasis is associated with reduced immune responses to infection. These patients need to be followed closely in the postoperative phase and to adhere to the regimen of complete lymphedema functional therapy, ClyFT [26]; this is essential to maintain the results obtained by the microsurgery and to continue to improve the long-term clinical outcome (Fig. 51.6). As advanced cases of lymphedema are associated with fibrotic adipose tissue deposits due to chronic lymph stasis and inflammation, an additional surgical approach may be applied and is discussed in a further section.

Regardless of the stage of disease, if patient compliance to the treatment program is poor, then the outcome may be less than satisfactory. Relative contradictions to lymphatic microsurgery are few and are represented by cases of lymphatic-lymph node aplasia (extremely rare), diffuse metastatic disease, and very advanced stage of lymphedema (stage IIIB) totally unresponsive to conservative therapy.

New Directions in Surgical Treatments for Peripheral Lymphedemas

In recent years, primary and secondary peripheral lymphedemas have become better understood, with the recognition of some genes involved in the disease onset and process, and increased awareness and detection of secondary causes

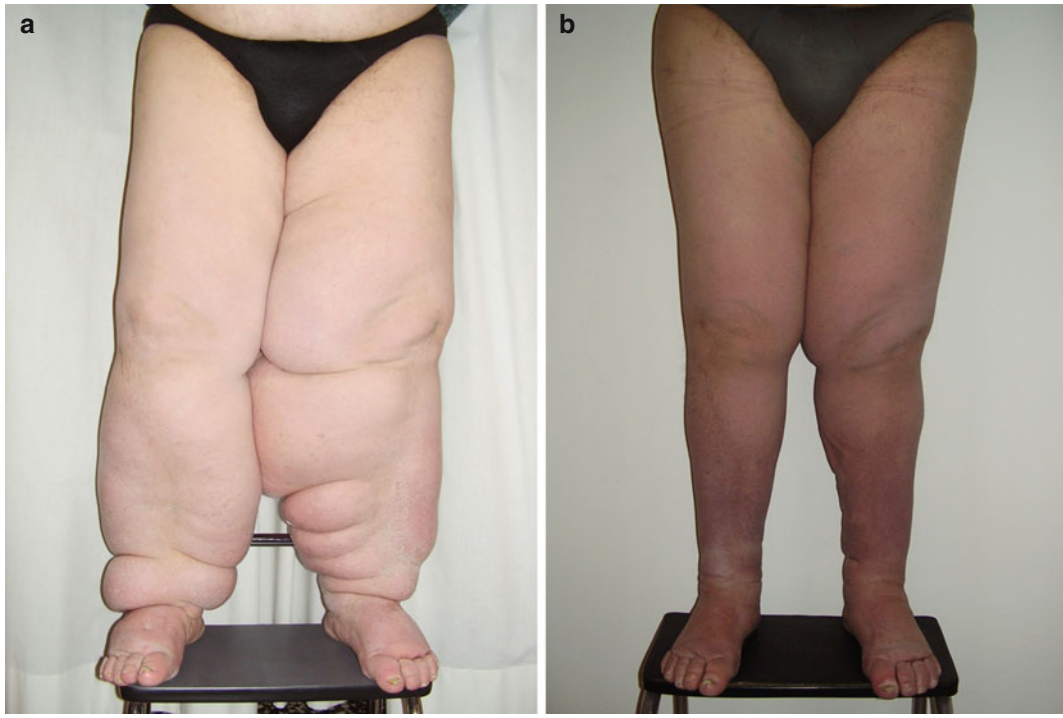

Fig. 51.6 Preoperative photo of a patient with advanced lower-limb lymphedema (**a**). Postoperative photo 1 year from surgery (**b**)

of lymphedema [27–31]. Notwithstanding this, conservative treatments are aimed at minimizing symptoms without addressing the cause of the underlying lymphatic drainage disturbance; which is chronic lymph stasis. Microsurgical derivative and reconstructive techniques are able to restore some, or all, lymphatic circulation in an affected limb by bypassing the obstruction in the lymphatic flow [9, 13, 32, 33]. Short- and long-term restoration of drainage is obtained, and the best results are obtained when the surgery is applied in the early stages of disease and is combined with conservative treatment measures.

In the past few years, we introduced a primary preventive approach using LVA and LVLA at the same time as lymphadenectomy in the surgical treatment of cancer (the lymphatic microsurgical preventive healing approach – LyMPHA [34–36]). Although this research primarily involves secondary lymphedema, which in general is caused by lymphadenectomy for oncological treatment, it is still applicable to a particular group of patients with primary lymphedema, namely, those undergoing surgery in vulnerable areas – regions involving the axillary/inguinal-crural-iliac-obturator lymph nodes. Initially, this approach was applied in a randomized control trial of patients undergoing axillary lymph node dissection for breast cancer treatment, where pre-surgery measures indicated a risk for lymphedema development (e.g., high BMI or suppressed lymphatic transport evident on lymphoscintigraphy; stage IA or subclinical lymphedema) [34–36]. In the patients who underwent the LyMPHA approach, only a slight transient edema was evident in 4.34 % of cases. In contrast, considering those in the treatment as usual group, 30.43 % developed permanent lymphedema. We have also applied this promising preventive technique to melanoma and vulvar carcinomas with axillary/inguinal-crural-iliac-obturator lymph nodal involvement, with excellent success [37].

Traditional debulking surgeries are currently used much less frequently in the treatment of lymphedema. Total excisional techniques, such as the Charles procedure, when employed as the

primary method of surgical treatment for advanced lymphedema have been technically successful in that there is a reduction in the size of the limb, but the results have been also associated with a poor cosmetic result, significant scarring, and sometimes serious complications such as infections [38–40]. Surgical resection of skinfolds and excess tissues can be appropriate in late-stage lymphedemas when there has been marked edema reduction after conservative and microsurgical methods, in body regions relatively inaccessible to conservative measures like the external genitalia, in advanced lymphatic filariasis often treated in combination with LVA or nodal anastomoses when lymphatic channels are widely dilated, or in localized lipolymphedema associated with massive obesity and consequent immobility [41, 42].

Recently, suction-assisted liposuction has been utilized as a less invasive procedure to remove this excess adipose tissue [43, 44]. Given the existing poor lymph drainage in patients with lymphatic diseases, extra caution needs to be taken to avoid damaging the lymphatic vessels further during liposuction. Investigations of lymph vessels in cadavers after dry and tumescent liposuction showed that significant injury to tissues occurred with the movement of the cannula and noted that a tumescent procedure and a parallel approach were necessary to avoid injury in people with normal lymphatic systems [45]. In patients with lymphedema, the lymph vessels and channels are often dilated and tortuous in the advanced stages of disease [46], which is exactly when liposuction is prescribed, and therefore may be more difficult to avoid with the liposuction cannula and more vulnerable to damage. We have recently developed a new lympho-lipo-aspiration technique (fibro-lipo-lympho-aspiration (FLLA) with lymph vessel sparing procedure (LVSP); Corrado Cesare Campisi) to improve the chronic swelling in patients with advanced lymphedema, taking a lymphatic sparing approach. Using blue patent violet (BPV), together with the photodynamic eye (PDE) method with indocyanine green (ICG) fluorescence, to highlight the lymphatic pathways in the limb, the excess adipose tissue is carefully aspirated.

Concluding Remarks

Primary lymphedema is regarded as a clinical manifestation of a lymphatic malformation that developed during the later stage of lymphangiogenesis, where the crucial symptom is chronic lymph stasis. Lymphatic microsurgery provides a means to restore lymphatic drainage, bypassing the obstruction in the lymphatic pathway and directing the flow of lymph into the veins (MLVA) or, in the case of an associated venous pathology, by using an analogous vein graft to bridge the gap in the lymphatic collectors around the obstruction (MLVLA). Lymphatic microsurgery offers excellent outcomes when applied early in the disease process, where a complete resumption of lymphatic flow in the long term is possible, and is a valuable tool in the combined treatment of advanced lymphedema in association with intensive conservative treatments and, when applicable, removal of the fibrotic tissue with an FLLA technique.

References

1. Morgan CL, Lee BB (2008) Classification and staging of lymphedema. In: Tretbar LL, Morgan CL, Lee BB, Simonian SJ, Blondeau B (eds) Lymphedema: diagnosis and treatment. Springer-Verlag Limited, London, pp 21–30
2. Lee BB (2004) Critical issues on the management of congenital vascular malformation. Ann Vasc Surg 18(3):380–392
3. Rutkowski JM, Boardman KC, Swartz MA (2006) Characterization of lymphangiogenesis in a model of adult skin regeneration. Am J Physiol Heart Circ Physiol 291:H1402–H1410
4. Goldman J, Le TX, Skobe M, Swartz MA (2005) Overexpression of VEGF-C causes transient lymphatic hyperplasia but not increased lymphangiogenesis in regenerating skin. Circ Res 96:1193–1199. (Comment: Circ Res. 2005;96:1132–1134)
5. Bastide G, Lefebvre D (1989) Anatomy and organogenesis and vascular malformations. In: Belov S, Loose DA, Weber J (eds) Vascular malformations. Einhorn-Presse Verlag, Reinbek, pp 20–22
6. Leu HJ (1989) Pathoanatomy of congenital vascular malformations. In: Belov S, Loose DA, Weber J (eds) Vascular malformations. Einhorn-Presse Verlag, Reinbek, pp 37–46
7. Witte MH, Jones K, Wilting J et al (2006) Structure function relationships in the lymphatic system and

implications for cancer biology. Cancer Metastasis Rev 25(2):159–184
8. Rockson SG (2008) Diagnosis and management of lymphatic vascular disease. J Am Coll Cardiol 52:799–806
9. Murdaca G, Cagnati P, Gulli R et al (2012) Current views on diagnostic approach and treatment of lymphedema. Am J Med 125:134–140
10. Lee BB, Andrade M, Antignani PL, Boccardo F, Bunke N, Campisi C et al (2013) Diagnosis and treatment of primary lymphedema consensus document of the International Union of Phlebology (IUP)-2013. Published online. http://www.lymphology2013.com/wp-content/uploads/2013/08/IUP-Cosensus-Pr-Lymph-Update-2013-Final-edition-07-10-13.doc
11. Rockson SG (2001) Lymphedema. Am J Med 110(4): 288–295
12. Campisi C, Boccardo F (2004) Microsurgical techniques for lymphedema treatment: derivative lymphatic-venous microsurgery. World J Surg 28:609–613
13. Campisi C, Bellini C, Campisi C et al (2010) Microsurgery for lymphedema: clinical research and long-term results. Microsurgery 30(4):256–260
14. Rutkowski JM, Davis KE, Scherer PE (2009) Mechanisms of obesity and related pathologies: the macro- and microcirculation of adipose tissue. FEBS J 276:5738–5746
15. Dixon JB (2010) Lymphatic lipid transport: sewer or subway? Trends Endocrinol Metab 21:480–487
16. Rutkowski JM, Markhus CE, Gyenge CC, Alitalo K, Wiig H, Swartz MA (2010) Dermal collagen and lipid deposition correlate with tissue swelling and hydraulic conductivity in murine primary lymphedema. Am J Pathol 176:1122–1129
17. Schneider M, Conway EM, Carmeliet P (2005) Lymph makes you fat. Nat Genet 10:1023–1024
18. Olszewski WL (1988) The treatment of lymphedema of the extremities with microsurgical lymphovenous anastomoses. Int Angiol 7:312–321
19. Campisi C, Boccardo F (2002) Lymphedema and microsurgery (invited review). Microsurgery 22:74–80
20. Ogata F, Narushima M, Mihara M, Azuma R, Morimoto Y, Koshima I (2007) Intraoperative lymphography using indocyanine green dye for near-infrared fluorescence labeling in lymphedema. Ann Plast Surg 59:180–184
21. Unno N, Inuzuka K, Suzuki M, Yamamoto N, Sagara D, Nishiyama M et al (2007) Preliminary experience with a novel fluorescence lymphography using indocyanine green in patients with secondary lymphedema. J Vasc Surg 45:1016–1021
22. Papendieck CM (1998) The big angiodysplastic syndromes in pediatric with the participation of the lymphatic system. Lymphology 31:390–392
23. Dellachà A, Boccardo F, Zilla A, Napoli F, Fulcheri E, Campisi C (2000) Unexpected histopathological findings in peripheral lymphedema. Lymphology 33:62–64
24. Campisi C, Eretta C, Pertrile D et al (2007) Microsurgery for the treatment of peripheral lymphedema: long-term out come and future perspective. Microsurgery 27:333–338
25. Campisi C, Boccardo F, Tacchella M (1995) Reconstructive microsurgery of lymphatic vessels: the personal methods of lymphatic-venous-lymphatic (LVL) interpositioned grafted shunt. Microsurgery 16:161–166
26. Campisi C, Boccardo F (2008) Terapia funzionale complete del linfedema (ClyFT; complete lymphedema functional therapy): efficace strategia terapeutica in 3 fasi. Linfologia 1:20–23
27. Bellini C, Boccardo F, Taddei G et al (2005) Diagnostic protocol for lymphoscintigraphy in newborns. Lymphology 38:9–15
28. Bourgeois P, Leduc O, Leduc A (1998) Imaging techniques in the management and prevention of posttherapeutic upper limb edemas. Cancer 83:2805–2813
29. Mariani G, Campisi C, Taddei G, Boccardo F (1998) The current role of lymphoscintigraphy in the diagnostic evaluation of patients with peripheral lymphedema. Lymphology 31:316
30. Pecking AP, Gougeon-Bertrand FJ, Floiras JL (1998) Lymphoscintigraphy: overview of its use in the lymphatic system. Lymphology 31:343
31. Witte C, McNeill G, Witte M (1989) Whole body lymphangioscintigraphy: making the invisible easily visible. In: Mitsumas N, Uchino S, Yabuki S (eds) Progress in lymphology XII. Elsevier, Amsterdam/London/Tokyo, p 123
32. Campisi C, Witte MH, Fulcheri E et al (2011) General surgery, translational lymphology and lymphatic surgery. Int Angiol 30:504–521
33. Campisi C, Da Rin E, Bellini C, Bonioli E, Boccardo F (2008) Pediatric lymphedema and correlated syndromes: role of microsurgery. Microsurgery 28: 138–142
34. Boccardo F, Casabona F, Friedman D, Puglisi M, De Cian F, Ansaldi F, Campisi C (2011) Surgical prevention of arm lymphedema in breast cancer treatment. Ann Surg Oncol 18:2500–2505
35. Boccardo F, Campisi CC, Molinari L, Dessalvi S, Santi PL, Campisi C (2012) Lymphatic complications in surgery: possibility of prevention and therapeutic options. Updates Surg 64(3):211–216. Epub 2012 Jul. 21
36. Campisi CC, Larcher L, Lavagno R, Spinaci S, Adami M, Boccardo F, Santi P, Campisi C (2012) Microsurgical primary prevention of lymphatic injuries following breast cancer treatment. Plast Reconstr Surg 130:749e–750e
37. Morotti M, Menada MV, Boccardo F, Ferrero S, Casabona F, Villa G, Campisi C, Papadia A (2013) Lymphedema microsurgical preventive healing approach for primary prevention of lower limb lymphedema after inguinofemoral lymphadenectomy for vulvar cancer. Int J Gynecol Cancer 23(4):769–774
38. Fujita T (2013) Optimizing surgical treatment for lymphedema. J Am Coll Surg 216:169–170
39. Mehrara B, Zampell JC, Suami H, Chang DW (2011) Surgical management of lymphedema: past, present, and future. Lymphat Res Biol 9:159–167

40. Ryan M, Campisi CC, Boccardo F et al (2013) Surgical treatment for lymphedema: optimal timing and optimal techniques. J Am Coll Surg 216:1221–1223
41. Narayanarao Y et al (2012) Pseudosarcoma-massive localized lymphoedema in morbidly obese – a rare entity: case report. Int J Surg Case Rep 3:389–391
42. Jensen V et al (2006) Massive localized lipolymphedema pseudotumor in a morbidly obese patient. Lymphology 39:181–184
43. Hoffman JN, Fertmann JP, Baumeister RG, Putz R, Frick A (2004) Tumescent and dry liposuction of lower extremities: differences in lymph vessel injury. Plast Reconstr Surg 113:718–724
44. Brorson H, Svensson H, Norrgren K, Throrsson O (1998) Liposuction reduces arm lymphedema without significantly altering the already impaired lymph transport. Lymphology 31:156–172
45. Schaverien MV, Munro KJ, Baker PA, Munnoch DA (2012) Liposuction for chronic lymphoedema of the upper limb: 5 years of experience. J Plast Reconstr Aesthet Surg 65:935–942
46. Lu Q, Delproposto Z, Hu A, Tran C, Liu N, Xu J, Bui D, Hu J (2012) MR lymphography of lymphatic vessels in lower extremity with gynecologic oncology-related lymphedema. PLos One 7:e50319