Peertechz®

CLINICAL GROUP

JOURNAL OF
Surgery and Surgical Research

ISSN: 2455-2968 DOI: https://dx.doi.org/10.17352/jssr

Review Article

Surgical research, staging-guided technical procedures and long-term clinical outcomes for the treatment of peripheral lymphedema: the Genoa Protocol

Corrado Cesare Campisi[1]*, Lidia Molinari[2], Caterina Sara Campisi[3], Giuseppe Villa[4], Ezio Fulcheri[5], and Corradino Campisi[6]

[1]MD, PhD, MRMES (CCC), Consultant Surgeon-in-Chief at Private Center of Clinical Lymphology, Lymphatic Surgery, Microsurgery, LASER-Assisted Surgery, and Outpatient Surgery, Genoa, Italy
*Adjunct Professor of Plastic, Reconstructive and Aesthetic Surgery, University of Catania, Master of Reconstructive Microsurgery-European School, Italy

[2]MD, Post-graduate on General-Alimentary Tract Surgery (LM), University of Genoa (confederated with Pisa and Siena). Consultant Surgeon at Private Surgical Clinic "Villa Montallegro" & Private Center of Clinical Lymphology, Lymphatic Surgery, Microsurgery, LASER-Assisted Surgery and Outpatient Surgery, Genoa, Italy

[3]MD, Post-graduate on Dermatology (CSC), University of Genoa, Consultant Dermatologist-in-Chief at Private Center of Surgical Dermatology, Oncological Dermatology, Aesthetic Dermatology, Cosmetics, LASER-Assisted Surgery, and Outpatient Surgery. Genoa, Italy

[4]MD, Post-graduate on Nuclear Medicine-Lymphoscintigraphy (GV), San Martino Polyclinic University Hospital, Genoa, Italy

[5]MD, Anatomo-Histopathology, Associate Professor (EF), School of Medical Sciences and Pharmaceutics, Department of Surgical Sciences and Integrated Diagnostics-DISC. University of Genoa, Italy

[6]MD,PhD,FACS,MD H.C., Prof. H.C., Professor of General Surgery (CC), Post-graduate on General, Vascular and Emergency Surgery, School of Medical Sciences and Pharmaceutics, Dpt. of Surgical Sciences and Integrated Diagnostics- DISC, University of Genoa, Consultant Surgeon-in-Chief at Private Surgical Clinic "Villa Montallegro" & Director of Private Center of Clinical Lymphology, Lymphatic Surgery, Microsurgery, LASER-Assisted Surgery, and Outpatient Surgery. Genoa, Italy

Received: 29 April, 2020
Accepted: 27 May, 2020
Published: 28 May, 2020

***Corresponding author:** Corradino Campisi, MD,PhD, FACS, MD H.C., Prof. H.C., Professor of General Surgery (CC), Consultant Surgeon- in- Chief at Private Center of Clinical Lymphology, Lymphatic Surgery, Microsurgery, LASER-Assisted Surgery, and Outpatient Surgery, via Assarotti 46/1, 16122 Genoa, Italy.
E-mail: campisi@unige.it; campisicorradino@tin.it

Keywords: Peripheral lymphedema; Lymphedema staging; Lymphatic Microsurgery; Derivative Multiple - Lymphatic- Venous-Anastomoses (MLVA); Reconstructive Lymphatic Microsurgery/Lymphatic-Venous-Lymphatic Bypass (MLVLA) - Interpositioned Autologous Vein Grafted Shunts; Single-Site Lymphatic Microsurgery; Liposuction; Lymph Vessel Sparing Procedure-LVSP; Indocyanine Green (ICG) Microlymphography; Blue Patent Violet-BPV Lymphochromic Test; Fibro-Lipo-Lymph-Aspiration (FLLA); Superficial and Deep Lymphoscintigraphy; Lymphedema Primary, Secondary and Tertiary Prevention

https://www.peertechz.com

Citation: Campisi CC, Molinari L, Campisi CS, Villa G, Fulcheri E, and Campisi C (2020) Surgical research, staging-guided technical procedures and long-term clinical outcomes for the treatment of peripheral lymphedema: the Genoa Protocol. J Surg Surgical Res 6(1): 041-050.
DOI: https://dx.doi.org/10.17352/2455-2968.000096

Abstract

The Author 's vast surgical experience in the treatment of primary and secondary peripheral lymphedema is reported. The objective is to describe the techniques and the long-lasting clinical outcomes based on more than 45 years research and clinical applications, with particular reference to staging-guided derivative and reconstructive lymphatic microsurgery at a single site, and to complementary, sequential, minimally invasive procedures of selective liposuction.

5.046 cases of patients (demographic characteristics are at length described) affected by upper and/or lower limb lymphedema, between 1973 and 2020, underwent lymphatic microsurgery and, between 2012 and 2020, Fibro-Lipo-Lymph-Aspiration according to Lymph Vessel Sparing Procedure (FLLA-LVSP), for latest stages of Lymphedema previously treated by Lymphatic Microsurgery with partial improvement of the disease. Derivative Multiple Lymphatic-Venous Anastomoses (MLVA) or, in selected cases of Phlebolymphedema absolutely contraindicating derivative procedures, lymphatic pathway reconstruction, using interpositioned vein grafted shunts (Multiple-Lymphatic-Venous-Lymphatic-Anastomose /MLVLA), above all at lower limbs, were performed at a single site, either the brachial-axillary or inguinal-crural region.

Adopted surgical techniques are described in detail. As far as exposition of results is concerned, patients were followed up for a minimum of 5 years to over 20 years. Clinical outcomes included excess limb volume (ELV), frequency of dermatolymphangioadenitis (DLA) attacks, lymphoscintigraphy, and use of conservative therapies.

Compared with preoperative conditions, patients obtained significant reduction in ELV of over 90%, with an average follow-up of 10 years or more. Over 96% of patients with earlier stages of disease (stage IB or IIA) progressively stopped using conservative therapies and over 80% of patients with later stages (stages IIB and III) significantly decreased the frequency of physical therapies and discontinued compressive garments or stockings. DLA attacks considerably reduced by over 95%.

MLVA or MLVLA techniques when performed at a single site produce excellent outcomes in the treatment of both primary and secondary lymphedemas, giving the possibility of a complete restoration of lymphatic flow in early stages of disease, when tissue changes are minimal. For late stages of lymphedema only partially responding to MLVA or MLVLA, FLLA-LVSP sequential procedures can significantly improve the long-term clinical outcomes.

Staging-guided treatment of peripheral lymphedema, according to Authors' Genoa Protocol, carries out contextual target of primary, secondary and tertiary prevention in the potential worsening of the disease.

Introduction

Peripheral lymphedema remains an often poorly recognized disease that causes significant morbidity in advanced cases, in terms of physical limitations, infection risk, and seriously compromised lifethreatening condition [1,2].

Chronic Lymphedema is associated with fibrotic tissue changes and adipose formation ("non-pitting" edema) that is irreversible when untreated or improperly managed [3-6].

Conservative treatments are time consuming and expensive, and can be ineffective in halting the progression of the disease [2,7].

The development, in the past 50 years, of surgical techniques to restore lymphatic flow offers a treatment that targets not only more than symptomatic relief, but also a functional repair of the underlying problem of lymph stasis.

Initial procedures involved lymph nodal-venous shunts, but these were associated with a high failure rate due to the thrombogenic effect of the lymph node pulp entering the venous system and re-endothelization of the lymph node surface [8-10].

Technical modifications improved the long-term outcomes of lymphatic microsurgery, but the efficacy, in terms of volume reduction and long-term stability, remains highly variable between surgical centers worldwide [11-14].

The Center of Clinical Lymphology, Lymphatic Surgery and Microsurgery, in Genoa, Italy, has obtained excellent stable clinical outcomes for more than 45 years by utilizing multiple lymphatic-venous anastomoses (MLVA) or, in selected cases, multiple lymphatic-venous-lymphatic-anastomoses (MLVLA) techniques, above all in lymphedemas at early stages (IB-IIA) and, starting from 2012, by additional sequential minimally invasive technique of selective liposuction (Fibro-Lipo-Lymph-Aspiration with Lymph Vessel Sparing Procedure-FLLA/LVSP), for lymphedemas at late stages (IIB-III) previously treated by Lymphatic Microsurgery with only partial improvement of the disease [14,15].

Anastomoses are performed at a single site using larger superficial and deep lymphatic vessels, attached to collateral branches of the main veins close to vein valves, to avoid backflow of blood and the closure of the anastomoses.

Microsurgical approach is planned on the guide of pre-operative superficial and deep lymphoscintigraphy, combined with calculation of Transport Index [16-18].

Blue Patent Violet (BPV) Lymphochromic Test and Indocyanine Green Microlymphography (ICG Test) are intra-operatively properly combined to select both superficial and deep lymph collectors.

A single-site approach minimizes the number of incisions and thereby potential entry sites for infections.

The retrospective evaluation of this considerable surgical experience is described with reference to the treatment of both primary and secondary peripheral lymphedemas.

Materials and methods

- Clinical registry, demographic characteristics, and description of surgical techniques.

Between 1973 and 2020, 5.046 cases have been treated by microsurgery for peripheral lymphedema in Genoa, Italy (Figure 1): both upper and lower limb lymphedema, with primary and secondary etiology, at early and late stages.

The two microsurgical techniques utilized in these procedures were derivative MLVA or reconstructive MLVLA (Figures 2,3).

Citation: Campisi CC, Molinari L, Campisi CS, Villa G, Fulcheri E, and Campisi C (2020) Surgical research, staging-guided technical procedures and long-term clinical outcomes for the treatment of peripheral lymphedema: the Genoa Protocol. J Surg Surgical Res 6(1): 041-050.
DOI: https://dx.doi.org/10.17352/2455-2968.000096

- Description of surgical techniques

In general, the MLVA technique was adopted.

Several healthy-appearing lymphatics located at the single operative site were directly introduced into the selected vein by a U-shaped stitch (using 8/0 to 10/0 prolene sutures, depending on the caliber of the vessels), and then adhered to the vein cut-end by means of additional stitches between the vein border and peri-lymphatic tissue. Finally, the U-shaped stitch was removed to avoid occluding the lymphatic collectors.

Blue Patent Violet dye (BPV, a sodium or calcium salt of diethylammonium hydroxide) stained the well-functioning lymphatics blue, allowing visualization under the operating microscope of the passage of the lymph into the vein, at the completion of the anastomoses, to ensure the patency of these joins (Figure 2).

Blue Patent Violet Lymphochromic Test and Indocyanine Green Microlymphography (ICG Test) can be properly combined in this procedure, to select both superficial and deep lymph collectors, allowing to identify 3 anatomic levels of the limb lymphatic network: level 1, superficial-subdermic; level 2, superficial-epifascial; level 3, subfascial or deep (Figure 4).

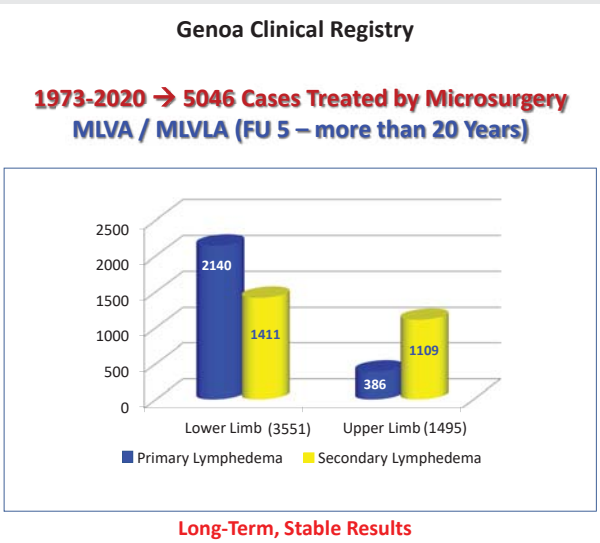

Figure 1: Genoa Clinical Registry (1973-2020).

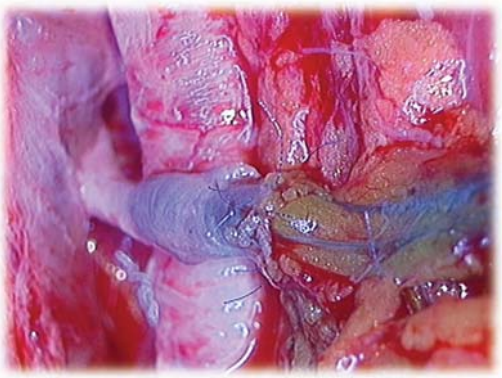

Figure 2: Single-Site Multiple Lymphatic Venous Anastomoses (MLVA).

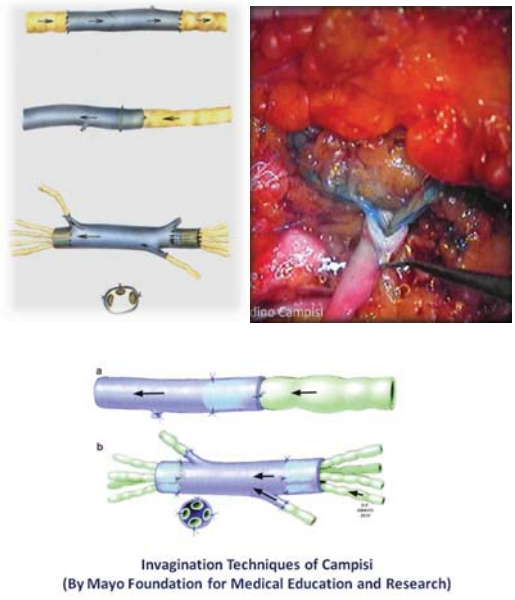

Figure 3: Reconstructive Lymphatic-Vein-Lymphatic Autologous Interpositioned Graft: Multiple LVLA (MLVLA).

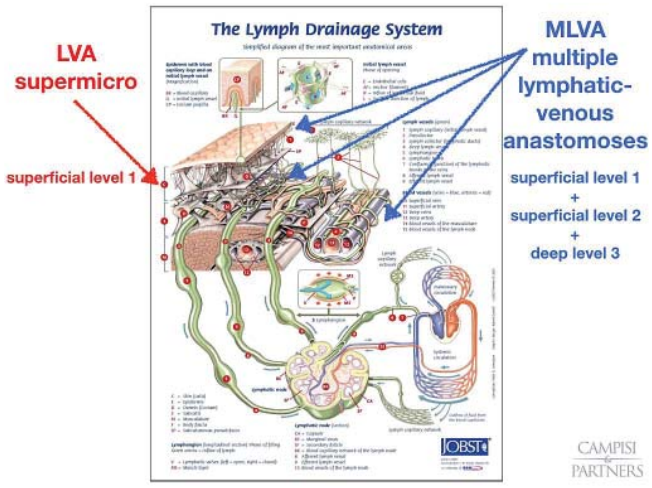

Figure 4: Anatomic levels of the limb lymphatic network.

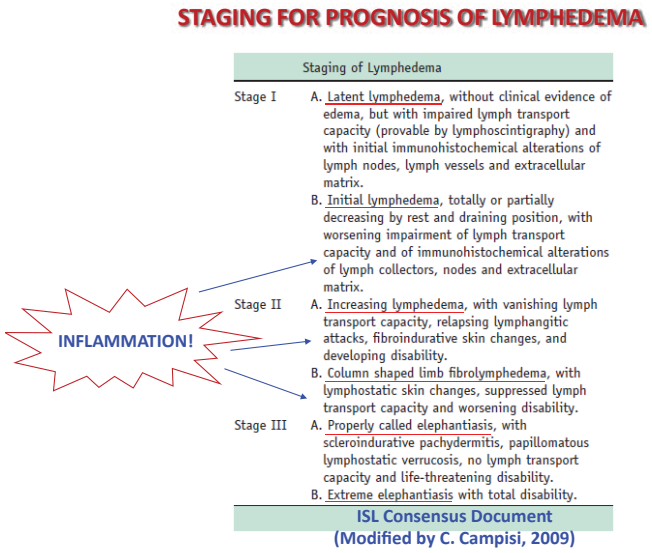

Figure 5: Lymphedema Staging.

Citation: Campisi CC, Molinari L, Campisi CS, Villa G, Fulcheri E, and Campisi C (2020) Surgical research, staging-guided technical procedures and long-term clinical outcomes for the treatment of peripheral lymphedema: the Genoa Protocol. J Surg Surgical Res 6(1): 041-050.
DOI: https://dx.doi.org/10.17352/2455-2968.000096

For lower limb lymphedema, the MLVAs were created at the site of a single incision made at the subinguinal region. Lymphatic-lymph nodal superficial and deep structures were isolated and all afferent lymphatics were used. Lymph nodal samples, together with lymph vessel biopsies and samples of the superficial and deep matrix, were obtained for subsequent histopathological examination. The typical findings in primary lower limb lymphedema were of varying grades of fibrosclerosis of the lymph nodes and thickening of the nodal capsule, but with sound afferent lymphatic vessels. In addition, the analysis of the matrix specimens showed various degrees of alterations. Histopathological analysis is, therefore, an essential component of lymphedema staging for prognosis (Figures 5,6)

For upper limb lymphedemas, MLVAs were created at the middle third of the volar surface of the arm, using both superficial and deep afferent lymphatic collectors, as visualized by the BPV Test properly combined with ICG Test. Deep lymphatics were located between the humeral artery, homonym veins and median nerve. A patent branch of one of the humeral veins containing a well-functioning valve was used for the anastomoses, adopting a telescopic technique.

In this way, performing simultaneous connections of superficial and deep lymph collectors with minor vein branches, by end-to-end telescopic MLVAs, a long lasting positive lymphatic venous one-way pressure gradient was ensured.

Primary lymphedemas were usually associated with lymph nodal dysplasias (LAD II, according to Papendieck's definition) (Table 1) [19], with hyperplastic lymph nodes, sinus histiocytosis, and a thick and fibrous capsule with micro-lymphangioadenomiomatosis. In these cases, lymphatic obstruction was evident due to alterations of the lymphatic vessels that appeared dilated with thickened walls and where the smooth muscle cells were reduced in number and fragmented with fibrotic elements [8].

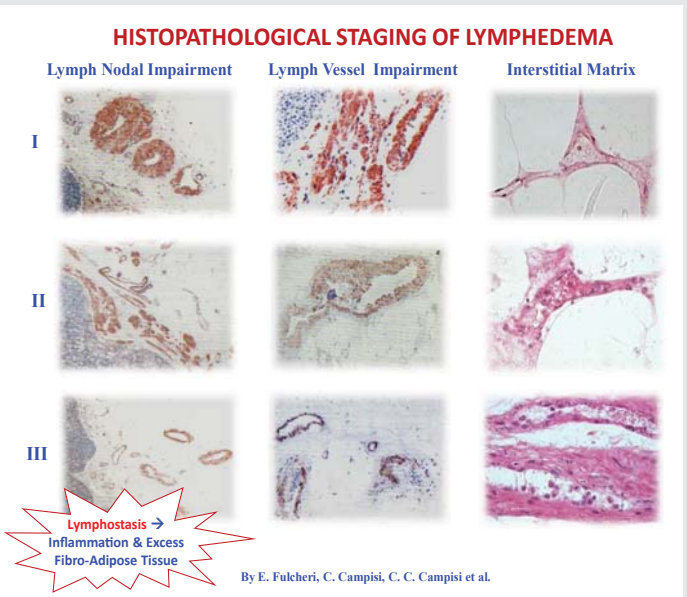

Figure 6: Histopathological Staging of Lymphedema.

Table 1: Classification of Lymphedema on etiological basis.

CLASSIFICATION OF LYMPHEDEMA ON ETIOLOGICAL BASIS	
CONGENITAL OR PRIMARY SECONDARY	**ACQUIRED**
FROM BIRTH - CONNATAL: 0-2 YEARS	POST-LYMPHANGITIS
SPORADIC / HEREDITARY – FAMILIAL	POST-SURGERY
PRAECOX < 35 yrs	POST-RADIATION
TARDIVE > 35 yrs	POST-TRAUMA
	POST-FILARIA
LAD I: LYMPHANGIODYSPLASIA	
LAD II: LYMPHADENODYSPLASIA	
LAAD: LYMPHANGIO-ADENO-DYSPLASIA	

C.Campisi - C. Papendieck (2001)

In Genoa clinical experience, secondary lymphedemas were generally due to lymphadenectomy and radiotherapy performed for oncological reasons (carcinoma of the breast, uterus, penis, bladder, prostate gland, rectum, and seminoma of the testis), or for complications of minor surgeries, for varicose veins, crural and inguinal hernias, lipomas, tendinous cysts, or inguinal and axillary nodal biopsies.

Most of the lymphedemas treated were at stages IIA (41%) and IIB (45%), with 5% at stage IB and 9% at stages IIIA and B, according to the personal (CC) staging system for lymphedema (Figure 5). There also exists a subset of patients, in Genoa clinical registry, where MLVAs were performed simultaneously with oncological surgery (for trunk melanoma or carcinoma of the breast, vulvar, uterus, prostate, bladder, with axillary or inguinal-crural-iliac-obturatory lymph nodal involvement), in a preventive approach, where preoperative examination indicated a risk of lymphedema development (stage IA or latent-subclinical lymphedema) [20,21].

Objective clinical measures of lymphedema consisted of limb water volumetry, circumferences and, above all, superficial and deep lymphoscintigraphy. This investigative procedure, performed with either ^{99m} Tc-labeled antimony sulfurcolloid or ^{99m} Tc-nanocolloid human serum albumin (90% of the particles > 80 nm in size), was employed in the diagnostic workup prior to surgery, to determine the eligibility for derivative or reconstructive lymphatic microsurgery.

Lymphoscintigraphy clearly indicates when the edema is of lymphatic origin and provides useful data about the etiology and lymphedema staging (Figure 5). A transport index (TI) can be calculated using the appropriate formula to categorize the lymphatic flow as normal or pathological:

$$TI = K+D+(0.04xT)+N+V$$

where K = transport kinetics (scored as 0-normal, 3-mild delay, 5-marked delay, 9-no transport);

D= distribution of the tracer (scored as 0-normal, 3-mild

Citation: Campisi CC, Molinari L, Campisi CS, Villa G, Fulcheri E, and Campisi C (2020) Surgical research, staging-guided technical procedures and long-term clinical outcomes for the treatment of peripheral lymphedema: the Genoa Protocol. J Surg Surgical Res 6(1): 041-050.
DOI: https://dx.doi.org/10.17352/2455-2968.000096

dermal diffusion, 5-marked dermal diffusion, 9-absent visualization); T=time to visualize the lymph nodes (minutes); N=visualization of lymph nodes (scored as 0-normal, 3-mild, 5-poor, 9-absent); and V= visualization of lymph vessels (scored as 0-normal, 3-mild, 5-poor, 9-absent).

A score of less than 10 signifies a normal TI, and a score ≥ 10 signifies a pathological TI [18].

Duplex scan was performed in all patients to identify any venous disorder that might be contributing to the edema. In most patients, it was possible to correct this venous dysfunction at the same time as the microsurgery such as performing valvular plasty for venous insufficiency with 6/0 nylon sutures. In the minority of cases non-surgically correctable venous pathology was a contraindication for undertaking MLVA. In these cases, it was possible to perform MLVLA to reconstruct a new lymphatic pathway.

The most commonly used technique was the Author's (CC) interposition of an autologous vein graft between the lymphatics above and below the site of obstruction in the lymphatic flow [22-24] (Figure 3). The venous segment can be harvested from the same operative site or from the forearm (typically the cephalic vein).

The length of the graft varied from 7 to 15 cm. It is very important to collect several lymphatics at the distal cut-end of the vein segment to maintain the vein segment full of lymph and to avoid closure of the anastomotic sites, distal and proximal cut-ends, by thrombosis. The valves of the vein segment are useful to address the flow of lymph in the correct direction and to prevent lymph gravitational back flow. As with the MLVAs, the lymphatic collectors were directly introduced into the vein cut-ends by means of a U-shaped stitch, which was then stabilized with additional peripheral stitches and, finally, removed, leaving lymph collectors free into the vein.

In the last 8 years, an evaluation of the lymphatic pathways in the affected limbs, at the same time as the lymphatic surgery,

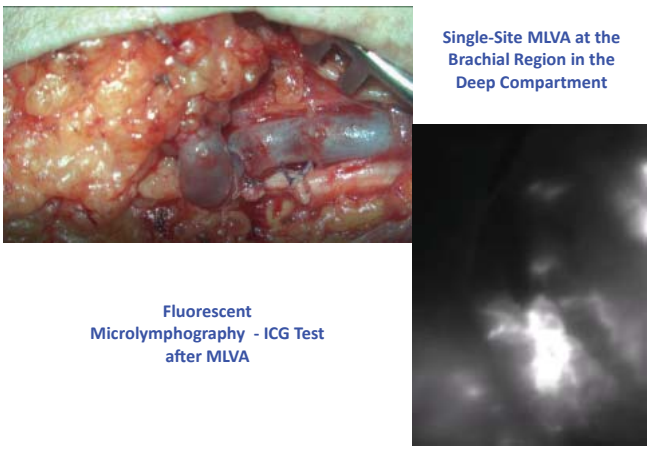

Figure 7: Peroperative fluorescent microlymphography (ICG) at completion of MLVA in the deep brachial compartment.

Figure 8: Peroperative fluorescent microlymphography (ICG) at completion of MLVA in the epifascial compartment of the inguinal-crural region.

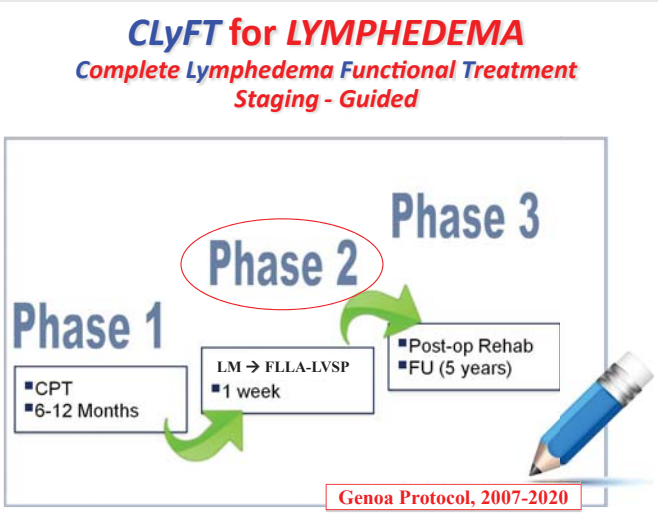

Figure 9: Genoa CLyFT Protocol.

based on ICG Test, has been usually combined with Blue Patent Violet (BPV) Lymphochromic Test, to properly select and to map both superficial and deep lymph collectors of the levels 1-2 and 3, thus planning the best surgical strategy by matching the operating results with pre-operative superficial and deep lymphoscintigraphic data and the related Transport Index.

ICG Test is performed by intradermal loco-regional injection of indocyanine green and subsequent survey of fluorescence by means of near-infrared (NIR) camera. Simultaneous use of ICG with BPV advantageously combines the two methods allowing to better visualize the loco-regional lymphatic flow at the surgical site and furthermore to check the patency of the anastomoses intraoperatively [25,26].

Single-Site MLVAs can be verified by BPV and ICG Tests at the brachial region, in the deep compartment (level 3), and in the inguinal-crural region (levels 2 and 3): Figures 7-8.

Microsurgical interventions (MLVA-MLVLA) and, starting from 2012, the additional sequential minimally invasive technique of selective liposuction (Fibro-Lipo-Lymph-

Citation: Campisi CC, Molinari L, Campisi CS, Villa G, Fulcheri E, and Campisi C (2020) Surgical research, staging-guided technical procedures and long-term clinical outcomes for the treatment of peripheral lymphedema: the Genoa Protocol. J Surg Surgical Res 6(1): 041-050.
DOI: https://dx.doi.org/10.17352/2455-2968.000096

Aspiration with Lymph Vessel Sparing Procedure: FLLA-LVSP), pointed out in Genoa (CCC), for lymphedemas at late stages (IIB-III), previously treated by Lymphatic Microsurgery with only partial improvement of the disease [14,15], are part of an integrated treatment protocol called "Complete Lymphedema Functional Therapy - CLyFT [22] (Figure 9).

The other elements of this protocol consist of manual and mechanical lymphatic drainage (according to Combined Physical Therapy-CPT system) [27] and intermittent negative pressure therapy, in conjunction with an innovative technological physical bio-circuit, digitally personalized for each patient, appropriate multilayered bandages and compressive garments or stockings. Mechanical lymphatic drainage basically refers to the use of uniform and sequential pneumatic devices. In addition, manual lymphatic drainage is performed by means of tailored LPG® System-Endermologie.

CLyFT Protocol is applied in 3 phases: 1- an intensive preoperative phase, for patients poorly responding to conservative treatment after 6-12 months. 2- Surgical phase (Lymphatic Microsurgery/FLLA-LVSP) of one week of length. 3- Postoperative Rehabilitation and Follow-up for a minimum of 5 years. The intensive preoperative phase 1 is targeted to reduce the size of the affected limb as much as possible prior to the surgical approach, followed by a gentle postoperative phase, in which the pressures of the lymphatic drainage are gradually increased as healing continues, and finally, by a long-term maintenance phase of daily (often self-managed) manual-mechanical lymphatic drainage and physical remedial exercises and activity, to strengthen the anastomotic joints over time.

Proper lifestyle, skin care, cosmetic measures, and tailored dietary habits with scientifically based functional foods are needed [28].

The timing of the treatment protocol depends on the preoperative stage of the disease, but in general there is 1 or 2 weeks of preoperative CLyFT, subsequently surgical intervention, and then 1 or 2 weeks of postoperative CLyFT, before patients initiate the maintenance phase.

Patients in this retrospective analysis were followed up for a minimum of 5 years to a maximum of 25 years postoperatively. The follow-up consisted of periodic clinical evaluations at 1,3,6 and 12 months after surgery, and then annually for a minimum of 5 years.

Postoperative lymphoscintigraphy has been performed on the average rate of 1, 3 and 5 years after operation. This close patient follow-up gives optimal control for the long-term clinical outcomes.

These data can be compared with other Authors' outcomes [29-34].

Results

Clinical outcomes improve the previous microsurgical techniques that are applied in the treatment of peripheral

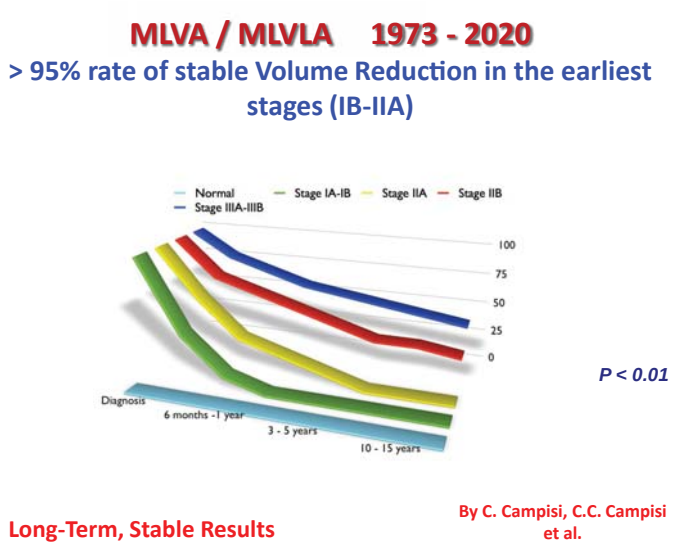

Figure 10: MLVA /MLVLA 1973-2020: Long-Term Results.

lymphedema, due to the absence of (or minimal) fibrosclerotic tissue changes in the lymphatic walls and surrounding tissues in the early stages of disease. Compared with preoperative conditions, patients obtained significant reduction in excess limb volume (ELV) of over 90%, with an average of 75% as measured by limb water volumetry and circumferences (Figure 10).

These results were stable over an average of 10 years of follow-up. Over 96% of patients with earlier stages of disease (stage I or IIA) progressively stopped using conservative therapies over the length of the follow-up period. In patients with more advanced lymphedema (stages IIB and III), above all those treated, as from 2012 up to the end of 2019 (in all 375), by previous lymphatic microsurgery with limited improvement, and subsequently by sequential additional FLLA-LVSP, over 80% significantly decreased the frequency of physical therapies and discontinued compressive garments or stockings.

In all patients, the frequency of dermatolymphangioadenitis attacks considerably reduced by over 95%, compared with preoperative conditions. There were no immediate significant postoperative complications, such as postoperative infections, lymphorrhea or worsening of edema. In the past 5 years, patency verifications was also performed postoperatively using ICG 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 ICG microlymphography is used immediately after surgery it is possible to verify microsurgical patency and provide evidence that no thrombosis of the anastomoses has occurred.

Lymphoscintigraphy was used to verify the patency of the microanastomoses in the long term by direct and indirect methods (Figures 11-12).

These included the following:

a. Reduced dermal backflow of the tracer and the appearance

Citation: Campisi CC, Molinari L, Campisi CS, Villa G, Fulcheri E, and Campisi C (2020) Surgical research, staging-guided technical procedures and long-term clinical outcomes for the treatment of peripheral lymphedema: the Genoa Protocol. J Surg Surgical Res 6(1): 041-050.
DOI: https://dx.doi.org/10.17352/2455-2968.000096

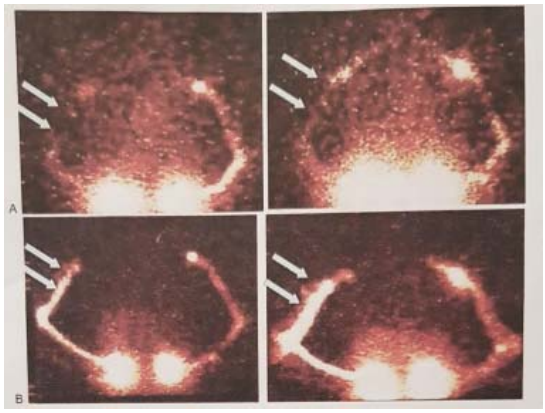

Figure 11: (A) Preoperative lymphoscintigraphy in a patient affected by right arm lymphedema secondary to breast cancer treatment. Poor lymphatic transport along the arm can be seen with dermal backflow (arrows). (B) Postoperative lymphoscintigraphy shows the appearance of preferential lymphatic pathways and disappearance of dermal backflow (arrows).

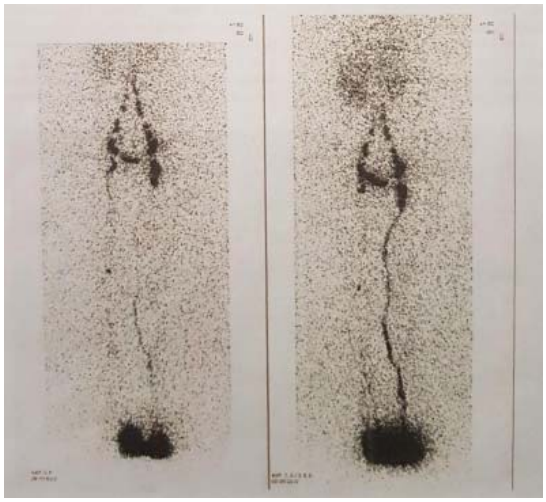

Figure 12: Preoperative lymphoscintigraphy in a patient affected by left leg lymphedema (left). Postoperative lymphoscintigraphy shows the appearance of preferential lymphatic pathways into the inguinal region (right).

of preferential lymphatic pathways, not discernible preoperatively.

b. The disappearance of the tracer at the site of the lymphatic-venous anastomoses (MLVA), indicating the passage of lymph into the bloodstream, or the visualization of the interpositioned autologous vein graft (MLVLA).

c. Earlier liver uptake of tracer, compared with preoperative parameters, taken as indirect evidence of the passage of lymph in the bloodstream.

In the long term, the ongoing reduction in ELV over time, together with follow-up lymphoscintigraphy, provided evidence of the patency of the anastomoses and absence of thrombosis.

No patient who was compliant with the CLyFT treatment protocol experienced a worsening of lymphedema. There was anecdotal evidence of significant patient satisfaction with the clinical outcomes achieved and this was supported by the fact that vast majority of patients completed the minimum 5-years follow-up regimen.

Discussion

Lymphatic microsurgery represents an effective and, most importantly, a functional repair of the lymphatic system, that treats the underlying cause of the disease, the lymph stasis resulting from an obstruction in the flow of lymph.

The ideal indications for lymphatic microsurgery include the following:

- Early stages of disease (IB, IIA, and early IIB).
- Superficial and deep lymphoscintigraphy, showing a low inguinal or axillary lymph node uptake, and minimal passage of tracer beyond the proximal node areas of the limbs.
- Excellent patient compliance.
- A Center for treatment of lymphatic diseases, where the patient can be visited for any necessity, related to the Center for Lymphatic Surgery where the Microsurgery is performed, with additional specialistic competence in complementary minimally invasive surgical options.

For patients with advanced stages of disease (late IIB, IIIA, and IIIB), as indicated by a significant impairment in the function of lymphatic channels and regional lymph nodes visualized by lymphoscintigraphy, BPV-Lymphochromic Test and ICG Fluorescent Microlymphography, it is necessary to reduce the stage of disease by conservative means prior to surgery (so called preoperative "destaging").

Lymphatic Microsurgery has an important role in the treatment not only of latent-subclinical lymphedema (stage IA), and of clinical lymphedema at early stages (IB, IIA, and early IIB), but also for the treatment of lymphedema at advanced stages (late IIB, IIIA, and IIIB), where addressing the lymph stasis helps with edema reduction ad also improving immune function in the affected limb [23], as recent research indicates that chronic lymph stasis is associated with reduced immune responses to infections [35-38].

According to this protocol, a complete functional staging-guided treatment of peripheral lymphedema consequently realizes primary, secondary and tertiary prevention (Figure 13).

Postsurgically, it is very important for the patients to be closely followed up by a Specialistic Team to improve the clinical outcome and maintain the results overtime. In the case of poor treatment compliance, results may be less than satisfactory.

Relative contraindications to lymphatic microsurgery are few, which include lymphatic-lymph nodal aplasia-agenesis (exceedingly rare), diffuse metastatic carcinomas, and extremely advanced lymphedema or elephantiasis (stage III B), unresponsive to conservative measures in non-compliant patients.

Citation: Campisi CC, Molinari L, Campisi CS, Villa G, Fulcheri E, and Campisi C (2020) Surgical research, staging-guided technical procedures and long-term clinical outcomes for the treatment of peripheral lymphedema: the Genoa Protocol. J Surg Surgical Res 6(1): 041-050.
DOI: https://dx.doi.org/10.17352/2455-2968.000096

In the Center of Clinical Lymphology, Lymphatic Surgery and Microsurgery in Genoa, Italy, treatment for peripheral lymphedema is conducted according to a prescribed protocol.

CLyFT represents the initial treatment for all patients (Figure 9).

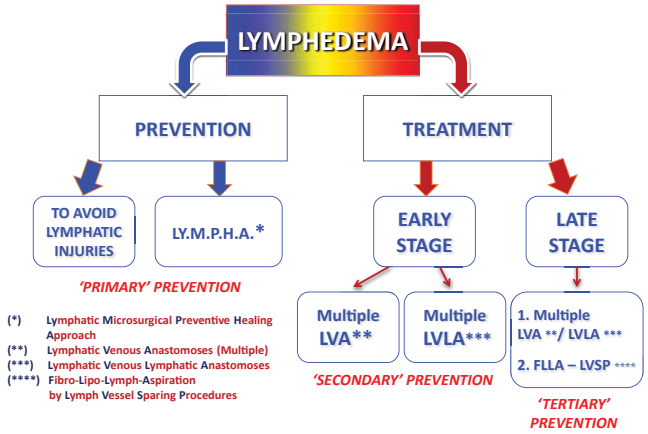

Figure 13: Genoa Algorithm for surgical prevention and treatment of lymphedema.

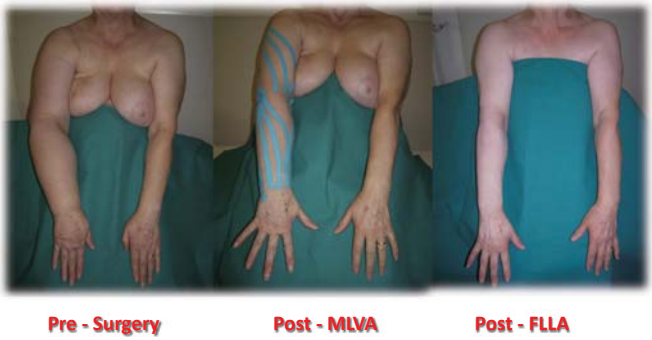

Figure 14: Long-term result (at 5 years follow-up) of complete surgical treatment for breast cancer-related lymphedema of right arm (MLVA+FLLA).

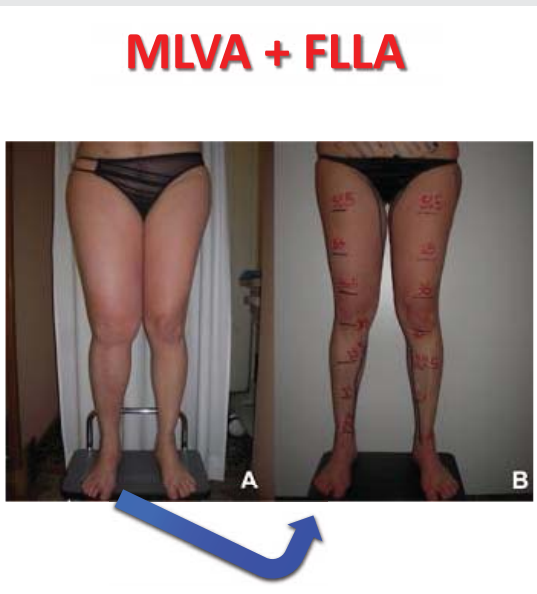

Figure 15: Long- term result (at 5 years follow-up) of complete surgical treatment for cervical-uterine cancer-related lymphedema of right lower limb (MLVA+FLLA).

The surgical timing is based on the clinical indications. In the initial stages of lymphedema, microsurgery is applied early in the treatment process before the progression to fibrosclerotic tissue changes and excess adipose deposition occurs. The patients undergo 1 or 2 weeks of CLyFT to minimize the edema prior to surgery.

In more advanced stages of lymphedema, where these tissue changes have already occurred, microsurgery is applied when the physical therapy component of CLyFT fails to obtain further edema reduction or prevent recurrent lymphangitis.

Lymphatic microsurgery applied at this time allows further amelioration of the pathology, but it needs subsequent additional and sequential minimally invasive technique of selective loco-regional liposuction, by Fibro-Lipo-Lymph-Aspiration with Lymph Vessel Sparing Procedure/FLLA-LVSP (Figures 14-15).

Lymphatic Microsurgery carried out in Genoa consists of MLVA or, in selected cases of severe phlebolymphedema, absolutely contraindicating derivative techniques, of the reconstructive MLVLA, by autologous interpositioned vein grafts (Figures 2-3).

MLVA and MLVLA are performed at a single tailored short incisional site [14,20,24,39].

Some plastic surgeons performing lymphatic microsurgery have adopted other techniques, making multiple scattered small incisions along the superficial-subdermic route of lymphatic pathways, distally down the lymphedematous limb, and performing a lymphatic-venular anastomosis at each incision [30-34]. However, such a so-called "supermicrosurgery" procedure implies many limitations and risks, as the following:

This technique is limited to the superficial-subdermic lymphatic pathways, not considering the basic role of epifascial-subfascial (deep) lymphatic circulation.

Such a technique does not consider the pathophysiological basic role of gravitational lymphatic reflux phenomenon in orthostatic/postural position of patient, with high risk of blood reflux into lymph vessels and subsequent risk of thrombotic occlusion of the anastomotic sites.

Many spaced out small incisions along the route of the superficial-subdermic lymphatic pathways can cut off communicating lymphatic connections, vital for the active working of collateral lymph pathways. Small superficial-subdermic lymph vessels have a poor valve availability.

Such a technique is often performed under local anesthesia, in day-surgery or out-patient surgical regimen, exceedingly simplifying the management of so critical lymphostatic pathology.

Such a technique involves operating costs, many operative microscopes for each single operation, and many surgeons simultaneously operating, too much expensive on the economic point of view, in comparison with Genoa single-site lymphatic

Citation: Campisi CC, Molinari L, Campisi CS, Villa G, Fulcheri E, and Campisi C (2020) Surgical research, staging-guided technical procedures and long-term clinical outcomes for the treatment of peripheral lymphedema: the Genoa Protocol. J Surg Surgical Res 6(1): 041-050.
DOI: https://dx.doi.org/10.17352/2455-2968.000096

microsurgery, requiring 1-2 surgeons and only 1 operative microscope.

The rationale behind using a single-site technique is twofold:

A proximal single-site surgery likely lowers the risk of infections, as there is less surface area for bacteria to breach the skin barrier. This is particularly relevant for advanced stages of disease with significant lymph stasis and impaired loco-regional immune function [35-38]. Incisions made in the distal area of a lymphedematous limb may increase the risk of postoperative infections.

The caliber of the lymphatic vessels increases proximally. Not only these vessels are easier to use for creating microanastomoses, but they also allow a greater amount of lymph to flow through each anastomosis, thus realizing a long-lasting positive lymphatic-venous one-way pressure gradient. This is very important when trying to redress the balance of fluid in and out of the limb [14].

Super-microsurgery using small caliber vessels, while technically very impressive and exciting, may not be sufficient to restore lymphatic flow in a limb, especially in late stage lymphedema.

There is an argument against the use of larger caliber lymph vessels and veins, however, it means that the pressure difference between the venous and lymphatic systems is too great for preventing thrombosis of the anastomoses when using these larger vessels. As matter of fact, Genoa MLVA technique takes measures to overcome this pressure difference by creating the anastomoses in close proximity to a valve in the vein. In this way, the valvular pumping creates a suction that pulls the lymph immediately through the anastomosis preventing thrombosis ("flutter valve mechanism", with subsequent "valve draining micro-pump" physiological phenomenon). The end-to-end approach realized in lymphatic-venular anastomoses, in contrast, allows the close contact of lymph and blood without this additional suction phenomenon and may, therefore, lead to thrombosis of the anastomoses.

The MLVA, using lymphatic vessels with the perilymphatic tissue, entirely ensure that these vessels are over time well functioning and this also helps to prevent thrombosis.

In addition, the administration of antithrombotic medications (low molecular weight heparin- LMWH, immediately postoperatively followed by low doses of aspirin for 1-2 years), and the application of the mechanical drainage components of CLyFT within 1 week from surgery, to assist in developing the flow of lymph through the anastomoses, are effective in maintaining the patency of the anastomoses in the long term.

Genoa Protocol shows to be able to achieve excellent results using a single-site approach for MLVA/MLVLA with no significant postoperative complications.

Conclusions

Lymphatic Microsurgery represents today a means to restore lymphatic drainage by bypassing the obstruction in the lymphatic pathways and directing the flow of lymph into the veins (MLVA) or, in the case of an associated serious venous pathology, by using an autologous vein graft to bridge the gap in the lymphatic collectors (MLVLA).

Lymphatic Microsurgery is able to offer excellent outcomes when applied early in the disease process, where a complete resumption of lymphatic flow in the long term is achievable.

For advanced cases of peripheral lymphedema, only partially responding to lymphatic microsurgery, FLLA-LVSP sequential, loco-regional and additional minimally invasive option can determine highly significant progress in the long-term control of the disease.

Preferably, microsurgery would be adopted as a preventive measure for all patients identified as "at risk for lymphedema" when undergoing surgery that may disrupt lymph flow in the axillary or inguinal-crural regions.

Genoa protocol is able to realize, by staging-guided lymphedema surgical treatment, the consequent Primary, Secondary and Tertiary Prevention in the potential progressive worsening of lymphostatic disease.

Acknowledgments

The Authors would like to acknowledge the significant contribution of all members of the Genoa Clinic Team, without whom they would not be able to offer such efficient and effective treatment to their beloved patients.

Conflict of Interest and Disclosure

All Authors declare no competing financial interests exist.

References

1. Gethin G, Byrne D, Tierney S, Strapp H, Cowman S (2012) Prevalence of lymphoedema and quality of life among patients attending a hospital-based wound management and vascular clinic. Int Wound J 9: 120-125. Link: https://bit.ly/36xZXTT

2. Morgan PA, Murray S, Moffatt CJ, Honnor A (2012) The challenges of managing complex lymphoedema/chronic oedema in the UK and Canada. Int Wound J 9: 54-69. Link: https://bit.ly/2X2Qe51

3. Rutkowsky JM, Davis KE, Scherer PE (2009) Mechanisms of obesity and related pathologies: the macro-and microcirculation of adipose tissue. FEBS J 276: 5738-5746. Link: https://bit.ly/2M3jeTL

4. Dixon JB (2010) Lymphatic lipid transport: sewer or subway? Trends Endocrinol Metab 21: 480-487. Link: https://bit.ly/3eqr1r9

5. Rutkowsky JM, Markhus CE, Gyenge CC, Alitalo K, Wiig H, et al. (2010) Dermal collagen and lipid deposition correlate with tissue swelling an hydraulic conductivity in murine primary lymphedema Am J Pathol 176: 1122-1129. Link: https://bit.ly/3ejD61d

6. Schneider M, Conway EM, Carmeliet P (2005) Lymph makes you fat. Nat Genet 37: 1023-1024. Link: https://bit.ly/3eoichu

Citation: Campisi CC, Molinari L, Campisi CS, Villa G, Fulcheri E, and Campisi C (2020) Surgical research, staging-guided technical procedures and long-term clinical outcomes for the treatment of peripheral lymphedema: the Genoa Protocol. J Surg Surgical Res 6(1): 041-050.
DOI: https://dx.doi.org/10.17352/2455-2968.000096

7. Lee BB, Laredo J, Neville RF (2011) Current dilemmas and controversy. In: Lee BB, Bergan J, Rockson S, eds. Lymphedema. London: Springerlink 381-385.

8. Dellachà A, Boccardo F, Zilli A, Napoli F, Fulcheri E, et al, (2000) Unexpected histopathological findings in peripheral lymphedema. Lymphology 33: 62-64.

9. O'Brien BM (1976) Replantation and reconstructive microvascular surgery. Part II. Ann R Coll Surg Engl 58: 171-182.

10. Campisi C, Boccardo F (2002) Lymphedema and microsurgery. Microsurgery 22: 74-78. Link: https://bit.ly/36y0lBP

11. Mehrara BJ, Zampell JC, Suami H, Chang DW (2011) Surgical management of lymphedema: past, present, and future. Lymphat Res Biol 9: 159-167. Link: https://bit.ly/3gsA4tt

12. Cormier JN, Rourke L, Crosby M, Chang D, Armer J (2012) The surgical treatment of lymphedema: a systematic review of the contemporary literature (2004-2010). Ann Surg Oncol 19: 642-651. Link: https://bit.ly/3ensKxf

13. Penha TR, Ijsbrandy C, Hendrix NAM, Heuts EM, Voogd AC, et al. (2013) Microsurgical techniques for the treatment of breast cancer-related lymphedema: a systematic review. J Reconstr Microsurg 29: 99-106. Link: https://bit.ly/36wdiw2

14. Campisi CC, Ryan M, Boccardo F, Campisi C (2016) A Single-Site Technique of Multiple Lymphatic-Venous Anastomoses for the Treatment of Peripheral Lymphedema: Long-Term Clinical Outcome. J Reconstr Microsurg 32: 42-49. Link: https://bit.ly/3er3nKP

15. Campisi CC, Ryan M, Boccardo F, Campisi C (2017) Fibro-Lipo-Lymph-Aspiration with a Lymph Vessel Sparing Procedure to Treat Advanced Lymphedema after Multiple Lymphatic-Venous Anastomoses. The Complete Treatment Protocol. Ann Plast Surg 78: 184-190. Link: https://bit.ly/2X61spa

16. Campisi CC, Ryan M, Villa G, Summa PD, Cherubino M, et al. (2019) Rationale for the study of deep subfascial lymphatic vessels during lymphoscintigraphy for the diagnosis of peripheral lymphedema. Clin Nucl Med 44: 91-98. Link: https://bit.ly/3gq5pwC

17. Villa G, Campisi CC, Ryan M, Boccardo F, Di Summa P, et al. (2019) Procedural recommendations for lymphoscintigraphy in the diagnosis of peripheral lymphedema: the Genoa Protocol. Nucl Med and Mol Imag 53: 47-56. Link: https://bit.ly/2XALvGz

18. Kleinhans E, Baumeister RGH, Siuda S, Büll U, Moser E (1985) Evaluation of transport kinetics in lymphoscintigraphy: Follow-up study in patients with transplanted lymphatic vessels. Eur J Nucl Med 10: 349-352. Link: https://bit.ly/36A41Tz

19. Papendieck CM (1998) The big angiodysplastic syndromes in pediatrics with the participation of the lymphatic system. Lymphology 31: 390-392.

20. Boccardo FM, Casabona F, Friedman D, Puglisi M, Campisi C, et al. (2011) Surgical prevention of arm lymphedema after breast cancer treatment. Ann Surg Oncol 18: 2500-2505. Link: https://bit.ly/2X27PtQ

21. Campisi CC, Larcher L, Lavagno R, Spinaci S, Adami M, et al. (2012) Microsurgical primary prevention of lymphatic injuries following breast cancer treatment. Plast Reconstr Surg 130: 749e-750e. Link: https://bit.ly/3gqTCOH

22. Campisi C, Bellini C, Campisi CC, Accogli S, Bonioli E, et al. (2010) Microsugery for Lymphedema: clinical research and long-term results. Microsurgery 30: 256-260. Link: https://bit.ly/2zxSus1

23. Campisi C, Campisi CC (2013) Lymphatic microsurgery: while the early bird catches the warm, the late riser still benefits. J Am Coll Surg 216: 506-507.

24. Campisi C, Davini D, Bellini C, Taddei G, Villa G, et al. (1984) Lymphatic or venous grafts in the microsurgical treatment of lymphedemas: first clinical trials. Microsurgery 4.

25. Ogata F, Narushima M, Mihara M, Azuma R, Morimoto Y, et al. (2007) Intraoperative lymphography using indocyanine green dye for near-infrared fluorescence labeling in lymphedema. Ann Plast Surg 59: 180-184. Link: https://bit.ly/3damcBW

26. Unno N, Inuzuka K, Suzuki M, Yamamoto N, Sagara D, et al. (2007) Preliminary experience with a novel fluorescence lypmphography using indocyanine green in patient with secondary lymphedema. J Vasc Surg 45: 1016-1021. Link: https://bit.ly/2Xwj0Kl

27. Földi M, Földi E (Eds. in Chief). Földi's Textbook of Lymphology. 2nd Edition, Elsevier GmbH, Urban & Fisher Verlag, Munich, Germany. Link: https://bit.ly/3ccqYOd

28. Campisi CC, Ryan M, Di Summa PG, Scarabosio A, et al. (2019) Inclusion of targeted skin products in the pre-surgical treatment regimen of peripheral lymphedema & lipedema. Lymphology 52: 194-201. Link: https://bit.ly/3gpNR3H

29. Koshima I, Nanba Y, Tsutsui T, Takahashi Y, Itoh S (2003) Long-term follow-up after lymphaticovenular anastomosis for lymphedema in the leg. J Recontr Microsurg 19: 209-215. Link: https://bit.ly/2M0nPq3

30. Koshima I, Nanba Y, Tsutsui T, Takahashi Y, Itoh S, et al. (2004) Minimal invasive lymphaticovenular anastomosis under local anesthesia for leg lymphedema: is it effective for stage III and IV? Ann Plast Surg 53: 261-266. Link: https://bit.ly/3c8v5dQ

31. Nagase T, Gonda K, Inoue K, Higashino T, Fukuda N, et al. (2005) Treatment of lymphedema with lymphaticovenular anastomoses. Int J Clin Oncol 10: 304-310. Link: https://bit.ly/2XsjAZy

32. Mihara M, Hayashi Y, Murai N, Moriguchi H, Iida T, et al. (2011) Regional diagnosis of lymphedema and selection of sites for lymphaticovenular anastomoses using elastography. Clin Radiol 66: 715-719. Link: https://bit.ly/2X5uzch

33. Maegawa J, Yabuki Y, Tomoeda H, Hosono M, Yasumura K (2012) Outcomes of lymphaticovenous side-to-end anastomosis in peripheral lymphedema. J Vasc Surg 55: 753-760. Link: https://bit.ly/3c20i2x

34. Mihara M, Hara H, Narushima M, Hayashi Y, Yamamoto T, et al. (2012) Lower limb lymphedema treated with lymphatico-venous anastomosis based on pre- and intraoperative icg lymphography and non-contact vein visualization: a case report. Microsurgery 32: 227-230. Link: https://bit.ly/3eqtTUX

35. Olszewski WL, Engeset A, Romaniuk A, Grzelak I, Ziolkowska A (1990) Immune cells in peripheral lymph and skin of patients with obstructive lymphedema. Lymphology 23: 23-33. Link: https://bit.ly/3d6REB4

36. Rockson SG (2001) Lymphedema. Am J Med 110: 288-295. Link: https://bit.ly/3c4sbqF

37. Beilhack A, Rockson SG (2003) Immune Traffic: A Functional Overview. Lymphat Res Biol 1: 219-234. Link: https://bit.ly/2AeKqfW

38. Szolnoky G, Dobozy A, Kemény L (2013) Decongestion improves cell-mediated immunity in postmastectomy arm lymphoedema: a pilot study. J Eur Acad Dermatol Venereol 27: 1579-1582. Link: https://bit.ly/3dhIOQQ

39. Campisi C (1991) Microvenous grafts in reconstructive lymphatic microsurgery: 7 years' clinical results. Vasc Surg 25: 345-352. Link: https://bit.ly/3gq8Gw6

Citation: Campisi CC, Molinari L, Campisi CS, Villa G, Fulcheri E, and Campisi C (2020) Surgical research, staging-guided technical procedures and long-term clinical outcomes for the treatment of peripheral lymphedema: the Genoa Protocol. J Surg Surgical Res 6(1): 041-050.
DOI: https://dx.doi.org/10.17352/2455-2968.000096