

**THE DIAGNOSIS AND TREATMENT OF
PERIPHERAL LYMPHEDEMA:
2013 CONSENSUS DOCUMENT OF THE
INTERNATIONAL SOCIETY OF LYMPHOLOGY**

This International Society of Lymphology (ISL) Consensus Document is the current revision of the 1995 Document for the evaluation and management of peripheral lymphedema (1) for discussion at the XXIV International Congress of Lymphology. It is based upon modifications: [A] suggested and published following the 1997 XVI International Congress of Lymphology (ICL) in Madrid, Spain (2) discussed at the 1999 XVII ICL in Chennai, India (3) and considered/confirmed at the 2000 (ISL) Executive Committee meeting in Hinterzarten, Germany (4); [B] derived from integration of discussions and written comments obtained during and following the 2001 XVIII ICL in Genoa, Italy as modified at the 2003 ISL Executive Committee meeting in Cordoba, Argentina (5); [C] suggested from comments, criticisms, and rebuttals as published in the December 2004 issue of Lymphology (6); [D] discussed in both the 2005 XX ICL in Salvador, Brazil and the 2007 XXI ICL in Shanghai, China and modified at the 2008 Executive Committee Meeting in Naples, Italy (7,8); and [E] modified from discussions and written comments from the 2009 XXII ICL in Sydney, Australia, the 2011 XXIII ICL in Malmo, Sweden and 2012 Executive Committee Meetings.

The document attempts to amalgamate the broad spectrum of protocols advocated worldwide for the diagnosis and treatment of peripheral lymphedema into a coordinated proclamation representing a "Consensus" of the international community. The document is

not meant to override individual clinical considerations for problematic patients nor to stifle progress. It is also not meant to be a legal formulation from which variations define medical malpractice. The Society understands that in some clinics the method of treatment derives from national standards while in others access to medical equipment and supplies is limited, and therefore the suggested treatments are impractical. Adaptability and inclusiveness does come at the price that members can rightly be critical of what they see as vagueness or imprecision in definitions, qualifiers in the choice of words (e.g., the use of "may... perhaps... unclear", etc.) and mention (albeit without endorsement) of treatment options supported by limited hard data. Most members are frustrated by the reality that NO treatment method has really undergone a satisfactory meta-analysis (let alone rigorous, randomized, stratified, long-term, controlled study). With this understanding, the absence of definitive answers and optimally conducted clinical trials, and with emerging technologies and new approaches and discoveries on the horizon, some degree of uncertainty, ambiguity, and flexibility along with dissatisfaction with current lymphedema evaluation and management is appropriate and to be expected. We continue to struggle to keep the document concise while balancing the need for depth and details. With these considerations in mind, we believe that this latest version presents a Consensus that embraces the entire ISL membership, rises above national

standards, identifies and stimulates promising areas for future research and represents the best judgment of the ISL membership on how to approach patients with peripheral lymphedema as of 2013. Therefore the document has been, and should continue to be, challenged and debated in the pages of Lymphology (e.g., as Letters to the Editor), and ideally will remain a continued focal point for robust discussion at local, national and international conferences in lymphology and related disciplines. We further anticipate as experience evolves and new ideas and technologies emerge that this "living document" will undergo further periodic revision and refinement as the practice and theories of medicine and specifically lymphology change and advance.

Keywords: consensus, lymphedema, diagnosis, treatment, ISL, International Society of Lymphology

I. GENERAL CONSIDERATIONS

As a fundamental starting point, lymphedema is an external (or internal) manifestation of lymphatic system insufficiency and deranged lymph transport. It may be an isolated phenomenon or associated with a multitude of other disabling local sequelae or even life-threatening systemic syndromes. In its purest form, the central disturbance is a *low output failure* of the lymphvascular system, that is, overall lymphatic transport is reduced. This derangement arises either from congenital lymphatic dysplasia (primary lymphedema) or anatomical obliteration, such as after radical operative dissection (e.g., axillary or retroperitoneal nodal sampling), irradiation, or from repeated lymphangitis with lymphangiosclerosis (secondary lymphedema) or as a consequence of functional deficiency (e.g., lymphangiospasm, paralysis, and valvular insufficiency) (primary or secondary lymphedema). The common denominator, nonetheless, is that lymphatic transport has

fallen below the capacity needed to handle the presented load of microvascular filtrate including plasma protein and cells that normally leak from the bloodstream into the interstitium. Swelling is produced by accumulation in the extracellular space of excess water, filtered/diffused plasma proteins, extravascular blood cells and parenchymal/stromal cell products. This process culminates in proliferation of parenchymal and stromal elements with excessive deposition of extracellular matrix substances and often, adipose tissue. *High output failure* of the lymph circulation, on the other hand, occurs when a normal or increased transport capacity of intact lymphatics is overwhelmed by an excessive burden of blood capillary filtrate. Examples include hepatic cirrhosis (ascites), nephrotic syndrome (anasarca), and deep venous insufficiency of the leg (peripheral edema). Although the final pathway is the manifestation of tissue edema whenever lymph formation exceeds lymph absorption, the latter entities should properly be distinguished from lymphedema, which is characterized by decreased lymphatic transport. In some syndromes where high output lymphatic transport failure is longstanding, a gradual functional deterioration of the draining lymphatics may supervene and thereby reduce overall transport capacity. A reduced lymphatic circulatory capacity then develops in the face of increased blood capillary filtration. Examples include recurring infection, thermal burns, and repeated allergic reactions. These latter conditions are associated with "safety valve insufficiency" of the lymphatic system and can be considered a mixed form of edema/lymphedema and as such are particularly troublesome to treat.

Peripheral lymphedema associated with chylous and non-chylous reflux syndromes is an infrequent but complex condition that requires specific diagnostic measures and treatment methods.

In the treatment of "classical"

lymphedema of the limbs (that is, peripheral lymphedema), improvement in swelling can usually be achieved by non-operative therapy. Because lymphedema most often becomes a chronic, generally incurable ailment, it generally requires, as do other chronic disorders, lifelong care and attention along with psychosocial support. The continued need for therapy does not mean a priori that treatment is unsatisfactory, although often it is less than ideal. For example, patients with diabetes mellitus continue to need drugs (insulin) or special diet (low calorie, low sugar) in order to maintain metabolic homeostasis. Similarly, patients with chronic venous insufficiency require lifelong external compression therapy to minimize edema, lipodermatosclerosis and skin ulceration (treatments may be preventative if initiated early). Compliance and commitment of the patient is also essential to an improved outcome. For example, in diabetes, poor compliance can result in weight loss, polyuria, and even coma and, long-term, also blindness, renal failure, and stroke. With chronic venous insufficiency, poor patient cooperation may be causally associated with progressive skin ulceration, hyperpigmentation, and other trophic changes in the lower leg. Similarly, failure to control lymphedema may lead to repeated infections (cellulitis/lymphangitis), progressive elephantine trophic changes in the skin, sometimes crippling invalidism and on rare occasions, the development of a highly lethal angiosarcoma (Stewart-Treves syndrome).

The recent promulgation of a list of risk factors for secondary lymphedema has become a highlighted issue due to publications of "do's and don'ts" lists. These are largely anecdotal and not sufficiently investigated. While some precautions rest on solid physiological principles (e.g., avoiding excessive heat on an "at risk" limb or trying to avert infections), others are less supported. It must be noted that most published studies on incidence of secondary lymphedema report less than 50% chance of developing

lymphedema. Therefore, standard use of some of these methods for "prevention" of lymphedema may not be appropriate and likely subjects patients to therapies which are unsupported until a point in the future when evaluation and prognostication evidence has demonstrated more clearly specific risks and preventative measures.

II. STAGING OF LYMPHEDEMA

Whereas most ISL members generally rely on a three stage scale for classification of a lymphedematous limb, an increasing number recognize Stage 0 (or Ia) which refers to a latent or sub-clinical condition where swelling is not yet evident despite impaired lymph transport, subtle changes in tissue fluid/composition, and changes in subjective symptoms. It may exist months or years before overt edema occurs (Stages I-III). Stage I represents an early accumulation of fluid relatively high in protein content (e.g., in comparison with "venous" edema) which subsides with limb elevation. Pitting may occur. An increase in various proliferating cells may also be seen. Stage II signifies that limb elevation alone rarely reduces tissue swelling and pitting is manifest. Late in Stage II, the limb may or may not pit as excess fat and fibrosis supervenes. Stage III encompasses lymphostatic elephantiasis where pitting can be absent and trophic skin changes such as acanthosis, further deposition of fat and fibrosis, and warty overgrowths have developed.

These Stages only refer to the physical condition of the extremities. A more detailed and inclusive classification needs to be formulated in accordance with improved understanding of the pathogenetic mechanisms of lymphedema (e.g., nature and degree of lymphangiodyplasia, lymph flow perturbations and nodal dysfunction as defined by anatomic features and physiologic imaging and testing) and underlying genetic disturbances, which are gradually being elucidated. Recent publications combining

both physical (phenotypic) findings with functional lymphatic imaging [by lymphangioscintigraphy (LAS) at this point) may be forecasting the future evolution of staging. In addition, incorporation of genotypic information, expanded from what is available even in current screening, would further advance staging and classification of patients with peripheral (and other) lymphedema.

Within each Stage, a limited but nonetheless functional severity assessment has utilized simple volume differences assessed as minimal (<20% increase in limb volume), moderate (20-40% increase), or severe (>40% increase). Clinicians also incorporate factors such as extensiveness, presence of erysipelas attacks, inflammation, and other descriptors or complications to their own individual severity determinations.

Some healthcare professionals focus on disability utilizing the World Health Organization's guidelines for the International Classification of Functioning, Disability, and Health (ICF). Quality of Life issues (social, emotional, physical disabilities, etc.) may also be addressed by individual clinicians and groups and note that these can positively or negatively impact therapy and compliance (maintenance).

III. DIAGNOSIS

An accurate diagnosis of lymphedema is essential for appropriate therapy. In most patients, the diagnosis of lymphedema can be readily determined from the clinical history and physical examination. In other patients confounding conditions such as morbid obesity, lipodystrophy, endocrine dysfunction, venous insufficiency, occult trauma, and repeated infection may complicate the clinical picture. Moreover, in considering the basis of unilateral extremity lymphedema, especially in adults, an occult visceral tumor obstructing or invading more proximal lymphatics needs to be considered. For these reasons, a thorough medical evaluation is indispensable before embarking on lymphedema treatment.

Co-morbid conditions such as congestive heart failure, hypertension, and cerebrovascular disease including stroke may also influence the therapeutic approach undertaken.

A. Imaging

If the diagnosis of lymphedema is unclear or in need of better definition for prognostic or therapeutic considerations, consultation with a clinical lymphologist or referral to a lymphologic center if accessible is recommended. The diagnostic tool of isotope lymphography (also termed lymphoscintigraphy or lymphangioscintigraphy) has proved extremely useful for depicting the specific lymphatic abnormality. Where specialists in nuclear medicine are available, lymphangioscintigraphy (LAS) has largely replaced conventional oil contrast lymphography for visualizing the lymphatic network. Although LAS has not been strictly standardized (various radiotracers and radioactivity doses, different injection volumes, intracutaneous versus subcutaneous injection site, epi-or subfascial injection, one or more injections, different protocols of passive and active physical activity, varying imaging times, static and/or dynamic techniques), the images, which can be easily repeated, offer remarkable insight into lymphatic (dys)function.

LAS provides dynamic images of both lymphatics and lymph nodes in the peripheral and central system as well as semi-quantitative data on radiotracer (lymph) transport, and it does not require dermal injections of blue-dye (as often used for example in axillary or groin sentinel node visualization i.e., lymphadenoscintigraphy). Dye injection is occasionally complicated by an allergic skin reaction or serious anaphylaxis. Moreover, clinical interpretation of lymphatic function after vital dye injection alone ("the blue test") is often misleading. Direct oil contrast lymphography, which is cumbersome and occasionally associated with

minor and even major complications, is usually reserved for complex conditions such as chylous reflux syndrome and thoracic duct injury. Non-invasive duplex-Doppler studies and occasionally phlebography are useful for examining the deep venous system and supplement or complement the evaluation of extremity edema. Other diagnostic and investigational tools used to elucidate lymphangiodysplasia/lymphedema syndromes include magnetic resonance imaging (MRI) – including MR lymphography and MR angiography techniques, computed tomography (CT), ultrasonography (US), indirect (water soluble) lymphography (IL), near infrared fluorescent imaging (NIFR) and fluorescent microlymphangiography (FM). DEXA, or bi-photon absorptiometry, may help classify and define a lymphedematous limb, but its greatest potential use may be to assess the chemical components of limb swelling (especially increased fat deposition, which by its added weight can lead to muscle hypertrophy). IL and FM are best suited to depict initial lymphatics and more superficial collectors and accordingly have limited clinical usefulness albeit valuable in research investigations. US has found its most practical value in depicting the dance of the living adult worms in scrotal lymphatic filariasis but also is increasingly used to highlight tissue alterations.

B. Genetics

Genetic testing has become practical and commercially available to screen for a limited number of specific hereditary syndromes with discrete gene mutations such as lymphedema-distichiasis (*FOXC2*), some forms of Milroy disease (*VEGFR-3*), and hypotrichosis-lymphedema-telangiectasia (*SOX18*) as well as a variety of chromosomal abnormalities. Other genes identified include Generalized Lymphatic Dysplasia (Hennekam syndrome) (*CCBE1*), Inherited Lymphedema Type 1C (*GJC2*), Lymphedema-Choanal Atresia (*PTPN14*), Emberger (*GATA2*), Milroy-like

lymphedema (*VEGFC*), and oculodento-digital syndrome (*GJA1*). The future holds promise that such testing for other known mutations and chromosomal defects as well as newly discovered ones, combined with careful phenotypic descriptions will become routine to classify familial lymphangiodyplastic syndromes and other congenital/genetic-dysmorphogenic disorders characterized by lymphedema, lymphangiectasia, and lymphangiomatosis. There are many other clinical syndromes with lymphedema as a component. Some of these have genes identified [Noonan (*PTPN11*, *KRAS*, *SOS1*, and others); microcephaly-chorioretinopathy-lymphedema-mental retardation (*MCLMR*) (*KIF11*)] while others still have no gene associated. In addition, recent and ongoing research is exploring a possible genetic (and epigenetic) basis underlying increased risk of developing secondary lymphedema after treatment involving injury to the lymphatic system.

C. Biopsy/Lymph Node Exam

Caution should be exercised before removing enlarged regional lymph nodes in the setting of longstanding peripheral lymphedema as the histologic information is seldom helpful, and such excision may aggravate distal swelling. Fine needle aspiration with cytological examination by a skilled pathologist is a useful alternative if malignancy is suspected. Use of sentinel node biopsy in the groin or axilla for staging malignancy such as breast and melanoma appears to have lessened the incidence of peripheral lymphedema by discouraging removal of normal lymph nodes; however, the number of sentinel nodes taken may be increasing possibly reducing this protective effect.

IV. TREATMENT

Therapy of peripheral lymphedema is divided into conservative (non-operative) and operative methods. Applicable to both

methods is an understanding that meticulous skin hygiene and care (cleansing, low pH lotions, emollients) is of upmost importance to the success of virtually all treatment approaches. Basic range of motion exercises of the extremities, especially combined with external limb compression, and limb elevation (specifically bed rest) is also helpful to virtually all patients undergoing treatment. Newer studies have indicated that more vigorous exercise can be undertaken under the proper conditions. As previously stated, even widely used methods have yet to undergo sufficient meta-analysis of multiple studies which have been rigorous, well-controlled, and with sufficient follow-up. Good studies comparing different methods of treatment do not exist, and advocates of all methods report that earlier treatment is optimal for the best results.

A. *Non-operative Treatment*

1. *Physical therapy and adjuvants*

a. Combined physical therapy (CPT) (also known as Complete or Complex Decongestive Therapy (CDT) or Complex Decongestive Physiotherapy (CDP) among others) is backed by longstanding experience and generally involves a two-stage treatment program that can be applied to both children and adults. The first phase consists of skin care, a specific light manual massage (manual lymph drainage-MLD), range of motion exercises and compression typically applied with multi-layered bandage wrapping. Phase 2 (initiated promptly after Phase 1) aims to conserve and optimize the results obtained in Phase 1. It consists of compression by a low-stretch elastic stocking or sleeve, skin care, continued "remedial" exercise, and repeated light massage as needed.

Prerequisites of successful combined physiotherapy are the availability of physicians (i.e., clinical lymphologists), nurses, and therapists specifically trained,

educated, and experienced in this method, acceptance of health insurers to underwrite the cost of treatment, and a biomaterials industry willing to provide high quality products. Compressive bandages, when applied incorrectly, can be harmful and/or useless. Accordingly, such multilayer wrapping should be carried out only by professionally trained personnel. Multiple manufactured devices/garments to assist in compression (i.e., pull on, velcro-assisted, quilted, etc.) may relieve some patients of the bandaging burden and perhaps facilitate compliance with the full treatment program and some clinics find that patient self-care and risk reduction strategies help maintain edema reduction (although neither of these has undergone rigorous study).

CPT may also be of use for palliation as, for example, to control secondary lymphedema from tumor-blocked lymphatics. Treatment is typically performed in conjunction with chemo- or radiotherapy directed specifically at producing tumor regression. Theoretically, massage and mechanical compression could promote metastasis in this setting by mobilizing dormant tumor cells, although only diffuse carcinomatous infiltrates which have already spread to lymph collectors as tumor thrombi might be mobilized by such treatment. Because the long-term prognosis for such an advanced patient is already dismal, any reduction in morbid swelling is nonetheless decidedly palliative.

A prescription for low stretch elastic garments (custom made with specific measurement if needed) to maintain lymphedema reduction after CPT is essential for long-term care. Preferably, a physician should prescribe the compression garment to avoid inappropriate usage in a patient with medical contraindications such as arterial disease, painful postphlebotic syndrome or occult visceral neoplasia. Generally the highest compression level tolerated (~20-60 mmHg) by the patient is likely to be the most beneficial.

Failure of CPT is confirmed only when intensive non-operative treatment in a clinic specializing in management of peripheral lymphedema and directed by an experienced clinical lymphologist has been unsuccessful.

b. Intermittent pneumatic compression. Pneumomassage is usually a two-phase program. After external compression therapy is applied, preferably by a sequential gradient "pump," form-fitting low-stretch elastic stockings or sleeves are used to maintain edema reduction. Newer devices that simulate manual massage and design improvements for area of coverage, ease of use, and sequence/actions may increase patient compliance. Displacement of edema more proximally in the limb and genitalia and the development of a fibrosclerotic ring at the root of the extremity with exacerbated obstruction of lymph flow needs to be assiduously avoided by careful observation. Combining pneumatic compression with manual lymph drainage has been reported but not sufficiently evaluated. Some published reports support the use of manual lymph drainage as a monotherapy in prevention after cancer surgery and in newly established and/or mild lymphedema without fibrosis.

c. Massage alone. Performed as an isolated technique, classical massage or effleurage, however, does not appear to be of benefit. Moreover, if performed overly vigorously, massage may damage lymphatic vessels. There are a few published studies demonstrating the utility of MLD monotherapy in specific populations (i.e., early breast cancer-related lymphedema), but there is a need for more robust studies to generate convincing evidence.

d. Wringing out. "Tuyautage" or wringing out performed with bandages or rubber tubes is probably injurious to lymph vessels and should seldom if ever be performed.

e. Thermal therapy. Although combinations of heat, skin care, and external compression have been advocated for and

successfully used by practitioners in Europe and Asia for thousands of patients, the role and value of thermotherapy alone without compression in the management of lymphedema remains unclear without further rigorous studies.

f. Low level laser. Recent reports with small numbers of patients have demonstrated efficacy of low level laser in reducing lymphedema. More studies with larger numbers of patients in diverse settings are needed to confirm these findings.

g. Elevation. Simple elevation (particularly by bed rest) of a lymphedematous limb often reduces swelling particularly in stage I of lymphedema. If swelling is reduced by antigravimetric means, the effect should be maintained by wearing of a low-stretch, elastic stocking/sleeve.

2. Drug therapy

a. Diuretics. Diuretic agents are of limited use during the initial treatment phase of CPT and should be reserved for patients with specific co-morbid conditions or complications. Long-term administration of diuretics, however, is discouraged for it is of marginal benefit in treatment of peripheral lymphedema and potentially may induce fluid and electrolyte imbalance. Diuretic drugs may be helpful to treat effusions in body cavities (e.g., ascites, hydrothorax) and with protein-losing enteropathy. Patients with peripheral lymphedema from malignant lymphatic blockage may also derive benefit from a short course of diuretic drug treatment.

b. Benzopyrones. Oral benzopyrones, which have been reported to hydrolyze tissue proteins and facilitate their absorption while stimulating lymphatic collectors, are neither an alternative nor substitute for CPT. The exact role for benzopyrones (which include those termed rutosides and bioflavonoids) as an adjunct in primary and secondary lymphedema treatment including filariasis is still not definitively determined including appropriate formulations and dose regimens. Coumarin,

one such benzopyrone, in higher doses has been linked to liver toxicity. Recent research has linked this toxicity with poor CYP2A6 enzymatic activity in these individuals.

c. **Antimicrobials.** Antibiotics should be administered for bona fide superimposed acute lymph stasis-related inflammations (cellulitis/lymphangitis or erysipelas). Typically, these episodes are characterized by erythema, pain, high fever and, less commonly, even septic shock. Mild skin erythema without systemic signs and symptoms does not necessarily signify bacterial infection. If repeated limb "sepsis" recurs despite optimal CPT, the administration of a prophylactic penicillin or broad spectrum antibiotic is recommended. Fungal infection, a common complication of extremity lymphedema, can be treated with antimycotic drugs (e.g., fluconazole, terbinafine). In most instances, washing the skin using a mild disinfectant followed by antibiotic-antifungal cream is helpful.

d. **Filariasis.** To eliminate microfilariae from the bloodstream in patients with lymphatic filariasis, the drugs diethyl-carbamazine, albendazole, or ivermectin are recommended. Killing of the adult nematodes by these drugs (macrofilaricidal effect) is variable and may be associated with an inflammatory-immune response by the host with aggravation of lymphatic blockage. Short and long-term efficacy of antibiotics (e.g., penicillin or doxycyclin) separate from skin hygiene in patients with lymphatic filariasis to prevent elephantine trophic changes remains to be determined.

e. **Mesotherapy.** The injection of hyaluronidase or similar agents to loosen the extracellular matrix is of unclear benefit and may actually be harmful.

f. **Immunological therapy.** Efficacy of boosting immunity by intraarterial injection of autologous lymphocytes is unclear and needs independent, reproducible evidence.

g. **Diet.** No special diet has proved to be of therapeutic value for uncomplicated peripheral lymphedema. In an obese patient,

however, reducing caloric intake combined with a supervised exercise program is of distinct value in decreasing limb bulk. Restricted fluid intake is not of demonstrated benefit for peripheral lymphedema. In chylous reflux syndromes (e.g., intestinal lymphangiectasia), a diet as low as possible or even free of long-chain triglycerides (absorbed via intestinal lacteals) and high in short and medium chain triglycerides (absorbed via the portal vein) is of benefit especially in children. Specific vitamin supplements may be needed in very low or no fat diets.

3. *Psychosocial rehabilitation*

Psychosocial support with a quality of life assessment-improvement program is an integral component of any lymphedema treatment.

B. *Operative Treatment*

Operations designed to alleviate peripheral lymphedema by enhancing lymph return have gained increased acceptance worldwide, but usually require combined physiotherapy or other compression after the procedure to maintain edema reduction and ensure vascular/shunt patency. These microsurgical procedures currently provide the closest chance at a cure for lymph flow disorders. In carefully selected patients, these procedures act as an adjunct to CPT or are undertaken when CPT has clearly been unsuccessful, and recent research has also focused on a preventive aspect in high risk patients.

Worldwide, surgical resection (in several forms) is the most widely used operative technique to reduce the bulk of lymphedema. Liposuction or "lipectomy" to reduce excess fat deposition is becoming more widespread with surgeons in multiple countries now performing the procedure.

In some specialized centers, operative treatment within specific guidelines may now be a preferred approach.

1. *Microsurgical procedures*

This operative approach is designed to augment the rate of return of lymph to the blood circulation. The surgeon should be well-schooled in both microsurgery and lymphology and utilize appropriate imaging tools to document efficacy.

a. *Reconstructive methods.* These sophisticated techniques involve the use of a lymphatic collector or an interposition vein segment to restore lymphatic continuity in lymphedema conditions due to a locally interrupted lymphatic system. Autologous lymph vessel transplantation mimics the normal physiology and has shown long-term patencies of more than 10 years. It generally has been restricted to unilateral peripheral lymphedema of the leg due to the need for one healthy leg to harvest the graft, but it has been utilized for bilateral upper extremity lymphedema where two healthy legs are available for lymphatic harvesting.

b. *Derivative methods.* Lymphatic-venous and lymph nodal-venous shunts are currently in use at multiple centers around the world, and these procedures have undergone confirmation of long-term patency and some demonstration of improved lymphatic transport (by objective physiologic measurements of long-term efficacy). Experience with these procedures over the last 25 years suggests that improved and more lasting benefit is forthcoming if performed early in the course of lymphedema before damage to the lymphatic wall and impaired lymphatic contractility has occurred.

2. *Liposuction*

Liposuction has been shown to completely or markedly reduce non-pitting, non-fibrotic, extremity lymphedema due to excess fat deposition (which has not responded to non-operative therapy) in both primary and secondary lymphedema (and limited studies in lipedema). Just like conservative treatment, long-term management requires

strict patient compliance with dedicated continuous wearing of low-stretch elastic compression garments, which may be challenging in warmer climates. This operation and follow-up should be performed by an experienced team of surgeons, nurses and physiotherapists to obtain and sustain optimal outcomes.

3. *Surgical Resection*

The simplest operation is "debulking," that is, removal of excess skin and subcutaneous tissue of the lymphedematous limb. The major disadvantage is that superficial skin lymphatic collaterals are removed or further obliterated. After intensive CPT, redundant skin folds may require excision. Debulking has been reported to be useful in treatment of advanced fibrosclerotic lymphedema (elephantiasis). Caution should be exercised in removing enlarged lymph nodes or soft-tissue masses (e.g., lymphangiomas) in the affected extremity as lymphedema may worsen thereafter.

Omental transposition, enteromesenteric bridge operations, and the implantation of tubes or threads to promote perilymphatic spaces (substitute lymphatics) have not shown long-term value and should be avoided without further published evidence.

4. *Lymph Node Transplantation*

Transplantation of superficial lymph nodes from an uninvolved area together with the vascular supply to sites of lymphadenectomy for cancer has been proposed both as a preventive and therapeutic approach to limb lymphedema. Long-term followup data on risk and efficacy is scant along with the role of adjunctive physical methods.

5. *Special Considerations*

Chylous and other reflux syndromes are special disorders which may benefit from CT-guided sclerosis, operative ligation of visceral

dysplastic lymphatics, and/or lymphatic to venous diversion after delineation by multimodal imaging.

C. *Treatment Assessment*

In each patient undergoing therapy, an assessment of limb volume should be made before, during and after treatment. This volume can be measured by water displacement, derived from circumferential measurements using the truncated cone formula, by perometer, or by other means. It is desirable, however, that treatment outcomes be reported in a standardized manner in order to compare and contrast the effectiveness of various treatment protocols. Additional assessments by imaging modalities such as lymphangioscintigraphy to document functional changes in lymphatic drainage, DEXA, ultrasound or magnetic resonance imaging to determine volume and tissue compositional changes, tonometry, bio-electrical impedance, and tissue dielectric constant to examine tissue alterations and fluid changes would add scientific rigor to analysis of the different treatment approaches. Psychosocial indices and visual analog scales of patient perceptions are also useful.

D. *Molecular Therapy*

Despite ongoing basic research and clinical trials, molecular treatments (e.g., administration of VEGF-C by various methods) have not yet been significantly translated to the clinic. While the addition of growth (or inhibitory) factors is attractive, the applicability of these treatments is uncertain at this time and should be examined carefully in the context of comorbid conditions (e.g., presence of cancer, cancer treatments, drug regimens).

V. *RESEARCH AGENDA*

While recognizing and encouraging individual investigators to pursue many

different avenues of investigation, some general directions can be formulated. Multinational collaborative studies and innovative clinical research designs in addition to randomized control trials should be encouraged with the aim of translating new and improved discoveries and approaches more rapidly into the clinical arena. Ongoing epidemiologic studies on the incidence and prevalence of lymphedema regionally and worldwide will benefit from the further development and establishment of standardized, secure, intercommunicating database-registries. Assessment of lymphedema risk and steps for lymphedema prevention in different groups of at risk patients need to be determined. Studies might include research on minimizing or preventing secondary lymphedema through altered operative/nodal sampling techniques (e.g., sentinel node biopsy or precise anatomical knowledge of derivative pathways), vector control (as demonstrated in China) and prophylactic drugs for filariasis, identification of patients with heritable genetic defects for lymphangiodysplasia (lymphedema), and use of massage or compression where lymphatic drainage is subclinically impaired as documented by imaging techniques (e.g., LAS). Research in molecular lymphology including lymphatic system genomics, proteomics, and "systemomics" should be encouraged. With the cellular and molecular basis of lymphedema-associated syndromes better defined, an array of specific biologically-based treatments including modulators of lymphatic growth and function should become available. Improved imaging techniques and physiological testing need to be devised to allow more precise non-invasive methods to measure lymph flow dynamics and lymphangion activity. Continuous improvement in imaging including molecular imaging techniques as well as development of new and improved technologies (e.g., NIRF and photoacoustics) to visualize the superficial and deep lymphatic system and soft tissues and also non-invasively intervene.

As knowledge accrues, the current crude classification of lymphedema should be revisited and modified to include a more encompassing clinical description based on genetic, anatomic, and functional disability. Accordingly, treatment, whether by designer drugs, gene or stem cell therapy, tissue engineering, physical methods or new operative approaches, should be directed at preventing, reversing or ameliorating the specific lymphatic defect and restoring function and quality of life.

VI. CONCLUSION

Lymphedema may be uncomplicated or complex but should not be neglected. Accurate diagnosis and effective therapy is now available, and lymphology itself is now recognized as an important speciality in which clinicians are carefully trained in the intricacies of the lymphatic system, lymph circulation, and related disorders. The emerging era of molecular lymphology should result in improved understanding, evaluation and treatment in clinical lymphology.

REFERENCES

1. International Society of Lymphology Executive Committee. The Diagnosis and Treatment of Peripheral Lymphedema. *Lymphology* 28 (1995), 113-117.
2. Witte MH, CL Witte, and M Bernas for the Executive Committee. ISL Consensus Document Revisited: Suggested Modifications. *Lymphology* 31 (1998), 138-140.
3. International Congress of Lymphology, Chennai, India. General Assembly discussion. ISL Consensus Document Revisited. September 25, 1999.
4. ISL Executive Committee Meeting, Földi Klinik, Hinterzarten, Germany. Discussions on modification of the ISL Consensus Document. August 30, 2000.
5. Discussions at the XVIII ICL in Genoa, Italy, September 2001 and over 50 written and verbal comments submitted to Executive Committee members. Changes discussed, modified, deleted, and confirmed at 2002 ISL Executive Committee meeting, May 2002, Cordoba, Argentina.
6. Consensus and dissent on the ISL Consensus Document on the diagnosis and treatment of peripheral lymphedema (M. Bernas and M.H. Witte); Remarks (M Földi); Liposuction and the Consensus Document (H. Brorson); Adipose tissue in lymphedema (H. Brorson); Liposuction in the Consensus Document (S. Slavin); A search for consensus on staging and lymphedema (T.J. Ryan); and Guidelines of the Società Italiana Di Linfangiologia: Excerpted sections (C. Campisi, S. Michelini, F. Boccardo). *Lymphology* 37 (2004), 165-184.
7. Changes discussed, modified, deleted, and confirmed at 2008 ISL Executive Committee meeting, June 2008, Naples, Italy.
8. The Diagnosis and Treatment of Peripheral Lymphedema: 2009 Consensus Document of the International Society of Lymphology. *Lymphology* 42 (2009), 51-60.