

Diagnosis and treatment of primary lymphedema. Consensus Document of the International Union of Phlebology (IUP)-2009

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Received on January 13, 2010; accepted for publication on April 8, 2010.

Primary lymphedema can be managed safely as one of the chronic lymphedemas by a proper combination of DLT with compression therapy. Treatment in the maintenance phase should include compression garments, self management including the compression therapy, self massage and meticulous personal hygiene and skin care in addition to lymph-transport promoting exercises. The management of primary lymphedema can be further improved with proper addition of surgical therapy either reconstructive or ablative. These two surgical therapies can be effective only when fully integrated with MLD-based DLT postoperatively. Compliance with a long-term commitment of DLT postoperatively is the most critical factor determining the success of any new treatment strategy with either reconstructive or palliative surgery. The future of management of primary lymphedema caused by truncular lymphatic malformation has never been brighter with the new prospect of gene-oriented management.

[Int Angiol 2010;29:00-00]

Key words: Lymphedema - Lymphatic abnormalities - Drainage - Reconstructive surgical procedures.

The management of chronic swelling of the limbs due to primary lymphedema remains a challenge for patients and clinicians worldwide. Progress over the past several decades has been significant in both the diagnosis and therapy of this disabling condition. The International Union

of Phlebology invited an expert multidisciplinary panel to convene and arrive at a consensus on the management of patients with primary lymphedema in 2009.

The goal of the document is not to overrule previously published expert guidelines from other specialty societies or boards. The charge of the panel was to bring together and evaluate the very best and most commonly used available diagnostic tests and therapies for primary lymphedema, which can ultimately be recommended to clinicians treating patients with this condition worldwide.

Recommendations in the document are graded according to scientific evidence. The panel adopted the system used by Guyatt *et al.*¹⁻³ and the document has two grades of recommendations: Grade 1 (strong) recommendation, which is reserved for those tests or procedures for primary lymphedema, where the benefits clearly outweigh the associated risks and Grade 2 (weak) recommendation, which is reserved for those diagnostic tests or procedures, where the benefits do not significantly outweigh the associated risks. The quality of evidence can be high (A), medium (B), low or very low (C) (Table I).

TABLE I.—Grading recommendations according to evidence.1 From Guyatt GH *et al*

Grade of recommendation/description	Benefit vs. risk and burdens	Methodological quality of supporting evidence	Implications
1A/strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A/weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

The document presents contemporary concepts encompassing a broad range of new and old diagnostic modalities and treatment options that are currently available in the management of primary lymphedema. We respect all of the currently available consensus documents, previously prepared by the many national and international societies, addressing all issues related to primary lymphedema. We strongly encourage the review of these expert documents as additional references in addition to this consensus document.⁴⁻⁸

This document is not meant to overburden the individual, local or national medical communities with specific recommendations, as these may be impractical to some where there is limited availability and access to the recommended technology. On the other hand, we hope that those with experience, knowledge and expertise beyond that described in this document will continue to offer their input to this consensus document.

The majority of the available data reviewed in the consensus belong to 2B or 2C, and at best, a small number belong to 1C or 2A. Only a few studies reviewed in this consensus have a strong recommendation based on low-quality or very low-quality evidence where the benefits clearly outweigh the associated risks. Because of problems associated with the methodology and quality of supporting evidence obtained from observational studies or case series, these data will be limited to a strong recommendation but may change when higher quality evidence becomes available.¹⁻³

With these considerations in mind, we support both manual lymphatic drainage (MLD) based decongestive lymphatic therapy (DLT)⁹⁻¹⁸ as the mainstay of treatment and management of primary lymphedema, and the surgical aspect of primary lymphedema care.¹⁹⁻²⁸ This should improve the brevity and precision of the document, while balancing the need for in depth analysis which should allow IUP members to exercise the best judgment as to how to approach patients with primary lymphedema as of 2009.

Although lymphedema is currently defined to be an external (or internal) manifestation of lymphatic system insufficiency and deranged lymph transport,⁶ the future of the diagnosis and classification of primary lymphedema is likely to be determined by the pathophysiology or genetic basis of the underlying condition²⁹⁻³⁸ which would

make the present classification³⁹⁻⁴¹ such as congenital /praecox /tarda, unnecessary.

It is our hope that this document will stimulate further inquiry and discussion regarding all aspects of primary lymphedema and that it will form a starting point for future discussions and ultimately become a "living document," where periodic updates and revisions are made incorporating new ideas, technologies and directions.

Definition and general consideration

Chronic lymphedema is a progressive and usually painless swelling of the limbs or genitals that is the result of decreased transport capacity of the lymphatic system. Chronic lymphedema can be primary or secondary. In patients with secondary lymphedema a specific cause (filariasis, previous surgery, radiation, malignancy, infection or inflammation, trauma, etc.) is identified.⁴²⁻⁴⁶ In patients with primary lymphedema the cause of decreased lymphatic transport can be an intrinsic "defect"⁴⁷⁻⁵¹ or a malfunction of the lymph conducting elements,⁵²⁻⁵⁶ which we believe is due to a genetically determined abnormality of lymph drainage.

The majority of chronic lymphedema cases classified as primary lymphedema, are due to inborn abnormalities of the lymphatic system, the most common of which is a truncular lymphatic malformation (LM)^{47, 49, 57} with an irregular or abnormal structural development caused by abnormal (mutant) genes.

LMs are a common type of congenital vascular malformations (CVM).⁵⁸⁻⁶² They occur as independent (predominant) malformations or can be combined with other CVMs such as venous malformations (VM),⁶³⁻⁶⁷ arterio-venous malformations (AVM),⁶⁸⁻⁷² and/or capillary malformations (CM).⁷³⁻⁷⁵ Combined malformations are classified as hemolymphatic malformations (HLM)⁷⁶⁻⁸⁰ according to the Hamburg Classification.⁸¹⁻⁸⁴

Primary lymphedema is believed to represent only a clinical condition due to truncular malformations of the lymphatic system with hypoplasia, aplasia, numerical hyperplasia, or dilation (lymphangiectasia) with valvular incompetence. There is some controversy where some experts believe that all lymphedema and lymphatic malformations are genetically derived and propose to define lymphedema as an abnormality of lymph

Guidelines 6.2.0 of the American Venous Forum on lymphoscintigraphy and lymphangiography

No.	Guideline	Grade of recommendation (1, we recommend; 2, we suggest)	Grade of evidence (A, high quality; B, moderate quality; C, low or very low quality)
6.2.1	We recommend lymphoscintigraphy for the initial evaluation of patients with lymphedema	1	B
6.2.2	We suggest lymphoscintigraphy, using visual interpretation of the images with a semiquantitative scoring index, to document response to treatment of lymphedema	2	B

Figure 1.—Guidelines of 62.0 of the American Venour Forum on lymphoscintigraphy and lymphangiography.

drainage where the predominant effect is on the tissue territory drained.

Milroy's disease is a genetic condition where patients present with congenital hereditary lymphedema or have a gene mutation at the locus 5q35.3: the gene mutated is *FLT4*, which codes for VEGFR3.^{36, 85-87} Milroy's disease is an inherited germ line mutation, whereas most asymmetrical and regionally limited genetic disorders (*e.g.* malformations) are due to a somatic mutation. In this situation, some tissue (*e.g.* skin) may be unaffected while the adjacent tissue (skin) may carry the mutation, representing the "mosaicism."

There are also different terminologies for this group of lymphedema but we prefer the term "primary" in preference to "essential or idiopathic" as recommended by the ISL document 2009.

The main concern here is "is it safe to say that all lymphedemas currently coined as primary are really primary?", which is hardly true. Some of them may be post-natal obliterations of lymph collectors and lymph nodes mimicking the congenital and prenatal condition, and not actually malformations, which, by definition, are found at birth.

Primary lymphedemas have been classified into three groups depending on the age of onset: Congenital (before age 2), Praecox (between age 2 and 25) and Tarda (after age 35). There is much doubt in classifying all lymphedema "tarda" as a primary disorder on the basis of conventional classification based on the age of the onset: congenital, praecox and tarda as one spectrum of the disease. The arbitrary age of 35 used to separate "tarda" from "praecox" is not clinically useful. How could it be

different if it starts at 34 or 36? How would we explain that congenital type of primary lymphedema is frequently associated with other edemas/malformations (heart, mental, renal etc) while praecox and tarda never show these features? Tarda is bilateral in most patients while bilateral involvement occurs in only 30% of patients with praecox, even though 70% of praecox patients have bilateral anomalies. This is likely due to mosaicism where a patient may clinically have only unilateral clinical symptoms with underlying bilateral pathology.

Gender distribution is also variable, not to say that scintigraphy shows wide variation. It is possible for tarda patients to have an idiopathic form of pumping insufficiency in anatomically normal lymphatic vessels and is therefore not a congenital lesion and should not be classified as a malformation.

Therefore, terms like tarda and praecox are outdated terms for the following reason. Lymphedema Distichiasis syndrome⁸⁸⁻⁹⁰ is caused by mutations in the *FOXC2* gene; patients with known mutations may develop lymphedema at puberty or not until 40 years. Therefore classifying lymphedema into praecox or tarda is potentially misleading in helping to understand the etiology of these forms of lymphedema.

Diagnosis

Clinical evaluation

Evaluation of patients with primary lymphedema must include a detailed history and clinical

evaluation along with a thorough physical examination.⁹¹⁻⁹³ History should include age at onset, travel to tropical countries and history of all causes that could result in secondary lymphedema. History of temporary edema of the affected limb or other areas must be noted and a detailed family history of limb swelling should also be recorded. Signs and symptoms of primary lymphedema should be documented. These include non-pitting edema, skin changes such as "peau d'orange, pinkish-red skin discoloration, hyperkeratosis, dermatitis, eczema, ulceration, varicosity, lymph vesicles, drainage of fluid, clear or milky, or yellow discoloration or other abnormalities of the nails. The presence of Stemmer sign (squaring of the toes) or puffiness of the forefoot (buffalo hump) should be noted. The presence of venous, arteriovenous, or capillary malformations, or any limb length discrepancy.^{94, 95} should be recorded. Finally, any complications, such as cellulitis, lymphangitis, malnutrition, immunodeficiency or, rarely, suspicion for malignancies (lymphangiosarcoma) must be documented.

Non-invasive evaluations

PLAIN X-RAYS

X-rays of bones will identify limb length discrepancies, bone abnormalities or phleboliths in patients with combined LMs and VMs.

DUPLEX SCANNING

Duplex scanning should include evaluation of the deep and superficial and local vasculature and the supra-facial structures. Venous duplex studies should confirm any associated venous anomalies (valvular incompetence, obstruction, ectasia or aneurysms) and/or exclude venous obstruction as etiology or contributing factor to lymphedema.

Minimally invasive evaluations

RADIONUCLIDE LYMPHOSCINTIGRAPHY

Scintigraphy is also a functional study in addition to an anatomical study such as phlebography.

There are no standardizations nor is there a gold standard.⁹⁶⁻¹⁰⁰

LSG, performed with injection of ^{99m}Tc-labeled human serum albumin or ^{99m}Tc-labeled Sulphur

Colloid subcutaneously into the first and second web-space of the toes or fingers, is the test of choice in 2009 to confirm or exclude lymphedema as the cause of chronic limb swelling.

Movement of the colloid from the injection site, transition time to the knee, groins or axilla, absence or presence of major lymphatic collectors, number and size of vessels and nodes, the presence of collaterals and reflux, symmetric activity with the opposite side are recorded and used for interpretation. Semiquantitative assessment has been reported, and most recently, the technique of quantitative assessment of transit time from the foot to the knee was also validated (Figure 1).¹⁰¹⁻¹⁰⁵

Basic initial diagnostic procedure of primary lymphedema should incorporate with those for secondary lymphedema in its early stage based on routine programs (e.g. routine volumetry, symptoms of the patients) to make early diagnosis in patients at risk.

An appropriate combination of non to minimally invasive tests normally should be able to provide all the information necessary to insure an adequate diagnosis and lead to the correct multidisciplinary, specifically targeted and sequenced treatment strategy. The tests and the information they provide are indicated below.

Basic/Essential tests:¹⁰⁶⁻¹¹⁰

- 1) Radionuclide lymphoscintigraphy;
 - 2) MRI with/without contrast for the differential diagnosis;
 - 3) CT scan to exclude underlying pathology;
 - 4) Duplex ultrasonography.
- Optional tests:^{67, 111-113}
- 1) whole body blood pool scintigraphy (WBBPS);
 - 2) MR and/or Ultrasound lymphography;
 - 3) volumetry;
 - 4) bio-impedence Spectrometry;
 - 5) air plethysmography;
 - 6) ultrasonographic lymphangiography: investigational for the reconstructive surgery candidate patient;
 - 7) MR lymphangiography: investigational for the reconstructive surgery candidate patient;
 - 8) microscopic fluorescent lymphangiography: investigational for the phlebolympedema.

Radionuclide lymphoscintigraphy (LSG) is the most essential part of the diagnosis of primary lymphedema in addition to clinical evaluation. LSG is extremely useful for identifying the specific lymphatic abnormality and has largely

Guidelines 6.3.0. of the American Venous Forum on lymphedema: medical and physical therapy

No.	Guideline	Grade of recommendation (1, we recommend; 2, we suggest)	Grade of evidence (A, high quality; B, moderate quality; C, low or very low quality)
6.3.1	To reduce lymphedema we recommend multimodal complex decongestive therapy that includes manual lymphatic drainage; multilayer short-stretch bandaging; remedial exercise; skin care; and instruction in long-term management	1	B
6.3.2	To reduce lymphedema, we recommend short-stretch bandages that remain in place for longer than 22 hours per day	1	B
6.3.3	To reduce lymphedema we recommend treatment daily, a minimum of 5 days per week, and continue until normal anatomy or a volumetric plateau is established	1	B
6.3.4	To reduce lymphedema we suggest compression pumps in some patients	2	C
6.3.5	For maintenance of lymphedema we recommend an appropriately fitting compression garment	1	A
6.3.6	For maintenance of lymphedema in patients with advanced (stages II or III) disease we recommend using short-stretch bandages during the night. Alternatively, compression devices may substitute for short-stretch bandages	1	B
6.3.7	For remedial exercises we recommend wearing compression garments or bandages	1	C
6.3.8	For cellulitis or lymphangitis we recommend antibiotics with superior coverage of Gram-positive cocci, particularly streptococci. Examples include cephalexin, penicillin, clindamycin, cefadroxil	1	A
6.3.9	For prophylaxis of cellulitis in patients with more than three episodes of infection we recommend antibiotics with superior coverage of Gram-positive cocci, particularly streptococci, at full strength for 1 week per month, Examples include cephalexin, penicillin, clindamycin, cefadroxil	1	C

Figure 2.—Guidelines 6.3.0. of the American Venous Forum on lymphedema: medical and physical therapy.

replaced conventional oil contrast lymphography for visualizing the lymphatic network. LSG can easily be repeated with minimal risk. Data and images obtained from the study identify lymphatic (dys)function, based on visualization of lymphatics, lymph nodes, and dermal backflow as well as semi-quantitative data on radiotracer (lymph) transport.

However, the LSG has not been standardized with regard to the various radiotracers and radioactivity doses, different injection volumes, intracutaneous versus subcutaneous injection site, epi-or sub-fascial injection, number of injections,

different protocols of passive and active physical activity, varying imaging times, static and/or dynamic techniques.¹¹⁴

The LSG remains the gold standard for lymphatic function evaluation since the LSG is the only test which can clearly indicate lymphatic function. Periodic radionuclide lymphoscintigraphy findings provide proper clinical and/or laboratory staging, which is essential for proper clinical management.

The suprafascial and the subfascial thickness of the edematous tissue with the high resolution echography (and/or computed tomography [CT])

Guidelines 6.4.0 of the American Venous Forum on principles of surgical treatment of chronic lymphedema

No.	Guideline	Grade of recommendation (1, we recommend; 2, we suggest)	Grade of evidence (A, high quality; B, moderate quality; C, low or very low quality)
6.4.1	All interventions for chronic lymphedema should be preceded by at least 6 months of non-operative compression treatment	1	C
6.4.2	We suggest excisional operations or liposuction only to patients with late stage non-pitting lymphedema, who fail conservative measures	2	C
6.4.3	We suggest microsurgical lymphatic reconstructions in centers of excellence for selected patients with secondary lymphedema, if performed early in the course of the disease	2	C

Figure 3.—Guidelines 6.4.0. of the American Venous Forum of principles of surgical treatment of chronic lymphedema.

scan) and tissue compressibility, are useful measurements that allow periodic assessment of the response to therapy and is useful in monitoring a patient's progress and determining prognosis.

On some occasions an invasive study is required to provide more information for an accurate differential diagnosis. These tests and the information they provide are indicated below:

Direct puncture percutaneous lymphangiography:

Standard (ascending) lymphangiography, as an optional to the reconstructive surgery candidate patients, if indicated

Indirect lymphography using water soluble contrast media Fine needle aspiration biopsy of lymph node

Skin biopsy in cases of suspected sarcoma, skin cancer or differential diagnosis of warty lesions

"Invasive" tests are seldom needed for the actual diagnosis but are occasionally needed for the differential diagnosis; Further studies with invasive tests such as direct puncture percutaneous lymphangiography can be generally deferred to later stages if there is need for refining the diagnosis or if surgical or other invasive therapeutic measures are considered. Otherwise, these should be reserved for road mapping for subsequent therapy if needed.

Conventional oil contrast lymphangiography, especially if coupled with CT scan, is still advantageously employed in selected patients with chylous dysplasia and gravitational reflux disorders

in order to define more clearly the extension of the pathologic alterations and sites of lymphatic and chylous leakage. It is the only diagnostic investigations that can clearly demonstrate pathologies of chylous vessels, chylous cyst and thoracic duct in cases of chylothorax, chylous ascites, protein losing enteropathy, etc.^{115, 116}

As a part of the diagnostic procedure, the systemic causes of edema (e.g. heart failure, hypoproteinemia, pulmonary hypertension, hypothyroidism, cyclic edema) should be ruled out. In addition to a complete history and physical examination, some tests should be ordered especially for the "tarda", lymphedema; for them it is an exclusion diagnosis and scintigraphy alone is insufficient to make a full diagnosis. Duplex ultrasonography should be included as the first test to be carried out, even before scintigraphy, in all forms of primary lymphedema including the congenital for differentiation from venous cause.

Proper diagnosis should allow appropriate clinical and laboratory staging¹¹⁷ of the disease for the assessment of progress of the condition and its response to treatment. Diagnosis should include a proper assessment of clinical and subclinical infections in the early and latent stages; such evaluation should be repeated aggressively not only for timely treatment but also for effective prevention of various conditions such as *tinea pedis*.

Diagnostic evaluation should include appropriate assessment of patient compliance since the

outcome of successful management is totally dependent on this crucial factor.

The diagnosis of lymphedema among children is mostly a primary origin in contrast to adults has unique problem; the lymphedema in children can be part of a syndrome if there are other concomitant phenotypic abnormalities and if a genetic defect is recognizable. However, it has to be made mainly on the basis of careful personal and family history and physical examination in initial phase.

Clinical evaluation will not be complete without documentation for the staging of lymphedema^{5-9, 117, 118} Stage 0 through Stage III, classification of severity of edema (volume): mild – moderate – severe, proper description on the skin and subcutaneous tissue changes, and functional assessment of limb affected by lymphedema. WHO guidelines for International classification of Functioning, Disability and health and Quality of Life issues can be used as a reference on this complex condition of social, emotional, physical disabilities.¹¹⁹⁻¹²¹

Treatment

General consideration

There have been substantial efforts to provide proper clinical staging of the lymphedema in conjunction with proper classification through decades. There are many different staging systems and none is perfect. The International Society of Lymphology (ISL) provides a three staging system (Stage 1 through 3) as the guideline to the lymphologists and recently reinforced with additional stage: Stage 0. But Italians use 6 stages, Germans 4 or 5, and Argentinians 5. It is very confusing to implement such different stagings; for example, how can we propose surgical treatment for initial stages for better outcome? Which are the initial stages? 0 and 1 for ISL or 0, 1, 2 and 3 for Italians?^{8, 9, 118, 122}

Most of the currently available staging systems reflect only tissue tenderness and limb shape, etc and neglect other substantial discrepancies (*e.g.*, upper limb with more fat than fibrosis). We would need more clinical information (*e.g.* number of major joints with tissue tenderness) as well as socioeconomic status to be incorporated to reflect the quality of life (QoL) properly.^{117, 118}

Therefore, many new proposals were made to compensate for such discrepancies, which includes

the Lymph CEAP classification by Europeans and US-based combined staging of two separate Clinical and Laboratory staging based on the lymphoscintigraphic findings.¹¹⁷

So we would need a new staging system which is easy to apply and easy to figure out how we could state that some forms of treatment are indicated in a certain stage of lymphedema, because we will never be sure what we do mean the “stage” with current staging system.

Patient involvement in the management is essential, especially for home maintenance. Patients should be encouraged to be aware of the disease nature and guided properly on how to be involved actively in the management of their own disease (self-management).

The treatment of the children with lymphedema has to be mostly conservative utilizing decongestive lymphedema therapy including compression therapy, directed exercises, massage and skin care. In the neonate, initial observation alone may be sufficient, as delayed lymphatic development and maturation can result in spontaneous improvement. The role of parents is crucial in providing the necessary input.

Proper management of various co-morbid conditions such as congestive heart failure, hypertension, and cerebrovascular disease including stroke is essential for the safe management of lymphedema since these co-morbid conditions will influence the therapeutic approach taken.

Physical & non-surgical/operative therapy

The ultimate goal of treatment is to improve the physical characteristics of the affected limb or area as well as the quality of life (QoL)^{119, 121} and thus achieving,

- Better social adaptation and a socially useful life,
- Better functional adaptation with physically normal activity, and
- Better psychological adaptation despite a psychologically unacceptable physical deformity.

Contemporary management of chronic lymphedema is now based on manual lymphatic drainage (MLD) and compression bandage-centered decongestive lymphatic therapy (DLT).^{14-19, 123-126}

DLT is now well established as the treatment of choice for lymphedema regardless of the underlying etiology (primary or secondary) or its clin-

ical stage. DLT consists of movement exercises, MLD, and compression (bandaging, garments, intermittent pneumatic compression) therapy in addition to basic skin care, and education for risk reduction. Appropriate pain management and psychosocial management should also be included in the treatment regimen.

Among the various components of DLT, exercise under multilayer non-elastic bandaging is the most important mode of therapy. Its efficacy has been documented in contrast to MLD.

However, DLT is an empirical strategy to control the edema and does not result in a "cure". DLT is only effective within the treatment program and to maintain control often means continuous commitment. Therefore, DLT requires a lifelong commitment.

MLD and compression bandage-based DLT with or without sequential intermittent pneumatic compression (SIPC)-based mechanical compression therapy,¹²⁷⁻¹³⁰ is still most effective treatment regimen for primary lymphedema.

The specific mechanism and efficacy of MLD however, has not been fully documented scientifically and remains to be proven with objective data. MLD has become an indispensable treatment modality. The MLD component of DLT is believed to reduce lymphatic congestion effectively by physiologic stimulation of a poorly functioning lymph-transporting system through the opening of collateral lymph pathways. In addition to improving lymphodynamics during treatment sessions and immediately after, it also moves accumulated fluids and may also reduce the fibrosclerosis of the involved soft tissues.

DLT is easy to apply with a minimum risk of complication and morbidity and gives the best outcome in the majority of patients regardless of the underlying etiology. It is more effective when started in the initial (fluid) stage of lymphedema, and in the compliant, motivated patient who is commitment to life-long therapy. In the later stages of lymphedema, the efficacy of DLT is very much limited to the maintenance of the current stage of lymphedema at best and prevention of progression. DLT is therefore, not curative but effectively prevents disease progression and produces a satisfactory outcome in the majority of cases. This is especially true when the patient is compliant and maintains a self-motivated home treatment schedule with a life-time commitment.

The treatment of lymphedema therapy, in the initial stages, should include short stretch bandaging between MLD sessions as well as meticulous skin care and exercises which reduce lymph formation and encourage uptake of accumulated fluids and promote lymph transport. The type and level of the bandaging and garments are still under evaluation. The treatment of lymphedema in more advanced stages should be based on a practical combination of compression garments (*e.g.* tailored flat knitted garments), self management (*e.g.* compression bandage and/or self massage), skin care and exercises to continue to reduce lymph formation, promote uptake of fluid and their contents from the interstitium and maintain lymph transport.

The efficacy of DLT in advanced stages of lymphedema is significantly reduced. In the recent past, its role has been limited to maintenance of the current stage of lymphedema at best and to prevent progression.

SIPC using a mechanical pumping device, is particularly useful in those cases where lymphedema is treated by physical passive therapy (*e.g.* elderly, patients in bed, with serious disabilities, etc.) in whom spontaneous/isotonic physical exercise is highly compromised or absent, and to maintain results (home self therapy).

Proper occupational therapy could improve the selected muscle exercises, often forgotten by the patients in most important clinical stages.¹²⁰ Psychological support is also extremely important in the lymphedema patient and is helpful for maintenance of compliance, especially for children and family members.

There are however a few contraindication to each component of the DLT; MLD with the risk of intravascular cancer metastases/thrombosis during the manipulation, compression therapy to the patient with cardiac failure, and pressure bandaging in advanced peripheral arterial disease of the limb.

A combined approach¹³¹ implementing conventional physical therapy, medical treatment using benzopyrones,¹³² and various physical¹³³ and surgical treatments remains the favored approach.

Surgical/operative therapy

GENERAL CONSIDERATION: CLASSIFICATION

There are four different surgical approaches to the treatment of primary lymphedema. Each sur-

gical approach has distinctively different indications regarding the various stages of primary lymphedema.

Reconstructive surgery with various lympho-venous anastomoses with microsurgical techniques:²¹⁻²⁶ it is best utilized in the early stages of lymphedema prior to the development and progression to the fatty fibrous stages where lymph vessels may show signs of fibrotic (functional) changes - clinical stage I & II (early stage)

Reconstructive surgery with free lymph nodes transplant surgery:^{27, 134} is best utilized in patients with lymphadenodysplasia - clinical stage II & III. It remains a controversial procedure and has not been fully accepted by lymphedema experts.

Debulking/Ablative (excisional) surgery:^{20, 28, 135-138} is best utilized when there are massive limb changes and when there is significant fibrotic induration. It is the least preferred approach of all of the surgical strategies - clinical stage III & IV (end stage)

Circumferential suction-assisted lipectomy:¹³⁹⁻¹⁴¹ is lipo-remediation techniques to remove adipose tissue when the patient is in the adipo-fibrous (mid) stage and DLT and MLD etc., have failed - clinical stage II & III. This procedure has been reported to be effective to the secondary lymphedema affecting upper limb following the mastectomy. But it remains with much controversy on the primary lymphedema regarding its timing and potential risk as a truncular lymphatic malformation (LM)^{48, 49} Its safety has not been proven especially when extratruncular LM^{61, 82} should coexist.

These surgical interventions require specialized techniques and experience as well as specific followup to achieve optimal outcomes. Those wishing to utilise these techniques should receive specific training with the relevant expert groups.

Among these surgical approaches, the reconstruction based on lymphatic-venous anastomosis (lymphatic-venous, lymphatic-lymphatic, and lymphatic-venous-lymphatic, etc) is the only procedure that has scientific merits while the other two lack this critical support/evidence.¹⁴²⁻¹⁴⁵

Lymphatic-venous anastomosis for reconstruction involves various technical aspects including the interposition of an autologous vein graft between lymphatics above and below the lymphatic obstruction. This technique is used in those cases involving the lower limbs, where surgically

uncorrectable disease exists (interpositioned vein grafted shunt or lymphatic-venous-lymphatic anastomosis - LVLA).¹⁴³

The first indication for additional surgical therapy is a well documented steady progression of the disease despite maximum of therapy over a two year period. But, two years of maximum therapy is generally considered to be too long and conservative before being declared a "treatment failure." Due to medicolegal and medicoethical issues involved in the treatment of primary lymphedema, while DLT remains first line treatment, two years is the generally accepted time period for the confirmation of the failed treatment by the IRB.

There remains significant controversy regarding this "waiting" period before considering reconstructive surgery. A delay of surgery for more than one year will increase the risk of surgical failure due to chronic lymphatic damage. Therefore, this waiting period should be shortened as much as possible especially in good compliant patients who stand to benefit the most from lymphatic reconstruction.

Surgical therapy for primary lymphedema should remain a treatment option as supplemental therapy in patients who have a non- to poor-response to DLT and/or compression therapy. This is especially true in the US where rigid criteria for the indication is influenced by medical-legal-ethical conflicts. In the good response group of patients in whom lymphedema relapses after DLT, notwithstanding the use of elastic garments, these patients can be excellent surgical candidates with outcomes similar to those in the early stage, treatment failure/non-responding group.

Patient compliance with life-long DLT therapy following surgical treatment is the single most important factor in ensuring successful management of lymphedema. In addition, the prevention and treatment of systemic and local infection such as cellulitis and erysipelas is equally important to prevent further injury to already jeopardized lymph vessels following successful reconstructive surgery.^{146, 147.}

The role of reconstructive surgery in early stage lymphedema and excisional surgery in late stage lymphedema remains a decision for the multidisciplinary management team. Full integration with DLT-based therapy can deliver effective control of the condition in both in early and late stage lymphedema. Life-long compliance and follow up

is necessary for successful treatment including postoperative DLT and compression garments.

Reconstructive surgery

Reconstructive surgery to restore lymphatic function with newly created lympho-venous or lympho-lymphatic bypass, lympho-lymphatic venous segmental reconstruction, or free lymph node transplantation of a damaged lymph-transport system to enhance lymph flow is more theoretically sound than DLT, with a definite chance of "cure" in early stage lymphedema.

In contrast, the LM as the cause of primary lymphedema accompanies an extremely variable number of lymph vessels and lymph nodes by the various forms of dysplasias such as lymphangiodyplasia, lymphadenodyplasia, and lymphangiadenodyplasia (Papendieck's classification).^{49, 148}

The proper candidates for reconstruction are therefore known to be much rarer among the primary lymphedemas due to such variation among the lymph nodes and lymph-transporting system (e.g. aplasia, hypoplasia and hyperplasia).^{47, 49, 57, 148} Reconstructive surgery outcomes are also known to be much more variable and generally not as effective as those seen when performed to treat secondary lymphedema, where a surgically correctable lesion is often found along the major lymphatics and collectors. Excellent results have been reported even among the primary lymphedema, claiming that there are many candidates with suitable lymph vessels for the reconstruction with the condition of lymphadenodyplasia than lymphangiodyplasia.^{49, 146} However, many others failed to confirm the same observation and this issue remains to be proved with further evidence.

Lymphatic surgical reconstruction is known to be technically demanding requiring microsurgical techniques and are often available only at specialized centers where lympho-venous procedures are routinely performed. These demands have hampered the widespread proliferation and acceptance of lymphatic reconstruction as a the first line treatment of lymphedema. This is especially true in the primary lymphedemas despite its one and only potential for cure. Only a handful of institutions throughout the world continue to devote the effort and resources required to maintain an

active lymphatic surgical reconstruction center. Access to these techniques is extremely limited.

Current DLT can provide satisfactory management of lymphedema in its early stage in the majority of cases. But, these cases of early stage lymphedema should be considered ideal candidates for reconstructive surgery, since there is a significant risk of lymphatic damage from progression of disease to fibrotic changes in the lymphedema patient.

Patients, however, become candidates for lymphatic reconstruction only when DLT-based therapy fails to prevent the progression of lymphedema and only when there is clear evidence of further damage to the lymphatic system. There is controversy regarding the timing of lymphatic reconstructive surgery where waiting until there is clear evidence of further damage to the lymphatic system may result in a higher likelihood of procedure failure.

In fact, the majority of candidates for lymphatic reconstruction have already had significant damage to lymph-transporting vessels caused by long term lymphatic hypertension. Therefore, postoperative maintenance of DLT following successful reconstructive surgery is essential for good long term outcomes. Without appropriate DLT assistance to partly damaged lymph vessels, even flawless technical surgical successes become futile.¹²

A majority of patients have very poor compliance and do not maintain postoperative DLT that is requisite to the long term success of belatedly performed surgery. Postoperative DLT totally depends upon patient compliance. Patient compliance is absolutely necessary for successful lymphatic surgery.¹²

Due to such many barriers, the reconstructive lymphatic surgery has remained an adjunctive therapy. Yet in most cases, when optimally performed, it can result in effective treatment of primary lymphedema.

Indications for lymphatic reconstructive surgery include:

- 1) failure to respond to proper therapy at clinical stage I or II;
- 2) progression of the disease to advanced stages such as stage I to stage II or stage II to III, despite proper treatment;
- 3) chylous-reflux combined with extremity lymphedema;
- 4) multiple recurrences of local or systemic infection; and

5) poor tolerance of CDP - based conservative treatment.

In reality, candidates for lymphatic reconstruction are generally selected only when DLT-based therapy fails to prevent the progress of lymphedema and when there is evidence of damage to the vessels of the lymphatic system. This scenario can often mean a passing of the optimal time for reconstruction.

In addition to the challenges of lymphatic reconstructive surgery as the only option to provide a therapeutic cure, there has been on the one hand many doubts and lack of convincing clinical evidence on the efficacy of this treatment.²²⁾ On the other hand, there have been reports of long term positive results over the past several decades.^{144, 145} A randomized controlled clinical trial is needed to determine the efficacy of lymphatic reconstructive surgery.

Ablative/excisional surgery

Ablative (cytoreductive) surgery is based on excisional techniques to reduce fibrosclerotic overgrowth, while liposuction can obliterate the epifascial compartment by removal of overgrown adipose tissue.

Several operations¹³⁵⁻¹³⁸ to treat lymphedema have been introduced throughout the decades (*e.g.* Charles procedure, Homan's procedure), but have ultimately been abandoned by the majority of vascular surgeons due to the associated morbidity and poor long term results. More recently however, modifications of the original techniques have resulted in significant improvements in morbidity with improved outcomes (*e.g.* Modified Auchincloss/Homan procedure).²⁸

Once the lymphedema advances to an irreversible stage, it has a tendency to progress steadily despite aggressive DLT with or without complementary compression therapy.

When the lymphedema progresses to its late end stages (stage III and IV of chronic lymphedema), the majority of patients will have an increased risk of recurrent local and systemic sepsis. In addition, due to the progressive deformity of the affected limbs, proper DLT becomes technically difficult. Therefore, once the multidisciplinary team admits its failure to arrest lymphedema progression toward the end stages with DLT and with evidence of steady deterioration despite maximum treatment, exci-

sional surgery can be offered as a supplemental measure of last resort to improve the efficacy of available DLT.^{19, 20}

Evaluation as candidates for palliative excisional surgery should be done when the clinical stage of chronic lymphedema reaches the end-stages of lymphedema (stage IV or late stage III) and accompanied by:

- increased difficulty to provide effective DLT due to a grotesquely disfigured limb and/or failure to be able to wrap adequately with a bandage for exercise therapy.

- increased frequency and severity of local and systemic sepsis.

Indications for ablative surgery include;

- 1) failure to implement proper care at clinical stage III or IV (end stage);

- 2) progression of the disease to end stages in spite of maximum available treatment; and

- 3) increased frequency and/or severity of local and/or systemic sepsis.^{19, 20}

However, compliance with maintenance DLT post-operatively becomes a major critical issue for long term success of excisional surgery. Without adequate postoperative DLT, excisional surgery alone cannot maintain the initial excellence of the surgical achievements and is doomed to fail in the long term.²⁰

Liposuction: Circumferential suction-assisted lipectomy

The current role of liposuction is a selective removal of excessive adipose tissue alone, which developed by secondary lymphedema involved to the upper limb following the mastectomy.¹³⁹⁻¹⁴¹ Therefore, control the lymphedema is mandated continuously with conventional bandage-based compression therapy following the liposuction. After all, the target for the suction ablation of swollen arm is the adipose tissue and NOT the lymphedematous tissue. And it has been reported that there is no risk involved to cause additional damage by the liposuction to the remaining lymphatic system.¹⁴⁰

The patient most likely to benefit from this procedure is one who has a unique condition of an excess fat accumulation to accelerate the progress of the postmastectomy lymphedema. But its efficacy has not been proven for the primary lymphedema which has entirely different background as a truncular lymphatic malformation (LM).

The clinical course of primary lymphedema, mostly affecting the lower extremity as a truncular LM, is not same as the secondary lymphedema affecting upper extremity; there is no clear evidence of selective overgrowth of the adipose tissue among this group. When the condition of “pitting” edema progresses to ‘non-pitting’ one to become feasible for the liposuction, whole tissue becomes fibrosclerotic with very limited amount of fat tissue available for the liposuction to improve local swelling.

Therefore, liposuction cannot be utilized in end stage of primary lymphedema as well, replacing current role of the excisional surgery.

Furthermore, primary lymphedema as a clinical manifestation of the truncular LM, accompanies significant risk of the extratruncular LM combined. When coexisting extratruncular LM is stimulated by the liposuction, it would respond to grow rapidly by its mesenchymal cell characteristics to make the condition worse.¹⁴⁹

Conclusions

Accurate diagnostic programs and tools and enhanced awareness of the early signs of lymphedema are essential. Primary lymphedema can be managed safely as one of the chronic lymphedemas by a proper combination of DLT with compression therapy regardless of the clinical stage of lymphedema. Treatment in the maintenance phase should include compression garments, self management including the compression therapy, self massage and meticulous personal hygiene and skin care in addition to lymph-transport promoting exercises. Prevention of chronic lymphedema in patients at risk is critical. Early diagnostic programs and enhanced awareness should be fully integrated.

The management of primary lymphedema can be further improved with proper addition of surgical therapy either reconstructive or ablative. These two surgical therapies can be effective only when fully integrated with MLD-based DLT postoperatively. Excisional surgery is a very effective method to control the progression of lymphedema initially, but ultimately becomes unable to maintain its initial success without additional DLT postoperatively. Liposuction for decompression will also have the same outcome; postoperative maintenance compression is mandated.

Compliance with a long-term commitment of DLT postoperatively is the most critical factor determining the success of any new treatment strategy with either reconstructive or palliative surgery. The future of management of primary lymphedema caused by truncular lymphatic malformation has never been brighter with the new prospect of gene-oriented management. .

“Molecular antidotes” to such pathological overgrowth of lymphangiomatosis such as the Klippel Trenaunay Syndrome should become major players with chance for cure in near future.

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Acknowledgements.—Authors are deeply grateful to Professor Hugo Partsch of Vienna, Austria and Professor Eberhard Rabe of Bonn, Germany, who volunteered to give their extraordinary efforts to help the consensus committee to reach to the proper conclusion on a few controversial issues.

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