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Diagnosis and management of secondary lymphedema

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ABSTRACT

Secondary lymphedema, more common than its primary variant is essentially a clinical diagnosis. Evaluation should include measurement of limb circumference and volume and appropriate staging protocols to determine the severity of the condition. Imaging studies such as magnetic resonance imaging and lymphoscintigraphy are invaluable in ruling out other causes of extremity swelling and for planning surgical treatment. Conservative measures such as combined decongestive therapy are of prime importance in reducing the limb volume and should be continued to maintain the results of surgical treatment. Pharmacotherapy does not have much role in lymphedema. Surgical options which were initially restricted to debulking procedures in chronic late stages are now gaining more relevance with the advent of physiological techniques to prevent further progression of the condition. Detailed counseling regarding the chronic nature of the disease and the need for regular follow-up along with rehabilitation programs will further improve the management of lymphedema.

Keywords: Complex decongestive therapy, Debulking surgery, Filariasis, Lymphedema, Lymphoscintigraphy, Secondary

INTRODUCTION

Secondary lymphedema, due to its myriad presentations and difficulties in clinical assessment, is under-reported and under-treated. Untreated lymphedema worsens with time and its negative effects on quality of life can be irreversible.^[1] A well-planned interdisciplinary approach from specialists including physicians, dermatologists, physiatrists, and vascular surgeons is crucial in the optimal care of these patients.^[2] Effective management of secondary lymphedema which includes clinical evaluation, investigations (especially imaging studies) and medical treatment options will be briefly discussed in this paper.

CLINICAL EVALUATION OF A PATIENT PRESENTING WITH LYMPHEDEMA

Management of secondary lymphedema needs a holistic approach with emphasis on the physical, functional and psychosocial issues faced by the patient. In addition to history and physical examination, staging of the condition and the assessment of the severity along with appropriate investigations are the pertinent steps in this direction.^[3]

HISTORY AND PHYSICAL EXAMINATION

History should include the age and mode of onset of complaints, most frequently the swelling of the affected area. Family history is an important aspect in ruling out primary lymphedema.

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Any previous or concomitant episodes of malignancy, surgical (lymphadenectomy included) or nonsurgical treatment (e.g., inguinal and axillary radiation), penetrating trauma, hypothyroidism, venous or lymphatic obstruction, hypoalbuminemia, travel to endemic areas of filariasis, infection, and sepsis should be noted. It is important to rule out causes of generalized edema such as heart failure or nephrotic syndrome because both lymphedema and generalized edema can coexist. Drug history should include intake of diuretics which are usually ineffective for lymphedema.^[2]

Presence and progression of associated symptoms such as aching pain, tightness, heaviness, and discomfort are also relevant. Similar to the limbs, the corresponding quadrant of the trunk may also be affected especially in malignancy. Asymmetry of the limbs is a vital clue toward lymphedema in a patient with generalized fluid retention.

Obesity has been identified as an independent risk factor for lymphedema, especially in cancer survivors.^[4] Morbid obesity has been known to be associated with a condition called massive localized lymphedema simulating lymphosarcoma histologically.^[5,6] Lipedema though having phonetic resemblance to lymphedema is a completely different entity.^[7] Caused by excessive deposition of adipose tissue, lipedema is exclusively seen in females, usually after puberty. The non-pitting swelling affects arms and legs (gynoid distribution) in a bilaterally symmetrical fashion sparing hands and feet.^[8,9]

Lymphedema of lower limbs usually begins in the distal extremity and progresses proximally resulting in a blunt squared-off appearance of the digits [Figure 1]. The swelling is typically soft and pitting in nature in the early stages. Kaposi Stemmer sign (thickened skin fold at the base of second toe or second finger leading to inability to pinch and lift the skin compared to the corresponding digit/toe of the contralateral limb) is a feature that can be positive in any stage of lymphedema.^[10] Although it has poor predictive value and false negatives can happen, a false positive Stemmer sign is rare.^[11] As lymphedema progresses, cutaneous fibrosis, dermal thickening, and adipose deposition set in and pitting disappears. The overlying skin gradually becomes dimpled (peau d'orange), hyperkeratotic and develops verrucous changes and woody fibrosis ending in elephantiasis nostras verrucosa [Figure 2].

CLINICAL STAGING OF LYMPHEDEMA

International Society of Lymphology developed a staging system combining two components on physical examination—softness or firmness of the limb (indicating fibrotic soft-tissue changes) and the effect of elevation [Table 1].^[12]

Within each stage, the severity of functional impairment is denoted on the basis of volume differences assessed as



Figure 1: Lymphedema of the right lower limb with pitting over the dorsum of the foot. The squared off appearance of the toes is also seen.



Figure 2: Elephantiasis nostras verrucosa of the lower limb in a case of filarial lymphedema.

minimal (5%–20% increase in limb volume), moderate (20%–40% increase), or severe (>40% increase).^[12]

EXTREMITY MEASUREMENTS

Measurements of affected area can aid in diagnosis, as well as in monitoring the response to therapy.^[13] The different methods for obtaining measurements can be circumferential measurements or calculation of limb volume.^[14,15]

Limb circumference

Measurements are taken using a flexible non-stretch tape. Four points each are described in both the affected and contralateral extremities with the limb in a relaxed position.^[16] For the upper extremity – at the metacarpal-phalangeal joints (if edematous), around the wrist, 10 cm below and 10 cm

Table 1: Clinical staging of lymphedema by International Society of Lymphology.^[12]

Stage 0 (Subclinical)	Stage 1 (Spontaneously reversible)	Stage 2 (Spontaneously irreversible)	Stage 3 (Lymphostatic elephantiasis)
<ul style="list-style-type: none"> • Swelling absent • Heaviness and discomfort may be present 	<ul style="list-style-type: none"> • Swelling present, subsides with limb elevation • Pitting edema • Soft edema without dermal fibrosis 	<ul style="list-style-type: none"> • Swelling does not resolve solely with limb elevation • Pitting may disappear • Dermal fibrosis has begun 	<ul style="list-style-type: none"> • Swelling does not resolve with elevation and pitting absent • Overlying skin shows verrucous changes • Recurrent soft tissue infections associated

above the olecranon process. For the lower extremity – at the metatarsal-phalangeal joints (if edematous), 2 cm superior to the medial malleolus, 10 cm above the superior pole of the patella, and 10 cm below the inferior pole of the patella. A discrepancy of more than 2 cm between the affected and contralateral limb is clinically significant.

Limb volume

Limb volume measurements give a better assessment of the extent and the severity of lymphedema. Different methods such as truncated cone formula,^[15] water displacement, and optoelectronic volumetry^[14] can be used for measuring limb volume.

Truncated cone formula

Volume differentials determined by circumferential measurements performed at 4 cm intervals beginning at the wrist and ankle on the affected and the contralateral sides are a simple and economic method to estimate the edema.^[17] Evidence suggests that volume measurements thus obtained correlate well with measurements by water displacement.^[15,18]

Water displacement volumetry

Water displacement can detect volume changes in the range of 1%. A volume difference of 200 ml or more between the affected and the opposite limb is taken as consistent with lymphedema.^[19] Although this is the preferred method in clinical trials, practical difficulties such as large size chambers, cumbersome steps, high cost, hygiene, and leakage issues limit its use.^[2,16]

Optoelectronic volumetry or Perometry

A Perometer uses infrared beams to scan the limb and calculates its volume by optoelectronic measurements. Perometry is more accurate and reliable but costly equipment, inability to measure hand and foot edema and need for maintaining a perpendicular position throughout the procedure are its disadvantages.^[2,19]

IMAGING STUDIES^[20-35]

In situations where diagnosis of lymphedema is not clear cut or differentiation from non-lymphatic causes of edema is not possible from the history and physical examination, imaging studies can be invaluable. Imaging is also indicated to assess the extent of involvement before deciding the appropriate therapeutic intervention, especially the surgical approach. Details of different imaging modalities used in evaluation of lymphedema are given in Table 2.

LABORATORY TESTS

A complete blood count should be done if possibility of infection exists. Analysis of blood parameters such as serum urea, creatinine, liver function tests, and albumin levels are indicated to assess hepatic and renal causes of extremity swelling.^[2,36] Blood culture is indicated in patients presenting with fever, erythema, pain, and sudden increase in swelling.^[37]

Microscopic examination for microfilaria in peripheral blood is an important step to diagnose filariasis as the cause for lymphedema. Enzyme linked immunosorbent assays that can identify circulating filarial antigens improve the diagnostic accuracy.^[12]

As histologic findings are nonspecific, a skin biopsy is rarely useful and rarely advised due to risk of poor wound healing. Light microscopy shows hyperkeratosis with areas of acanthosis and diffuse dermal edema. In chronic stage, dermal fibrosis, and infrequent foci of inflammatory infiltrate can be seen.^[38]

TREATMENT OF LYMPHEDEMA

The objectives of lymphedema treatment are alleviation of the symptoms, reduction of the morbidity, and improvement in the quality of life. Earlier, the treatment is instituted, better the outcome. Education and training of the patient form the cornerstone of treatment. A follow-up assessment every 3–6 months is advisable since non-compliance eventually leads to poor treatment outcomes. General measures such as weight reduction and obesity control should be duly stressed.

Table 2: Imaging studies for the evaluation of secondary lymphedema.

Method	Technique & Findings	Remarks
Lymphangioscintigraphy (LAS) or Lymphoscintigraphy or Isotope scintigraphy ^[21-24]	Radioactive tracers like water-soluble technetium-labelled colloid injected the web space of affected extremities. The flow of lymph through the lymphatic network from the skin to the lymph nodes is visualized [Figure 3].	Specificity-100% Sensitivity-73% for quantitative accumulation of tracer in lymph node Expensive Time-consuming Risk of radiation exposure
Indo Cyanine green (ICG) lymphangiography or Near Infrared Fluorescent Imaging (NIRF) ^[25-27]	Flow of dye visualizes anatomy of the superficial peripheral lymphatic system and aberrations if any.	Superior to LAS in identifying early stages and predicting the progression of lymphedema. No risk of radiation exposure. Needs specialized sensors for imaging.
Blue (Patent Blue V dye) Test or Lymphadenoscintigraphy ^[28]	Sentinel node visualization by dye injection in peritumour area, carried by lymphatics	Combination with isotope LAS improves detection rates
Magnetic resonance imaging (MRI) ^[29-31]	Demonstrate accumulation of fluid within soft tissues. Absence of oedema within the muscular compartment, honey comb pattern in subcutaneous tissue. Beaded appearance of lymphatics and higher signal intensity on contrast injection.	Uptake of contrast by veins can impair the findings. MR lymphography increases specificity
Computerised tomography (CT) ^[32,33]	Skin thickening, subcutaneous edema, honey combed appearance	Sensitivity -93% Specificity -100% ^[37]
Ultrasonography (USG) - duplex mode ^[12]	Identification of causes of secondary lymphedema like obstruction and tumours, co-existing conditions like venous insufficiency, reflux or deep venous thrombosis. Secondary changes of skin and subcutaneous tissue	Identify living adult worms in scrotal filariasis
Dual Energy X-ray Absorptiometry (DEXA) ^[12]	Assesses the chemical composition of a swelling	Differentiates lymphedema from fat deposition and secondary muscle hypertrophy.
Bioimpedance spectroscopy ^[34-36]	Measure fluid components within an extremity by recording resistance of the tissue to flow of electric current.	Non-invasive, simple, quick, accurate and early detection possible

Patients with higher body mass index have a higher risk of treatment failure.^[39,40] There is no role for restricted fluid intake or any special diet in lymphedema management.^[12]

The therapeutic options are divided into conservative (non-surgical) and surgical measures. A combined approach may be necessary in some cases.

Conservative (non-surgical) measures

Pharmacotherapy

Pharmacotherapy does not have much role in the management of lymphedema, except in active lymphatic filariasis. Mostly pharmacotherapy is limited to treatment/prevention of secondary bacterial infections and superadded fungal infections [Table 3].^[41-50]

Elevation

Bed rest and simple elevation of a lymphedematous limb reduces swelling especially in stage I of lymphedema. A low-stretch, elastic compression garment should be worn to maintain the reduction of swelling.^[2,12]

Complex Decongestive Therapy or Complete Decongestive Therapy (CDT) or Complete Physical Therapy

CDT is regarded as the standard treatment method for lymphedema. It is a multi-step approach consisting of two phases – an initial intensive reductive phase and a maintenance phase.^[12]

The reductive phase consists of instituting proper skin care regimen, manual lymphatic drainage (MLD), muscle

Table 3: Pharmacotherapy of lymphedema.

Drug	Indication	Comments
Diethyl carbamazine (6 mg/kg/day orally in 3 divided doses for 12 days)	Active lymphatic filariasis	Effectiveness against adult filarial worms is variable ^[42]
Ivermectin as a single dose of 150 microgram/kg body weight or albendazole 400 mg single oral dose	Active lymphatic filariasis	Effective against microfilariae as well as adult worms ^[43]
Doxycycline 200 mg/day for 4-8 weeks	Active lymphatic filariasis	Effective against microfilariae as well as adult worms ^[44]
Amoxycillin clavulanate 500 mg of every 8 hours	Cellulitis	Streptococci and <i>Staphylococcus aureus</i> are the common pathogens ^[45,46]
Oral penicillin 250-500 mg twice daily	Prophylactic treatment in patients with more than 3 episodes per year of cellulitis.	Fewer recurrences for one year when compared to placebo, but the beneficial effect diminishes progressively once the prophylactic therapy is stopped ^[47,48]
Topical antifungals	Tinea pedis, webspace intertrigo	Treatment of superadded fungal infection ^[2,12]
Oral antifungals	Severe superadded fungal infection	Treatment of superadded fungal infection ^[2,12]
Diuretics	Initiation phase of complex decongestive therapy, effusion in body cavities	Not indicated generally since fluid accumulated is protein rich lymph in interstitial spaces (not in vasculature), long term use may cause fluid electrolyte imbalance ^[39,49]
Oral benzopyrones (coumarin, rutosides, bioflavonoids)	? reduce lymphedema and elephantiasis	Hepatotoxicity in higher doses especially in patients with liver enzyme defects ^[50,51]

pumping exercises, and external compression therapy. The second phase should be initiated promptly after the first and is aimed to maintain and improve the results from phase one. Compression therapy is continued along with optimum exercises and MLD as required.^[51] It can reduce the limb volume and provide long-term benefits by arresting the pathological process of progressive lymphedema.^[2,21,38]

Skin care

Gentle but thorough cleansing of the affected sites should be done regularly and the area should be dried properly after each wash, especially the toes, to avoid fungal infection due to the retained moisture. Bland emollients can be used to prevent skin dryness and secondary eczematization. Keratolytics can reduce the epidermal thickening and delay the secondary changes.^[4,40]

Exercise programs

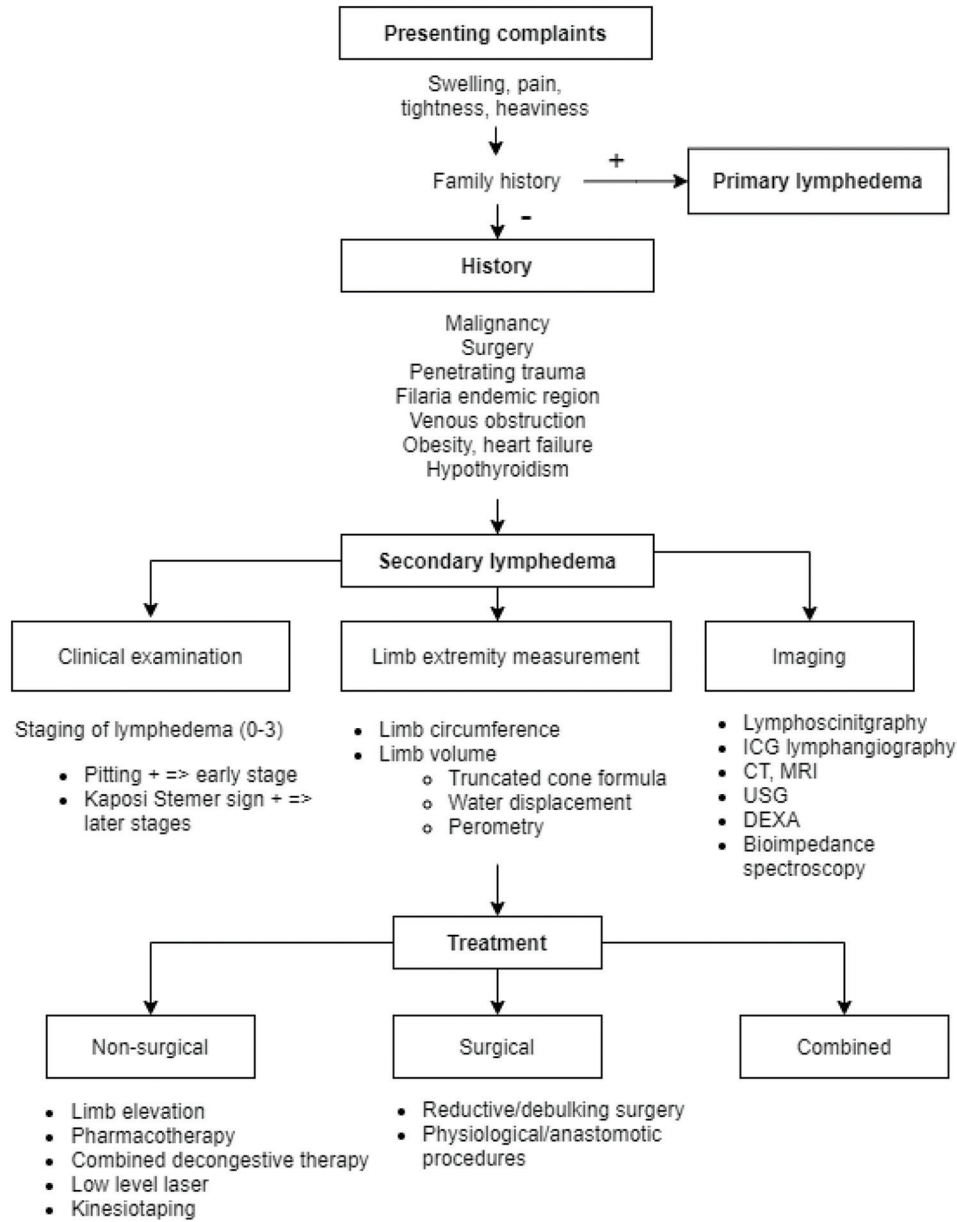
Lymphedema exercises include a series of repetitive movements which stimulate musculoskeletal activity and compression. This improves the lymph flow and increases the protein absorption. The exercise program should be customized according to the functional status of each patient and a general advice is to exercise for minimum 30 minutes a day wearing compression garments. Resistance training is particularly advantageous.^[2,52] Walking, Nordic walking using poles, weight lifting, yoga, swimming, and other aerobic and aquatic exercises are also beneficial.^[53,54]

MLD

MLD is performed by a specially trained physical therapist and low pressure (30–40 mm Hg), low frequency circular or spiral massaging techniques are applied. It is more beneficial in patients with mild-to-moderate lymphedema. The results are further improved when combined with compression bandage techniques. The massaging boosts the contractility of the lymphatics and redirects the flow through the affected cutaneous channels. Non-elastic high pressure (40–80 mm Hg) compressive bandages or undergarments are applied after each session of MLD and during exercise to prevent re-accumulation of fluid in the area.^[12,36,55] It is administered by specially trained physiotherapists or lymphologists.^[38]

Compression therapy

Application of external compression is a pivotal step in the treatment of all stages of lymphedema and can reduce the limb volume by 60%.^[52] Compression can improve lymphatic flow and venous return, control the volume of the limb, reduce accumulation of protein and debris, protect the limb from external trauma and maintain a scaffold for shape of the limb. Compression therapy can be achieved by (a) compression bandages and garments or (b) pneumatic compression devices (PCDs).



Flow Chart 1: Algorithm - Management of secondary lymphedema. ICG: Indo Cyanine green, CT: Computerized tomogram, MRI: Magnetic resonance imaging, USG: Ultrasonogram, DEXA: Dual energy X-ray absorptiometry.

Compression bandages and garments

Multilayer compression bandage consists of a layer of protective cotton bandage next to the skin, a middle layer of soft foam or synthetic wool underpadding and an outermost layer of minimum of two stretchable outer bandages. Compression is applied on the affected area for 24 hours during the intensive phase and changes to single layer bandages during the day in the maintenance phase.^[55] Compression garments had been found to be especially beneficial in the prevention and treatment of breast

cancer-related lymphedema if initiated as early as stage I with minimal volume change. Elastic garments with graduated compression from distal to proximal are preferred and advised to be worn throughout the day. When removed, the affected area should be kept elevated. The compression provided by the garments is determined by the severity of lymphedema, a minimum pressure of 40 mm Hg is essential, and the highest compression tolerated by the patient is most beneficial.^[56] The garments should be properly fit and comfortable without causing tourniquet effect and must be replaced when they lose their elasticity. Contraindications such as peripheral arterial

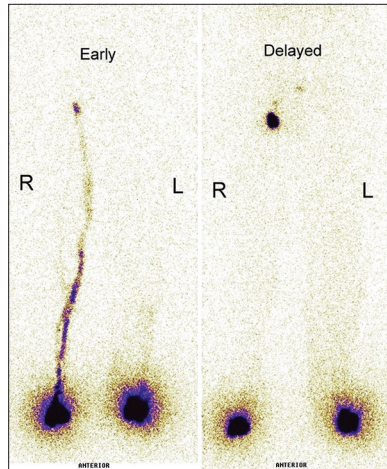


Figure 3: Lymphoscintigraphy images showing few superficial lymphatic channels in the right limb but absent in the left limb characteristic of moderate obstruction in the right lower limb and total obstruction of lymphatic flow in the left lower limb (Image Courtesy – Dr Shamily George, MBBS, DNB(Nuclear Medicine) Consultant, Department of Nuclear Medicine, Medical Trust Hospital, Cochin).

insufficiency and occult neoplasia must be ruled out before prescribing such garments. Open wounds or infection at the site are not absolute contraindications. Complications include irritant and allergic contact dermatitis to the materials used and swelling distal to the compression application.^[9,57]

PCDs

PCDs provide intermittent pneumatic compression which squeezes the edema tissue fluid to the regions with normal lymphatic drainage. These devices are filled with air and active sequential compression is applied from distal to proximal part of the limb mimicking the normal lymph flow. This helps in reducing the limb volume and prevents further swelling and development of fibrotic complications.^[58] PCDs can be used both in hospitals and at home, for a minimum period of 2 hours a day. Intermittent use of PCDs is useful add on approach to MLD and it can reduce the need for labor intensive MLD which can be delivered only by specially trained practitioners. Advanced PCDs (APCDs) can be programmed to deliver pneumatic compression identical to MLD and patients can get customized and more efficient treatment at home.^[59] MLD and pneumatic compression therapy are contraindicated in patients with uncontrolled hypertension, acute deep vein thrombosis, active infection or acute inflammation at the site.^[12]

Integrated management of lymphedema

Developed in South India, this protocol is devised using therapeutic measures from biomedicine, Ayurveda, and yoga. In addition to herbal medicines, Indian MLD (IMLD) and pre- and post-IMLD yoga exercises are successfully

incorporated in the management of lymphedema (especially filarial) in a rural community setting.^[60]

Low level laser therapy

Low level lasers or photobiomodulation are described to be effective in breast cancer related lymphedema.^[61] In addition to volume reduction, improvement is noted in terms of pain, skin changes, and limb mobility. But more studies are needed to validate its role.^[62]

Kinesiotaping

Kinesiotaping is a therapeutic taping method. Small studies on breast cancer related lymphedema therapy show promising results especially in patients in whom compression therapy is not practical.^[63]

Conservative management of podoconiosis

Protective footwear is useful to some extent but a change of occupation may be warranted. Maintaining limb hygiene and using compression bandages and limb elevation can help in alleviating the swelling and further complications.^[64,65]

Surgical measures

In carefully chosen patients, surgical measures can be either an adjunct to CDT (after the fluid component has been removed) or indicated when CDT fails. Recent research shows that operative interventions can also have a preventive role in avoiding complications of chronic disease.^[66,67]

There are two categories of surgeries – (a) reductive techniques and (b) physiological techniques

Reductive techniques

Reductive techniques are debulking surgeries aimed at reducing the fibrotic swelling and surface changes and restoring the volume of the limb. The different methods include direct excision, suction assisted protein lipectomy or radical reduction with perforator preservation. Although successful in restoring the limb size and shape, these techniques are associated with high rate of recurrences and graft associated complications.^[67,68] Liposuction is another surgical approach mainly used in the chronic stage of extremity lymphedema.^[69] Standard liposuction without skin excision and modified liposuction with skin excision are the two variants, successfully employed to reduce the soft-tissue hypertrophy and limb volume.^[70]

Physiological techniques

Physiological techniques are useful in the management in the early stages of lymphedema and restore the lymphatic

circulation at the affected site (e.g., microsurgical procedures such as vascularized lymph node transfer and lymphaticovenous anastomosis).

Performed by specially trained microvascular surgeons, these procedures have good immediate and long-term benefits with regard to reduction in limb volume and improvement of quality of life.^[71,72]

A combination of two approaches is used in selective cases and CDT along with other conservative measures as discussed above should be continued to maintain the results.^[62,73]

CONCLUSION

Secondary lymphedema is a complex condition in terms of etiology, clinical presentation, evolution, and treatment. A comprehensive approach is required in tackling the same because progressive disease leads to irreversible changes and puts severe psychosocial and economic burden on the patients. The multimodality approach which can be followed for efficient management of lymphedema has been outlined in algorithm 1 [Flow chart 1]. Ongoing research in investigative and therapeutic options will hopefully improve the treatment outcome for secondary lymphedema.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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