
TOPIC: The Diagnosis And Treatment Of Lymphedema

Introduction

Lymphedema is caused by an abnormality of the lymphatic system leading to excessive build up of tissue fluid that forms lymph, known as interstitial fluid. Stagnant lymph fluid contains protein and cell debris that causes swelling of affected tissues. Lymph is responsible for transporting essential immune chemicals and cells. Left untreated, lymphedema leads to chronic inflammation, infection and hardening of the skin that, in turn, results in further lymph vessel damage and distortion of the shape of affected body parts.^{1-4,199,201}

Interstitial fluid can build up in any area of the body that has inadequate lymph drainage and cause lymphedema. Lymphedema is a condition that develops slowly and once present is usually progressive.^{143,192} People can be born with abnormalities in the lymphatic system. This type of lymphedema is known as Primary Lymphedema. Depending on how severe the condition is, swelling can be present at birth or may develop later in life.¹⁹⁸ Most lymphedema in the United States is Secondary Lymphedema. This type of lymphedema occurs from damage to the lymphatic system, commonly from cancer and its treatment but also from trauma to the skin such as from burns or infections.^{5,189} Lymphedema after breast cancer has been studied the most, but lymphedema can occur as a result of other cancers, including melanoma, gynecologic cancer, head and neck cancer and sarcoma.^{76-78, 185-187} The overall risk of lymphedema for all cancers is reported to be 15.5%.¹⁸⁶ The risk of developing lymphedema does not diminish over time but is a lifelong risk.^{6,143} Progressive lymphedema is complicated by recurrent infections, non-healing wounds, discomfort or pain, difficulty with daily tasks, emotional and social distress.⁷⁻⁹

Effective treatment for lymphedema is available. Early diagnosis is important since treatment is most effective when lymphedema is diagnosed at the earliest stage.^{188,193,194} Every patient with lymphedema should have access to established effective treatment for this condition. Lymphedema has no cure but can be successfully managed when properly diagnosed and treated.

Diagnosis of Lymphedema

Since lymphedema is progressive and early diagnosis leads to more effective treatment, the diagnosis of lymphedema at the earliest possible stage is very important. Treatment of lymphedema is based on correct diagnosis. Many conditions that cause swelling (edema) are not lymphedema. True lymphedema is swelling caused by abnormality in the lymphatic system. Lymphedema can also co-exist with other medical and swelling conditions. Correct diagnosis of lymphedema may require evaluation by a physician or other health-care provider with expertise in lymphedema who can, when needed, perform specialized diagnostic testing.^{10,198} Diagnostic tests for lymphedema come under the following categories:

- History and physical examination
- Soft tissue imaging
- Lymph vessel and lymph node imaging
- Measures of volume
- Changes in electrical conductance
- Changes in biomechanical properties
- Genetic testing

- Other vascular imaging
- Blood tests for other conditions that can look like lymphedema

History and Physical Examination

A history and physical examination by a health-care provider who has experience with diagnosis and treatment of lymphedema is important for all patients with chronic swelling.^{193,194,198} Primary and Secondary lymphedemas have characteristic features that can be seen over time. The history should include age of onset, location(s) of swelling, pain and other symptoms, medications that can cause swelling, the course of progression of the swelling, and factors associated with swelling onset such as cancer, injury, or infection. A family history is important to the diagnosis of inherited forms of lymphedema. The physical examination includes an assessment of the vascular system (lymphatics, veins and arteries), skin and soft tissues in the swollen body part(s), palpation of lymph nodes, and looking for changes in body systems associated with various forms of inherited lymphedemas.^{181,182,202} Diagnostic tests and imaging must be paired with the information from the history and physical examination to make a correct diagnosis. For trunk, breast, genital, head and neck lymphedema, the history and physical examination is the currently accepted method of diagnosis.^{76,78}

Soft Tissue Imaging

Magnetic resonance imaging (MRI), computed tomography (CT) and some types of ultrasound (US) are able to detect the presence of extra fluid in the tissues.^{159,160,170} Fluid that is outside of cells (extracellular) and also outside of vessels (extravascular) is called tissue fluid or interstitial fluid. Lymphedema is one type of interstitial fluid build up that occurs when fluid is not being removed effectively by the lymph vessels. MRI, CT and US can show the presence of increased interstitial fluid but cannot tell the cause. These imaging techniques have to be put together with history, physical examination and sometimes other imaging tests.¹⁹⁴ Other conditions such as heart failure or low proteins in the blood from liver disease or malnutrition can cause fluid to build up in the tissues. MRI, US and CT scans may be required to determine the cause of lymphedema, especially if there is a concern that the lymphedema might be the result of an untreated cancer.

Lymph Vessel Imaging

Lymphoscintigraphy is a nuclear medicine study used for imaging lymph vessels and lymph nodes.¹⁹⁵ Radio-labeled particles of protein are injected just under the skin of the area of the body to be imaged. Usually technetium labeled sulphur colloid is used. Lymphoscintigraphy is accurate for detecting abnormalities of the lymphatic system in the extremities regardless of the cause.^{163,165,189} It demonstrates slow or absent lymph flow and areas of reflux (backflow). Lymphoscintigraphy can reveal abnormalities of lymph uptake in lymph nodes with some forms of lymphedema.¹⁶⁸ Lymphoscintigraphy can predict response to treatment.¹⁶⁷ Lymphoscintigraphy shows the main, larger lymph vessels and nodes. It shows the basic architecture of the peripheral lymphatic system. It does not show the deep transport lymph vessels carrying lymph from the nodes back to the blood circulation. Lymphoscintigraphy identifies lymphatic abnormalities at a late stage, after lymphedema has occurred. The type of lymphoscintigraphy done for the diagnosis of lymphedema is not available at all radiology departments. Most radiology departments, however, can do a form of lymphoscintigraphy used to identify the sentinel lymph node for cancers such as breast and melanoma. These studies for the sentinel lymph node are different from the lymphoscintigraphy studies done for diagnosis of lymphedema. Before undergoing a lymphoscintigraphy study the patient should inquire if the radiologist performing and reading the study has a large amount of experience with lymphoscintigraphy studies for the diagnosis of lymphedema. Lymphoscintigraphy, in combination with other vascular studies, can differentiate venous edema from lymphedema.^{190,196} Lymphoscintigraphy may not be necessary in some forms of secondary lymphedema where the diagnosis is clear from the history and physical examination or other imaging. In order to diagnose primary lymphedema, however, a lymphoscintigraphy must be done. Especially in children, a detailed study must be done that includes all potential areas of involvement and the contralateral normal limb or body part for comparison.^{166,169} These studies must be done by a radiologist familiar with primary lymphedema

and genetic forms of edema. In children being evaluated for lymphedema, other vascular and imaging studies are necessary because primary lymphedema can occur in combination with many vascular abnormalities and other organ defects. The specific tests needed should be determined by a specialist in lymphedema.

A new technique for imaging lymph vessels is Near Infra-Red Florescence Imaging (NIR) using a substance known as indocyanine green (ICG).^{82,171-175} The ICG is injected into the skin and immediately imaged with a dynamic (real time) infrared florescence camera. With NIR-ICG, even very small lymphatic vessels can be seen. The study is dynamic which means that the actual function of the lymphatic vessels can be analyzed. Diseased lymphatics that do not contract (or pulse) normally can be seen with NIR-ICG. ICG is a green dye that has been used safely in other areas of the body such as the liver and eyes. It can be used in very small amounts to image the lymphatics. NIR-ICG can diagnose lymphedema and find abnormalities at an early stage, possibly before swelling is obvious. Although this technique shows promise for the diagnosis of lymphedema, it is currently available at very few centers, most of which are involved in research.

Measures of Volume

Measures of limb (arm and leg) volume have been the standard way of detecting lymphedema for years and have been shown to be accurate when properly done.^{156,157,161,170} Enlargement of the limb (increase in volume) is the end result of fluid building up in the tissues. Therefore, volume measurements are used to quantify the presence and severity of lymphedema and follow the response to treatment. Volume is measured by 3 main methods: tape measurements, perometry, and water displacement.¹⁷⁰ Tape measurements are taken at defined intervals, using geometric formulas to calculate the total volume. This technique can be accurate if it is done in precisely the same way each time, and is most accurate when the same person takes the measurements each time. Perometry uses an infra-red optical electronic scanner and computer to calculate the volume of the body part. Perometry is accurate if the body part is positioned exactly the same way each time and the machine has been calibrated for accuracy. Perometry has been used for a decade in research on lymphedema and has been accurate when compared to the long used 'gold standard' of water displacement.¹⁴⁹ Perometry has been demonstrated to detect as little as a 3% change in limb volume in breast cancer survivors followed over time.²⁰⁷ Water displacement, the bench 'gold standard' for assessing volume, is rarely used these days due to its inconvenience. The body part to be measured is immersed in a large cylinder and the water that is pushed out (displaced) is measured. All of these volume methods are effective and accurate when done properly.¹⁷⁰ They are most accurate on arms and legs. Measures of volume cannot differentiate lymphedema from other types of edema and do not determine when temporary post-operative arm edema becomes chronic lymphedema. Although tape measurements have been developed for head and neck,⁷⁸ they are not true volume measurements, nor have they been standardized. They are best used for following the effects of treatment rather than making a diagnosis.

Electrical Conductance Testing (BIS)

Bioimpedance Spectroscopy (BIS) is a method for measuring water content in tissues. It has been used for many years to assess the total water content of the body and body composition for fitness and weight loss purposes. BIS is now available to measure interstitial fluid as a component of assessment leading to the diagnosis of lymphedema.^{144,148,149} BIS has been shown to provide reliable data to be used in the diagnosis of breast cancer-related lymphedema.¹⁵⁰ BIS can detect early changes associated with lymphedema.^{162,164} BIS is done by passing a small, painless, electrical current through the limb and measuring the resistance to current (impedance). The machine uses certain electrical current frequencies to determine if more fluid exists as compared to the contralateral limb. It does this by comparing the difference in resistance to electricity passed through interstitial fluid compared to intracellular fluid. BIS currently is done on the whole limb since the resistance to current flow for standard technique is calculated to the length of the body part. The higher the water content in the interstitial tissue, the lower the resistance (impedance). BIS may show promise for detecting smaller areas of localized lymphedema, but this application has not been subjected to adequate study to recommend it.²⁰⁶ BIS is not as accurate in advanced, fibrotic edema. As in measures of volume, BIS cannot differentiate lymphedema from other types of edema and does not determine when temporary post-operative arm edema becomes chronic lymphedema.^{145,170,191}

Changes in Biomechanical Properties of Tissues

Lymphedema causes the affected skin and subcutaneous tissues to become inflamed and hardened (fibrotic).¹⁹⁹ Lymphedema is graded clinically, not just by increased size or volume, but also by the progressive change in the skin texture as it becomes denser and harder.^{10,158} Currently, these skin changes are documented by physical examination of tissue texture, pitting, enlarged skin folds and other dermatologic conditions such as wounds or papillomas (benign growths on the skin in areas of lymphedema). Methods available for measuring skin texture and resistance quantitatively are: tissue dielectric constant¹⁵¹⁻¹⁵³ and tonometry.^{148,152,154,155} The tissue dielectric constant is a measure of tissue water content. The test is performed with a device that passes an electrical current of a specific frequency to one location of the skin and measures the reflected wave that returns. The reflected wave form indicates the amount of water present in the tissue. Tonometry uses a device that measures the amount of force required to indent a tissue which gives a specific measurement value to the degree of firmness or fibrosis. There are some technical difficulties to the use of these tools and a number of environmental factors and operator differences can give variable values. These measures of the biomechanical properties of tissues are important for research. Hopefully continued development will lead to better tools for clinical use so that diagnostic methods will include quantitative methods of skin and subcutaneous tissue changes associated with progressive lymphedema.

Genetic Testing

For patients who have been diagnosed with primary lymphedema, genetic counseling and genetic testing may be appropriate.^{176-178,184,202} All young children diagnosed with primary lymphedema should have a karyotype test performed. The karyotype determines the presence of chromosome abnormalities such as Turner's syndrome that can be associated with lymphedema. Other types of primary lymphedema involve specific genes. For example, Milroy's disease has a specific defect of the FLT4 gene that is responsible for producing a protein called vascular endothelial growth factor receptor 3 (VEGFR-3). The FOXC2 and SOX18 genes are also associated with lymphedema. Most forms of inherited lymphedema are not detected on gene or chromosome tests. Children diagnosed with primary lymphedema should be referred to a Medical Geneticist or a Genetic Counselor to determine which tests are indicated for that child's condition. With late onset of primary lymphedemas, genetic testing is of limited benefit, but Genetic Counseling may be offered on a case-by-case basis.

Other Vascular Imaging

Some forms of edema are caused by diseases or abnormalities in the cardiovascular system (heart, arteries veins). For children, and some adults, diagnosed with primary lymphedema, it is important to evaluate for other vascular abnormalities.^{179,180} Conditions such as congestive heart failure, vein clots known as deep venous thrombosis (DVT), damaged vein valves known as venous insufficiency, and some arterial conditions can lead to swelling or exist concurrent with lymphedema. With secondary lymphedema from cancer, obstruction of a vein can contribute to the severity of edema.¹⁹⁶ Imaging studies of the heart, veins or arteries may be needed to get a complete and accurate diagnosis of the cause and proper treatment for edema.¹⁹⁰ The most common cardiovascular studies ordered for the evaluation of complex edemas are: echocardiogram, venous ultrasound and arterial ultrasound with ankle brachial index (ABI). Ultrasound studies of veins looking for a clot can be done lying down. To accurately diagnose venous insufficiency (incompetent valves) the ultrasound must be done standing or on a tilt table that can be tipped into a standing position (for patients who cannot stand for the test). If there is a concern for abnormalities of blood vessels in the chest, abdomen or pelvis, more advanced imaging, such as computed tomography venograms or arteriograms, may be recommended.

Other Diagnostic Tests

There is no blood test for lymphedema. Other medical conditions such as hypothyroidism (myxedema) or low protein (hypoproteinemia) can cause edema and need to be done in a complete evaluation of swelling. Standard plain x-rays may be ordered for some inherited lymphedemas to evaluate for orthopedic conditions.^{182,183}

Treatment of Lymphedema: Complete Decongestive Therapy (CDT)

Complete Decongestive therapy is also called Combined, Complex or Comprehensive Decongestive Therapy. All refer to the same method known as CDT. CDT is the main treatment for lymphedema. Experts who treat lymphedema consider CDT the “gold standard” of treatment.^{11,12} CDT has been shown to be safe and effective.^{13-19,197} CDT consists of an initial reductive phase (Phase I) followed by a maintenance phase (Phase II).^{11, 20-23} In Phase I, the main goals are reducing the size of the affected part and improving the skin. After Phase I, the person with lymphedema needs to continue into Phase II, an ongoing, individualized self- management phase to make sure the gains of Phase I are maintained long term.²⁴

Effects of CDT are to:

1. decrease swelling^{25,26}
2. increase lymph drainage from the congested areas^{27,28}
3. reduce skin fibrosis and improve the skin condition¹
4. enhance patient's functional status²⁹
5. relieve discomfort and improve quality of life^{8,25,26,30-34}
6. reduce the risk of cellulitis and Stewart-Treves-Syndrome, a rare form of angiosarcoma^{35-45,197}

Components of CDT

1. manual lymph drainage (MLD)
2. multi-layer, short-stretch compression bandaging
3. lymphatic exercise
4. skin care
5. education in lymphedema self-management, and elastic compression garments^{22,46}

Frequency and Duration of Phase I (Reductive) CDT

Optimally, CDT is performed daily (5 days/week) until the reduction of fluid volume has reached a plateau, which can take 3 to 8 weeks.^{22,47} Some patients may have good results from CDT with modifications of the frequency and duration of treatment.⁴⁹ CDT frequency and duration should be individualized to produce the greatest reduction of swelling and improvement of skin condition in the shortest period of time.

Maintenance (Phase II) CDT

At the completion of Phase I CDT, the person with lymphedema is set up on a self-management program that includes self-lymph drainage (sometimes called Simple Lymphatic Drainage), home lymphatic exercises, a skin care regimen, and compression garments or bandages that the individual learns to apply. Some individuals may require additional measures at home to maintain the gains achieved in Phase I. These measures may include garments with Velcro, specialized foam construction garments, and pneumatic compression devices.¹³⁶ Phase II maintenance must be monitored and changed periodically, just as treatment for any other chronic medical condition. Compression garments must be replaced every 4-6 months to be effective. Specialized equipment requires maintenance and replacement according to manufacturers' guidelines. Phase II CDT and periodic medical monitoring are essential to the long-term success of lymphedema treatment.^{16,22-24}

Therapist Training

Therapists providing CDT should have completed at least 135 hours of training as recommended by the Lymphology Association of North America® (LANA®). (See NLN Position Paper: Training of Lymphedema Therapists.²⁰⁵) Additional specialty training may be required for therapists treating facial, truncal, and genital lymphedema, or lymphedema in people with complex illnesses or disabilities.

Manual Lymph Drainage (MLD)

Manual lymph drainage is an essential part of CDT. It is a specialized manual (hands-on) technique that appears to work by two mechanisms. It stimulates superficial lymphatic vessels to remove excess interstitial fluid and it moves it through subepidermal (under the skin) fluid channels that form when lymphatics are damaged.^{47,201} Some people refer to MLD as massage, but it is different from the usual types of muscle or myofascial massage commonly known to the public. MLD is a light, skin technique learned by certified lymphedema therapists designed to improve fluid removal from congested areas where the lymphatics are not working properly and into lymph vessels and lymph nodes that are functioning.⁴⁸

Compression Bandaging

Compression bandaging refers to a specific technique⁵⁴ utilizing multiple layers of several materials to create safe and effective gradient compression. The necessary components of compression bandaging are:

1. Tubular bandage lining
2. Digit bandages
3. Polyester, cotton, or foam under-cast padding
4. Multiple layers of short-stretch bandages with 50% overlap and 50% stretch to cover the entire limb

In some patients, it is also necessary to utilize polyurethane foam in various densities and configurations within the bandaging system. These materials are applied according to standard technique to body parts with lymphedema. Short-stretch bandages have limited stretchability when pulled. They can stretch 40-60% from resting length, compared to long-stretch bandages such as Ace® bandages that stretch to greater than 140% of resting length. To achieve an effective compression gradient, short-stretch bandages must be strategically applied with low-to-moderate tension using more layers at the ends of the extremities than higher up.⁵⁰⁻⁵⁵ Pressure within the short-stretch bandages is low when the patient is not moving (“resting pressure”). Muscle contractions increase interstitial fluid pressure to assist the fluid to move out of congested areas (“working pressure”), as muscles expand within the limited space of the short-stretch bandages.⁵⁶ The cycling between low-resting and high-working pressures in the interstitial fluid areas under the bandages creates an internal pump-like action. This action encourages movement of congested interstitial fluid into the vascular circulation. The short-stretch bandages also prevent refilling of the fluid into the tissues. Another property of short-stretch bandages is to reduce the tissue hardening (fibrosis).¹ Compression Bandaging is always a part of Phase I CDT. Some individuals with more severe forms of lymphedema may need to use home compression bandaging longer term as part of Phase II. Some locations of the body, such as the head and neck, are not amenable to standard short-stretch bandaging so other compression techniques have to be used.²⁰⁴

Exercise (including lymphatic “Remedial Exercise”)

With lymphedema, specific exercise is beneficial for all patients.²⁰³ Although heavy activity may temporarily increase fluid load, appropriate exercise enables the person with lymphedema to resume activity while minimizing the risk of exacerbation of swelling.^{29,57-60,139} For people who have lymphedema, compression garments or compression bandages must be worn during exercise (except in aqua therapy) to counterbalance the build up of interstitial fluid.^{58,61} (See NLN Position Paper: Exercise for Lymphedema Patients.²⁰⁵) Since exercise has been shown to have major positive effects during and after cancer treatment, safe exercise must be a goal for all cancer-related lymphedema.^{60,62} For other forms of lymphedema, exercise also has positive effects. People with or at-risk for lymphedema are encouraged to work with a lymphedema specialist to incorporate an individualized exercise program into lymphedema management.

Skin and Nail Care

Meticulous hygiene is recommended to decrease the amount of fungus and bacteria on the skin. Low pH moisturizers should be applied to keep skin from drying and cracking.⁶³ Cracks and dry areas of the skin are entry points for bacteria and fungus, which can result in infections and wounds.^{64,65} Skin infections are known as cellulitis (or

erysipelas). Cellulitis is a serious infection of the skin that requires antibiotic treatment in people with lymphedema.³⁶⁻³⁸ (See NLN Position Paper: Lymphedema Risk Reduction Practices.²⁰⁵)

Compression Garments

Following achievement of maximal volume reduction with Phase I CDT, patients should be fitted with a compression garment. The patient should receive two garments at a time for each affected body part: one to wear and one to wash and dry. Having two garments insures that the patient does not wear a dirty or wet garment which promotes bacterial or fungal infection. Garments may be sleeves, stockings, bras, compression shorts, face or neck compression wear, etc. The type of garment depends upon the body part with lymphedema. Properly-fitted garments are essential for long-term control of lymphedema.^{4,66} Garment style and compression strength should be prescribed according to the patient's ability to manage the garment and maintain the best volume control and skin health.⁶⁷ Ready-made garments come in a variety of sizes and can be fitted to many individuals. Custom garments are made specifically for the individual who cannot fit a ready-made garment. They are more expensive than ready-made garments. Custom garments may be required for patients with irregularly-shaped limb(s) or body parts, wounds, lack of sensation or difficulty with hand dexterity. Custom garments are often a necessity for growing children. Custom garments allow for options such as special linings to reduce the risk of skin breakdown and fastening devices which can help the patient put on and remove the garment. Garments should be washed daily so the garment lasts as long as possible and does not lose its compression strength. Manufacturer instructions must be followed for washing and drying to prolong the life of the garment. Most daily garments must be replaced every 4-6 months to maintain compression strength. Compression garments for children must be replaced when growth necessitates, which is usually multiple times per year for babies and younger children.

In addition to the day garments used in Phase II, some patients with more severe forms of lymphedema will need night garments or advanced day garments to maintain the reductions obtained in Phase I. There are a variety of options for advanced and night garments that may be required for control of lymphedema, such as Velcro closure garments and specialized foam compression garments.^{68,136,137}

Patient Education

Since lymphedema is a life-long condition, patient education in self-management is very important.⁶⁹ To reduce the risk of developing lymphedema or having lymphedema worsen, all patients with lymphedema or at-risk for lymphedema should be instructed in essential self care. The important areas of education include risk-reduction practices, self-lymph drainage, skin care, signs and symptoms of infection, proper fit and care of garments, and the importance of good nutrition, exercise and weight control.

Weight Loss

Lymphedema risk increases with obesity, so weight loss should be a part of lymphedema treatment in overweight individuals, as well as maintenance of optimal weight in normal-weight individuals.^{45,70-74} In one study, weight loss alone was shown to reduce arm volume in the lymphedema arm more than the uninvolved arm of obese women with post-mastectomy lymphedema.⁷⁵

Modifications and Individualization of CDT

CDT programs should be individualized based on the presence of other medical conditions or patient abilities. Patients with wounds, scars, or musculoskeletal conditions; palliative care patients; or patients with post-radiation fibrosis may require adaptations of CDT. If there is limited mobility of the body part with or near the swelling, the patient may require other therapies, such as scar massage or myofascial therapy, in addition to CDT, to have a benefit from CDT.^{49,64,65,68}

Decongestive Therapy for Head and Neck Lymphedema

Lymphedema can be a complication of treatment for head and neck cancer. Manifestations of lymphedema in patients with head and neck cancer are both internal (difficulty swallowing, vocal cord swelling) and external (swelling

of the face, jaw and neck). Modifications of CDT have been shown to be beneficial, especially manual lymphatic drainage and modified garments.⁷⁶⁻⁷⁸

Intermittent Pneumatic Compression Therapy (IPC)

IPC, also known as compression pump therapy, can be useful in some patients as an adjunct to Phase I CDT⁷⁹⁻⁸⁸ or a necessary component of a successful home program (Phase II CDT).⁸⁹⁻⁹¹

Single-chamber pumps, used in the past, are not used for lymphedema now. Single chamber pumps can cause fluid to move in both directions, meaning fluid can build up in the already-swollen area. Also, the pressure in single-chamber pumps does not stimulate lymphatic flow as sequential pumps do.⁹² Acceptable pumps should have appliances (pump garments) with multiple chambers and have a sequential pressure delivery with the chambers compressing in a specific pattern determined individually for the patient's diagnosis and pattern of lymphedema.⁹³ Since lymphedema is a condition involving a quadrant of the body (upper or lower trunk, chest, abdomen), and not just the limb with the swelling, many patients who require IPC will need a pump that treats the trunk of the body and not just the limb with the swelling.

Recommended pump pressures generally range from 30-60 mmHg, although lower or higher pressures may be indicated.²⁰⁰ The pressure displayed on the pump may not accurately reflect what is delivered to the skin surface. One study demonstrated considerable differences in skin/device interface pressure patterns and magnitude which may have an impact on therapeutic outcomes.⁹⁴ This is a significant concern because superficial structures may be harmed if the pressures applied in therapy are too high.⁹⁵ In general, lower pressures are considered to be safer, but the pressure has to be individualized to the patient's diagnosis and skin condition.^{95,200} The length of each treatment is usually one hour. IPC is not a "stand-alone" treatment. It is utilized along with standard CDT to maintain control of lymphedema at home.^{90,91} (Phase II). To maintain edema control, a compression garment, or short-stretch bandages, should be worn between pump treatments and also when IPC therapy is discontinued.¹³⁶

Patients being considered for IPC therapy must be evaluated by a physician or health-care provider with expertise in lymphedema. It is important to insure safe selection of the proper device and appropriateness of IPC. The prescription must include the intensity of pressure and pattern of pressure needed, taking into consideration several aspects of the patient's situation including determination of need for programmable pressure to treat fibrotic areas,^{200,201} address treatment of ulcers, and adjust for patient's level of pain and skin sensitivity. If trunk, chest or genital swelling is present, the physician must determine whether a pump that provides appliances to treat those areas is necessary or if the patient can manage the trunk swelling through self-MLD or garments. If a pump with only extremity attachments is used, close monitoring should be instituted to detect an increase in edema or fibrotic (hard) tissue above the device sleeve, called a fibrosclerotic ring.⁹⁶ If this occurs, consideration should be given to using a device that treats the trunk in addition to the extremities. Additionally, the physician or health-care provider must evaluate the impact of various other medical conditions that are usually considered contraindications for pneumatic compression therapy, including acute infection, severe arterial vascular disease, acute superficial or deep vein phlebitis (inflammation or clot), recurrent cancer in the affected area, or uncompensated congestive heart failure.

Surgical Treatment of LE

Surgery for lymphedema is not curative, but it has been used in specific circumstances for control of a severe condition. Circumstances where surgery may be considered are: reducing the weight of the affected limb, minimizing the frequency of inflammatory attacks, improving cosmetic appearance, or fitting the limb into garments. As with all surgical procedures, the risks and benefits must be weighed against the individual needs of the patient, and the expertise of the surgical team. Surgery is usually only considered when adequate trials of all usual methods of treatment have failed.^{97,98} There are several types of surgical procedures available that have been used for lymphedema: (a) excisional operations, including debulking and liposuction, (b) tissue transfers, and (c) microsurgical lymphatic reconstruction. There are very few surgeons who perform these procedures. It is extremely important that patients with lymphedema are treated by surgeons experienced in the care of lymphedema and who work

with certified lymphedema providers for the patient's on-going care after surgery. Surgery for lymphedema must be done in conjunction with CDT.¹⁴⁷

Debulking

Debulking surgery removes the hard connective tissue and any large folds of fatty tissue associated with the lymphedema-affected body part.⁹⁹⁻¹⁰¹ The potential risks of this surgery include prolonged hospitalization, poor wound healing, nerve damage or loss, significant scarring, destruction of the remaining lymphatic vessels in that body part, loss of limb function, return of swelling, poor cosmetic results, and decrease in quality of life. Post-operatively, compression garments are still necessary for the maintenance of the limb and must be worn life-long due to the lymphatic scarring from these surgeries and lymphatic insufficiency.

Liposuction

Liposuction involves the circumferential removal of fatty tissue deposits in the body part affected by long-standing lymphedema. It is generally performed under general anesthesia and involves the creation of many small incisions. Tubular suction devices are inserted into the incisions by the surgeon to break up, liquefy, and suction out the fat.¹⁰²⁻¹⁰⁴ Liposuction for lymphedema is similar, but not exactly the same, as cosmetic liposuction. Tight bandaging is necessary to stop the bleeding after liposuction for lymphedema. Life-long compression garments are generally needed to prevent lymphedema from coming back due to the scarring of lymph vessels that can occur from the procedure. The risks of liposuction include bleeding, infection, skin loss, abnormal sensation (such as numbness, tingling, "pins and needles" feeling), and lymphedema returning.

Tissue Transfers

Tissue transfers (grafts) have been attempted to bring lymph vessels into a congested area to remove excess interstitial fluid. There are few studies of the long-term effectiveness of tissue transfers for lymphedema. Published articles are either outdated, done on animals, or describe lymph vessel function in breast reconstruction flaps.^{104,105}

Microsurgical Lymphatic Reconstruction

Microsurgical and supramicrosurgical (much smaller vessels) techniques have been developed to move lymph vessels to congested areas to try to improve lymphatic drainage. Surgeries involve connecting lymph vessels and veins, lymph nodes and veins, or lymph vessels to lymph vessels. Reductions in limb volume have been reported and a number of preliminary studies have been done, but there are no long-term studies of the effectiveness of these techniques.¹⁰⁶⁻¹¹⁵

Summary on Surgical Treatments

In general, surgical treatment is associated with significant risks, may result in reduced swelling for an unknown time, and is done by very few surgeons with experience in lymphedema. Surgical management of lymphedema should always be done in conjunction with CDT and does not stop the need for compression garments and Phase II maintenance. Since CDT, and other adjunctive therapies such as advanced garments and IPC, can usually produce good management in compliant patients, surgery is rarely a necessary consideration.¹³⁸

Pharmaceutical Approaches

Lymphedema should not be exclusively treated with drugs or dietary supplements. Diuretics are ineffective for removal of interstitial fluid from the tissues. Excess diuretic use can lead to dehydration, electrolyte imbalance, and tissue damage. However, diuretics may be medically indicated in patients with lymphedema who have other medical conditions such as high blood pressure and heart disease. Therefore, diuretic use must be assessed on a case-by-case basis. Individuals with lymphedema should not stop diuretics before checking with their physician or health care provider.

Some drugs such as Coumarin (not coumadin) and Diosmin have been tried for lymphedema. They have not been found to be effective and have adverse side effects.¹¹⁶⁻¹²³

Natural Supplements

There is limited evidence from rigorously-designed studies on the use of natural supplements for lymphedema. Studies have indicated American horse chestnut may help venous edema but not lymphedema.¹²⁴ Selenium has been reported to improve lymphedema in head and neck cancer.^{125,126} Bromelain, a substance found in pineapple, has anti-inflammatory, anticoagulant, enzymatic, and diuretic effects. Some have wondered if there might be a benefit for bromelain use with lymphedema, but it has not been studied for use specifically for lymphedema.¹²⁷⁻¹³²

Due to potential interactions with prescription drugs and other negative side effects, patients should check with their physician or health-care provider before taking any natural supplement.

Complementary, Integrative and Alternative Treatments

A number of promising treatments have been reported, but they have not yet been subjected to sufficient rigorous research to recommend as the standard of care. These treatments include cold laser, electrical stimulation, vibratory therapy, oscillation therapy, endermologie and aqualymphatic therapy.^{133-142,146} All of these techniques are done in combination with components of CDT. Acupuncture has shown benefit for some symptoms of cancer and cancer treatment, including fatigue, hot flashes, muscular or joint pain, neuropathy and nausea. There are no rigorous studies on using acupuncture for treating lymphedema or using acupuncture on lymphedema extremities (see NLN Position Paper on Risk Reduction.²⁰⁵). Rebounder trampolines have been advocated by some for treating lymphedema, but there are no published studies on this treatment. Rebounding is good exercise, it but is not known to be superior to other forms of aerobic exercise in individuals with lymphedema.

Summary on Treatment and Diagnosis of Lymphedema

Treatment of lymphedema should be undertaken only after a thorough diagnostic evaluation has been done according to accepted guidelines by qualified practitioners. CDT is the current international standard of care for managing lymphedema. CDT has been shown to be effective in large numbers of case studies demonstrating limb volume reductions of 50-70% or more, improved appearance of the limb, reduced symptoms, improved quality of life, and fewer infections after treatment. Even people with progressive lymphedema for 30 years or more before starting CDT have been shown to respond. Patient adherence during Phase II CDT is critical for preserving volume reduction. It is recommended that CDT adaptations or other lymphedema treatments be used on a case-by-case basis under the supervision of a health-care provider (physician, nurse, physician assistant, therapist) with demonstrated expertise in lymphedema management. IPC is a demonstrated effective adjunct to CDT. All interventions for lymphedema must have the goals of inducing and maintaining volume reduction, preventing medical complications, improving skin condition, reducing infection, enhancing patient adherence, and improving comfort and quality of life.

This document has been written and reviewed by members of the 2010-2011 NLN Medical Advisory Committee (MAC). MAC members have disclosed no relevant financial arrangements or affiliations.

REFERENCES

1. Foldi E, et al. (2005). The Science of Lymphoedema Bandaging in Calne, S. Editor. European Wound Management Association (EWMA). Focus Document: Lymphoedema Bandaging in Practice. London: MEP Ltd, 2-4
2. Casley-Smith, J. (1995). Alterations of untreated lymphedema and its grades over time. *Lymphology*, 28,174-185
3. MacLaren, J. (2001). Skin changes in lymphoedema: pathophysiology and management options. *Int J Palliat Nurs*, 7, 381-388
4. Yasuhara, H. (1996). A study of the advantages of elastic stockings for leg lymphedema. *Int Angiol*, 15, 272-277

5. Gordon, K (2007). A guide to lymphedema. *Expert Review of Dermatology*, 2 (6) 741-752
6. Armer J et al.(2009) 30-month post-breast cancer treatment lymphoedema. *J Lymphoedema*, 4,14–18
7. Ridner, S.(2009) The PsychoSocial Impact of Lymphedema. *Lymphat Res Biol*. 7, 109–112
8. Ahmed, R. J (2008) Lymphedema and Quality of Life in Breast Cancer. *Survivors: The Iowa Women's Health Study*. *Clin Oncol* 26, 5689-5696
9. Shih, Y. (2009) Incidence, Treatment Costs, and Complications of Lymphedema After Breast Cancer Among Women of Working Age: A 2-Year Follow-Up Study. *JCO* 27, 2007-2014
10. Executive Committee of International Society of Lymphology (2009) The Diagnosis and Treatment of Peripheral Lymphedema. Consensus Document of the International Society of Lymphology. *Lymphology*, 42, 51-60
11. Mayrovitz HN (2009)The standard of care for lymphedema: current concepts and physiological considerations. *Lymphat Res Biol* 7,101-8
12. Szuba, A (2000) Decongestive lymphatic therapy for patients with cancer-related or primary lymphedema. *American Journal of Medicine*,109, 296-300
13. Godette, K. (2006) Can Manual Treatment of Lymphedema Promote Metastasis? *J Soc Integrat Oncol*. ,4, 8-12
14. Pinell, XA et al.(2008) Manipulative therapy of secondary lymphedema in the presence of locoregional tumors. *Cancer* 112, 950–954,
15. Hinrichs CS, et al. (2004) The effectiveness of complete decongestive physiotherapy for the treatment of lymphedema following groin dissection for melanoma. *J Surg Oncol*. 85: 187–192
16. Lasinski, B. (2002). Comprehensive lymphedema management: results of a five-year follow-up. *Lymphology*, 35, 301-305.
17. Morgan, R.G. (1992). Complex physical therapy for the lymphoedematous arm. *J Hand Surg*, 17, 437-441
18. Thomas, RC et al. (2007) Reduction of lymphedema using complete decongestive therapy: roles of prior radiation therapy and extent of axillary dissection. *J Soc Integrat Oncol*.5, 87-91
19. Koul et al. (2007) Efficacy of complete decongestive therapy and manual lymphatic drainage on treatment related lymphedema in breast cancer. *Int. J. Radiation Oncology Biol. Phys*, 67, 841–846.
20. Foldi, E. (1989). The lymphedema chaos: a lancet. *Ann Plast Surg*, 22, 505-515.
21. Foldi E, (1998) The Treatment of Lymphedema. *Cancer* 83 Suppl 12B, 2833-2834.
22. Ko, D. (1998). Effective treatment of lymphedema of the extremities. *Arch Surg*, 133, 452-458
23. Boris M, et al (1994). Lymphedema reduction by noninvasive complex lymphedema therapy. *Oncology*. 9, 95-106
24. Johnstone, PA et al. (2006) Role of patient adherence in maintenance of results after manipulative therapy for lymphedema *J Soc Integr Oncol*. 4, 125-9
25. Mondry T et al (2004) Prospective trial of complete decongestive therapy for upper extremity lymphedema after breast cancer therapy, 10, 42-8
26. Hammer JB et al. (2007) Lymphedema Therapy Reduces the Volume of Edema and Pain in Patients with Breast Cancer. *Annals of Surgical Oncology* 14, 1904–1908.
27. Ferrandez, J. (1996). Lymphoscintigraphic aspects of the effects of manual lymphatic drainage. *J Mal Vasc*, 21, 283-289
28. Franzcek U et al (1997) Combined physical therapy for lymphedema evaluated by fluorescence microlymphography and lymph capillary pressure measurements. *J Vasc Res*, 34, 306-311
29. Hayes, S et al.(2008) Lymphedema After Breast Cancer: Incidence, Risk Factors, and Effect on Upper Body Function. *J Clin Oncol* 28, 3536-3542
30. Weiss, J. (2002). The effect of complete decongestive therapy on the quality of life of patients with peripheral lymphedema. *Lymphology*, 35, 46-58.
31. Kim SJ et al. (2007) Effect of Complex Decongestive Therapy and the Quality of Life in Breast Cancer Patients with Unilateral Lymphedema. *Lymphology* 40, 143-151.

32. Cormier, JN et al. (2009) Minimal limb volume change has a significant impact on breast cancer survivors. *Lymphology* 42, 161-175
33. Hormes, JM et al. (2010) Impact of lymphedema and arm symptoms on quality of life in breast cancer survivors. *Lymphology* 43, 1-13
34. Fu, M et al (2009) Breast Cancer Survivors' Experiences of Lymphedema-Related Symptoms *J Pain Symptom Manage*;38:849e859.
35. Vignes, S (2006) Recurrence of lymphoedema-associated cellulitis (erysipelas) under prophylactic antibiotherapy: a retrospective cohort study *JEADV*,20:, 818–822
36. Cooper, R et al. (2009) Cutaneous Infections in Lymphoedema. *Journal of Lymphoedema*, 4, 44-48
37. Al_Niaini, F et al.(2009) Cellulitis and Lymphoedema, A Vicious Cycle. *Journal of Lymphoedema*. 4, 38-42
38. Godoy J et al. (2007) Prevalence of cellulitis and erysipelas in post-mastectomy patients after breast cancer. *Arch Med Sci*, 3, 249-251
39. Chamilos, G (2006) Refractory Cellulitis in a Woman With Chronic Lymphedema *Infectious Diseases in Clinical Practice*, 14 ,244-245
40. Schwartz, RA (2010) Stewart Treves Syndrome: Follow Up. <http://emedicine.medscape.com/article/1102114-followup>
41. Chopra, S et al. (2007) MRI of angiosarcoma associated with chronic lymphoedema:Stewart–Treves syndrome *The British Journal of Radiology*, 80 e310–e313
42. Tomita, K et al.(1988) Lymphangiosarcoma in postmastectomy lymphedema (Stewart-Treves syndrome): ultrastructural and immunohistologic characteristics. *J Surg Oncol*. 38, 275-82.
43. Ruocco V, et al (2002) Lymphedema: an immunologically vulnerable site for development o f neoplasms. *J Am Acad Dermatol*. 47, 124 -127.
44. McHaffie, DR et al. (2010) Stewart-Treves Syndrome of the Lower Extremity. *JCO* 28, e351-e352
45. Gur, A et al. (2009) Risk factors for breast cancer-related upper extremity lymphedema. *Central European Journal of Medicine*. 4, 65-70
46. Didem, K et al (2005) The comparison of two different physiotherapy methods in treatment of lymphedema after breast surgery *Breast Cancer Research and Treatment* 93, 49–54
47. Williams, AF et al (2002) A randomized controlled crossover study of manual lymphatic drainage therapy in women with breast cancer-related lymphoedema. *European Journal of Cancer Care* 11, 254–261
48. McNeely, M. (2004). The addition of manual lymph drainage to compression therapy for breast cancer related lymphoedema: a randomized controlled trial *Breast Cancer Res Treat*, 86, 95-106.
49. Yamamoto et al. (2008) Study of Edema Reduction Patterns During the Treatment Phase of Complex Decongestive Physiotherapy for Extremity Lymphedema. *Lymphology* 41 80-86
50. Foldi E, et al. (2005)The Science of Lymphoedema Bandaging. In Calne, S. Editor. *European Wound Management Association (EWMA). Focus Document: Lymphoedema bandaging in practice*. London: MEP Ltd, 2-4
51. King, T. (2001). Physical properties of short-stretch compression bandages used to treat lymphedema. *Am J Occup Ther*, 55, 573-576
52. Partsch, H. (2007) Assessing the Effectiveness of Multilayer Inelastic Bandaging. *Journal of Lymphoedema*. 2, 55-61
53. Forner-Cordero I et al. (2010) Predictive factors of response to decongestive therapy in patients with breast cancer-related lymphedema. *Ann Surg Oncol*. 17, 744-751
54. Williams, A (2005) Practical Guidance on Lymphoedema Bandaging of the Upper and Lower Extremities. In Calne, S. Editor. *European Wound Management Association (EWMA). Focus Document: Lymphoedema bandaging in practice*. London: MEP Ltd, 10-14
55. Lerner R (2000) Effects of compression bandaging. *Lymphology* 33: 69
56. Hafner J et al (2000) A Comparison of Multilayer Bandage Systems During Rest, Exercise,and Over 2 Days of Wear Time *Arch Dermatol*. 136:857-863

57. McKenzie, D. (2003). Effect of upper extremity exercise on secondary lymphedema in breast cancer patients: a pilot study. *J Clin Oncol*, 21, 463-466
58. Schmitz, KH et al. (2009) Weight Lifting in Women with Breast-Cancer-Related Lymphedema. *N Engl J Med* 361:664-73.
59. Moseley AL et al: (2005) The Effect of Gentle Arm Exercise and Deep Breathing on Secondary Arm Lymphedema. *Lymphology* 38 136-145
60. Schmitz KH. Balancing lymphedema risk: exercise versus deconditioning for breast cancer survivors. *Exerc. Sports Sci. Rev.* 2009; 38:17-24
61. Johansson K, et al. (2005) Low intensity resistance exercise for breast cancer patients with arm lymphedema with or without compression sleeve. *Lymphology* 38,167-80
62. Mustian, K et al. (2009). Exercise for the Management of Side Effects and Quality of Life among Cancer Survivors. *Curr Sports Med Rep* 8; 325-330
63. Vaillant, L. (2002). Infectious complications of lymphedema. *Rev Med Interne*, 23, 403-407
64. Mallon, E. (1994). Lymphedema and wound healing. *Clin Dermatol*,12, 89-93
65. Macdonald, J. (2001). Wound healing and lymphedema: a new look at an old problem. *Ostomy Wound Manage*, 47, 52-57.
66. Badger CM, et al (2000) A randomized, controlled, parallel-group clinical trial comparing multilayer bandaging followed by hosiery versus hosiery alone in the treatment of patients with lymphedema of the limb. *Cancer* 88, 2832-37
67. Cornu-Thenard, A et al. (2007) Superimposed Elastic Stockings: Pressure Measurements *Dermatol Surg* 33:269-275
68. Lund, E. (2000). Exploring the use of CircAid legging in the management of lymphoedema. *Int J Palliat Nurs*, 6, 383-391
69. Fu, M.R et al. (2008). Breast Cancer-Related Lymphedema: Information, Symptoms, and Risk Reduction Behaviors. *J Nurs Scholarsh*, 40, 341-348.
70. Fife, C et al. Lymphoedema in Bariatric Patients. *J Lymphoedema*. 4, 29-37,
71. Petrek, JA (2001) Lymphedema in a Cohort of Breast Carcinoma Survivors: 20 years after diagnosis. *Cancer*. 92, 1368-77
72. Soran, A et al. (2006) Breast Cancer Related Lymphedema-What are the Significant Predictors and how they affect the severity of lymphedema. *Breast J*, 12, 536-43,
73. Mahamaneerat, K et al. Breast Cancer Treatment, BMI, PostOp swelling/lymphoedema. *J Lymphoedema*. 3, 38-44.
74. Helyer LK, et al. (2010) Obesity is a risk factor for developing postoperative lymphedema in breast cancer patients. *Breast J.*; 16, 48-54
75. Shaw, S et al. (2007) A Randomized Controlled Trial of Weight Reduction as a Treatment for Breast Cancer-related Lymphedema. *Cancer*, 110, 1868-74
76. Lewin, J et al. (2010) Preliminary Experience With Head and Neck Lymphedema and Swallowing Function in Patients Treated for Head and Neck Cancer. *Perspectives on Swallowing and Swallowing Disorders. Dysphagia* 19, 45-52
77. Murphy, B et al. 2010, Late-effect laryngeal oedema/lymphoedema. *Journal of Lymphoedema*, 5, 92-93
78. Smith B et al. (2010) Lymphedema Management in Head and Neck Cancer. *Current Opinions in Otolaryngology and Head and Neck Surgery*. 18,153-158
79. Szolnoky et al.(2009) Intermittent Pneumatic Compression Acts Synergistically With Manual Lymphatic Drainage In Complex Decongestive Therapy. *Lymphology* 42,188-194
80. Miranda F et al. (2001) Effect of Sequential Intermittent Pneumatic Compression On Both Leg Lymphedema Volume and On Lymph Transport As SemiQuantitatively Evaluated by Lymphoscintigraphy. *Lymphology* 34 135-141.
81. Johansson, K. (1988). A randomized study comparing manual lymph drainage with sequential pneumatic compression for treatment of postoperative arm lymphedema. *Lymphology*, 31, 56-64.

82. Adams, KE et al. Direct Evidence of lymphatic function improvement after advanced pneumatic compression device treatment of lymphedema. *Biomedical Optics Express* 1, 114
83. Pappas, C. (1992). Long-term results of compression treatment for lymphedema. *J Vasc Surg.* 16(4). 555-564.
84. Yamazaki, A. (1988). Clinical experience using pneumatic massage therapy for edematous limbs over the last 10 years. *Angiology.* 39. 154-163.
85. Dini, D. (1998). The role of pneumatic compression in the treatment of postmastectomy lymphedema. A randomized phase III study. *Ann Oncol.* 9. 187-190.
86. Szuba, A. (2002). Decongestive lymphatic therapy for patients with breast carcinoma-associated lymphedema. A randomized, prospective study of a role or adjunctive intermittent pneumatic compression. *Cancer,* 95, 2260-2267
87. Szolnoky, G et al. (2008) Complete Decongestive Physiotherapy With and Without Pneumatic Compression For Treatment of Lymphedema: A Pilot Study. *Lymphology* 41: 40-44
88. Partsch, H. (1980). Experimental observations on the effect of a pressure wave massage apparatus (Lympha-Press) in lymphedema. *Phlebologie Proktologie.* 80. 124-128
89. Wilburn, O. (2006). A pilot, prospective evaluation of a novel alternative for maintenance therapy for breast cancer-associated lymphedema. *BMC Cancer.* 6, 84
90. Hammond, T et al. (2009) Programmable Intermittent Pneumatic Compression as a Component of Therapy for Breast Cancer Treatment-Related Truncal and Arm Lymphedema Home Health Care Management Practice Online First, doi:10.1177/1084822309343421
91. Ridner, S et al. (2008) Home-based lymphedema treatment in patients with cancer-related lymphedema or noncancer-related lymphedema. *Oncol Nurs Forum.* 35, 671-80
92. Adams, KE et al. Direct Evidence of lymphatic function improvement after advanced pneumatic compression device treatment of lymphedema. *Biomedical Optics Express* 1, 114
93. Pilch et al. (2009) Influence of Compression Cycle Time and Number of Sleeve Chambers on Upper Extremity Lymphedema Volume Reduction During Intermittent Pneumatic Compression. *Lymphology* 42 26-35
94. Mayrovitz, HN. (2007) Interface pressures produced by two different types of lymphedema therapy devices. *Phys Ther* 87, 1379-1388
95. Segers P, Belgrado JP, LeDuc A, et al. Excessive pressure in multichambered cuffs used for sequential compression therapy. *Phys Ther.* 2002; 82:1000-1008
96. Boris, M. (1998). The risks of genital lymphedema after pump treatment for lower limb lymphedema. *Lymphology.* 31. 50-20.
97. Gloviczki, P. (1999). Principles of surgical treatment of chronic lymphoedema. *International Angiology,* 18 42-46.
98. Vignes, S. (2002). Role of surgery in the treatment of lymphedema. *Rev. Med Interne.* 23, 426-430.
99. Miller, T.A. (1998). Staged skin and subcutaneous excision for lymphedema: a favorable report of long-term results. *Plast Reconstr Surg,* 102,1486-498.
100. Kim, D.I. (2004). Excisional surgery for chronic advanced lymphedema. *Surgery Today,* 34, 134-137
101. Salgado CJ, Sassu P, Gharb BB, et al. Radical reduction of upper extremity lymphedema with preservation of perforators. *Ann Plast Surg.* Sep 2009;63(2):302-6
102. Brorson, H. (2003). Liposuction in arm lymphedema treatment. *Scand J Surg.* 92, 287-95.
103. Brorson H, Ohlin K, Olsson G, Svensson B. Liposuction of leg lymphedema: Preliminary 2 year results. *Lymphology* 2006; 39
104. Fazhi Q et al, (2009) Treatment of upper limb lymphedema with combination of liposuction, myocutaneous flap transfer, and lymph-fascia grafting: A preliminary study. *Microsurgery.* 29, 29-34.
105. Slavin SA et al.(1999) Return of lymphatic function after flap transfer for acute lymphedema. *Ann Surg.* 229,421-7
106. Weiss M, et al (2003) Dynamic lymph flow imaging in patients with oedema of the lower limb for evaluation of the functional outcome after autologous lymph vessel transplantation: an 8-year follow-up study. *Eur J Nucl Med Mol Imaging;* 30, 202-206.

107. Becker C, et al (2006) Post mastectomy lymphedema: long-term results following microsurgical lymph node transplantation. *Ann Surg*; 243, 313-315)
108. Koshima, I. (2000). Supermicrosurgical lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. *J Reconstr Microsurg*, 16, 437-442.
109. Baumeister, R.G. (2003). The microsurgical lymph vessel transplantation. *Handchir Mikrochir Plast Chir*, 35, 202-209.
110. Abalmasov, K.G. (2003). Lymphedema of the extremities: prospects of microsurgical treatment. *Angiol Sosud Khir*, 9, 66-79.
111. Vignes, S. (2003). Quantitative evaluation and qualitative results of surgical lymphovenous anastomosis in lower limb lymphedema. *J Mal Vasc*, 28, 30-35.
112. Chang, D. (2010): Lymphaticovenular Bypass for Lymphedema Management in Breast Cancer Patients: A Prospective Study. *Plastic & Reconstructive Surgery* 126, 752-758.
113. Campisi C, et al, (2006) Lymphatic microsurgery for the treatment of lymphedema. *Microsurgery*; 26(1): 65-69.
114. Campisi C et al (2004) Microsurgical techniques for lymphedema treatment: derivative lymphatic-venous microsurgery. *World J Surg* 28(6): 609-13.
115. Narushima M, et al (2010) The intravascular stenting method for treatment of extremity lymphedema with multiconfiguration lymphaticovenous anastomoses. *Plast Reconstr Surg*. 125, 935-943
116. Casley-Smith, J. (1993). Treatment of lymphedema of the arms and legs with 5, 6 benzo-a-pyrone. *N Engl J Med*, 329, 1158-1163.
117. Casley-Smith, J. (1993). Treatment of filarial lymphodema and elephantiasis with 5, 6 benzo-a-pyrone (coumarin). *Br Med J*. 307, 1037-1041.
118. Loprinzi, C. (1999). Lack of effect of coumarin in women with lymphedema after treatment for breast cancer. *N Engl J Med*. 340, 346-50.
119. Taylor, H. (1993). A double blind clinical trial of hydroxyethylrutosides in obstructive arm lymphodema. *Phlebology*, 8, 22-28.
120. Mortimer, P. (1995). A double-blind, randomized parallel-group, placebo-controlled trail of O-(β -hydroxyethyl)-rutosides in chronic arm oedema resulting from breast cancer treatment. *Phlebology*.10, 51-55.
121. Kendall, S. (1993). Effects of hydroxyethylrutosides on the permeability of microvessels in t frog mesentery. *Br J Pharmacol*. 110, 199-206.
122. Bouskela, E. (1999). Effects of diosmin-hospieridin on inceased microvascular permeability in the hamster cheek pouch. *International Journal of the Microcirculation: Clinical and Experimental*, 14, 79.
123. Cotonat, A. (1989). Lymphangogue and pulsatile activities of Daflon 500 mg on canine thoracic lymph duct. *International Angiology*, 8, 15-18
124. Siebert U, et al. (2002) Efficacy, routine effectiveness, and safety of horsechestnut seed extract in the treatment of chronic venous insufficiency. A meta-analysis of randomized controlled trials and large observational studies. *Int Angiol*. 4, 305-315
125. Micke O, et al. (2003) Selenium in the treatment of radiation-associated secondary lymphedema. *Int J Radiat Oncol Biol Phys* . 56, 40-9
126. Bruns F, et al.(2004) Selenium in the treatment of head and neck lymphedema. *Med. Princ Pract*. 13:185-90.
127. Cirelli, M. (1962). Treatment of inflammation and edema with bromelain. *Delaware Med J*, 34,159-167.
128. Seligman, B. (1969). Oral bromelains as adjuncts in the treatment of acute thrombophlebitis. *Angiology*, 20, 22-6.
129. Schafer A. (1985). Plasma inhibition of platelet function and of arachidonic acid metabolism. *J Clin Invest*, 75, 456-461.
130. Kelly, G. (1996). Bromelain: a literature review and discussion of its therapeutic applications. *Altern Med Rev*, 1, 243-257.
131. Munzig, E. (1995). Bromelain protease F9 reduces the CD44 mediated adhesions of human peripheral blood lymphocytes to human umbilical vein endothelial cells. *FEBS Lett*, 351, 215-218.

132. Gaby, A. (1995). The story of bromelain. *Nutr Healing*, 3, 4-11.)
133. Piller et al Placebo controlled trial of mild electrical stimulation. *Journal of Lymphoedema*, 2010, Vol 5, No 1. 15-25.
134. Moseley AL et al. The Sun Ancon Chi Machine Aerobic Exerciser: A New Patient Focused Home Based Therapy For People with Chronic Secondary Leg Lymphedema. *Lymphology* 37 (2004) 53-61.
135. Carati C, et al. Treatment of Postmastectomy Lymphedema with Low-Level Laser Therapy. *Cancer* 2003;98:1114-22
136. Hafner, A et al. (2005) Combined modality treatment of lymphedema using the Reid Sleeve and the Biocompression Optiflow system. *Journal of Clinical Oncology*. 23(s), 592.
137. Lawrence, S. (2008) Use of a Velcro Wrap System in the management of lower limb lymphoedema/oedema. *Journal of Lymphoedema*, 3, 65-70
138. Warren, A et al. (2007) Lymphedema: A comprehensive review. *Annals of Plastic Surgery*, 59, 464-472
139. Tidhar, D et al. (2010) Aqualymphatic therapy in women who suffer from breast cancer treatment-related lymphedema: a randomized controlled study. *Support Care Cancer*. 18: 383-392
140. Jahr, S et al. (2008) Effect of treatment with low intensity and extremely low frequency electrostatic fields (deep oscillation) on breast tissue and pain on patients with secondary breast lymphoedema. *J Rehabil Med*. 40, 645-650
141. Omar A et al. (2010) Treatment of Post Mastectomy Lymphedema with laser therapy: double blind placebo control randomized study. *J Surg Research*, 165, 82-90
142. Kozanoglu E et al, (2009) Efficacy of Pneumatic Compression and Low Level Laser Therapy in the treatment of post mastectomy lymphoedema: a randomized controlled trial. *Clin Rehabil*. 23, 117-124
143. Armer J et al. (2010) Post Breast Cancer Lymphedema: Incidence Increases from 12 to 30 to 60 months. *Lymphology* 43, 118-127.
144. Ward, L, (2006) Bioelectrical Impedance Analysis: Proven Utility in Lymphedema Risk Assessment and Therapeutic Monitoring. *Lymph Res Biol*. 4, 51-56
145. Moseley A et al (2007) Endermologie (with and without compression bandaging)--a new treatment option for secondary arm lymphedema. *Lymphology*, 40, 129-137.
146. Lee B et al.(2010) Diagnosis and treatment of primary lymphedema. Consensus document of the International Union of Phlebology (IUP)-2009. *Int Angiol* 29,454-70
147. Moseley A et al. (2008) Reliability of bioimpedance spectroscopy and tonometry after breast conserving cancer treatment. *Lymphatic Res Biol*, 6, 85-7
148. Moseley A et al. (2002) Combined opto-electronic perometry and bioimpedance to measure objectively the effectiveness of a new treatment intervention for chronic secondary leg lymphedema. *Lymphology*. 35. 136-43
149. Rockson, S et al. (2007) Bioimpedance analysis in the assessment of lymphoedema diagnosis and management. *J Lymphoedema*. 2, 44-48.
150. Mayrovitz, H (2009) Suitability of single tissue dielectric constant measurements to assess local tissue water in normal and lymphedematous skin. *Clin Physiol Imaging* 29: 123-127
151. Mayrovitz, H (2009) Assessing lymphedema by tissue indentation force and local tissue water. *Lymphology* 42, 88-98
152. Mayrovitz, H (2007) Assessing local tissue edema in postmastectomy lymphedema. *Lymphology* 40, 87-94
153. Corica, GF et al (2006) Objective measurement of scarring by multiple assessors: is the tissue tonometer a reliable option? *J Burn Care Res*. 27, 520-523
154. Mirnajafi, A et al. (2004) A New Technique for Measuring Skin Changes of Patients with Chronic Postmastectomy Lymphedema. *Lymph Res Biol*. 2, 82-85
155. Ridner S, et al. (2007) Comparison of upper limb volume measurement techniques and arm symptoms between healthy volunteers and individuals with known lymphedema *Lymphology* 40, 35-46
156. Chen Y et al. (2008) Reliability of Measurements For Lymphedema in Breast Cancer Patients. *Am J Phys Med Rehabil*. 87, 33-38

157. Chevillet A et al. The Grading of Lymphedema in Oncology Clinical Trials. (2003) *Seminars in Radiation Oncology*. 13, 214-225
158. Gniadecka, M.(1996) Localization of dermal edema in lipodermatosclerosis, lymphedema, and cardiac insufficiency: High frequency ultrasound examination of intradermal echogenicity. *J Amer Acad Derm* 35, 37-41
159. Astrom K et al.(2001) Imaging of primary, secondary and mixed forms of lymphedema. *Acta Radiol*. 42 409-416
160. Deltombe T et al. (2007) Reliability and limits of agreement of circumferential, water displacement and optoelectric volumetry in the measurement of upper limb lymphedema. *Lymphology* 40, 26-34
161. Hayes S et al. (2005) Comparison of Methods to Diagnose Lymphoedema among breast cancer survivors: 6 month follow up. *Br Ca Res Treat*. 89, 221-226
162. Pecking A et al. (2008) Relationship between lymphoscintigraphy and clinical findings in lower limb lymphedema: toward a comprehensive staging. *Lymphology* 41, 1-10
163. Hayes S et al. (2008) Lymphedema secondary to breast cancer: how choice of measure influences diagnosis, prevalence, and identifiable risk factors. *Lymphology* 41,18-28
164. Kramer E. (2001) Lymphoscintigraphy: Defining a Clinical Role. *Lymph Res Biol*. 2, 32-7
165. Bellini C et al (2005) Diagnostic Protocol for Lymphoscintigraphy in Newborns. *Lymphology* 38, 9-15
166. Hwang et al (2007) Lymphoscintigraphy predicts response to complex physical therapy in patients with early stage extremity lymphedema. *Lymphology* 40-172-176
167. Szuba (2007) Presence of Axillary lymph nodes and lymph drainage within arms of women with and without breast cancer-related lymphedema. *Lymphology* 40-81-86
168. Bellini C et al. (2008) Lymphatic Dysplasias in Newborns and Children: the role of lymphoscintigraphy. *J Pediatr* 152. 587-9
169. Ng, M et al. (2010) Clinimetrics of volume measurement in upper limb LE. *J Lymphoedema*. 5, 62-67
170. Unno, N et al. (2008) Quantitative Lymph Imaging for Assessment of Lymph Function using Indocyanine Green Fluorescence Lymphography. *Eur J Vasc Endovasc Surg* 36, 230-236
171. Unno N et al. (2010) A novel method of measuring human lymphatic pumping using indocyanine green fluorescence lymphography. *J Vasc Surg* 52, 946-52
172. Rasmussen J et al.(2009) Lymphatic Imaging in Humans with Near-Infrared Fluorescence. *Curr Opin Biotechnol*. 20-74-82
173. Rasmussen J et al (2010) Human Lymphatic Architecture and Dynamic Transport Imaged Using Near-infrared Fluorescence. *Transl Oncol.*; 3362–372
174. Maus, E. (2010) Near-infrared fluorescence imaging of lymphatics in head and neck lymphedema. *Head and Neck*. Online November 12, 2010. DOI: 10.1002/hed.21538
175. Damstra, R (2008) Diagnosis and Therapy in Children with Lymphoedema. *Plebology* 23: 276-286
176. Ferrell RE (2008) Candidate Gene Analysis in Primary Lymphedema. *Lymphat Res Biol* 6, 69-76
177. Connell, FC (2009) et al Analysis of the coding regions of VEGFR3 and VEGFC in Milroy disease and other primary lymphoedemas. *Hum Genetics* 124, 625-631
178. Boon, L (2011) Pathogenesis of Vascular Anomalies. *Clinics in Plastic Surgery*. 38, 7-19. Online ahead of print November 2010
179. Schumacher, M, et al. (2008) Treatment of Venous Malformations-comparison to lymphatic malformations. *Lymphology*. 41, 139-146
180. Bellini C. (2005) Pulmonary Lymphangiectasia. 38, 111-121
181. Wang, Z. (2005) Clinical Report of congenital lymphatic malformations and partial gigantism of the hands associated with a heterogenous karyotype. *Am J Medical Genetics* 132A, 106-107
182. Gupta, N et al. (2006) A female with hemihypertrophy and chylous ascites- Klippel Trenaunay Syndrome or Proteus Syndrome: a diagnostic dilemma. *Clin Dysmorphol*. 15: 229-231

183. Bellini C et al. (2009) Congenital lymphatic dysplasias: genetics review and resources for the lymphologist. *Lymphology* 42, 36-41
184. Starritt, E et al. (2004) Lymphedema after complete axillary node dissection for melanoma. *Ann Surg* 240, 866-874
185. Cormier, J et al (2010) Lymphedema beyond breast cancer: A systematic review and meta-analysis of cancer-related secondary lymphedema. *Cancer* 116 5138-5149.
186. Chang, S et al (2010) Prospective assessment of postoperative complications and associated costs following inguinal lymph node dissection (ILND) in melanoma patients. *Ann Surg Oncol.* 17, 2764-72
187. Lacomba, M (2010) Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: randomised, single blinded, clinical trial
188. Soo, J et al (2008) Lymphatic abnormalities demonstrated by lymphoscintigraphy after lower limb cellulitis. *BrJDermatol.* 158, 1350-1353
189. Piller, N, (2009) Phlebolympoedema/chronic venous lymphatic insufficiency: an introduction to strategies for detection, differentiation and treatment. *Phlebology* 24:51-55
190. Cornish, B et al. (2007) Can bioimpedance spectroscopy tell us about the form of lymphoedema? In Scharfetter and Merwa (Eds) 13th International Conference on Electrical Bioimpedance and 8th Conference on Bioimpedance Tomography. Springer. 795-798.
191. Bar-Ad, et al (2008) Time Course of Mild Arm Lymphedema After Breast Conservation Treatment for Early-Stage Breast Cancer, *Intl Journal Radiation Oncology Biology Physics* 78, 85-90
192. Lawenda, B et al (2009) Lymphedema: A primer on the identification and management of a chronic condition in oncologic treatment. *CA: A Cancer Journal for Clinicians.* 59, 8-24.
193. Bernas, M et al (2010) Lymphedema: How do we diagnose and reduce the risk of this dreaded complication of breast cancer treatment? *Curr Breast Cancer Rep* 2, 53-58.
194. Szuba, A et al. (2003) The third circulation: radionuclide lymphoscintigraphy in the evaluation of lymphedema. *J Nucl Med*, 44, 43-57
195. Szuba, A et al (2003) Diagnosis and treatment of concomitant venous obstruction in patients with secondary lymphedema. *J Vasc Intervent Radiol.* 13,799-803
196. Szuba, A et al (2000) Decongestive lymphatic therapy for patients with cancer-related or primary lymphedema. *Am J Med.* 109, 296-300
197. Szuba, A et al (1998) Lymphedema: classification, diagnosis and therapy. *Vasc Med*, 3, 145-156
198. Szuba, A et al (1997) Lymphedema: anatomy, physiology and pathogenesis. *Vasc Med*, 4,321-6
199. Olszewski, W. (2010) Tissue fluid pressure and flow in the subcutaneous tissue in lymphedema-hints for manual and pneumatic compression therapy. *Phlebolympology.* 17, 144-50
200. Olszewski, W (2009) Anatomical distribution of tissue fluid and lymph in soft tissues of lower limbs in obstructive lymphedema-hints for physiotherapy. *Phlebolympology.* 16, 283-289.
201. Brice, G et al (2002) Analysis of the phenotypic abnormalities in lymphoedema-distichiasis syndrome in 74 patients with FOXC2 mutations or linkage to 16q24. *J Med Genet*, 39, 478-483.
202. Moseley A, et al. (2008) Exercise for Limb Lymphoedema: evidence that it is beneficial. *J Lymphoedema.* 3,51-56
203. Gultig, O (2005) Lymphoedema bandaging for the head, breast and genitalia. In Calne, S. Editor. *European Wound Management Association (EWMA). Focus Document: Lymphoedema bandaging in practice.* London: MEP Ltd, 2-4
204. National Lymphedema Network Position Papers, www.lymphnet.org
205. Czerneic, S et al (2010) Segmental measurement of breast cancer-related arm lymphoedema using perometry and bioimpedance spectroscopy. *Support Care Cancer.* Online DOI: 10.1007/s00520-010-0896-8
206. Gergich, N et al (2008) Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. *Cancer.* 112, 2809-2819.

Additional References:

1. Weissleder, H and Schuchhardt, C. Lymphedema
2. Diagnosis and Therapy, 4th edition. ViaVital, Verlag 2008
3. American Cancer Society, ACS Complete Guide to Lymphedema: Understanding & Managing Lymph edema after Cancer Treatment, ACS 2006
4. Foldi, M, Foldi, E, Kubik, S. Textbook of Lymphology, 6th Edition, Elsevier 2005
5. Kurz, I Textbook of Dr Vodder's Manual Lymph Drainage Vol 2: Therapy 4th edition, 1997.
6. Wittlinger, H & W., Textbook of Dr Vodder's Manual Lymph Drainage Vol 1, 7th Edition. 2004
7. Foldi, M, Strobenreuther, R. Foundations of Manual Lymph Drainage 3rd edition, Elsevier, 2005
8. Zuther JE. Lymphedema Management: The Comprehensive Guide for Practitioners. 2nd ed. New York, NY: Thieme; 2009