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Lymphedema: A Primer on the Identification and Management of a Chronic Condition in Oncologic Treatment

Brian D. Lawenda, MD[1], Tammy E. Mondry, DPT, MSRS, CLT-LANA[2], Peter A. S. Johnstone, MD[3]

Abstract

The primary goals of oncologic therapy are the compassionate care of cancer patients, eradication of disease, and palliation of symptoms. Advances in various targeted therapies such as highly conformal and image-guided radiotherapy techniques, sentinel lymph node dissection, and molecularly targeted agents hold the promise of allowing those goals to be reached with fewer treatment-related complications. Unfortunately, certain side effects remain problematic due to the inability to completely avoid injuring normal tissues. Lymphedema, a chronic condition that occurs as a result of the body's inability to drain lymph fluid from the tissues, is a common treatment-related side effect experienced by cancer patients. In this review, many of the important aspects of lymphedema with which clinicians who treat cancer patients should be familiar are outlined, including the anatomy, pathophysiology, diagnosis, and management of this condition. The authors also identify some of the resources available both to cancer patients with lymphedema and to the clinicians who treat them. It is hoped that this review will convey the importance of the early identification and management of this incurable disorder because this is essential to minimizing its complications. **CA Cancer J Clin 2009;59:8-24. ©2009 American Cancer Society.**

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Introduction

It is estimated that between 3 and 5 million patients in the United States suffer from lymphedema, with a significant proportion developing the disease as a consequence of cancer or its treatment.[1] In oncology, the most common etiology for the development of lymphedema is the impaired or disrupted flow of lymph fluid through the draining lymphatic vessels and lymph nodes, usually as a consequence of surgery and/or radiation therapy. If the uninjured lymphatic vessels are unable to accommodate the increased lymphatic load, an accumulation of lymph fluid develops in the dependent tissues. Without intervention, lymphedema can lead to progressive swelling, fibrosis of the soft tissues, neurologic changes (eg, pain and/or paresthesias), and infection. Early identification of the signs and symptoms of lymphedema should be integral to the management of all patients who have received surgery and/or radiation, and are thus at high risk. When treated in the earliest stages, complications of this condition may be minimized.

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General Lymphatic Anatomy and Physiology

The lymphatic system is composed of lymphatic vessels and lymphatic tissues. When tissue fluid from the interstitium enters the lymphatic system, it is considered lymph fluid.[2] For the purpose of this article, the interstitial fluid will be referred to as lymph fluid. Lymph fluid consists primarily of protein, water, fatty acids, salts, white blood cells, microorganisms, and foreign debris.[2] It is absorbed from the interstitial spaces into the lymphatic vessels, where it is transported into the venous system.[2]

Topographically, there are 2 separate systems of lymphatic drainage. The superficial system drains the skin and subcutaneous tissues, and the deep system drains the tissues deep to the fascia. The lymphatic vessels in the superficial system are located in the subcutaneous fatty tissues, whereas those of the deep system follow the blood vessels. These two systems are connected via perforating vessels that traverse the fascia; the lymphatic system comprises the following structural components: lymphatic capillaries, precollectors, lymph collectors, and lymphatic trunks (Fig. 1.)[3,4] The lymphatic capillaries of the superficial system are interconnected and cover the entire surface of the body.[3,4] They are structurally different from blood capillaries in that they are larger and their endothelial junctions more permeable; this enables them to absorb fluids and macromolecules from the interstitium.[2-4] These vessels are able to stay open even under high interstitial tissue pressures through a structural support network called "anchoring filaments." These filaments connect the subendothelium of the lymphatic vessel with the surrounding connective tissues.[2-4] Whenever fluid builds within the interstitial tissues, increasing tissue pressure develops causing the tissues to expand and pull on the anchoring filaments. As the anchoring filaments stretch, they open the lymphatic endothelial junctions, thereby allowing the interstitial fluid to enter the lower pressure lumen of the lymphatic vessels.[2-4] The lymphatic capillaries do not have valves, so lymph flows in the direction of lower pressure.[2-4] This process creates a flow gradient for lymph from the interstitium into the lower pressure lymphatic capillaries and subsequently into the larger precollectors.[2-4]

The precollectors have a varied wall structure with sections of tight endothelial junctions and smooth muscle, and some sections of open endothelial junctions that allow for the absorption of fluid.[3,4] Unlike lymphatic capillaries, some precollectors contain valves.[3,4] The precollectors connect the lymphatic capillaries with the collectors. The collectors are structurally similar to veins, and transport lymphatic fluid to the lymph nodes and lymphatic trunks.[3,4] The collectors have valves to promote the direction of flow proximally. They have three distinct layers: intima, media, and adventitia.[3,4] The media layer is comprised of smooth muscle, with less muscle adjacent to valvular regions. The sections between a proximal and distal pair of valves are called "valve segments" or "lymphangions."[2-4] Lymph collectors transport lymph fluid via the pumping mechanism of the lymphangion. Lymphangions are innervated by the sympathetic nervous system, and contract at a rate of 10 to 12 contractions per minute.[4] This contractile rate can increase to accommodate an increased lymphatic load.[2,4] Adjacent collectors connect with each other to create anastomoses, which allow for collateral lymph flow in cases of increased lymphatic load.[3]

Similar to the lymph collectors, the lymphatic trunks have a three-layer structure, valves, and sympathetic innervation.[3,4] The major lymphatic trunks drain lymph directly into the venous system (Fig. 2.) The right and left lumbar trunks (which drain the lower extremities, pelvis, and genitalia) and the gastrointestinal trunk (which drains the digestive system) merge to form the cisterna chyli, the origin of the thoracic duct. The jugular trunk (draining the head and neck), subclavian trunk (draining the upper extremities, chest wall, upper back, shoulders, and breasts), supraclavicular trunk (draining the shoulders and breasts), and bronchomediastinal trunks enter the thoracic duct and right lymphatic duct ipsilaterally. The thoracic duct is the largest of the lymphatic trunks, and is responsible for emptying approximately 3 liters of lymph per day into the left venous angle, which is comprised of the left internal jugular and left subclavian veins.[3,4] The bilateral lower quadrants and the left upper quadrant of the body drain into the left venous angle via the thoracic duct, whereas the right upper quadrant of the body drains into the right

Lymph Capillaries→Precollectors→Lymph Nodes→Lymphatic Trunks→Venous Angles

FIGURE 1. Lymph Fluid Return Pathway From the Lymph Capillaries to the Venous System.

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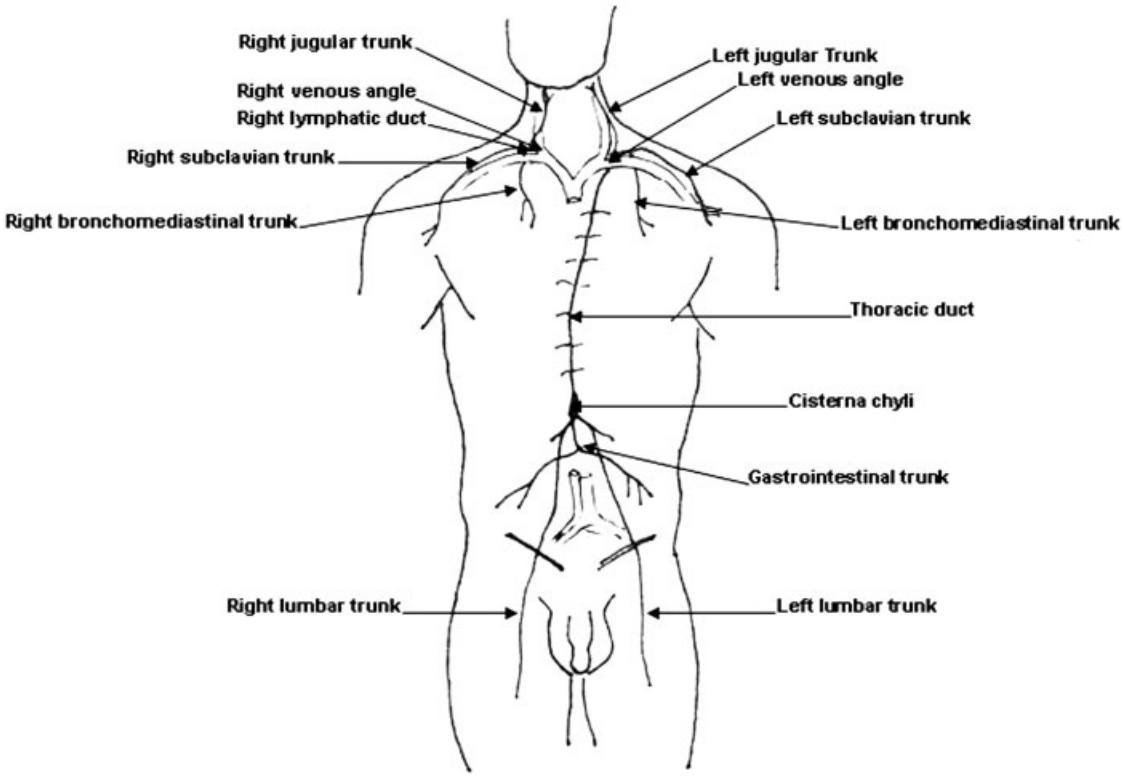

FIGURE 2. Lymphatic Trunks. Artwork Courtesy of Alicia B. Minns, MD.

venous angle via the right lymphatic duct. The right lymphatic duct is formed by the right jugular, right supraclavicular, right subclavian, and right parasternal trunks, and is the second largest of the lymphatic trunks; it delivers into the right venous angle, which is formed by the right internal jugular and subclavian veins.[3,4] The parasternal trunks, which drain the internal mammary lymph nodes and parts of the pleura, diaphragm, liver, pericardium, and chest/abdominal wall, each drain into their respective ipsilateral venous angles.[3,4]

Regional lymph nodes are the first echelon lymph nodes responsible for the drainage of specific territories of the body. Lymphatic fluid travels from these regional lymph node areas through a series of lymphatic vessels and lymph nodes into the venous system. The major regional lymphatic areas include the head and neck; thoracic, abdominal, and pelvic cavities; retroperitoneum; trunk wall; and upper and lower extremities.[3,4]

Lymphedema of the skin and subcutaneous tissues is the most common clinically significant presentation of this condition, and thus a brief discussion of the lymphatic drainage of the skin is important. The skin has initial lymph vessels connecting to vertical precollectors.[3] These areas, which are drained by a common lymphatic collector, form skin zones. Adjacent skin zones, which are connected to all of the collectors of a single lymph vessel bundle, join together to create a territory.[3] Between adjacent skin territories, lymphatic vessel anastomoses occur infrequently, thereby creating linear zones on the surface of the body called lymphatic watersheds.[4] There are two collateral pathways that, under conditions of increased intralymphatic pressure, permit the flow of lymph across the watersheds from one territory to another: 1) the initial lymphatic vessel plexus and 2) interterritorial anastomoses.[4]

Pathophysiology of Lymphedema

The predominant component of lymphatic fluid is interstitial water and protein filtrate, which is not reabsorbed back into the arteriovenous capillary system. In a normal physiologic state, the lymphatic system is able to absorb and transport this fluid back into the venous system. The ability of the lymphatics to function sufficiently is dependent on the lymphatic load and transport capacity.[2,5] Lymphatic load is the volume of lymph fluid, which includes lymphatic protein and water, cell, and fat loads, as well as hyaluronan.[2] Transport capacity is the maximum

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amount of lymph volume that can be transported by the lymphatics in a given period of time.[2,5] The difference between the transport capacity and the lymphatic load is called the functional reserve. When increases in the lymphatic load exceed the maximum transport capacity, the lymphatic system becomes overwhelmed, causing lymphatic insufficiency or failure, which leads to interstitial edema.[2,5]

There are three forms of lymphatic insufficiency that can occur: 1) dynamic insufficiency or high-output failure; 2) mechanical insufficiency or low-output failure; and 3) combined insufficiency.[2,5] Dynamic insufficiency occurs when the lymphatic load surpasses the transport capacity of a functional and intact lymphatic system.[2,5] Alternatively, a functional or anatomic abnormality in the lymphatic system can lead to a reduction in the transport capacity. This state is called mechanical insufficiency. The remainder of this article will focus primarily on this subtype of lymphatic insufficiency because this is the most common etiology of cancer treatment-related lymphedema. Finally, combined insufficiency develops when dynamic and mechanical insufficiencies occur simultaneously. This happens in circumstances in which there is both a reduction in the transport capacity and an increase in the lymphatic load.[2,5]

Edema can be classified by its protein content. Low-protein edema is composed of <1 g of protein per 100 mL of fluid, and high-protein edema is composed of >1 g of protein per 100 mL of fluid.[2] Some groups claim that high-protein edema always develops with mechanical insufficiency.[2] The dysfunctional lymphatics are unable to completely reabsorb the large protein molecules and therefore they remain within the interstitial spaces, progressively leading to an increasing accumulation of a high-protein edema fluid also known as lymphedema.[2] This view is contradicted by data that demonstrate that interstitial fluid from edematous limbs actually contains a lower protein concentration compared with that from nonedematous limbs.[6] One of the proposed explanations for this finding is that capillary pressure rises and increases the capillary filtration rate due to hemodynamic abnormalities in the affected limb.

Hyperproliferative and inflammatory skin changes can develop in chronic lymphedema, resulting from prolonged exposure to accumulated interstitial debris, proteins, and elevated interstitial pressure.[1] This condition is termed lymphostatic fibrosis.[1] Another consequence of the stagnant fluid is that it impedes the circulation of macrophages and lymphocytes, thereby leading to a greater risk of infection, most typically cellulitis.[5]

Causes of Lymphedema

As previously mentioned, the development of lymphedema occurs when the lymphatic load exceeds the transport capacity.[5] There are two general classifications of lymphedema: primary and secondary. Primary lymphedema develops as a consequence of a pathologic congenital and/or hereditary etiology. These various conditions include: 1) reduced numbers of lymphatic collectors and the decreased diameter of existing lymph vessels (hypoplasia); 2) increased diameter of lymphatic collectors (hyperplasia); 3) absence of lymphatic system components (aplasia); and 4) inguinal lymph node fibrosis (Kinmonth syndrome).[1] Significantly more common at the time of presentation than primary lymphedema is secondary lymphedema. This classification of lymphedema is caused by mechanical insufficiency due to surgery, radiation, trauma, infection, tumoral blockage, chronic venous insufficiency, immobility, or tourniquet effects.[1] Once damage has occurred to the lymphatic system, transport capacity is permanently diminished in the affected region, thereby predisposing that region to lymphedema. In the United States, the most common cause of secondary lymphedema is a consequence of breast cancer treatment, especially with the combination of axillary surgery and radiation.[1]

Stages and Severity of Lymphedema

Lymphedema is not considered to be a curable condition due to the permanent damage to, or absence of, various lymphatic system components. The accumulation of lymph fluid in the interstitium may not be clinically evident in the early stages of the disease, but will occur if the lymphatic load increases above the reduced transport capacity of the lymphatic system. Therefore, a subclinical lymphedema exists after surgery or radiation therapy. This stage is frequently referred to as the "latency stage" or "Stage 0."[1] In this stage, there are no clinical signs of lymphedema because the reduced transport capacity exceeds the lymphatic load of the tissues. Patients may report a feeling of heaviness in the limb, but many patients are asymptomatic in this latency stage. Education is critical to help prevent, slow, or diminish progression to more advanced stages.

Stage I lymphedema is referred to as "reversible lymphedema" (Figs. 3 and 4). In this stage, the patient

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presents with very soft, pitting edema with no fibrosis. Prolonged elevation of the limb leads to complete resolution of the clinically evident swelling.[1]

Stage II lymphedema, also called "spontaneously irreversible lymphedema," (Figs. 5 and 6) presents with intradermal fibrosis that decreases tissue suppleness and reduces the ability of the skin to indent ("pit") with pressure. Applying firm pressure into the tissue for at least 5 seconds assesses pitting edema.[7] If an indentation remains after the pressure is released, pitting edema is present. It is measured on a scale of 0 to 3+, in which 0 indicates not present, 1+ indicates minimal, 2+ indicates moderate, and 3+ indicates severe pitting edema.[7] In this stage, resolution of clinically evident lymphedema is not possible with elevation.[1] The patient will often present with a positive Stemmer sign, in which the skin of the dorsum of the fingers and toes cannot be lifted, or lifted with difficulty, compared with the uninvolved limb.[1] Skin infections are more common in this stage, due to the diminished ability of the immune system to respond to foreign bacteria and debris. Infections can predispose the affected lymphatic channels to both an increased lymphatic load due to the inflammatory response and decreased transport capacity, potentially leading to Stage III disease.[1]

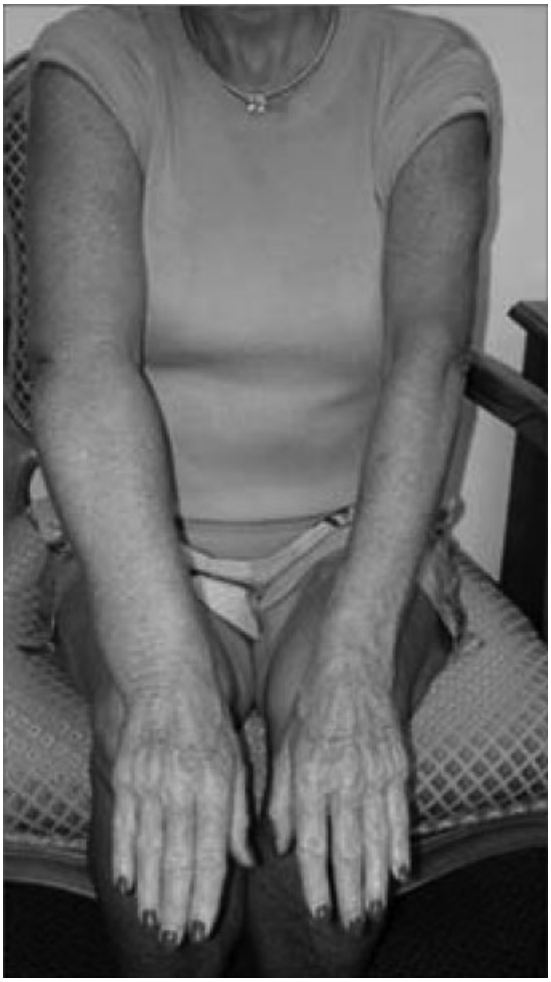

FIGURE 3. Stage I: Reversible Lymphedema of the Upper Extremity.

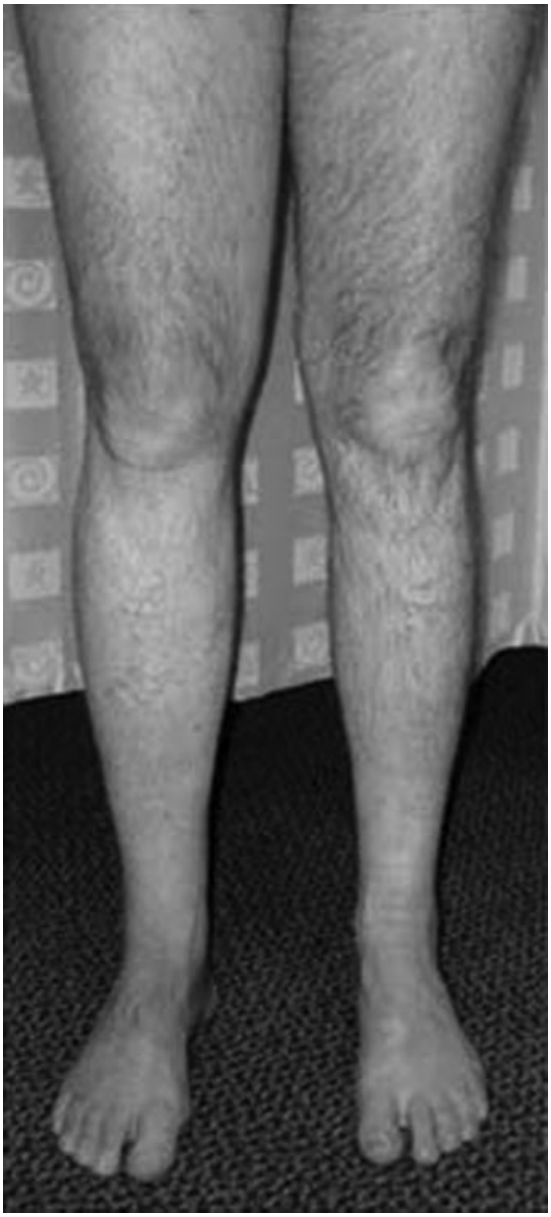

FIGURE 4. Stage I: Reversible Lymphedema of the Lower Extremity.

Stage III lymphedema is also called "lymphostatic elephantiasis" (Figs. 7 and 8). It is associated with a significant increase in the severity of the fibrotic response, tissue volume, and other skin changes such as papillomas, cysts, fistulas, and hyperkeratosis.[1] Skin folds on the wrists and ankles deepen, the patient may present with slight or no pitting, and the Stemmer sign

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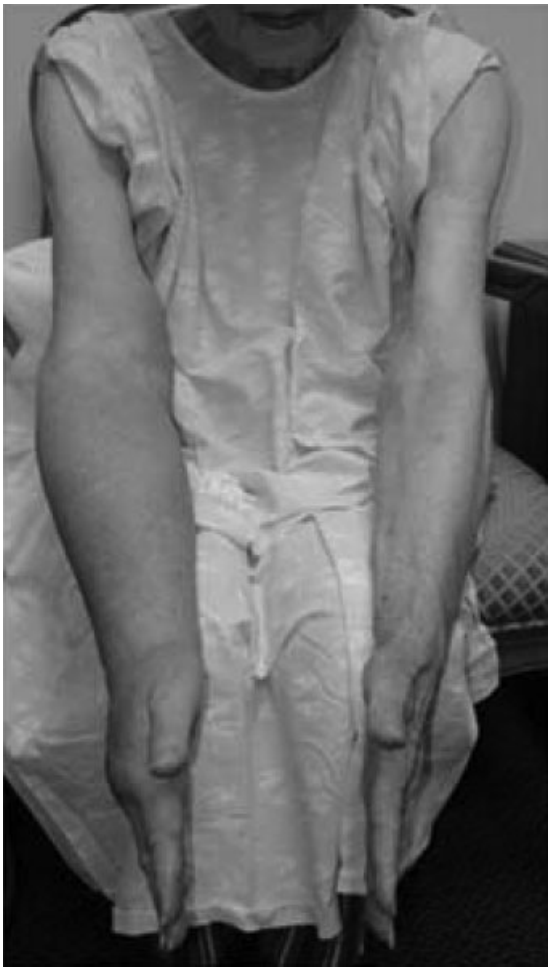

FIGURE 5. Stage II: Spontaneously Irreversible Lymphedema of the Upper Extremity.

becomes more prominent.[1] Recurrent bacterial and fungal infections of the skin and nails are more common in this stage of lymphedema.[1] In Stage II and Stage III lymphedema, the formation of adipose tissue is mainly responsible for the excess volume in swollen limbs that do not present with pitting.[8,9]

Although not a component of the lymphedema staging system, comparative volumetric differences between the affected versus the unaffected limb can be used as a supplement to further characterize the severity of each stage. "Minimal" severity represents a situation in which the affected limb has a measured volume that is <20% greater than the unaffected limb. A 20% to 40% difference in volume represents "moderate" severity, and a difference of >40% is considered "severe."[1]

Lymphedema as a Consequence of Cancer Treatment

As previously stated, the most common cause of secondary lymphedema in the United States is surgery and radiation therapy for the treatment of cancer.[10] The most commonly reported context is following breast cancer treatment, but lymphedema can result from the treatment of cervical, endometrial, vulvar, head and neck, and prostate cancers, as well as sarcomas and melanoma. The exact incidence rate of cancer treatment-related lymphedema is difficult to assess accurately due to a lack of standardized definitions and measurement techniques for the disorder.

The breast cancer patient who undergoes lymph node dissection and/or radiation therapy is not only at risk for lymphedema of the upper extremity but also edema developing in the ipsilateral upper quadrant, including any remaining breast tissue. The frequency of upper extremity lymphedema (Table 1) is influenced by the type of surgery performed and whether it is combined with radiation therapy to the regional lymph nodes.[11-33] There are several variables that have been identified as potential risk factors for the development of upper extremity lymphedema after the management of breast cancer (Table 2).[12,27,34,35]

Lymphedema of the breast is an often overlooked side effect of breast cancer treatment. The causes of

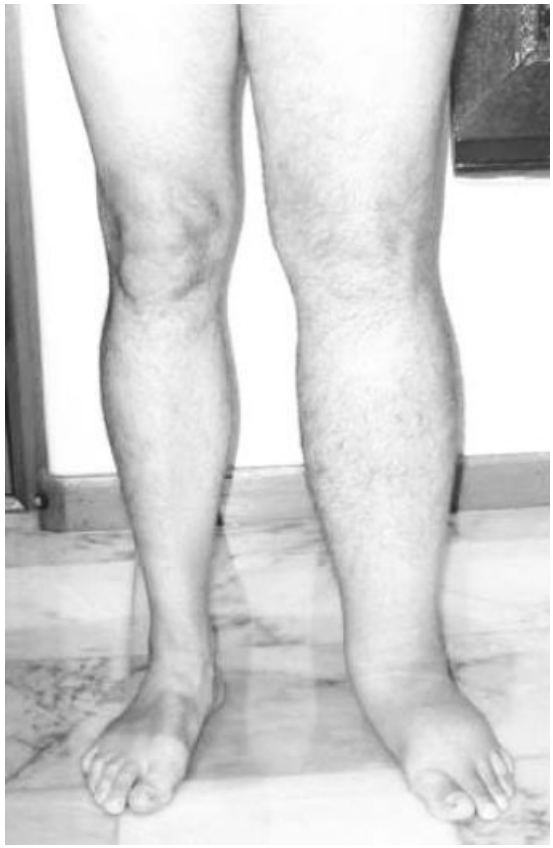

FIGURE 6. Stage II: Spontaneously Irreversible Lymphedema of the Lower Extremity.

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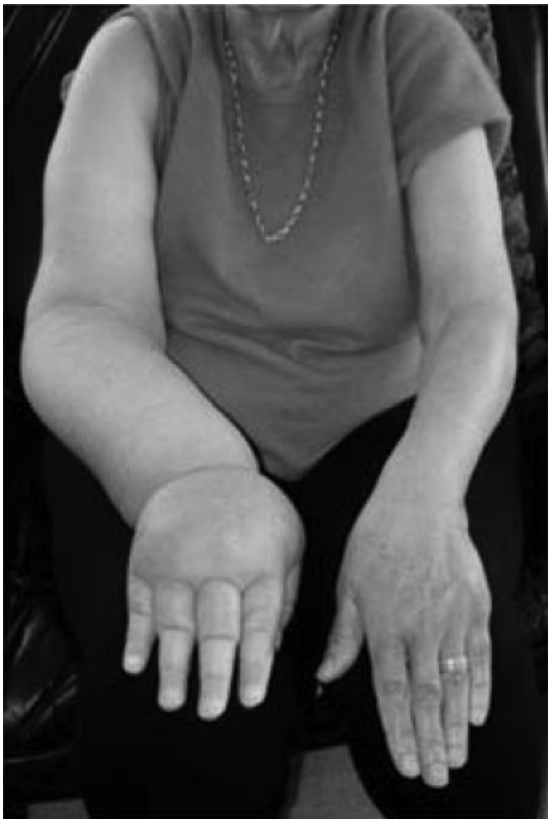

FIGURE 7. Stage III: Lymphostatic Elephantiasis of the Upper Extremity.

breast lymphedema include surgery, radiation therapy, malignancy, and, rarely, heart failure.[36-38] Although this mechanical insufficiency can be due to the development of scar tissue from surgery or radiation therapy blocking the lymphatic pathways, tumor blockage can also disrupt lymph flow, leading to the clinical presentation of lymphedema. Breast lymphedema occurs most commonly in patients who have undergone both axillary radiation therapy and surgery[39]; when both surgery and radiation therapy are performed, the frequency of breast edema ranges from 6% to 48%.[27,40,41] If a lumpectomy is performed alone, the frequency is approximately 6%.[40] A drastic increase in incidence is noted when a lymph node dissection and radiation therapy are performed. With a sentinel lymph node biopsy (SLNB) and radiation therapy, the frequency of breast lymphedema rises to 23%.[41] If the patient undergoes an axillary lymph node dissection (ALND) with radiation therapy, the lymph node status may affect the development of lymphedema (35% in lymph node-negative patients and 48% in lymph node-positive patients).[41] Factors that are reported to significantly increase the risk of breast lymphedema include an increased body mass index (BMI) and tumor location in the upper outer quadrant.[27] A level 2 lymph node dissection or wound infection after SLNB have been noted to increase the risk of breast edema in women undergoing breast-conserving therapy.[42]

An analysis was performed to explore the differences in the signs and symptoms of postbreast cancer lymphedema experienced by survivors aged <60 years in comparison with older women.[43] This study found that women aged <60 years had a higher likelihood of lymphedema (41.2% versus 30.6%) in comparison with women aged >60 years.[43] Approximately 15% of patients with a bra cup size of A or B developed breast edema, whereas approximately 48% of patients with a bra cup size of C, D, or DD presented with edema.[44] With these risk factors in mind, the prompt treatment of soft tissue infections and weight loss in obese patients may contribute to the prevention of breast edema.[39]

In the treatment of cervical cancer, the incidence of lower extremity lymphedema is reported to be approximately 21% to 49% after surgery and radiation therapy.[45-47] A retrospective study of patients with early stage cervical carcinoma who were treated with preoperative radiation therapy and radical hysterectomy found that 21% of the patients developed lymphedema during the first year.[46] If postoperative radiation therapy was performed, 31% of patients developed lower extremity lymphedema[47]; another study quoted a frequency of 49% at 10 years.[45]

Lower extremity and genital lymphedema can be a side effect of therapy for patients with melanoma and pelvic cancers. In a retrospective review of 517

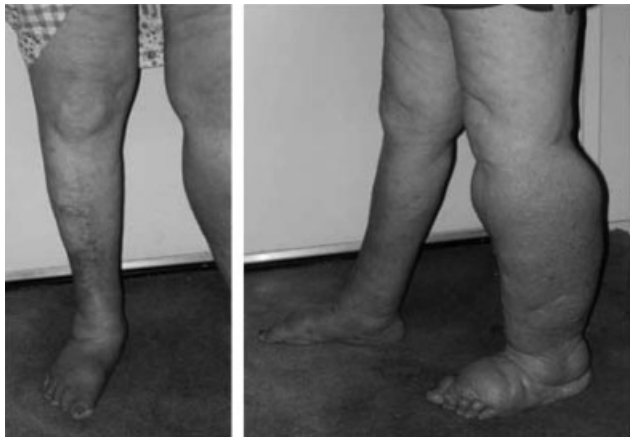

FIGURE 8. Stage III: Lymphostatic Elephantiasis of the Lower Extremity.

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TABLE 1. Frequency of Developing Upper Extremity Lymphedema After Surgical and Radiotherapeutic Management of the Axilla

PROCEDURE	FREQUENCY
Lumpectomy and breast radiation or total mastectomy and sentinel lymph node biopsy (SLNB) alone (no axillary radiation)	2.6–3.0%[11,12]
Axillary lymph node dissection (ALND) and/or axillary radiation (these data incorporate various surgical procedures to the primary site)	● ALND and axillary radiation: 31.7%[13] ● Total mastectomy and ALND or partial mastectomy, ALND, and breast radiation: 30% (vs. 0% with "axillary sampling" instead of ALND)[14] ● ALND (no difference in lymphedema incidence noted with or without axillary radiation): 11% (objectively measured), 23.4% (patient subjectively reported)[15] ● Axillary radiation alone: 8.3%; "axillary sampling" and axillary radiation: 9.1%; "axillary clearance" and axillary radiation: 38.3%[16] ● Segmental mastectomy and ALND (no difference noted with or without the addition of breast radiation): ≥10 dissected lymph nodes (20% incidence at 36 mo); increasing relative risk) (RR) with each dissected lymph node (RR of 1.1)[17] ● ALND (17% [range, 6%-39%]) vs. ALND and axillary radiation (41% [range, 21%-51%])[18]
Lumpectomy alone (no axillary surgery or radiation)	3%[19] and 0%[20]
Lumpectomy, ALND, and breast radiation	1.0%,[21] 11%,[22] and 19%[23]
Lumpectomy, ALND, and breast/axillary radiation	10.7%[21] and 42.4%24
Lumpectomy and axillary radiation (no axillary surgery)	2%[20]
Lumpectomy and SLNB (no radiation)	9.9%[25]
Lumpectomy and ALND (no radiation)	2%,[20] 13.4%,[24] and 14%[26]
Lumpectomy, SLNB, and breast radiation	7.6%,[27] 6%,[22] 7%,[26] and 4%[23]
Lumpectomy, ALND, and axillary radiation	9%[20] and 27.5%[28]
Lumpectomy and axillary radiation (no axillary surgery)	4% (patient subjectively reported) and 11% (objectively measured)[29]; 1.2%[30]
Total mastectomy alone (no axillary surgery)	15.5%[31]
Total mastectomy and axillary radiation (no axillary surgery)	14.8%[31]
Halstead-type radical mastectomy alone (includes levels 1-3 ALND)	30.7%[31]
Modified radical mastectomy (MRM) alone (includes ALND)	7%,[32] 28.2%,[28] and 10%[14]
MRM and axillary radiation (includes ALND)	17%[32] and 44%[14]
MRM and chest wall and axillary radiation	27%[33]

patients, 11% of endometrial cancer patients undergoing surgery and postoperative radiation therapy were reported to develop lower extremity lymphedema.[48] The type of therapy used in the treatment of vulvar cancer was determined to make a difference in the incidence rate of lymphedema. Patients undergoing bilateral inguinal irradiation had a 6% frequency, versus 12% in patients undergoing unilateral or bilateral inguinofemoral lymph node dissection.[49] These findings are emphasized in a Cochrane review of chemoradiation in the management of vulvar cancer.[50]

The risk of postirradiation lymphedema was found to be strongly dependent on the extent of lymph node dissection performed during treatment of prostate cancer.[51] The types of dissection performed included biopsy only, limited or diagnostic dissection, and complete or therapeutic dissection. Patients undergoing a limited or diagnostic dissection followed by pelvic irradiation had a 25% to 30% incidence of lower extremity lymphedema, versus a 66% incidence in patients undergoing pelvic irradiation after a complete or therapeutic dissection.[51]

In the treatment of melanoma, the incidence of lymphedema is dependent on the type and degree of lymph node dissection performed. When SLNB was used for patients with cutaneous melanoma, the incidence of lymphedema was reported to be 1.7%.[52] A study of upper extremity lymphedema resulting from ALND for melanoma found a 10% risk after a complete level I to III ALND, rising to 53% after additional axillary radiation therapy.[53] Finally, a retrospective review reported that lymphedema occurred in 30% of melanoma patients after inguinal lymph node dissection.[54]

Signs, Symptoms, Diagnosis, and Evaluation

It is important for healthcare practitioners to be aware of signs and symptoms that may be precursors to the clinical diagnosis of lymphedema. A study of patients with breast cancer treatment-related lymphedema was performed to ascertain the predictive and discriminatory validity of using their

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TABLE 2. Risk Factors for Developing Upper Extremity Lymphedema after Management of Breast Cancer

Tumor located in the upper outer quadrant[12]
Postoperative axillary trauma, infection, hematoma, and seroma[12,34]
Axillary radiation after axillary lymph node dissection (ALND)[35]
Extent of ALND (inclusion of level 3)[34]
Axillary recurrence[27]
Large no. of positive axillary lymph nodes[27,34]

symptom experiences with limb volume change to determine the presence of clinically measurable lymphedema.[55] This would allow for the detection of lymphedema at an earlier stage of development using self-reported symptoms. The study found that the symptoms of "heaviness in the past year" and "swelling now" were predictive of a maximal limb circumference difference of 2 cm.[55] Incorporating the findings of this study into daily practice may provide the best clinical assessment data for the identification of changes associated with postbreast cancer lymphedema by using both symptom assessment and limb volume measurements.

Signs and symptoms that the patient may present with include a feeling of heaviness or tightness in the limb, aching or discomfort of the limb, restricted range of motion of the limb, and swelling in a portion of the limb or the entire limb. Swelling may also be present in the adjacent upper quadrant of the trunk. Lymphedema patients do not usually present with severe pain. The color of the skin is generally normal, and the temperature of the skin typically feels normal to touch. The swelling is usually unilateral and may include the dorsum of the hand or foot. A deepening of the natural skin folds may be noted. The patient may also present with a Stemmer sign.[56] It is possible to have a false-negative Stemmer sign, but to our knowledge, there cannot be a false-positive.[56]

The risk for lymphedema is lifelong; therefore, the onset may occur at the time of the initiation of treatment or be delayed for several decades.[57] If a patient does present with a new onset of swelling after undergoing surgery or radiation therapy, a through history and physical examination should be performed to rule out recurrent or metastatic disease that may be causing tumor blockage of the lymphatic system, as well as to rule out deep vein thrombosis. Once the physician eliminates these possibilities, the patient should be referred to physical therapy for an evaluation to confirm the diagnosis of lymphedema and to objectively quantify the amount of edema present in the limb.

The evaluation of lymphedema should begin with a thorough medical and surgical history. Observation of the limb, including inspection of the skin and palpation, should be performed with the skin mobility, tissue consistency, and the presence or absence of fibrosis noted, as well as whether the edema is pitting or nonpitting. Pain level should be noted as well as the presence of the Stemmer sign. Digital photography and measurements of girth and volume should be performed. Some practitioners consider a maximum girth difference of $\geq$2.0 cm or a volume difference of $\geq$200 mL in the involved limb versus the uninvolved limb to indicate a positive diagnosis of lymphedema.[43] Other practitioners prefer to use a 10% girth or volume difference between the affected and unaffected limb because the former definition does not take into account the patient's body habitus (slim or obese).[14,58] Girth measurements are determined through circumferential assessment using a tape measure at predetermined sites on the involved versus the uninvolved limb. The sites of measurement should be determined by the practitioner, and should be a standard point of reference that is reproducible. Anatomic landmarks can be used, or measurements can be taken in intervals along the limb. For example, the leg may be measured circumferentially at 2-inch intervals from the heel proceeding proximally. Volume measurements can be assessed using several different methods: calculation of estimated volume, water displacement, bioimpedance, and infrared optoelectronic assessment. Reliable volume estimates can be calculated using the disk model method on circumferential measurements.[59] A volumeter can be used for water displacement with the assessment of the displaced water measured in mL using graduated cylinders. Bioimpedance spectroscopy determines volume by comparing the composition of fluid compartments within the body using resistance to electrical current. This type of impedance analysis has been found to be a reliable and accurate tool with which to measure volume of both the upper and lower extremities in the evaluation of lymphedema.[60] Infrared optoelectronic volumetry is a computerized analysis that also can be used in the assessment of

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volume. The disk model method and optoelectronic volumetry have been found to have better reliability than water displacement volumetry or the frustum sign method of calculation for volume.[59] When the diagnosis of lymphedema is confirmed, the patient should quickly begin a treatment program, regardless of the stage or severity of the disease.

An evaluation of the breast tissue in the involved quadrant should also be performed. The onset of breast lymphedema can be early or late. An early onset occurs within two months of surgery, whereas a late onset occurs ≥20 months after surgery or radiation therapy.[61] After breast conservation therapy, all patients are considered to be in a latency stage of lymphedema because there has been some alteration to the mechanical structure of the lymphatic system. Although there may be no visible or palpable edema, the patient may have subjective complaints of breast heaviness or fullness, aches, pains, or a sensation of "pins and needles" (paresthesias). When there is a clinical presentation of lymphedema of the breast, it should be noted whether it is pitting versus nonpitting; whether there is increased volume of adipose tissue[8,9]; fibrotic versus nonfibrotic changes; peau d'orange skin changes; and subjective complaints of painful, heavy breasts or nipple pain.[40] To our knowledge, information regarding the assessment and treatment of breast lymphedema is lacking. Breast edema may be assessed during clinical examination using a subjective classification of mild, moderate, or severe or by comparison to the contralateral breast and determining whether the involved breast is equal, smaller, or larger in size.[41] The clinical assessment of breast edema should include clinical history; observation of skin texture, integrity, and color changes; and digital photography.

Management of Lymphedema

The management of lymphedema should begin with efforts to prevent the disorder. A preoperative evaluation and prevention education should occur with all patients who will undergo treatment that puts them at risk for the development of lymphedema. This initial encounter with the patient should include baseline girth and volume measurements of the affected and unaffected limbs, educating the patient concerning arm or leg care guidelines, and noting any risk factors that may put the patient at an increased risk for the development of lymphedema.

The early detection and treatment of lymphedema is of the utmost importance. Baseline measurements of girth and volume will assist in finding any significant changes in the size of the limb, allowing the intervention to occur as early as possible. Currently, to our knowledge there is no accepted standard for the definition of lymphedema with regard to girth and volume. The different criteria that have been used to define lymphedema to date are not equivalent, and include 2.0-cm circumferential difference, a 200-mL limb volume change, and a 10% change in limb volume.[43] As previously mentioned, a 10% change in limb volume is considered by many lymphologists as a more useful definition of lymphedema because it takes into account the body habitus of the patient.[58] These are some of the most reported criteria, although many more exist. This lack of a standard definition is largely responsible for the wide variation in the reported incidence of lymphedema.

If lymphedema is diagnosed, intervention should occur as soon as possible. If treatment is not provided, lymphedema will slowly progress, causing tissue damage and advancement through all three stages of the disorder. Treatment can be provided at any stage of lymphedema, but the outcomes are less optimal in the later stages due to adipose and fibrotic changes within the tissue. To our knowledge, no curative treatments for lymphedema are currently available; therefore, the goal of treatment is to decrease the excess volume as much as possible and maintain the limb at its smallest size. This reduces the amount of stagnant fluid in the tissues, thereby potentially preventing or eliminating infections. To achieve maximal results and maintain the gains from treatment, the patient's participation is crucial. Therefore, before the initiation of any intervention, the patient must have a thorough understanding and firm commitment to all components of the treatment and maintenance program to achieve clinical success.

There are some data to suggest that hyperbaric oxygen therapy and possibly low-level laser therapy (LLLT) may be useful adjunctive treatment options for patients with chronic lymphedema of the breast and arm.[62-66] LLLT has been reported by some groups to decrease lymphedema in the affected limbs of patients who have undergone mastectomy.[62,65,66] This technique involves the use of low-energy laser devices that are focused on the lymphatic channels in

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the axilla with the intent of improving the lymphatic flow. Studies, including 2 small placebo-controlled randomized trials, have shown that short courses (3-10 weeks) of LLLT were able to reduce limb volume, extracellular fluid, tissue hardness, and pain.[62,66] These trials should be validated with larger numbers of patients, varying laser parameters (wavelength, pulse duration, frequency, dose, and treatment schedule), and longer follow-up. However, the results are certainly intriguing. Basic science research on LLLT has demonstrated various cellular and chemical modifying effects, including stimulation of mitochondria, macrophages, and lymphocytes; increased or decreased fibroblast proliferation (wavelength-dependent); and increased production of vascular endothelial growth factor and endothelial cell proliferation.[62] Further research is encouraged to better understand the potential mechanisms of action that may explain the modifying effects of LLLT on lymphedema.

Microsurgical lymphatic-venous anastomoses (LVA) may be an effective treatment for lymphedematous conditions that have been minimally responsive to nonsurgical techniques, such as complete decongestive therapy (CDT), manual lymph drainage (MLD), and compression. One group with extensive experience in this specialized surgical technique reported that >83% of patients who underwent this procedure maintained significant limb volume reductions at 10 years of follow-up,[67] although a recent review of the literature has demonstrated that LVA may not be an effective treatment for lymphedema.[68] Another surgical technique used in the treatment of lymphedema is microsurgical lymphatic grafting. Some groups have reported this to be an effective surgical option in the management of lymphedema.[69] Although not commonly used in the United States for the treatment of chronic, nonpitting arm and leg lymphedema, some groups have reported success using liposuction with the long-term use of postoperative compression garments (controlled compression therapy.).[70-72] In the United States, these procedures are usually undertaken only in patients with the most advanced stages of lymphedema; however, there is likely a role at earlier stages.

The gold standard treatment for lymphedema is CDT.[73] In one of the larger studies of CDT reported to date, the examination of 299 patients undergoing CDT for the treatment of upper and lower extremity lymphedema found an average reduction in volume of 59.1% for upper extremity lymphedema, and an average reduction in volume of 67.7% for lower extremity lymphedema.[74] Patients in this study underwent an average of 15.7 days of treatment with volume measurements performed at the beginning and end of the treatment phase, as well as during follow-up at 6 months and 12 months. Both patients with upper and lower extremity lymphedema who were adherent during the maintenance phase were found to retain 90% of the initial reduction, whereas nonadherent patients regained on average 33% of the initial reduction.[74] Other smaller studies with subject numbers ranging from 14 to 138 patients reported volume reductions of 22% to 73%, with the number of treatment sessions varying from 6 to 36 visits.[75-81]

CDT is a two-phase program that consists of a treatment phase and a maintenance phase. Phase 1, the treatment phase, lasts 2 to 4 weeks in duration. During this time, the patient receives treatment on a daily basis, 5 days per week, with girth and volume measurements of the limb performed at the end of each week. The girth and volume measurements are compared with those of the previous week to determine whether a reduction has occurred or a plateau has been reached. The span of the treatment phase is dependent on the patient's response to therapy. Once the patient's girth and volume measurements have plateaued and maximal benefit is achieved, the patient begins phase 2, the maintenance phase, which consists of life-long self-care to maintain the size of the limb. The treatment phase consists of 4 components: skin and nail care, MLD, compression bandaging, and therapeutic exercise. Although the effectiveness of MLD is controversial, many lymphologists believe that to be effective, the patient must be adherent to all 4 parts of the therapy.

The skin and nail care component consists of inspecting the limb to confirm that it is free of any cuts, scratches, areas of irritation, or signs of infection. A pH-balanced moisturizer is applied to the entire limb before compression bandaging. The patient is also educated throughout the treatment phase so that self-care of the skin and nails can be carried out in the maintenance phase.

MLD is a manual technique that is performed to stimulate the smooth muscle sheath of the superficial lymphatic vessels and thereby increase their pumping rate. This procedure requires a light application of pressure secondary to the location of the superficial lymphatic vessels just below the skin. If the pressure

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is too great, it may result in a spasm of the smooth muscular sheath surrounding the superficial lymph vessels or lead to damage of the thin anchoring filaments.[82] MLD is a massage-like technique that is performed for 30 to 60 minutes not only on the affected limb but also other areas of the body, such as the lymph node basins, to improve lymphatic flow. The direction of movement with this technique is always distal to proximal, with the sequence and type of manual techniques being determined for each patient on an individual basis depending on the specific area of increased edema as well as the stage of lymphedema present. An animal study has shown that applying this type of manual manipulation to the tissue, even to areas of the body distant to the location of the affected limb, enhances lymph uptake.[83] It is this stimulation of the lymphatic vessels that leads to the evacuation of fluid from the limb. As previously mentioned, the effectiveness of MLD in CDT remains an area of controversy because some groups have demonstrated that MLD provides no additional benefit when added to compression therapy.[84,85] A Cochrane review on this topic concluded that the benefit of MLD is not known at this time due to insufficient evidence in the form of well-designed, prospective, randomized controlled trials.[86]

After MLD is performed, compression bandaging is applied to the limb. This is a multilayer bandage that is worn 24 hours per day during the treatment phase. It consists of padding materials and short-stretch bandages. Short-stretch bandages are used because they apply pressure during movement and not at rest. This allows for the stimulation of the superficial lymphatic vessels during movement via the muscle-joint pump. The muscle-joint pump is created between the muscle of the limb and the compression bandage when the pressure exerted by the contraction of the muscle within the bandage causes a mechanical stimulation of the smooth muscle of the lymph vessels, thereby increasing the pumping rate of the lymph vessel. The multilayer compression bandage also helps to soften the indurated tissues, making the MLD techniques more effective.

The final component of CDT is therapeutic exercise. Exercises are performed with the compression bandages in place to facilitate the muscle-joint pump. The patient performs the exercise at regular intervals throughout the day to engage the pumping mechanism. These exercises involve movement of the limb through a comfortable range of motion with the bandaging in place, whereas some incorporate diaphragmatic breathing to enhance the lymphatic pumping rate. Although to our knowledge no studies to date have shown that diaphragmatic breathing alone leads to a reduction in lymphedema, a study of gentle arm exercises in combination with deep breathing did demonstrate a significant decrease in secondary arm lymphedema.[87] This study found not only a statistically significant reduction in arm volume, but also noted a statistically significant decrease in reported arm heaviness and tightness.[87] There is speculation that resistive exercise may exacerbate lymphedema, thereby causing some controversy regarding whether patients should be instructed to avoid this type of exercise.[88] The effects of upper and lower body weight training on breast cancer treatment-related lymphedema were examined in a randomized controlled trial.[89] This study assessed self-reported symptoms and circumferential measurements at baseline and at 6 months. The results found no change in self-reported symptoms or arm circumference at 6 months, and therefore concluded that the 6-month resistive exercise program did not increase the risk or exacerbate symptoms of upper extremity lymphedema.[89]

There are both relative and general contraindications for the use of CDT (Table 3). Relative contraindications include hypertension, paralysis, diabetes, and bronchial asthma. General contraindications include acute infections of any kind, the presence of deep venous thrombosis, or congestive heart failure. Some practitioners perceive malignant disease as a general contraindication for treatment to an area with known tumor. The perception is that MLD will lead to dissemination of the cancer by forcing malignant cells through the lymph nodes into the blood stream, and eventually spreading cancer cells throughout the entire body.[90]

The promotion of metastasis by mobilizing dormant tumor cells through massage and mechanical compression is a theoretic concept that has been published in the consensus document of the International Society of Lymphology (ISL).[73] It has been stated in several documents regarding the treatment of lymphedema that active malignancy is a contraindication for the use of CDT.[56,90-93] Foldi et al stated that malignancy is a relative contraindication for CDT pending 2 recommendations: 1) the patient must be receiving treatment for the cancer and 2) MLD should not be performed in the area of the body directly affected by the tumor.[94] It is important to note that these authors clearly state that metastasis is not caused by CDT and that the treatment

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TABLE 3. Contraindications for Complete Decongestive Therapy and Potential Pathophysiologic Mechanisms*

RELATIVE CONTRAINDICATIONS	
Hypertension	Complete decongestive therapy (CDT) increases central venous blood volume
Paralysis	A flaccid limb may offer insufficient resistance for the application of compression bandages and garments; the limb will also be unable to create a muscle-joint pump with the absence of a muscle contraction; any decrease in sensation my result in injury from the compression bandages or garment
Diabetes	Diabetic vasculopathies and neuropathies may decrease the sensation of pain of improperly fitted compression garments, leading to injury and infection
Bronchial asthma	Parasympathetic stimulation can occur with CDT, which may result in an asthma attack
ABSOLUTE CONTRAINDICATIONS	
Acute infections	CDT may exacerbate the symptoms or spread the infection; acute infections should be treated prior to the initiation of CDT because the infection itself provides an increased burden on the lymphatic system (CDT may decrease circulation in the area of the infection, diminishing access to the immune-fighting lymphocytes and macrophages)
Congestive heart failure (CHF)	CHF may be exacerbated by any increase in central venous volume or pressure (patients with mild CHF are still eligible for treatment, but the patient's cardiologist should be consulted for clearance of the patient prior to the initiation of treatment)
Deep vein thrombosis	CDT may lead to embolism from dislodging of a clot

*Disclaimer: This table of contraindications for CDT is not all inclusive. Consideration of CDT must be under the guidance of a trained lymphologist and clinician.

should be used to improve the patient's quality of life.[95] Conversely, cancer research supports the use of therapy for patients with metastasis, contending that CDT does not contribute to the spread of disease.[96]

Several studies of various types of cancer have demonstrated that tissue exposure to cancer cells does not guarantee metastasis will occur.[96] It is the biologic properties of cancer cells and the condition of the immune system that are responsible for metastasis.[94] It is therefore important to state that elevations in venous pressures caused by MLD do not provide individual cancer cells with capabilities that do not exist at lower pressures.[96] Recently, cancer survivors with lymphedema in the presence of locoregional masses were compared with those with lymphedema in the absence of such masses after undergoing CDT.[77] The findings indicated that relief could be obtained with CDT regardless of whether locoregional disease was a contributing factor. Therefore, patients who have persistent or recurrent disease in the draining anatomic bed should not be denied therapy.[77]

During the treatment phase, it is important that the patient adhere to all 4 components of therapy and, more importantly, maintain the compression bandages on the limb 24 hours per day. A prospective study examined the use of low-stretch compression bandaging alone and in conjunction with MLD in patients with breast cancer treatment-related lymphedema.[97] It found that the volume reductions between the two groups were not significantly different, but the percentage reduction was significantly greater for patients whose treatment included MLD.[97] It is important to note that both groups reported a decrease in the feeling of heaviness and tension in the arm, but only the group that received both therapies reported a significant decrease in pain.[97] Although the effectiveness of MLD remains controversial, many lymphologists believe that the patient will benefit most from receiving both compression bandaging and MLD intervention.

Once the patient reaches a plateau in volume reduction for the affected limb, the patient begins the maintenance phase. The maintenance phase is a life-long, self-care program. The patient must have a very clear understanding of the importance of the maintenance phase, and that all reductions gained during treatment will be lost without consistent care. During this phase, the patient continues with a daily home maintenance program that includes self-MLD (please note that to our knowledge there are no studies published to date demonstrating the effectiveness of self-MLD), skin and nail care, compression garments worn during waking hours, compression bandaging at night if necessary, and a home exercise program that should include both aerobic and low-load resistance exercises. If the patient has difficulty with self-bandaging, there are several companies offering alternatives for nighttime bandaging during the maintenance phase to assist the patient in achieving appropriate compression of the limb. Because it may be challenging for some patients to bandage themselves, some lymphologists recommend using compression garments at night and changing to a washed garment the next day. Washing the garment restores the elasticity, thus improving compression.[72] Because there is no cure for this disorder, lymphedema must be monitored over the patient's lifetime. Reassess-

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ment of girth and volume measurements should be performed every 6 months to allow monitoring of the condition so that care can be modified and redirected as appropriate. The reassessment should include review and modification of the patient's home maintenance program if necessary, and replacement of the compression garments as indicated.

When the patient begins their home maintenance program, their adherence is crucial to maintain the results achieved during the treatment phase. It has been shown that the self-report of adherence by the patient is significantly correlated with better outcomes at the time of follow-up at a median of 7.5 months after therapy.[98] Patients reporting self-adherence presented with a continued loss of edema compared with those patients reporting nonadherence, who presented with a gain in edema.[98] It has also been demonstrated that the duration of CDT does affect adherence. A longer duration of therapy results in decreased patient adherence over time.[99]

A study was performed to compare quality of life and symptoms between breast cancer survivors who had developed and undergone treatment for chronic lymphedema and those who had not.[100] The results found that those with lymphedema had a symptom cluster that included alteration in sensation of the limb, loss of body confidence, decreased physical activity, fatigue, and psychologic distress.[100] A comprehensive literature review identified both psychologic and social sequelae that resulted in a reduction of quality of life.[101] The psychologic sequelae included frustration, distress, depression, and anxiety.[101] The social sequelae included changes in role function, lack of social support, and pain and disability.[101] It has been shown that both quality of life and pain are improved by CDT and continue to improve after the treatment has ended.[99]

Precautions and Prevention of the Exacerbation and Progression of Lymphedema

The patient should be educated regarding precautions to decrease the risk of the development of lymphedema. Instruction in arm or leg care guidelines should include skin care, modification of activity and lifestyle, avoiding limb constriction, using compression garments as appropriate, and avoiding extreme temperatures.[102] A retrospective study of women with and without breast cancer treatment-related lymphedema revealed that individuals with lymphedema consistently recalled receiving less education about this disorder.[103] The study concluded that breast cancer survivors' recall of the educational information received concerning lymphedema may be improved through pretreatment lymphedema education, and thereby influence their risk of developing lymphedema.[103]

It should be noted that there is little evidence-based literature regarding precautions to decrease the risk of lymphedema, and therefore the majority of the recommendations are based on knowledge of the pathophysiology and decades of clinical experience by experts in the field.[102] The information in the following two paragraphs regarding suggested risk reduction practices have been retrieved from the National Lymphedema Network (NLN).[102] The NLN is an internationally recognized, nonprofit organization that provides education and guidance to lymphedema patients, healthcare professionals, and the general public.

Skin care should include keeping the extremity clean and dry, applying moisturizer on a daily basis to prevent chapping or chafing of the skin, and using sunscreen and insect repellents. The patient should be instructed to avoid cutting or clipping out cuticles during nail care because this allows easy access for bacteria. Any punctures to the skin, including injections and blood draws, should be avoided. Although some clinicians have demonstrated no detrimental effects from blood pressure monitoring and venipuncture when performed on lymphedematous limbs,[104] we suggest a primum non nocere (first, do no harm) approach and recommend using the unaffected limb whenever possible. The patient should wear gloves when performing activities that could cause injury to the skin, such as gardening or working with household cleaners. The patient should generally avoid injury and contact their physician if any signs of infection occur in the ipsilateral quadrant, including rash, itching, redness, pain, and increased skin temperature, or if the patient is experiencing fever or flu-like symptoms.

The recommendations for activity and lifestyle are that the patient should gradually increase the duration and intensity of any activity or exercise. The patient should take frequent rest periods during activity to allow for limb recovery. The patient should avoid any type of limb constriction on the affected side, including tight jewelry or clothing, and, as noted previously, blood pressure assessment on that limb. The patient should avoid exposure to extreme temperatures, including extreme cold (which can be

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associated with rebound swelling or chapping of the skin) and prolonged exposure to heat (including use of hot tubs and saunas for more than 15 minutes). More specifically for patients with lower extremity lymphedema, prolonged standing, sitting, or crossing of the legs should be avoided. The patient should be encouraged to wear well-fitted footwear and hosiery.

There is some controversy regarding whether compression garments or bandaging should be worn during air travel to prevent lymphedema. Patients at risk for developing lymphedema should understand the risk factors associated with air travel and should make a decision to wear compression garments based on their individual risk factors.[105] Patients with lymphedema should follow all risk reduction activities to avoid exacerbation of the swelling, and should use compression garments during air travel once lymphedema has been diagnosed.[102,105]

Additional factors that influence a patient's risk of developing lymphedema include stage of cancer at the time of diagnosis, age, BMI, blood pressure, and whether the patient has undergone chemotherapy.[39] Patients with more advanced lymph node disease are likely to undergo more extensive axillary surgery along with axillary radiation therapy, which increases the risk of lymphedema.[39] Older age has been found to be associated with an increased risk of lymphedema subsequent to radiation therapy.[39] Obesity is a strong predictor of arm edema, and hypertension has also been noted to increase the risk of arm lymphedema after axillary surgery and radiation therapy.[39] Chemotherapy has been reported in some series to increase the complication rate of breast radiation therapy, including arm edema.[39] With these risk factors in mind, it is important that the patient focus on whole-body health to control risk factors that can be managed, including weight and hypertension. The patient should be instructed to follow a heart-healthy diet and exercise regimen.

TABLE 4. Nonprofit Lymphedema Information Resources

Online information is available from several nonprofit lymphedema informational resources:
American Cancer Society: http://www.cancer.org
Circle of Hope Lymphedema Foundation, Inc.: http://www.lymphedemacircleofhope.org
Lymphedema Research Foundation (LRF): http://www.lymphaticresearch.org
Lymphology Association of North America (LANA): http://www.clt-lana.org
National Cancer Institute (NCI): http://www.cancer.gov/cancertopics/pdq/supportivecare/lymphedema
National Lymphedema Network (NLN): http://www.lymphnet.org

Summary

Conventional oncologic therapies, including radiation therapy and surgery, have made significant improvements in the outcomes of patients' lives. Nevertheless, despite numerous advances in techniques to improve outcomes and decrease toxicity, many of these interventions can leave patients with untoward complications, such as lymphedema. Lymphedema is a chronic and incurable condition that must be discussed with each at-risk patient. It is our responsibility as oncologists and patient educators to become familiar with the early signs and symptoms of lymphedema, the basic pathophysiology, prevention/risk reduction behaviors, and general management techniques. There are numerous informational resources available to educate practitioners and patients about lymphedema and to help find reputable lymphedema management specialists (Table 4.) Importantly, with the early identification and management of lymphedema, we can help many of our patients maintain their quality of life by minimizing cosmetic, functional, psychoemotional, and potentially life-threatening complications. ■

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