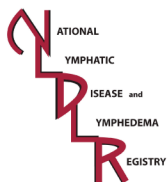


# Recent Advances in Breast Cancer-Related Lymphedema Detection and Treatment



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## Introduction

On April 19, 2011, the Avon Foundation for Women, in partnership with the Lymphatic Research Foundation and the National Lymphedema Network, assembled a group of leading scientists and clinicians expert in breast cancer-related lymphedema to discuss the advances being made in the early-detection and early-intervention of upper extremity lymphedema, how such advances are improving management of the impairment and the need for clinical standardization of care.

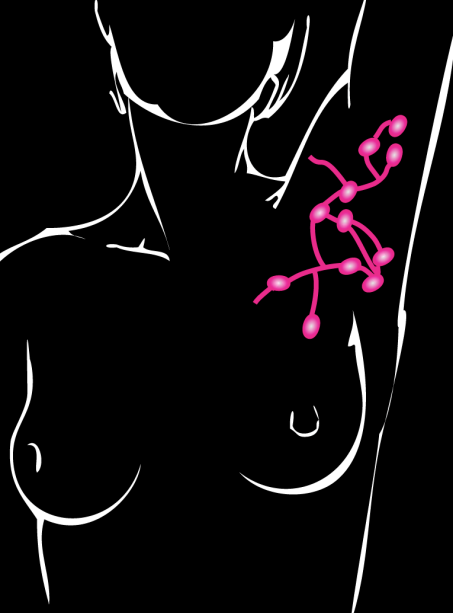
Breast cancer-related lymphedema (BCRL) is a chronic, debilitating disorder that is frequently misdiagnosed, treated too late or not treated at all.<sup>i</sup> Lymphedema (LE) is an abnormal accumulation of protein-rich fluid in the interstitium, which leads to limb swelling, chronic inflammation and reactive fibrosis of the affected tissues resulting from damage to lymphatic circulation following surgery, chemotherapy and/or radiation therapy. Failure of lymph fluid to circulate normally promotes stagnation of extracellular fluid and subsequent inflammatory response and injury to the surrounding tissues. This process can occur quite early in the course of breast cancer treatment and has devastating physical and emotional consequences to breast cancer survivors. Adverse effects commonly seen include the risk of infection, loss of strength and functional limitation of movement, as well profound psychosocial consequences including loss of body image and self-esteem, vocational issues, onset of affective disorders and anxiety. Recently published evidence and expert clinical opinion favor early detection and timely intervention of LE as holding the greatest promise of reducing the incidence of late-stage lymphedema.<sup>ii</sup>

## Primary and Secondary Lymphedema

Although the literature often categorizes LE as being either primary or secondary, the division may be somewhat artificial. There is an increasing awareness that genetic and anatomic variances suggest predisposition of certain individuals to the development of LE, although the exact etiology is unknown. LE risk also appears to increase with obesity and higher body mass index.<sup>iii</sup> Consequently, optimal LE treatment has been noted to be more effective when combined with weight loss strategies.<sup>iv</sup>

The disorder is common among the 2.3 million U.S. survivors of breast cancer<sup>v</sup>, affecting approximately between 19-33% of survivors following axillary lymph node dissection (ALND) and radiation therapy (RT)<sup>vi,vii</sup> and between 3.5-22% of survivors following sentinel node (SLN) biopsy and RT.<sup>vi,vii,viii</sup> The wide variation in incidence and prevalence is often due to differences in measurement techniques and definitions employed in the identification or diagnosis of LE and/or when it is reported after treatment.<sup>i</sup> While refinements in surgical and RT interventions have led to reduction in overall incidence of LE in certain subgroups of patients, even the most conservative

strategies have not resulted in a complete elimination of the disorder.<sup>ix</sup> Essentially anyone with a BC diagnosis that undergoes surgery, chemotherapy and/or RT is at relative risk for LE.



### Staging Systems used for Lymphedema

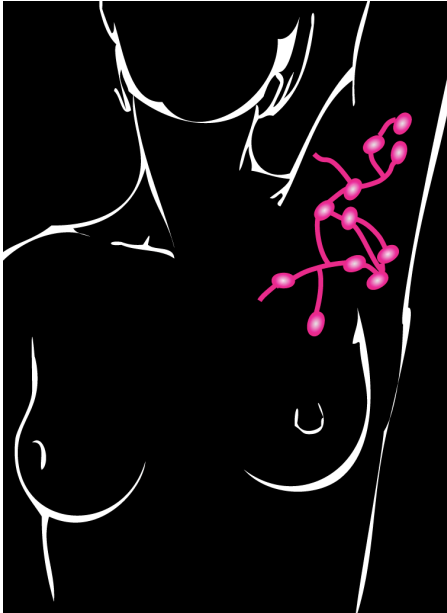
**ISL Stage 0 (Latent, subclinical)**

- No apparent swelling
- Patient may report vague "heaviness"
- Excess accumulation of extracellular fluid
- Slower flow on Lymphoscintigraphy
- Detectable with Perometry or Bioimpedance Spectroscopy
- Non-pitting

**ISL Stage 1 (CTC 4.0 Grade 1, Mild)**

- Mild swelling (< 20% volume)
- Reversible with elevation of the arm
- Protein-rich extracellular fluid
- Detectable with all techniques
- Mild pitting

Onset of BCRL is commonly seen within the first three years following the definitive surgical procedure, with persistent, diminished risk occurring five years later and beyond.<sup>x,xi</sup> The amount of edema can range from mild to severe, and once the condition starts the possibility of progression to more severe stages of edema increases<sup>xi</sup>, adversely impacting survivors' quality of life. As such, early detection of the condition allowing for early intervention appears imperative in reducing the severity of this disorder. In addition, because patients may be anatomically predisposed to developing LE, early stage disease (Stage 1 and 2) may continue to exist in a latent or sub-clinical state even when successfully treated at initial onset, sometimes presenting at later stages ten or more years after initial diagnosis. Minor physical traumas, including cuts, burns, tight jewelry or other injuries to the fingers or hands, may transform a latent condition into active LE requiring treatment. Excessive exposure to the sun can also lead to an inflammatory stimulus that overtaxes an already impaired lymphatic system, resulting in recurrent LE.



**Staging Systems used for Lymphedema**

**ISL Stage 2 (CTC 4.0 Grade 2, Moderate)**

- Mild to moderate swelling (20-40% volume)
- Minimal or no decrease with elevation
- Expanded extracellular fluid compartment
- Fibrosis: lifelong CDT (too late for prevention)
- Moderate pitting and peau d'orange

**ISL Stage 3 (CTC 4.0 Grade 3, Severe)**

- Severe swelling (Elephantiasis) (>50% volume)
- No change with elevation
- Fibrosis and fat have replaced most of the fluid
- Non-pitting
- Little response to CDT

### Early Detection and Intervention of Lymphedema: A Prospective Study

In most cases, in the common practice patterns that are currently employed, a clinical diagnosis of LE is made when the condition becomes visually evident and is usually classified as “mild” LE, often defined as an initially reversible, two-centimeter (cm) circumferential difference between the affected and unaffected arms. Unfortunately, by the time LE is visually detectable it has already evolved into the irreversible advanced stages of the disorder. Undiagnosed, or not treated effectively, LE can progress into later stages of the condition resulting in a severe form of swelling called elephantiasis.

Between 2001 and 2006, a prospective observational study to identify factors affecting morbidity in BC patients was conducted as a collaboration between the National Institutes of Health (NIH) and the National Naval Medical Center (NNMC) Breast Care Center. The study accrued 196 newly diagnosed BC patients over a five year period.<sup>xii</sup> The study collected data on the subjects prior to their surgery and in three-month intervals following their surgery for up to one year. During that time, researchers were able to identify the development of subclinical lymphedema in 43 women (22%) using perometry (an optical-electronic infrared measuring device, which detects small changes in limb volume). At that point, the LE was not visible to the naked eye, and the majority of patients were not complaining of any symptoms. A conservative, low-cost intervention was used once the volume change equated to approximately 100 ml or a three percent volume change compared to the pre-op measure. LE patients were treated with an off-the-shelf sleeve and gauntlet, which was worn daily except during sleeping hours.

Significant reduction in volume and return to nearly their pre-surgical baseline value was noted in all patients over an average period of 4.4 weeks.

Among the conclusions cited in the published article by Stout Gergich et al.<sup>xii</sup>

- Preoperative assessment, prospective surveillance and early intervention may have prevented the progression to more advanced stages of LE in this cohort of 43 patients.
- The compression sleeve significantly reduced affected limb volume to nearly that of the unaffected limb and, therefore, provides effective treatment when sub-clinical LE (prior to the development of obvious swelling) is detected.

## Preventing Lymphedema

In 2010, a randomized, single blinded clinical trial conducted by Maria Torres Lacomba, et al, reported on 116 BC patients who had undergone breast surgery involving dissection of axillary lymph nodes that were divided into two groups.<sup>xiii</sup> Fifty-nine of the women were given early physiotherapy, which included manual lymph drainage, massage of scar tissue, assisted shoulder exercises and educational strategies. The control group, which was composed of 57 women, was given educational strategies only. LE was operationally defined as a 2 cm difference in arm circumference between affected and unaffected side of the breast cancer. At the one-year follow-up, of the 116 women, 18 (16 percent) developed secondary LE:

- 14 in the control group (25 percent)
- 4 in the intervention group (7 percent)

*Conclusions cited by the authors:*

Early physiotherapy could be an effective intervention in the prevention of secondary LE for at least one year after breast cancer surgery. However, treating 116 women to benefit 18 may not be feasible both in terms of cost effectiveness and patient and physician compliance.

## New Tools for Early Detection

Currently, there appears to be some confusion about the most appropriate methods and tools to identify early vs. late stages of LE and when to use them.<sup>xiv,xv</sup>

Tools for early detection of LE include:

- Bioimpedance Spectroscopy (BIS)— A direct clinical method which measures extracellular fluid based on the impedance to the flow of an imperceptible, low level electric current; accurately measures extracellular fluid volume differences between the arms to aid in the clinical assessment of unilateral lymphedema; the device is portable and it is easy to position patient. The L-Dex medical devices utilize BIS to quantify changes in extracellular fluid in a patient's arms. As fluid accumulates in the at-risk arm, the L-Dex value increases. The L-Dex number provides an easy way for clinicians to track extracellular fluid change in the patient's arm over time. An increase of ten (10) L-Dex units from a patient's baseline value represents a change of three (3) standard deviations. BIS is FDA cleared and has been assigned a Category III CPT code.
- Optoelectronic Volumetry (Perometry)— An indirect clinical method which uses infrared light in computer calculation of volume; measures size, not extracellular fluid. Perometry is capable of detecting three percent volume difference in limbs, however it lacks portability and positioning some patients may be difficult. Perometry is not FDA cleared and no CPT code has been assigned.

Late-stage LE, with visible swelling, is typically assessed using a tape measure to quantify circumferential girth. However, due to the insensitive nature of the tape measurement, incidence rates of LE may actually be higher than reported. Tape measurement is most accurate when done in precisely the same manner each time and by the same person. In tape measurement:

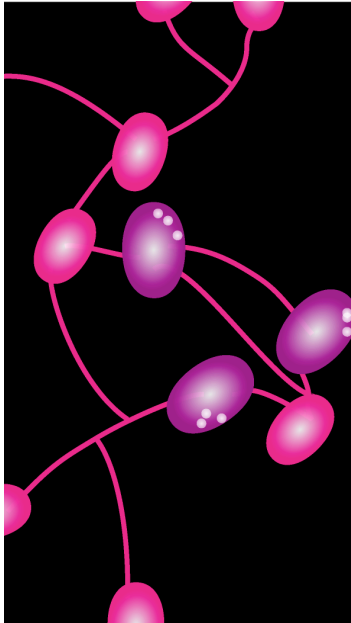
- Circumferential measurements are done incrementally on the affected and unaffected limbs. As reported in the literature, a two centimeter inter-limb difference is the most common method used but maybe a poor indicator of LE due to variability in measurement procedures.
- Volume is calculated based on the formula for a truncated cone (frustum method).
- BMI is recorded.

## Developing Oncology-Rehabilitation Systems

A prospective cohort study assessing limb volume change (LVC) and quality of life in breast cancer survivors published in 2008 by J.N. Cormier, et al<sup>xvi</sup>, found that even a small amount of volume change (between five percent and ten percent, when LE is barely perceptible) was associated with a significant decline in quality of life. Subsequently, Patricia Ganz, MD, Director, Cancer Prevention & Control Research at the Jonsson Comprehensive Cancer Center, UCLA, noted that clinicians must anticipate sequelae of breast cancer treatment and initiate preventative interventions.<sup>xvii</sup>

While advances have been made in primary medical treatment for BC, outpatient medical rehabilitation services to address the physical consequences of that treatment lags behind.<sup>xviii</sup> Necessary strategies required to implement or improve rehabilitation services for BC survivors include:

- Development of more effective systems to recognize rehabilitation needs, provide rehabilitation care and facilitate evidence-based outcomes of rehabilitation in the cancer population.<sup>xix</sup>
- Development of interdisciplinary breast care programs that utilize comprehensive and pre-emptive surveillance programs consistent with current standards used for accreditation by the National Accreditation Program for Breast Centers (NAPBC) and supported by the American College of Surgeons (ACS).
- Implementation of newly developed clinical practice guidelines based on evidenced based literature and current best practices.
- Evaluation and education of patients at risk for lymphedema by competent, well-trained and/or certified lymphedema therapist to ensure safety to proceed with exercise to the affected body part and to provide the proper fit of compression garments.<sup>xx</sup>



Rehabilitation issues for breast cancer patients are considerable, including:

- Post-mastectomy pain
- Radiation fibrosis
- Lymphedema
- Postural instability-balance dysfunction
- Neck pain syndromes
- Sexual dysfunction
- Cognitive decline
- Muscle weakness and tissue contractures after reconstruction
- Cancer Related Fatigue (CRF)

## Interventions for Breast Cancer-Related Lymphedema

The current standard of care for BCRL includes the following:<sup>xx,xxi</sup>

- Complete Decongestive Therapy (CDT): Short stretch compression bandages to contain edema; manual lymphatic drainage; good skin hygiene; lymphatic exercises
- Patient referral to competent, trained lymphedema therapists skilled in CDT

## Weight Lifting and BCRL

Recent studies in weight lifting, exercise and weight loss are also showing benefit in the prevention of lymphedema in at-risk patients and in patients with lymphedema.<sup>xxii,xxiii</sup>

The first study, conducted on BCRL patients, called for 90 minutes of circuit exercise that included stretching, aerobics and arm and leg weights and found that the BCRL patients who adhered to the exercise protocol fared better than those who did not.

Participants:

- Experience fewer lymphedema flares
- Were treated more quickly
- Were more physically fit
- Demonstrated greater weight reduction

## Exercise for At-Risk BCRL Patients

In another study, at-risk BCRL patients followed the same 90-minute exercise protocol used on the patients with LE, they:

- Did not wear a compression sleeve unless they developed LE
- Had significantly less (70%) development of LE at one year follow-up

## The Connection between Obesity and Lymphedema

- Lymphedema risk increases with weight gain
- Lymphedema treatment is more effective if combined with a weight-loss program
- Lymphedema volume measurements done in therapy must be correlated with BMI

## Advancing Toward Targeted Treatment for Breast Cancer

Treatment of BC is moving toward “targeting” optimal therapy for each patient based on maximum benefit and minimal side effects consistent with the physician’s Hippocratic oath to “First, do no harm.” Although personalized medicine is not yet a complete reality, there are examples of how targeted medicine, such as Herceptin for HER2-positive BC patients, provides larger proportional benefit for specific patients than would be derived if the drug were given to every patient. Radiation therapy also needs to be targeted and used appropriately in order to reduce morbidity. A similar targeted approach is needed for lymphedema surveillance and intervention. The results of the Lacomba prospective randomized control trial using tape measurement and physical therapy for everyone in the treatment arm showed a two-thirds reduction in preventing lymphedema through intervention and education vs. education alone (25% control group vs. 7% in intervention group). The reduction observed with this intervention yields even greater effect than other targeted interventions including Herceptin for HER2 positive breast cancer and most surgical approaches to treat breast cancer.

Routine use of perometry or the validated and more economical alternative of bioimpedance spectroscopy (BIS) holds great promise as an aid to clinicians in the early detection of LE and identifying who needs physiotherapy.

Early detection and intervention methods for BC patients at risk for lymphedema should be developed analogous to the model used in screening mammography. Similar to the rationale for mammography, a surveillance model of early detection and early intervention (at early stages) in BCRL can prevent progression. Currently there are no clinical guidelines for early intervention of LE and these procedures are often not reimbursed by managed care providers. However, the Avon Foundation for Women

Breast Cancer Crusade and other nonprofit foundations make funds available to hospitals to enable at-risk BCRL patients to access these new technologies with the anticipation that managed care providers will soon provide coverage.

## Case Studies in Long-Term Care for BCRL Patients: What We Are Learning<sup>xxiv</sup>

There are many questions that science needs to answer in the treatment of BCRL patients, including:

### Case Study I

- How often do patients have recurring LE and require the compression sleeve or physiotherapy again?

A 37-year-old woman presented with invasive ductal carcinoma (IDC) of the right breast. She underwent a partial mastectomy and axillary dissection, which revealed seven of twelve positive nodes for residual disease. Her L-Dex score (BIS) was 1.0 preoperatively. The patient received radiation and chemotherapy. Her L-Dex score remained stable for a few months with a mild shift to 6.0 in August of 2009. In February of 2010, her L-Dex score rose to 11.7. She was treated with an off-the-shelf compressive sleeve, and arm volume returned to normal in four weeks. However, since that time, the patient was reevaluated periodically and was found to again have subclinical lymphedema. She was put back on a compression sleeve and again the edema resolved. BCRL patients should be monitored periodically for LE and may have to be treated intermittently to prevent progression of LE.

### Case Study II

- Should patients with preexisting lymphedema be periodically evaluated? Yes.

A 72-year-old woman presented with h/o lymphedema diagnosed by tape measure following a lumpectomy and axillary node dissection. She had been wearing a compression sleeve for five years. After the five years, she was measured and had a normal L-Dex (BIS) score. It turned out that her LE had not recurred for two-and-a-half years and she did not need to constantly wear a sleeve.

### Case Study III

- Has subclinical lymphedema progressed during treatment? Of the cases that presented with subclinical lymphedema, identified with a baseline measurement and followed by NIH protocol, none have progressed to later stages of lymphedema except for the case study below. The following case is a typical example of outcomes when lymphedema is not detected in the early, reversible stage.

A 58-year-old woman presented with 3.4 cm IDC. She was treated with neoadjuvant chemotherapy and underwent a partial mastectomy and axillary dissection. Ten of 15 nodes were positive for residual disease. Her initial L-Dex score was normal. The patient was non-compliant with scheduled follow-up visits. She was subsequently seen by her oncologist 18 months later and presented with stage II lymphedema and an L/Dex score of 65.

## Summary

- Breast cancer-related lymphedema remains a significant problem for survivors even when conservative treatment strategies, such as the sentinel lymph node technique, and refinements in surgical and radiotherapy interventions are employed.
- Breast cancer-related lymphedema adds to the aggregate cost of cancer care for these patients.<sup>xxv</sup>
- Appropriate surveillance for lymphedema onset is essential and medically necessary due to documented risk in breast cancer survivors following treatment and for regular intervals afterward. Although BC survivors have a lifetime risk of developing late onset lymphedema, scheduling frequent, regular perometry or BIS screenings (i.e., regular surveillance) in the years after successful cancer treatment can improve quality of life and reduce fear and the development of irreversible LE. Guidelines are needed to firmly establish recommended intervals to screen survivors for early and late onset lymphedema.
- The National Lymphedema Network (NLN) in April 2011 issued its position paper on lymphedema screening and treatment. NLN recommends all breast cancer patients receive pre- and post-treatment measurements on both arms, consistent measurements throughout treatment, and use of bioimpedance spectroscopy or infrared perometry as alternatives to tape measure to reduce the occurrence of false negative and false positive results that can be obtained with the tape measure.<sup>xxvi</sup>
- Bioimpedance spectroscopy (BIS) is a technology currently used in the early clinical assessment of LE and has been shown in clinical trials to detect very early increases in extra cellular fluid volume, correlated with findings from perometry. BIS has been FDA cleared as an aid in the assessment of unilateral arm lymphedema in women, is coming into routine clinical use and has been granted a CPT Category III code (0239T). Adoption and implementation may be limited by some insurance carriers' current coverage and reimbursement policies.

- Perometry, which uses an infrared optical electronic scanner and computer to calculate the volume of a body part, has been shown to detect as little as a 3 percent change in limb volume in BC survivors over time. However, perometry equipment is not universally available and it is generally not reimbursable.
- Complete Decongestive Therapy (CDT) and properly fitted sleeve may benefit early edemas when volume is less than 5 percent or in the first year.
- A 5-year prospective observational study enrolled 196 newly diagnosed breast cancer patients and identified 43 (22%) with subclinical LE at 6.9 months post-surgery. Those identified with subclinical LE were treated on average for 4.4 weeks with an off-the-shelf compression sleeve and gauntlet, and all returned statistically to their pre-surgical baseline.
- Universal guidelines for the standard of care for early-stage LE are needed to treat the problem effectively. Early detection and intervention hold the greatest promise of reducing the incidence of lymphedema. A greater emphasis on patient education, such as patient education brochures, is also needed to help BC survivors reduce their risk of developing LE and better manage the condition if it does develop. For example, BC survivors should be made aware of the physical triggers, such as cuts or burns on the fingers that may transform latent disease into active disease and the importance of maintaining meticulous skin care hygiene, optimal body weight and a regular exercise routine. The National Lymphedema Network (NLN) issued the Position Paper “Lymphedema Risk Reduction Practices”.
- At the same time, lymphedema fear, which impacts quality of life, should be addressed with the news that early detection is now available and can facilitate resolution of fluid accumulation in the reversible stage, before swelling is obvious.
- Greater lobbying efforts by medical and breast cancer advocacy organizations are needed to inform health insurance carriers about the evidence-based research showing the benefits of emerging diagnostic tools in the detection of early-stage lymphedema.

## Calls to Action

- Updated educational materials need to be created to provide breast cancer survivors with the latest information about the risks of lymphedema and current evidence-based strategies to detect and treat the condition.
- A joint letter should be issued from advocacy groups such as the Avon Foundation Breast Cancer Crusade, Living Beyond Breast Cancer, Lymphatic Research Foundation, National Coalition for Cancer Survivorship, National Lymphedema Network, Susan G. Komen for the Cure, Y-Me National Breast Cancer Organization, Young Survival Coalition and other advocacy groups to the American Society of Breast Surgeons, the American Society of Clinical Oncology and other organizations such as the United States Preventative Screening Task Force urging support in promotion of early detection and intervention of BCRL.
- The publication of a white paper position statement is needed on standard of care guidelines for BCRL from the American Society of Clinical Oncology, American Society of Breast Surgeons and the National Comprehensive Cancer Network.
- There are no standards of care for clinicians in the treatment of BCRL. In order to address all the concerns of BCRL patients, including physical, psychosocial and financial, the disorder has to be tackled from the perspective of cancer survivorship as a whole. Universal systems have to be adopted to detect patients at increased risk for developing BCRL, prevent complications of the condition and enhance survivors' quality of life. To standardize care and improve quality of life for survivors, rehabilitation care must include a survivorship care model in collaboration with various departments of medicine, including surgery medical and radiation oncology, primary and palliative care. Strategies needed to implement or improve rehabilitation services for BC survivors in individual cancer institutions include:
  - Surveillance for BCRL in all at-risk patients by their oncology or surgical providers using a pre-emptive surveillance approach.
  - The development of more effective systems to recognize rehabilitation needs, provide rehabilitation care and facilitate evidence-based outcomes of rehabilitation in the cancer population.
  - The development of system-wide breast care programs that deliver lymphedema care according to accepted guidelines based on current best practices.
  - Based on pre-emptive guidelines for early lymphedema, referral to competent, trained and/or certified lymphedema providers who are knowledgeable in assessment and management of all stages of lymphedema to ensure early intervention, safety with exercise of the affected body part and to provide the proper fit of compression garments.<sup>xx</sup>

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