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INTRODUCTION

Breast cancer treatment is recognized as the most common cause of secondary lymphedema (LE) in the developed countries of the world. LE occurs as both an acute and chronic health condition in which significant and persistent swelling is associated with an abnormal accumulation of protein-rich fluid. The impact of LE is significant on a wide range of daily activities and survivorship quality of life. Measurement and quantification of LE has been problematic despite the fact that various methods have been used to measure limb volume (LV). Perhaps in part because of difficulties in measurement and diagnosis, the reported incidence of LE varies greatly among persons treated with surgery and radiation for breast cancer. Through increased measurement accuracy, LE incidence and prevalence following current therapeutic approaches for breast cancer treatment will be better understood, and more informed decisions about risk factors, treatment interventions, and recovery will be made. Further identification of epidemiological and clinical factors associated with risk and incidence will provide the necessary foundation for preventive intervention. Bilateral measurements at pre-op and over time are necessary to assess LV changes during follow-up, as it is important as part of the differential diagnosis to note whether volume change has occurred in the affected limb alone or in both limbs. Application of rigorous measurement protocols, assessment of symptom experience, and establishment of a data base on bilateral LV at pre-op for later comparison are essential components of a solid foundation for intervention studies. Through multidisciplinary collaboration with rigorous scientific approaches feasible to be carried out in the clinical setting, we have the opportunity to better target risk factors for development of LE, design data-based interventions, and improve post-treatment quality of life.

Definition and Impact of Lymphedema

LE occurs as both an acute and chronic health condition in which significant and persistent swelling is associated with an abnormal accumulation of protein-rich fluid that is both observable and palpable in the affected area. In addition, the swelling often causes discomfort and disability. Following the onset of limb swelling, the patient is predisposed to infection, cellulitis, and lymphangitis, which is then sometimes followed by life-threatening septicemia. Huffman and others have noted a wide impact of LE on women’s daily lives, such as: 1) problems with sleeping as women try to position their arms; 2) restrictions on carrying items, such as heavy pots or groceries; 3) many forms of exercise (even walking) can lead to further symptoms; 4) difficulty in performing and completing family-related and occupational responsibilities; and 5) fit and comfort of clothing. Thus, the impact of LE is significant on a wide range of daily activities.

Diagnosis of Lymphedema

Measurement and quantification of LE has been problematic despite the fact that various methods have been used to measure limb volume (LV). Clinically and often in research studies, subjective observation is the basis of the judgment about presence of LE. Perhaps the most common...
clinically applied objective criterion for diagnosis has been a finding of 2 cm or more difference in arm circumference (or 200 ml limb volume difference [LVD]) between affected and nonaffected limbs. LE can be categorized as mild, moderate, or severe. Three stages are identified: Grade I, in which pitting occurs upon application of pressure and edema reverses with limb elevation; Grade II, in which the edematous limb becomes larger and harder and no longer pits under pressure; and Grade III, in which swelling worsens and skin changes occur—the skin may become very thick and develop huge folds associated with elephantiasis. LE also may be classified as acute (lasting less than 6 months) or chronic (lasting longer than 6 months).

**Incidence of Lymphedema**

Perhaps in part because of difficulties in measurement and diagnosis, the reported incidence of LE varies greatly among persons treated with surgery and radiation for breast cancer. The most recent reviews of the literature have estimated the incidence of LE from 6% to 30% and from 6% to 62.5%. Not surprisingly, since we understand LE can occur from weeks to years following treatment, Petrek and Heelan noted that the study with the shortest follow-up (12 months) reported the lowest incidence (6%); likewise, one of the studies with the longest follow-up (11 years) reported the highest incidence. This broad statistical range of findings probably reflects major recent breakthroughs in breast cancer treatment, including progress in breast conservation and therapeutic combinations leading to increased survival rates, inconsistent criteria for defining and diagnosing LE, and small samples, retrospective analyses, and the psychometric difficulties (particularly reliability) in assessing LE.

Although common medical assumptions imply LE is not a problem of the present or future due to modern procedures such as sentinel lymph node biopsy (SLNB) and breast conservation surgical approaches, the latest data reported in 2003 reveal LE occurrence at a significant level of concern in spite of these improved techniques. Two national cooperative clinical trials are now in design and approval stages, aimed at investigating LE occurrence and prevention in breast cancer patients (Cancer and Leukemia Group B: CALGB; American College of Surgeons Oncology Group: ACOSOG), evidence that clinicians recognize the continuing breadth and impact of this posttreatment complication on survivors’ quality of life (L. Jacobs, M.D., co-investigator and ACOSOG member, personal communication, January 12, 2004). Clinicians and researchers report modest estimates of LE following breast cancer surgery even for SLNB-only patients (L. Jacobs, M.D., co-investigator and ACOSOG member, personal communication, January 12, 2004). This group with node-negative disease (SLNB-only) represents the group at lesser risk for LE and this LE occurrence is commonly reported by clinical observation rather than objective limb measurement.

Posing a high probability of underrepresentation of the condition. Further, current protocols require further nodal dissection for node-positive disease. A 2003 study by Deutsch and Flickinger reports LE at 7% at 6-month follow-up after post-lumpectomy radiotherapy (n=265). In the same year, Coen and colleagues estimate up to a 10% 10-year risk of developing LE (highest with axillary irradiation), as compared to a 26% prevalence reported by Voogd et al. in a sample of 332 women receiving axillary lymph node dissection (ALND) but no axillary radiation in the Netherlands; 28% in a group (n=240) undergoing ALND at 18 months post-surgery in Turkey by Ozaslan and Kuru and a prevalence of 38% self-reported postsurgical arm or hand swelling (n=145) by Geller and colleagues. The incidence of LE among breast cancer patients, even using the lowest estimates, affects hundreds of thousands of women and represents a major societal problem.

It is hoped that newer breast cancer treatment approaches will reduce the long-term treatment effects of the past such as LE. Indeed, it is believed that a lower percentage of breast cancer patients without radiation or surgery to the axilla will develop LE; however, the risk of LE following treatment of breast cancer still exists. Post-surgical infection or radiation skin reaction (even in radiation to the breast), as well as co-morbid conditions and co-treatment effects such as seroma, may increase risk of LE. Even in radiation treatment directed toward the breast alone, not directed at the axilla, some radiation scatter may impact the axillary lymphatics. Although chemotherapy or hormonal therapy is not known to cause LE, some studies and clinical practice guidelines hint at association of weight gain during treatment with risk of LE; chemotherapy and hormonal therapy are known to impact fluid balance changes. It is conservatively estimated that 20–40 of every 100 persons (or 1 in 4) treated for breast cancer with contemporary treatment modalities will experience LE in their lifetimes. Indeed, in the author’s preliminary work, 39% of the 103 women returning for follow-up after breast cancer treatment (mean time since diagnosis=36 months) had ≥2 cm circumferential difference between the affected and nonaffected limbs at one or more points.

Over the past decade, breast conservation techniques, most often coupled with radiotherapy, have been used widely in an effort to diminish unpleasant, lasting side effects (such as LE) associated with more radical treatments. Similar medical optimism regarding reduction in LE has been associated in recent years with the advent of sentinel lymph node biopsy (SLNB) procedures that spare the breast cancer patient the more invasive and traumatic axillary lymph node dissection (ALND). However, preliminary observations and data indicate that LE incidence following breast conservation surgical methods, such as lumpectomy and partial mastectomy combined with radiotherapy, may be equal to or in fact greater than the incidence following traditional surgical treatment (mastectomy with or without radiation). The impact of
SLNB on LE occurrence is not yet known because too little time has elapsed to observe LE that may occur up to 20 years after treatment.\textsuperscript{19} It is important to note current protocols continue to call for ALND in node-positive disease; thus, a large cohort of women continue to require axillary dissection—alone or in addition to SLNB.\textsuperscript{17,19,20} Indeed, SLNB in combination with lumpectomy is typically followed by radiation therapy—again (even if limited to the breast), incurring additional LE risk. Both breast conservation techniques and SLNB are generally components of a program of treatment including radiotherapy to the breast and/or axilla.\textsuperscript{14,29} Since radiation exposure is associated with trauma to the lymphatic system, risk for LE likely continues for women treated with state-of-the-art treatment modalities. Through increased measurement accuracy, LE incidence and prevalence following current therapeutic approaches for breast cancer treatment can be better understood, and more informed decisions about risk factors, treatment interventions, and recovery will be made. In addition, appropriate sampling decisions can be made for the next stage of intervention research.

**Management of Lymphedema**

A range of clinical approaches with varying levels of success in LE management has been reported in the literature.\textsuperscript{19,20} Certain comprehensive approaches in therapy and self-management, such as complete decongestive physiotherapy (including manual lymph drainage, bandaging, exercise, and meticulous skin care), have become the standard in managing LE.\textsuperscript{13,34} Early detection and intervention hold the greatest promise of reducing this widespread condition.\textsuperscript{17,33} Further identification of epidemiological and clinical factors associated with risk and incidence will provide the necessary foundation for preventive intervention.

It is noted here that axillary tumors sometimes cause LE, requiring treatment of the malignant tumors, a scenario to be ruled out before LE is diagnosed as secondary to cancer treatment. Treatment in this case generally is chemotherapy or hormone treatment targeting the tumor, rather than LE-specific treatment.

**Lymphedema Risk and Compliance**

While personal and historical characteristics such as age, weight, co-morbid conditions, infection, ALND, and radiation are believed to affect survivors’ risk for onset of LE,\textsuperscript{14,16,17,24} patient compliance has been identified as the most important factor in treating LE.\textsuperscript{13,24} Even so, little is known about factors influencing patient compliance and effective self-management strategies for LE symptoms. For example, many of the most promising LE management techniques are time-consuming, very difficult to accomplish by the patient alone, and may be vulnerable to incomplete patient compliance without strong support and practical assistance from family or friends. Investigations with increased precision in LE measurement to establish its current incidence and prevalence among breast cancer survivors and identification of protective mechanisms are crucial to the development of intervention research directed at prevention, early detection, treatment, and management of signs and symptoms of LE.\textsuperscript{12,37}

**MEASUREMENT OF LYMPEDEMA**

**Measurement Issues in Lymphedema**

Among the issues relevant to measurement of LE are those of: 1) reliable instruments which are appropriate in the clinical setting; 2) timing of measurements for most efficacious and informative data gathering for diagnosis and follow-up; 3) underlying assumptions about limb volume symmetry; and 4) assessment of symptom experience in combination with anthropometric limb measurement.

**Instrumentation**

The ideal anthropometric measurement for LE would be described as easy to use, noninvasive, hygienic, inexpensive, reliable, quantifiable, suitable for any portion of the limb, and capable of providing information on shape.\textsuperscript{12,38} Existing measures that are easy to use and inexpensive have limited reliability and do not address the functional impact of LE.\textsuperscript{12}

![FIG. 1. Water displacement.](image-url)
Currently, there is no standard clinical protocol (a clinical "gold standard") that is easy to use, noninvasive, and reliable for the measurement of the affected limb in the clinical setting.\textsuperscript{[12,34,39]} Although water displacement (Figure 1) has been regarded as the sensitive and accurate "gold standard" for volume measurement in the laboratory setting, it is little used clinically because it is cumbersome and messy. It is usually limited to measuring a certain part of the limb and does not provide data about edema localization or the shape of the extremity.\textsuperscript{[38,39]} Moreover, a standard deviation of 25 ml for repeated measures of the arm is reported by Swedborg.\textsuperscript{[32,40]} Finally, water displacement is contraindicated in patients with open skin lesions. Disinfecting equipment and replacement of water between patients is necessary to prevent infection—a requirement which makes water displacement impractical in many clinical settings.

Circumferences (Figure 2) at various anatomic points are used most frequently to quantify LE, but several problems exist.\textsuperscript{[31]} Limits for acceptable difference between repeated circumferential measurements of the normal adult arm, forearm, and wrist are 0.2 cm,\textsuperscript{[13]} a standard rarely met clinically in between-rater comparisons. Although circumferences may appear to be simple measures, control of intra- and interrater reliability is difficult. These rigorous standards are especially difficult to meet with an edematous limb. Volume estimate calculations most often assume a cylindrical circumference, which is seldom the case. This systematic methodological error gives a slightly higher volume than the true value. Studies report correlations with water displacement ranging from 0.70 to 0.98,\textsuperscript{[12,13,38]} Because of its irregular shape, circumference of the hand is an inaccurate way of determining volume. There are severe limitations for these methods when skin damage exists. Handling of the extremity and contact with equipment raise hygienic concerns.\textsuperscript{[38]} The circumferential method is time-consuming and requires considerable experience.

The perimeter (Figure 3) is an optoelectronic device developed to meet the need for a quick, hygienic, and accurate method of volume calculation. It works similarly to computer-assisted tomography, but uses infrared light instead of x-rays.\textsuperscript{[38]} An array of 360 light beams is emitted perpendicular to the axis of and sequentially along the limb. Where the path of the beams is interrupted by the limb, the receivers in the limb's shadow are not hit, allowing the perimeter to calculate a precise transsection. Dimensions along the x- and y-axes are measured to an accuracy of \(10^{-4}\) m.\textsuperscript{[38]} Transsections are measured every 3 mm (as compared to every 4 cm in a typical circumferential protocol) and summed to the volume by a computer.\textsuperscript{[38]} The perimeter has a standard deviation with repeated measures of 8.9 ml, less than 0.5% of the arm volume.\textsuperscript{[38,39]} In addition, the volume and transsection of any part of the limb can be measured, the shape of the limb or limb segment can be displayed, and accurate calculations of change in volume can be made in seconds. Until recently, testing of the perimeter on limbs with LE had been limited to Europe and largely to the horizontal leg unit, but it has shown very promising results.\textsuperscript{[39]} The perimeter now in use in a National Institutes of Health-funded prospective longitudinal study at the University of Missouri-Columbia has not been previously applied in the U.S. for this purpose.\textsuperscript{[38,39,41,42]} Its potential application for baseline and follow-up measurements of LE is promising. Given the expected precision of the perimeter and our research protocol, we have conceptualized LE as a continuous (rather than dichotomous) variable, supporting a more robust test of the link between severity of LE (measured in percent of LVD between affected and non-
affected limbs) and selected psychosocial processes and functional health.

Timing of Measurements for Lymphedema Assessment

Assessment of limb volume change (LVC) following breast cancer treatment cannot be accurately carried out without a pre-treatment limb baseline measurement. Limb volume measurements need to be done routinely, pre-operatively as well as at follow-up. Ideally, this measurement would be done at pre-op when other pre-op activities are carried out (e.g., physical assessment, lab, EKG, chest x-ray, anesthesia assessment). Alternatively, data could be gathered at immediate post-op. The greatest disadvantage to forgoing the pre-op measurement is that surgical edema may cloud the baseline measurements at immediate post-op. By definition, acute LE lasts less than 6 months, but delaying treatment to allow spontaneous resolution of edema (surgical or lymphatic) may predispose to a less-optimal LE outcome. Only with passage of time can surgical edema be differentiated from early-onset (acute or chronic) LE. A useful step in differentiating generalized surgical edema from post-op LE is the assessment of bilateral LV both at baseline and at follow-up. If both limbs have increased by a similar percentage of volume or circumferences in the follow-up period, this is a clue to overall fluid retention rather than isolated lymph congestion in the affected limb. This LVC is likely to be associated with body weight increase as well. Comparison of the affected limb volume with the contralateral limb volume provides evidence of LVC associated with LE, with certain caveats, as discussed below.

Underlying Measurement Assumptions

It has long been assumed (although not always spoken or written) that the limbs are symmetrical and of similar, if not identical, volume. Indeed, the basis of LE diagnosis leading to eligibility for third-party payment for LE treatment is the underlying assumption that the two limbs are symmetrical in circumferences and volume. As noted earlier, the most common criteria for LE diagnosis is 2 cm circumferential difference or 200 ml LVC (affected versus non-affected limbs). These criteria are based on the underlying assumption that the limbs are symmetrical and identical in volume. When this assumption is challenged and the potential of asymmetry considered, the next assumption is that the dominant limb is larger than the non-dominant limb—with this LVC sometimes estimated to be up to 200 ml due to dominance. In preliminary measurement studies, LVD up to 160 ml have been noted between healthy limbs and in some few cases (3 of 10 initial participants) non-dominant limbs have been found to have larger volume than dominant limbs. These incidental findings provide further justification for the bilateral baseline limb measurements. Further, continued bilateral measurements over time are necessary to assess LVC during follow-up, as it is important as part of the differential diagnosis to note whether volume change has occurred in the affected limb alone or in both limbs.

Symptom Experience in Combination with Anthropometric Limb Measurements

Frequently, the patient’s subjective experience of sensation changes is the first sign of LE, sometimes prior to observable LVC. Research into symptom experience reveals certain symptoms (swelling, heaviness, and numbness) differentiate between women with breast cancer LE and healthy women. When these three symptoms were used to examine a group of survivors with and without LE at the 2 cm circumferential difference, swelling and heaviness differentiated group membership (c statistic=0.952). In an earlier preliminary analysis of this second set of data, participants who were breast cancer survivors with LE experienced more symptoms than those without limb swelling at the recognized criterion. It is recommended that LV measurements routinely be accompanied by symptom assessment.

State-of-the-Art Lymphedema Research

Since the “critical weakness” in previous incidence research is lack of knowledge about the total pool of participants, a National Institutes of Health-funded study now in progress aims to consecutively sample all breast cancer patients scheduled for breast cancer treatment (surgery, radiation, and/or chemotherapy) at one midwestern cancer center. Participants are being followed at routine quarterly (Year 1) and semianual (years 2-3) follow-up appointments over a 30-month period (Time 2-Time 9). This longitudinal study uses a much more sophisticated LV measurement, the perimeter, as well as a rigorously developed measurement protocols for circumferential limb measurement. This modality supports increased sensitivity and specificity of measurement findings. This also allows a more robust test of the link between severity of LE (measured in percent of LVD between affected and non-affected limbs), symptom experience, and selected psychosocial processes, operationalized with up-to-date, psychometrically strong assessment tools. We also are now able to assess LVC over time from pre-op through immediate post-op through post-treatment follow-up (30 months follow-up currently funded; funding request pending for 7 years follow-up).

The theoretical model (Figure 4) for our research reflects our conceptualization of LE in terms of both objective and subjective indicators—specifically LVC and associated signs and symptoms—and coping effectiveness, respectively. Because LVC measurement has been problematic in the past, we included two measurement methods, the traditional circumferential arm measurement and infrared perometry. Likewise, because very little is known about coping with LE, we examine coping through measurement of LE coping efficacy. Objective and subjective assessments describe different dimensions of LE, which may help to further our
understanding of not only the physical aspects of LE, but also the cognitive and affective components associated with coping with this disease. Further, we examine potential protective mechanisms such as problem solving and social support that are believed to impact general well-being and may influence adaptation to or inhibit progression of post-breast cancer outcomes such as LE. Finally, we examine these assessments in relationship to multiple dimensions of post-breast cancer treatment outcomes, namely psychosocial adjustment, specifically psychosocial distress, quality of life, and adjustment to chronic illness, as well as functional health status. Tracking changes in these variables over time, along with changes in functional health status and psychosocial adjustment, will allow the investigation of selected variables (e.g., problem solving ability, social support, and coping effectiveness) as predictors of LVC, psychosocial adjustment outcomes (e.g., quality of life), and functional health status over time.

Our goal is to identify variables that influence disease progression and psychosocial outcomes/functional health status, which can inform subsequent interventions. This study will provide foundational knowledge for research developing early-intervention strategies to reduce incidence and complications of LE among women treated for breast cancer. Such study is essential for further systematic research to evaluate the effectiveness of interventions in preventing, controlling, and resolving LE in women treated for breast cancer. Without a LV measurement protocol such as has been developed and applied in this study, accurate comparisons of treatment effectiveness across multiple sites, therapeutic modalities, and patient characteristics remain impossible. Furthermore, measurement of LE as a dichotomous variable (generally ≥2 cm difference between limbs) using often-precise and -reliable measurement tools such as circumferenceal tape measure has not allowed examination of LVC that may begin immediately after surgery and/or radiation and that are not easily detected with current measurement strategies. The added measurement precision in this study provides a more stringent examination of the relationships among protective mechanisms (problem solving and social support), LE coping effectiveness, LVC, and post-breast cancer treatment psychosocial adjustment and functional health status. Moreover, the prospective longitudinal design allows examination of these relationships over time.

Ultimately, this program of research has the potential to influence clinical practice guidelines for persons undergoing treatment for breast cancer. The findings from this study will have potentially widespread clinical applications in developing and testing a protocol for consistent, accurate, noninvasive, and labor- and cost-effective measurement of the lymphedematous limb. Potential application is considerable for both upper and lower extremity LE attributable to surgery, radiation, and other adjunct treatment for malignancy, including breast, melanoma, prostate, ovarian, and other cancers involving lymph node dissection and irradiation. Moreover, examining the link between protective mechanisms, LVC, coping effectiveness, and psychosocial outcomes/functional health status will lead to a more complete understanding of the consequences of LE, and subsequently to more appropriate care. In addition, identification of potential protective mechanisms could greatly inform clinical treatment and preventive interventions. Accurate and consistent anthropometric measurements are essential to scientific evaluation of the effectiveness of LE treatments, as well as to sound clinical assessment of disease management and progression.

**Directions for Future Research**

Comparisons of LE incidence and treatment effectiveness across multiple sites, therapeutic modalities, and patient characteristics are necessary to better understand this complex issue. It becomes increasingly imperative that clinicians and researchers across disciplines collaborate to establish multi-site
research programs focused on incidence and prevalence of post-breast cancer treatment LE with the aim of developing multi-site randomized intervention programs. Application of rigorous measurement protocols, assessment of symptom experience, and establishment of a data base on bilateral LV at pre-op for comparison are essential to the foundation for intervention studies. Through multidisciplinary collaboration with rigorous scientific approaches feasible to be carried out in the clinical setting, we have the opportunity to better target risk factors for development of LE and improve post-treatment quality of life.

SUMMARY

Of two million women with breast cancer in the U.S., at least one in four is likely to have LE within 11 years and experience a wide range of potentially debilitating outcomes as a result. At this point, much remains unknown about the measurement, incidence, and correlates of LE, including effective and ineffective health care self-management strategies.

REFERENCES

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