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Lymphedema Following Treatment for Breast Cancer: A New Approach to an Old Problem

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Abstract

Lymphedema following treatment for breast cancer can be an irreversible condition with a profound negative impact on quality of life. The lack of consensus regarding standard definitions of clinically significant lymphedema and optimal methods of measurement and quantification are unresolved problems. Inconsistencies persist regarding the appropriate timing of intervention and what forms of treatment should be the standard of care. There are reports that early detection and intervention can prevent progression, however the Level 1 evidence to support this hypothesis has yet to be generated. To assess these controversies, we propose the implementation of a screening program to detect early lymphedema in conjunction with a randomized, prospective trial designed to generate Level 1 evidence regarding the efficacy of early intervention and appropriate treatment strategies. Collaboration among institutions that manage breast cancer patients is essential to establish a standardized approach to lymphedema and to establish guidelines for best practice.

Keywords

lymphedema; screening; perometer; breast cancer

1. INTRODUCTION

Lymphedema is a chronic swelling caused by accumulation of fluid in the interstitial tissues due to the inability of the lymphatic system to adequately transport lymph fluid [1, 2]. In the

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9. CONFLICT OF INTEREST STATEMENT

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era when axillary lymph node dissection (ALND) was routine practice, the incidence of lymphedema in patients treated for breast cancer was reported as high [3]. Due to advancements in care and surgical techniques such as the sentinel lymph node biopsy (SLNB), incidence rates have decreased substantially, with a 5–8% incidence in patients who undergo SLNB and a 14–16% incidence in patients who undergo ALND, including only levels I and II [4, 5]. Reports on cohorts with longer follow up report incidence rates as high as 34%–94% [2, 6] depending on the methods of lymphedema measurement and quantification.

The discrepancies in definitions, measurement techniques, and quantification methods of lymphedema have been cited as limitations in multiple previously published reports [7–9]. The various methods of measurement, quantification, and definition that have previously been used and reported in the literature are not interchangeable, preventing the comparison of data across studies [10]. This lack of standardization has created a major hindrance in the interpretation of data that ultimately needs to be applicable to the entire breast cancer population.

The detrimental effects of lymphedema on a breast cancer survivor's physical and psychosocial health can be overwhelming, particularly because lymphedema is a risk that lasts for the survivor's life [7, 9, 11]. Physical morbidities caused by lymphedema include recurrent infections, skin changes, and symptoms of heaviness and numbness [12]. While physical distortion is characteristic of advanced lymphedema, even low-level swelling can cause a patient to be symptomatic and result in physical impairment [8] (Figure 1). Quality of life (QOL) may also be compromised due to emotional distress, anxiety and disturbance of body image accompanying the development of lymphedema [11]. The fear of developing lymphedema has been reported to influence survivors' function and activity, as those at-risk may alter their lifestyle and impose restrictions on their activity in hope of preventing the condition [13]. With survivorship from breast cancer increasing, attention to the QOL challenges that survivors face, such as lymphedema, is also increasing. Furthermore, patients with lymphedema have significantly more medical costs than those who do not have this condition. In a review of medical claims for 1877 breast cancer patients, Shih et al. reported that the costs for those with lymphedema were $14,877– $23,167 higher than were the claims for those patients who did not have lymphedema [14].

A surveillance approach to this condition is being strongly advocated for in the literature [15–17]. However, the hypothesis that early detection and early intervention can minimize lymphedema progression presently lacks the Level 1 evidence to support this approach. To date, the lack of a uniform approach to assess lymphedema has limited the level of accurate data necessary to test the premise that a surveillance approach should become the standard of care. This, in turn, has hindered the generation of Level 1 evidence that is needed to determine appropriate intervention for this condition. Standardization is imperative for surveillance programs to be designed in such a manner that data can be shared and generalized.

In this work we sought to emphasize the need for all providers involved in the care of breast cancer patients to be aware of the risk of lymphedema and the negative impact it has on their patients' QOL. We aimed to explore current controversies in the field of lymphedema following treatment for breast cancer, emphasize the need to generate Level 1 evidence regarding intervention, suggest the implementation of screening programs and encourage collaboration in the effort to develop a standardized approach to this dreaded side effect of breast cancer treatment.

2. METHODS

For the purposes of this critical review, an extensive literature research was conducted. Multiple websites and patient educational brochures were also utilized to assess the recommendations presently available to patients regarding lymphedema prevention, management, and treatment strategies.

3. FACTORS CONTRIBUTING to LYMPHEDEMA FOLLOWING TREATMENT for BREAST CANCER

ALND unequivocally increases the risk of developing lymphedema. Many reports cite that this vulnerability increases with the number of nodes excised, as well as with the number of positive nodes in the dissection [4, 5, 18–21]. Radiation is another treatment-related risk factor for lymphedema, with lymphedema risk rising when more nodal fields are radiated [19, 20, 22, 23, 24]. Post-operative infection is often not included in analyses on risk factors for lymphedema, but when considered, it has been reported as contributing to the risk of developing lymphedema [20, 25]. There has also been reference to lymphedema developing during treatment secondary to chemotherapy regimens [21, 24, 26]. The rationale for this association remains unclear and is a phenomenon that requires further study.

Many lifestyle risk factors appear on pamphlets and websites, cautioning patients with and without lymphedema to avoid repetitive activity, lifting weighted objects, having injections or blood drawn in the arm on the side of surgery and to use a compression sleeve for any air travel. However, to date, there is no robust data to support any of these activities as risk factors for developing lymphedema [27–29]. Although well intentioned, these warnings could potentially result in patients unnecessarily altering their lifestyle and decreasing their overall QOL [30]. In fact, there is an increasing body of data indicating that a gradually progressive exercise program does not increase the risk of lymphedema either for survivors with established lymphedema or for those considered to be at-risk [31–33]. Recent work by Schmidt et al. demonstrated that a slowly advanced weight lifting program did not increase the risk of lymphedema in breast cancer survivors. For those women with lymphedema, exercise was shown to decrease symptoms of lymphedema [34, 35]. This information is important, especially given the many and various health-related and QOL reasons women should exercise. Investigating the lifestyle risk factors that contribute to lymphedema is a research area ripe for study.

A high body mass index (BMI) at diagnosis is consistently cited as a risk factor for lymphedema development [21, 24, 36, 37]. Although BMI at diagnosis cannot be modified, these patients may benefit from close monitoring for lymphedema during their years of follow up. An unresolved question worthy of study is whether losing weight after breast cancer treatment decreases lymphedema risk, as post-treatment weight loss would be something survivors could pursue as a risk reduction strategy.

4. IMPACT of LYMPHEDEMA on QUALITY OF LIFE

Data abounds on the negative impact lymphedema following treatment for breast cancer has on a person's QOL [11, 38–41]. Lymphedema is frequently referred to as a "dreaded" and "feared" side effect of treatment [9, 42]. Body image can be profoundly affected as the limb becomes distorted, the sleeves in clothing no longer fit properly or a swollen finger prevents a wedding ring from being worn. Symptoms of heaviness in the upper quarter and difficulty using the limb for functional activities are routinely reported. Cormier et al. reported on the association of symptoms and lymphedema in a cohort of 269 breast cancer patients,

demonstrating that even a 5% volume difference significantly increased symptoms and compromised QOL [8].

The fear of developing lymphedema has also been reported [13]. This fear can influence how patients who have been treated for breast cancer approach activity during their survivorship years and can be a constant reminder of their disease. Although most lymphedema occurs in the first 3–4 years, long-term follow up reports show that edema development can present many years after that time [43]. In a 6-year follow up, Hayes et al. reported some new cases at that time, albeit much less than in the first 2 years [2]. Data from Armer et al.'s 60-month follow up demonstrated that cases of lymphedema continued to develop at 5 years [6]. The risk of developing lymphedema lasts for a lifetime [6], so this sense of vulnerability can be difficult for many patients to overcome.

5. UNRESOLVED CONTROVERSIES in the LYMPHEDEMA FIELD

Table 1 summarizes the main data from each of the sections described below (5.1 – 5.5).

5.1. Definition of Lymphedema Following Treatment For Breast Cancer

A significant and unresolved dilemma in the lymphedema field is the level of swelling considered to be clinically significant for lymphedema [6, 8, 44]. Reports by Cheville et al. and Tsai et al. illustrate this problem [45, 46]. The current lack of consensus regarding lymphedema definition contributes to the difficulty of obtaining uniformity in reports of incidence, risk factors, and intervention strategies [47].

Circumferential differences considered indicative of lymphedema vary from 1.0 cm to 3.0 cm [46, 48]. If changes in arm volume are utilized instead, a 200 ml difference is considered indicative of lymphedema [16, 46]. Edemas deemed to be significant by percent change have ranged from 3–20% [7, 46, 49]. The work of Armer et al. demonstrated how edema incidence varies widely within the same cohort when comparing a 2.0 cm circumferential difference, a 200 ml difference, a 10% volume difference and self-report [6].

In addition to defining the impact of lymphedema as an objective change in arm size, the work of many authors illustrates the role of assessing functional compromise and pain when evaluating a patient for lymphedema. Reports by Dawes et al., Tsauo et al. and Hormes et al. clearly illustrate that only addressing arm volume, without managing other symptoms, may not improve QOL [50–52]. Thus, there is a need for universal recognition that upper quarter symptoms, physical function, fear avoidance behavior, and QOL may need to be included in the definition of clinically significant lymphedema, helping to facilitate comparison of outcome data. Hence, it is our recommendation that adopting one of the well-validated questionnaires capable of assessing upper quarter function and pain should be considered in developing a uniform approach to evaluating lymphedema following treatment for breast cancer.

5.2. Measurement Methods

The different methods utilized to measure lymphedema are continually cited as a significant limitation when interpreting data from multiple studies [7–9, 44]. These measurement methods include circumferential tape measurement, water displacement, bioimpedance spectroscopy (BIS), perometry and self-report.

Utilizing a flexible tape to measure a circumferential difference between the affected and unaffected arm is convenient and cost-effective, but is subject to error if the technique of the examiners is not consistent [10]. Circumferential measurement has been referred to as "marginally accurate" [53]. Measurement by water displacement is based on Archimedes'

principle and has been cited as a reliable method [54]. Although it has been referred to as "the gold standard," reports by Deltombe et al. and Smoot et al. challenge this assumption [10, 55]. It has also been reported as messy and inappropriate for patients with open wounds on their arms [54]. It is also time-consuming because of the need to clean the equipment between patients amid a busy clinical setting [55–57]. BIS utilizes resistance to electrical current to assess interstitial fluid differences between a patient's arms, with the difference expressed as an impedance value of standard deviations from normative data (Figure 2). BIS is utilized in some settings, reported in several works and is considered a reliable and sensitive measurement method for detecting early changes in interstitial fluid [55, 58, 59]. However, this method may not be optimal for measuring late-stage lymphedema when much of the fluid has become fibrotic tissue. Additionally, BIS involves the continued expense of purchasing the costly electrodes that are required for each use. The Perometer is another instrument that ensures reliable and reproducible data for quantifying lymphedema as a volume change between arms (Figure 3). The utility of the Perometer has been well-documented and it is a device suited for a busy clinical setting that manages a large volume of patients each day [53, 60, 61]. It is, however, an expensive piece of equipment to purchase, requires a properly trained individual to conduct measurements, and necessitates a dedicated space in the clinic.

Many studies have utilized a patient's self-report of lymphedema as the method to assess incidence. Norman et al. published their results with confidence in a validated self-reporting tool [62]. Conversely, McLaughlin et al. found a patient's report of lymphedema "significantly discordant" when compared to objective measurement of lymphedema [4]. The work of Czerniec et al. supports this discrepancy, finding that self-report was only "moderately" reliable when compared to objective measurement [63]. It is clear that, without consensus on a standard approach to measure lymphedema, progress in this field will continue to be thwarted.

5.3. Quantification Methods

Lymphedema is very frequently quantified as an absolute volume change, typically a 200 ml difference between arms demonstrated by water displacement or a 1.0 – 3.0 cm difference assessed by tape measurement [4, 5, 46, 48]. Absolute volume measurement lacks specificity and is inherently flawed because the magnitude of absolute volume change depends upon the body size of each patient [64]. A relative volume difference between the affected and the unaffected arm expressed as a percent change is a more reliable method as it does not vary with body size and shape [64]. We advocate that volume should only be expressed as a relative volume difference between arms, and that the use of an absolute difference, expressed in centimeters or milliliters should be abandoned.

An ideal quantification method for lymphedema in patients who undergo unilateral breast surgery would utilize percent change between arms with incorporation of pre-operative measurements. Ancukiewicz et al. developed a mathematical model to quantify volume changes in the affected arm as compared to the unaffected arm, known as the relative volume change (RVC) formula [65]. This formula compares the ipsilateral arm to the contralateral arm at follow-up, taking into account a patient's pre-operative measurements. Specifically, Equation 1: $\mathrm{RVC}=(A_2/U_2)/(A_1/U_1)-1$, where A represents the ipsilateral arm, and U represents the contralateral arm which serves as a control for arm volume changes that may be unrelated to lymphedema, including fluctuations in patient weight. The numeral 1 indicates the pre-operative measurement and numeral 2 refers to the follow-up measurement. The use of RVC to quantify lymphedema has been shown to have the reliability and specificity required for accurate reporting [64, 65].

Lymphedema assessment remains particularly challenging for patients with bilateral breast cancer as they may be bilaterally at-risk for lymphedema and lack a control arm to use for comparison. An equation based on weight adjustment has been developed to calculate unilateral arm volume changes for detection and monitoring of lymphedema in patients who undergo bilateral breast surgery. Weight-adjusted arm volume change (WAC) can be calculated according to Equation 2: $\mathrm{WAC}=(A2^{*}W1)/(W2^{*}A1)-1$ where A1 is pre-operative arm volume on the affected side and A2 is post-operative arm volume on the affected side, and W1, W2 are the patient's weights at these time points (unpublished data). This formula is applicable for quantifying lymphedema in patients who undergo bilateral breast surgery since it does not rely on the contralateral arm volume as a control. The research community still needs to come to agreement on this topic. Until consensus is reached regarding methods of measurement and quantification, the problem of data incongruence will continue.

5.4. Appropriate Timing of Measurement

In addition to the varied methods of defining, measuring, and quantifying lymphedema, there is a lack of consistency with regard to the timing and sequencing of screening. The necessity of obtaining pre-operative arm volume measurements has been well demonstrated, as it allows for the normal asymmetry which may exist between arms to be considered when assessing post-operative changes [6, 49, 66]. The analysis of the pre-operative baseline perometer measurements of 677 patients at our institution demonstrated that 11.2% of patients present with a >5% pre-operative difference in arm volume between arms, and 1.5% of patients present with a >10% pre-operative difference in arm volume between arms (Figure 4) [65]. The National Lymphedema Network has recommended that pre-operative assessment be done routinely [67]; however, reports on lymphedema incidence that do not have baseline data continue to be published [68, 69].

5.5. Optimal Management Strategies

Complex Decongestive Therapy (CDT) has been cited as the recommended treatment for lymphedema following treatment for breast cancer [70, 71]. It consists of skin care, manual lymphatic drainage, compression strategies and exercise. Although there have been small trials aimed at assessing this type of intervention, no Level 1 evidence exists to support it. A systematic review by Lasinski et al. demonstrated that although CDT was considered to be effective in reducing swelling, further study was needed to determine if the components of CDT could be effective as stand-alone treatments [72].

Devoogdt et al. pre-operatively enrolled 160 breast cancer patients and randomized them into two groups for post-operative management. They reported that manual drainage did not have a significant impact on edema development when compared to exercise and precautionary advice [73]. Stout Gergich et al. assessed 196 patients pre-operatively and followed them post-operatively using the Perometer to evaluate for lymphedema. The 46 patients whose arm volume increased to 3% postoperatively were reported to be successfully managed with use of a compression sleeve and no CDT. Importantly, this trial utilized a small cohort of patients and did not involve randomization [49]. The recommendations of an expert panel led by Partsch et al. in 2010 were that more clinical trials are required to adequately assess the use of compression to treat lymphedema [74].

Pneumatic compression devices have been another treatment modality utilized and reported over the years. However, the evidence regarding the utility of this device with respect to long-term outcomes is not robust [75, 76]. Low-level laser treatment has also been suggested, but lacks the data to support its use [77]. In 2009, Devoogdt et al. reviewed the treatment options for lymphedema and concluded that high quality, well-powered

randomized trials that included symptoms, QOL and large cohorts are needed to inform clinical decision making when developing a plan of care for these patients [78].

6. A PROSPECTIVE SURVEILLANCE APPROACH

The prospective screening of medical conditions to allow for early intervention has become the standard of care for many diseases, such as breast and colorectal cancer. Such surveillance has been increasingly advocated for breast cancer patients who are at-risk for lymphedema. The 2012 National Lymphedema Network Position Paper, "Screening and Early Detection of Breast Cancer-Related Lymphedema: The Imperative," [79] addresses the rationale for lymphedema screening as a method to detect and subsequently treat lymphedema at an early, even subclinical, stage so as to "reverse the progression to chronic, irreversible lymphedema." If early identification of increased fluid in the arm (by BIS, volume or circumference) allows a patient to be identified and managed in a manner that minimizes lymphedema progression, then the screening for lymphedema would be advantageous. As outlined in a recent report by Cheville et al. this model has yet to be fully evaluated for its application, cost and outcome [80]. Should it be for all survivors or targeted only for those patients who are at high risk for developing lymphedema? In 2011, Stout et al. reported on the direct costs involved with a surveillance approach, compared to the traditional approach of treating lymphedema after it has developed [81]. Using a 2009 Medicare physicians' fee schedule, the projected cost of managing early stage lymphedema, per patient per year was $636.19, compared to $3,124.92 per patient per year in a more traditional manner. Thus, a surveillance approach to lymphedema through prospective screening would not only have a positive impact on the patient, but also reduce financial burden on the health care system.

It has been our experience that a lymphedema screening program can be successfully implemented even in a busy clinical environment. Such a screening program, in which patients are continuously monitored for arm volume changes via perometer measurements pre-operatively and every few months post-operatively, was implemented at our institution in 2005. Since the screening program's initiation in 2005, we have screened 3110 patients at their pre-operative baseline. Data from the first few years allowed us to assess the natural history of lymphedema, evaluate rates of progression, and determine the relative volume change to test for appropriate intervention. With this necessary information, we were able to design and implement a prospective clinical lymphedema screening trial in tandem with a randomized-controlled Phase III intervention trial (ClinicalTrials.gov Identifiers: NCT01521741 and NCT00959985, respectively).

The primary objective of the lymphedema screening trial is to identify patients with early lymphedema who can subsequently be enrolled in the randomized intervention trial. The intervention trial is designed to generate Level 1 evidence regarding early intervention and optimal treatment strategies. Subjects on the clinical lymphedema screening trial are assessed for lymphedema objectively via perometry to assess limb volume changes and subjectively via a questionnaire to evaluate symptoms, arm function and QOL. The questionnaire is a compilation of questions from the following previously validated assessment tools: the Lymphedema Breast Cancer Questionnaire (LBCQ) [12]; the Disability of the Arm, Hand and Shoulder (DASH) [82]; the Survey of Arm Care Following Breast Cancer [83]; and the Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B) [84]. Assessments occur pre-operatively, at the completion of chemotherapy and/or radiation therapy, and every 3–8 months thereafter. This framework will allow us to analyze data on symptoms, function, fear of edema and QOL in a large sample size.

When a patient on the clinical lymphedema screening trial exhibits a RVC≥5% at two consecutive visits that are one to two months apart, they are recruited into a Phase III randomized-controlled intervention trial designed to produce Level 1 evidence by testing the hypothesis that early treatment of low-level increases in arm volume after treatment for breast cancer will reduce the likelihood of lymphedema progression. One of the primary objectives of the trial is to evaluate the efficacy of early intervention using compression garments for low-level arm volume changes (RVC 5–<10%) and using compression garments with or without night compression bandaging for moderate-level arm volume changes (RVC 10–<20%). Another primary objective is to assess symptom clusters, treatment adherence, upper extremity function, fear avoidance behavior, and QOL as they are associated with varying degrees of lymphedema.

Specifically, participants in Group 1 are randomized to either exercise or exercise with compression. Participants in Group 2 are randomized to either exercise with compression or exercise with compression plus night bandaging. The study endpoints for Groups 1 and 2 are time to progression of RVC ≥10% and failure to regression of RVC<10% at weeks 8 and 12. Figure 5 displays the intervention trial schema.

The sample size for Groups 1 and 2 of the intervention trial was calculated to provide 85% power to detect treatment response differences using 2-sided Fisher exact test, with an overall type I error of 0.05. The sample size for the 5–<10% group is 208 subjects. The sample size for the 10–<20%" group is 128 subjects. Thus, the total sample size for the intervention trial is 336 subjects. Based upon screening data collected thus far, 7446 patients must be screening in order to achieve a total sample size of N=336 on the intervention trial. To date, since its initiation in 2009, the screening trial has accrued 1028 subjects, with a 72% accrual rate for 2012 (293 enrolled of 408 eligible). The 2012 accrual rate most accurately represents current accrual, since inclusion criteria have been modified since trial initiation. As the screening trial serves as a conduit for the intervention trial, the sample size for the screening trial was calculated based upon the sample size for the intervention trial. We have not yet reached target accrual for the intervention trial, but have recently expanded to multiple other institutions and continue to actively accrue eligible participants.

Our two-part screening and intervention trial is an example of how a surveillance approach can serve as a conduit for a Phase III trial to assess the efficacy of early intervention and identify optimal treatment interventions. To our knowledge, there are no other prospective randomized-controlled trials in a cohort of this size assessing early intervention. More screening programs and clinical trials are needed to respond to the call of researchers and organizations such as the National Lymphedema Network to generate rigorous research that will yield Level 1 evidence for "Best Practices in surveillance and early intervention for post-breast cancer lymphedema" [79].

7. CONCLUSION

Lymphedema following treatment for breast cancer is a major concern for most patients who experience it, and for many patients who fear its development. The challenges that patients with lymphedema face on a daily basis are further exacerbated by the lack of a standard approach to measure, quantify and define their condition. Inconsistencies also persist regarding the appropriate timing and type of treatment intervention that should be the standard of care. Not only do such discrepancies significantly inhibit the ability to compare data across studies and to develop a universal understanding of lymphedema incidence, but they also limit our ability to effectively and optimally treat patients who suffer from lymphedema. We endorse a unified effort among providers caring for breast cancer patients to work together to arrive at a consensus regarding these dilemmas.

Early detection and intervention have been increasingly advocated to prevent lymphedema progression; however, Level 1 evidence to support this hypothesis has yet to be generated. We support the design and implementation of prospective surveillance programs in conjunction with prospective, randomized Phase III trials capable of generating Level 1 evidence regarding the efficacy of early intervention and appropriate treatment strategies. To accrue a sample size of significance and to include patients from diverse populations, national and/or international collaboration is pivotal. Such collaboration will allow healthcare professionals to provide breast cancer patients who suffer from or who are at-risk for lymphedema with clinical decisions grounded in robust evidence that should ultimately guide clinical practice on a universal level.

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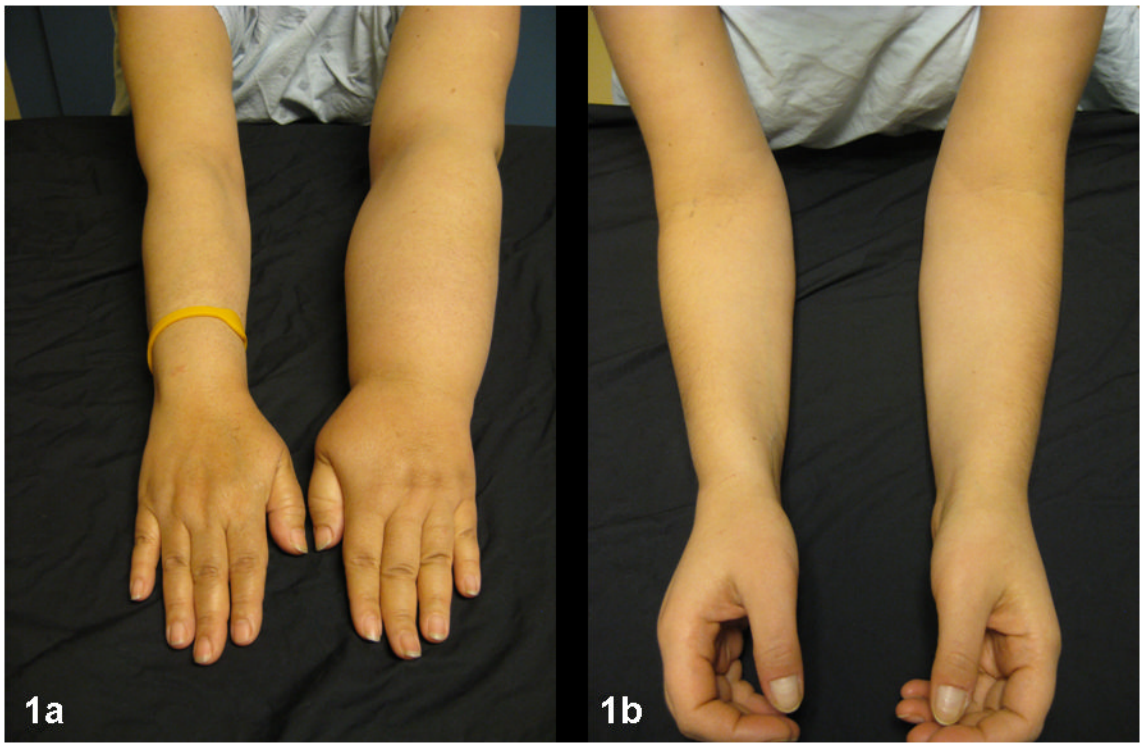

Figure 1.
(a) Advanced lymphedema. By perometry, this woman's left arm is 44% larger than her right and is physically distorted, which makes fitting into clothing with sleeves a challenge. The weight of the arm results in difficulty with functional reaching activities. (b) Low-level edema. This women's left arm is 9% larger than her right arm. Despite her low-level swelling, she reports symptoms of discomfort from ""fullness and tightness." She verbalizes a great fear that the swelling will increase.

Figure 2.
Lymphedema measurement by bioimpedance spectroscopy (BIS). BIS utilizes electrical current to assess interstitial fluid differences between arms and has been shown to be an effective method for detecting early changes in interstitial fluid. Source: http://german.l-dex.com/what-is-l-dex/.

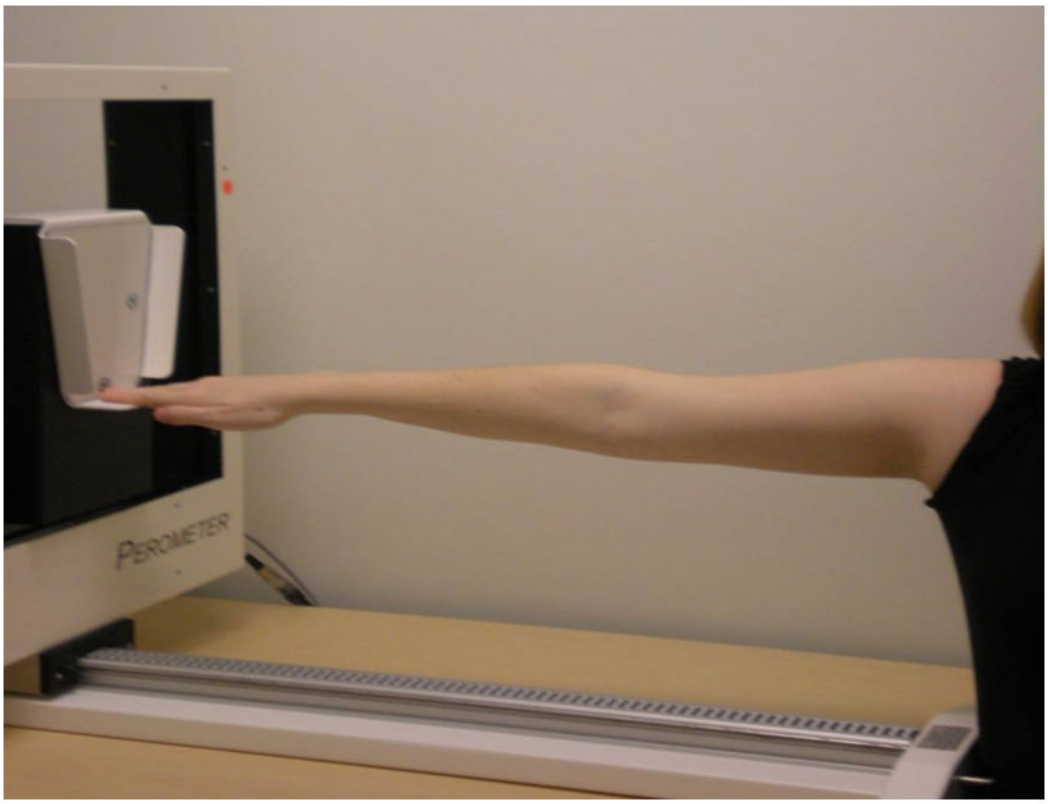

Figure 3.
Lymphedema measurement by perometry. The Perometer is a device that measures patient arm volumes with accuracy and inter-rater reliability, allowing for the valid quantification of lymphedema.

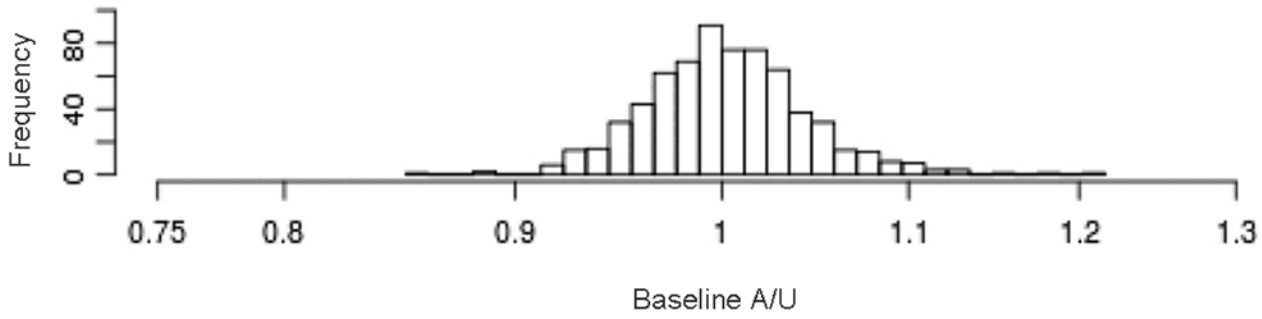

Figure 4.
Histogram assessing pre-operative volume differences between arms among a cohort of 677 patients at our institution. 11.2% of patients presented with a >5% pre-operative difference between their arms [59].

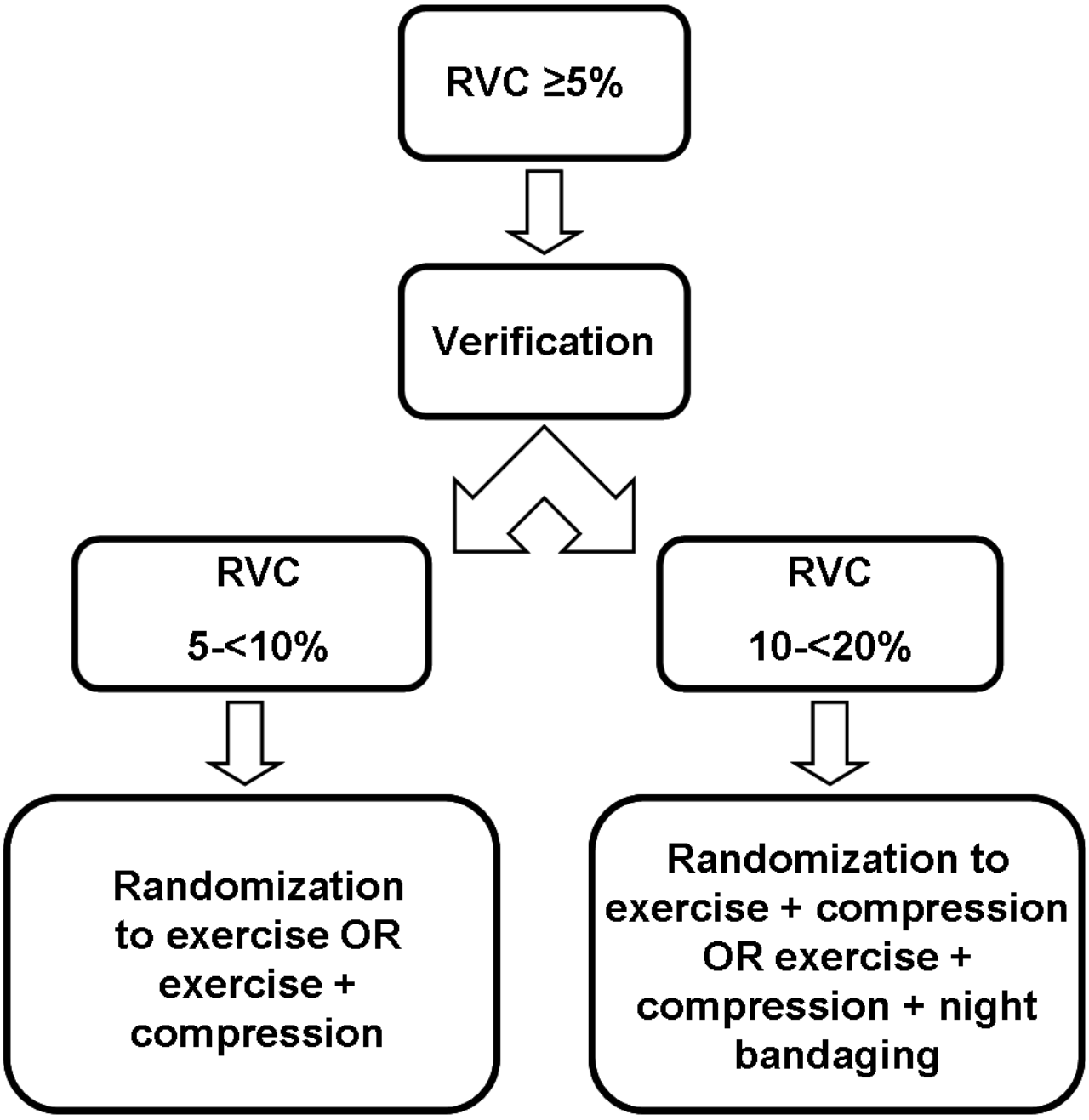

Figure 5.
Schema for a prospective, randomized Phase III lymphedema intervention trial (ClinicalTrials.gov Identifier: NCT00959985). This trial is being conducted at our institution and is testing the hypothesis that early treatment of low-level increases in arm volume after treatment for breast cancer reduces the likelihood of lymphedema progression.

Table 1

Summary of the various methods used to define, measure, quantify, and manage lymphedema following treatment for breast cancer, as well as the appropriate timing of assessment.

Topic	Details	References	
Definition	Circumferential Difference	1.0 – 3.0 cm	Tsai 2009 [46], Wernicke 2011 [48]
	Volume Difference	200 ml	Boccardo 2009 [16], Tsai 2009 [46]
	Percent Difference	3 – 20%	Armer 2009 [7], Tsai 2009 [46], Stout Gergich 2008 [49]
	Self-Report		Armer 2010 [6], Norman 2009 [62]
Measurement	Tape Measurement	Arm circumference	Deltombe 2007 [10], Jain 2010 [53]
	Water Displacement	Volume	Deltombe 2007 [10], Tewari 2008 [54], Smoot 2011 [55], Fu 2009 [56], Ridner 2007 [57]
	Bioimpedance Spectroscopy	Impedance value	Smoot 2011 [55], Ward 2011 [58], Ridner 2009 [59]
	Perometry	Volume	Jain 2010 [53], Stanton 1997 [60], Petlund 1991 [61]
	Self-Report		McLaughlin 2008 [4], Norman 2009 [62], Czerniec 2010 [63]
Quantification	Absolute Volume Difference	ml or cm difference	McLaughlin 2008 [4], Ashikaga 2010 [5], Tsai 2009 [46], Wernicke 2011 [48]
	Relative Volume Difference	Percent difference between arms	Ancukiewicz 2012 [64]
	Relative Volume Change (RVC)	Percent change between arms as compared to baseline	Ancukiewicz 2012 [64], Ancukiewicz 2011 [65]
Timing	Pre-operative Arm Volume Measurements	Accounts for any normal asymmetry between arms	Armer 2010 [6], Stout Gergich 2008 [49], Ancukiewicz 2011 [65], Harris 2001 [66], NLN Position Paper 2011 [67]
	Continuous Post-operative Screening	Prospective surveillance may allow for early detection and treatment, but has not been fully evaluated for its application, cost and outcome	NLN Position Paper 2012 [79], Cheville 2012 [80], Stout 2011 [81]
Management	Complex Decongestive Therapy (CDT)	Recommended and considered effective; lacks Level 1 evidence to support its use; further study needed to determine efficacy as stand-alone treatment	Vignes 2011 [70], Forner-Cordero 2009 [71], Lasinski 2012 [72]
	Manual Lymphatic Drainage	No signficant impact on edema development when compared to exercise and precautionary advice	Devoogdt 2011 [73]
	Compression Sleeve without CDT	Assessed in a small cohort study without randomization; further study needed	Stout Gergich 2008 [49], Partsch 2010 [74]
	Pneumatic Compression	No robust evidence about long-term outcomes	Fife 2012 [75], Wilburn 2006 [76]
	Low-Level Laser Treatment	Lacks data to support its use	Omar 2012 [77]