

# Preoperative Assessment Enables the Early Diagnosis and Successful Treatment of Lymphedema

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**BACKGROUND.** The incidence of breast cancer (BC)-related lymphedema (LE) ranges from 7% to 47%. Successful management of LE relies on early diagnosis using sensitive measurement techniques. In the current study, the authors demonstrated the effectiveness of a surveillance program that included preoperative limb volume measurement and interval postoperative follow-up to detect and treat subclinical LE.

**METHODS.** LE was identified in 43 of 196 women who participated in a prospective BC morbidity trial. Limb volume was measured preoperatively and at 3-month intervals after surgery. If an increase >3% in upper limb (UL) volume developed compared with the preoperative volume, then a diagnosis of LE was made, and a compression garment intervention was prescribed for 4 weeks. Upon reduction of LE, garment wear was continued only during strenuous activity, with symptoms of heaviness, or with visible swelling. Women returned to the 3-month interval surveillance pathway. Statistical analysis was a repeated-measures analysis of variance by time and limb ( $P \leq .001$ ) comparing the LE cohort with an age-matched control group.

**RESULTS.** The time to onset of LE averaged 6.9 months postoperatively. The mean ( $\pm$ standard deviation) affected limb volume increase was 83 mL ( $\pm$ 119 mL; 6.5%  $\pm$  9.9%) at LE onset ( $P = .005$ ) compared with baseline. After the intervention, a statistically significant mean 48 mL ( $\pm$ 103 mL; 4.1%  $\pm$  8.8%) volume decrease was realized ( $P < .0001$ ). The mean duration of the intervention was 4.4 weeks ( $\pm$ 2.9 weeks). Volume reduction was maintained at an average follow-up of 4.8 months ( $\pm$ 4.1 months) after the intervention.

**CONCLUSIONS.** A short trial of compression garments effectively treated subclinical LE. *Cancer* 2008;112:2809–19. Published 2008 by the American Cancer Society.\*

**KEYWORDS:** breast cancer, lymphedema, early detection, physical therapy, early intervention, compression, optoelectronic volumetry, subclinical lymphedema.

**B**reast cancer (BC)-related lymphedema (LE) is a chronic condition that diminishes quality of life and contributes to impairments in limb range of motion (ROM), loss of strength, and functional limitations with activities, such as lifting and reaching.<sup>1–3</sup> The frequency of BC-LE is approximately 33% to 47% after axillary lymph node dissection (ALND) and radiation therapy (XRT)<sup>4–6</sup> and 4% to 17% after sentinel lymph node biopsy (SLNB) and XRT.<sup>5,7–10</sup> Other risk factors associated with the onset of BC-related LE include obesity,<sup>11</sup> postoperative infection,<sup>12</sup> venapuncture<sup>9</sup> to the affected extremity, race, and level of hand use.<sup>9,13,14</sup>

Clinically apparent LE presents as visible or palpable tissue swelling and may be associated with a perception of fullness and heaviness in the limb.<sup>15–17</sup> The progressive nature of LE requires life-long,

costly treatment to control the condition and to prevent associated secondary impairments, such as infection, shoulder morbidity, and pain.<sup>13,18,19</sup>

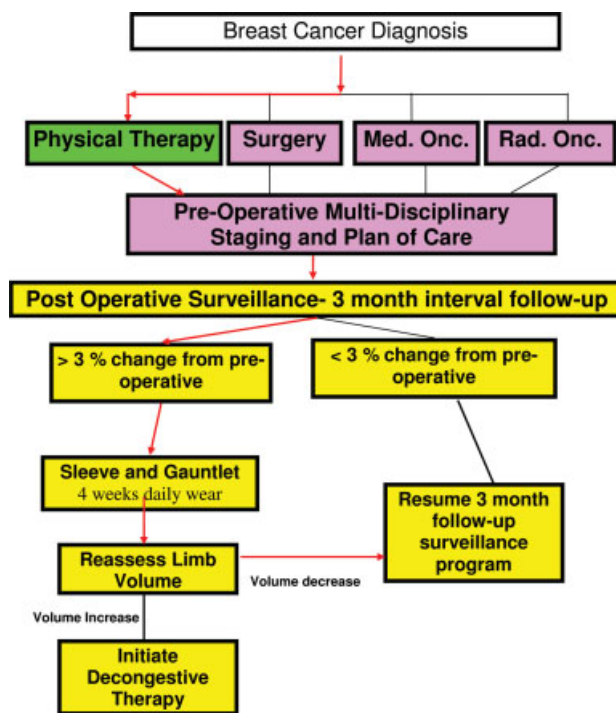
Upper limb (UL) volume measurement is used routinely to identify LE. Limb volume can be measured by using circumferential limb girth,<sup>20</sup> water displacement,<sup>21</sup> optoelectronic perometry,<sup>22</sup> and bioelectrical impedance.<sup>23</sup> These methods are reliable and valid to accurately quantify and monitor LE; however, significant variability exists in their use among research trials, prohibiting valid comparison of incidence reports and treatment outcomes and, thus, inhibiting extrapolation to the greater population.<sup>9,21,24–30</sup>

Further disparity exists among the criteria used to diagnose LE in clinical trials. Various diagnostic definitions exist, including a difference between limbs of >200 mL, >8% to 10%, and >2 cm and/or subjective reports of limb heaviness.<sup>24,29,31–34</sup> Armer and Stewart report that these criteria are not interchangeable and cite 10% of limb volume change from baseline as the most accurate threshold to diagnose clinically apparent LE.<sup>35</sup> However, this is not sufficiently discriminatory for diagnosis, because it neglects to capture up to 150 mL of subclinical fluid accumulation in the tissue.<sup>36,37</sup> Detection and management of LE at this early stage may prevent the condition from progressing to a chronic, disabling stage<sup>18,38</sup> and may enable a more cost-effective, conservative intervention.

The objective of the current case-control study was to investigate the efficacy of a surveillance method for the diagnosis and management of subclinical LE in patients with early-stage BC. We hypothesized that, on diagnosis of subclinical LE, a light-grade compression garment worn daily for a short trial would alleviate subclinical LE and eventually could be discontinued.

## MATERIALS AND METHODS

A large, observational, Institutional Review Board-approved study (National Institutes of Health Protocol 02-CC-0044; National Naval Medical Center [NNMC] Protocol B01-052) that was conducted at the NNMC Breast Care Center (Bethesda, Md) from 2001 to 2006 used a surveillance model to identify BC treatment-related morbidity. All women with newly diagnosed, unilateral, early-stage BC (stage I-III) were screened by a physical therapist preoperatively to determine eligibility. Patients were excluded if they had a previous history of BC, bilateral BC, or prior severe trauma or surgery of the affected UL. All women who met the inclusion criteria and agreed to



**FIGURE 1.** Clinical pathway for the Prospective Physical Therapy Model of Care. Med. indicates medical; Onc., oncology; Rad., radiation.

participate were consented before participation ( $n = 196$  patients). Bilateral UL strength, ROM, and volume were assessed at the preoperative visit and reassessed at 1 month, 3 months, 6 months, 9 months, 12 months, and 18 months postoperatively. The surveillance model clinical pathway is illustrated in Figure 1.

The inclusion criterion for this compression intervention was a diagnosis of subclinical LE. Diagnostic criteria for LE included a volume increase  $\geq 3\%$  in the affected UL compared with the patient's preoperative measurement and with consideration of the contralateral limb volume changes. The threshold for diagnosis was set below the criteria currently outlined in the medical literature to facilitate early treatment of LE before a clinically apparent onset. Women were excluded from the intervention if they experienced an onset of LE related to an infection or blood clot ( $n = 5$  patients).

Through the surveillance trial, 43 women ages 34 to 82 years (mean  $\pm$  standard deviation [SD],  $55.3 \pm 12.1$  years) were diagnosed with subclinical LE. An age-matched control group (CG) of women without LE was selected from the trial for comparison. The CG was comprised of 43 women ages 33 to 81 years (mean  $\pm$  SD,  $53.5 \pm 12.3$  years). The physical characteristics of these groups are outlined in Table 1. The groups were significantly different

**TABLE 1**  
**Lymphedema Group and Control Group Physical Characteristics**

| Characteristic                        | Mean±SD             | Range      | P*                |
|---------------------------------------|---------------------|------------|-------------------|
| Age, y                                |                     |            | .965              |
| Control group                         | 53.4 ± 12.3         | 33–81      |                   |
| Lymphedema group                      | 55.3 ± 12.1         | 34–82      |                   |
| Baseline weight, kg                   |                     |            | .530 <sup>†</sup> |
| Control group                         | 69.7 ± 16           | 46.7–137.9 |                   |
| Lymphedema group                      | 71.8 ± 14.3         | 48.1–105.3 |                   |
| Weight at intervention, kg            |                     |            | .364              |
| Control group                         | 69.9 ± 15.4         | 44.5–138.4 |                   |
| Lymphedema group                      | 72.8 ± 14.7         | 48.1–117.1 |                   |
| Weight at follow-up, kg               |                     |            | .277              |
| Control group                         | 70 ± 15.6           | 44–134.8   |                   |
| Lymphedema group                      | 73.5 ± 14.6         | 47.4–113.4 |                   |
| Height, m                             |                     |            | .017*             |
| Control group                         | 1.66 ± 0.06         | 1.52–1.75  |                   |
| Lymphedema group                      | 1.62 ± 0.06         | 1.52–1.75  |                   |
| 80% Arm length, cm                    |                     |            | .977              |
| Control group                         | 41.6 ± 3.3          | 33.9–49.6  |                   |
| Lymphedema group                      | 41.7 ± 2.7          | 36–47.2    |                   |
| BMI at baseline, kg/m <sup>2</sup>    |                     |            | .135 <sup>†</sup> |
| Control group                         | 25.4 ± 6            | 17.1–55.6  |                   |
| Lymphedema group                      | 27.2 ± 5            | 20–39.1    |                   |
| BMI at follow-up, kg/m <sup>2</sup>   |                     |            | .051 <sup>†</sup> |
| Control group                         | 25.6 ± 5.9          | 16.2–54.3  |                   |
| Lymphedema group                      | 27.9 ± 5.1          | 19.1–40.3  |                   |
| Affected limb:                        | No. of patients (%) |            | .009 <sup>‡</sup> |
| Right                                 |                     |            |                   |
| Control group                         | 29 (67)             |            |                   |
| Lymphedema group                      | 16 (37.2)           |            |                   |
| Left                                  |                     |            |                   |
| Control group                         | 14 (33)             |            |                   |
| Lymphedema group                      | 27 (62.8)           |            |                   |
| Dominant limb:                        | No. of patients (%) |            | .018 <sup>‡</sup> |
| Right                                 |                     |            |                   |
| Control group                         | 17 (40)             |            |                   |
| Lymphedema group                      | 28 (65.1)           |            |                   |
| Left                                  |                     |            |                   |
| Control group                         | 26 (60)             |            |                   |
| Lymphedema group                      | 15 (34.9)           |            |                   |
| BMI classification:                   | No. of patients (%) |            |                   |
| Normal: <25 kg/m <sup>2</sup>         |                     |            |                   |
| Control group                         | 23 (53.5)           |            |                   |
| Lymphedema group                      | 15 (34.9)           |            |                   |
| Overweight: 25–29.9 kg/m <sup>2</sup> |                     |            |                   |
| Control group                         | 16 (37.2)           |            |                   |
| Lymphedema group                      | 15 (34.9)           |            |                   |
| Obese: >30 kg/m <sup>2</sup>          |                     |            |                   |
| Control group                         | 4 (9.2)             |            |                   |
| Lymphedema group                      | 13 (30.2)           |            |                   |

SD indicates standard deviation; BMI, body mass index.

\*  $P < .05$  is significant with all interval data tested by univariate analysis of variance (ANOVA) at baseline between groups.<sup>†</sup> Weight and BMI were tested by repeated-measures ANOVA (baseline, onset of intervention, and follow-up).<sup>‡</sup>  $P < .05$  is significant with nominal data tested by the chi-square test.

physically for height (mean ± SD,  $1.66 \pm 0.06$  meters hand dominance, and affected extremity ( $P \leq .05$ ).

Table 2 shows the BC-related characteristics of the lymphedema group (LG) and the CG. No randomization occurred, because as this was a population-based morbidity trial. Women were included in the LG upon LE diagnosis. Therefore, the CG highlights treatment-based differences between the groups that may be associated with LE onset. The reference periods for the CG were based on their 3-month interval follow-up at 6 months, 9 months, and 12 months to closely approximate the measurement times of the LG. We classified lymph node dissection as only SLNB (CG,  $n = 0$  patients; LG,  $n = 5$  patients), ALND (CG,  $n = 36$  patients; LG,  $n = 35$  patients), or none (CG,  $n = 7$  patients; LG,  $n = 3$  patients). Patients with positive SLNB who went on to undergo completion ALND were included in the ALND group.

Measurements for both ULs were taken in a standard position (Fig. 2A,B) with the Perometer (Pero-System Messgerate, Wuppertal, Germany).<sup>22</sup> UL volume was calculated by using 80% of the total limb length, which was measured from the ulnar styloid process to the tip of the acromion for standardization. Body weight was recorded at each visit to control for weight change.

### Early Intervention

When women were diagnosed with LE, a conservative compression intervention was introduced. We hypothesized that light-grade compression garments worn daily for a short trial would alleviate subclinical LE and eventually could be discontinued. The garment provided was a Jobst (BSN-Jobst, Inc., Charlotte, NC) ready-made, 20- to 30-mm Hg compression sleeve and gauntlet fitted by the physical therapist. Two patients required custom-fitted garments because their limbs exceeded in length the size range of ready-made garments. Garments were prescribed for daily wear, and women were advised to follow-up for repeated measures in 1 month. No activity limitations were placed on the patients for the duration of the intervention.

At follow-up, when limb volume decreased as indicated by the Perometer, women were advised to continue wearing the garment only when completing strenuous exercise or activity, during air travel, with symptoms of heaviness, or if visible swelling appeared.<sup>39–41</sup> Women were instructed to follow-up at their next interval 3 month surveillance visit for repeated measures or sooner if symptoms were exacerbated.

**TABLE 2**  
Control Group and Lymphedema Group: Breast Cancer-related Characteristics

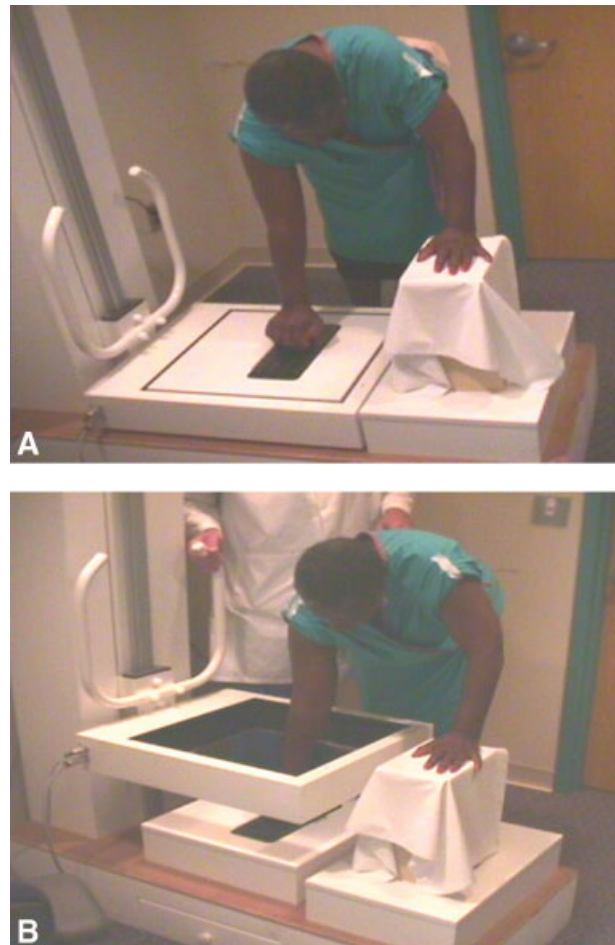
| Characteristic              | No. of patients (%) |                  | P     |
|-----------------------------|---------------------|------------------|-------|
|                             | Control group       | Lymphedema group |       |
| Type of BC                  |                     |                  |       |
| DCIS                        | 8 (18.6)            | 5 (11.6)         | .128  |
| IDC                         | 26 (60.5)           | 16 (37.2)        |       |
| DCIS and IDC                | 6 (14)              | 15 (34.9)        |       |
| Other                       | 3 (7)               | 7 (16.1)         |       |
| Stage of BC                 |                     |                  |       |
| 0                           | 8 (18.6)            | 3 (7)            | .024* |
| I                           | 16 (37.2)           | 12 (27.9)        |       |
| II                          | 14 (32.5)           | 23 (53.5)        |       |
| III                         | 5 (11.6)            | 5 (11.6)         |       |
| Surgery                     |                     |                  |       |
| MRM                         | 21 (48.8)           | 19 (44.2)        | .522  |
| BCT                         | 21 (48.8)           | 24 (55.8)        |       |
| Lymph node dissection       |                     |                  |       |
| None                        | 7 (16.3)            | 3 (7)            | .037* |
| ALND                        | 36 (83.7)           | 35 (81.4)        |       |
| SLNB                        | 0 (0)               | 5 (11.6)         |       |
| Radiotherapy                |                     |                  |       |
| No                          | 14 (32.6)           | 10 (23.3)        | .336  |
| Yes                         | 29 (67.4)           | 33 (76.7)        |       |
| Hormone therapy             |                     |                  |       |
| No                          | 10 (23.3)           | 13 (30.2)        | .852  |
| Yes                         | 33 (76.7)           | 30 (69.8)        |       |
| Chemotherapy                |                     |                  |       |
| No                          | 24 (55.8)           | 14 (32.6)        | .013* |
| AC                          | 16 (37.2)           | 15 (34.9)        |       |
| TAC                         | 2 (4.7)             | 13 (30.2)        |       |
| Other                       | 1 (2.3)             | 1 (2.3)          |       |
| Seroma                      |                     |                  |       |
| No                          | 39 (90.7)           | 34 (79.1)        | .132  |
| Yes                         | 4 (9.3)             | 9 (20.9)         |       |
| Axillary web syndrome       |                     |                  |       |
| No                          | 36 (83.7)           | 28 (65.1)        | .048* |
| Yes                         | 7 (16.3)            | 15 (34.9)        |       |
| No. of lymph nodes sampled  |                     |                  | .100† |
| Mean ± SD, %                | 10.9 ± 9.9          | 14.5 ± 9.8       |       |
| Range                       | 0–37                | 1–48             |       |
| Risk/lymph node sampled‡    |                     |                  | .112  |
| Mean ± SD, %                | 32 ± 29.7           | 42.4 ± 29.7      |       |
| Range                       | 0–111               | 0–144            |       |
| No. of positive lymph nodes |                     |                  | .320† |
| Mean ± SD, %                | 1.2 ± 4.4           | 2.4 ± 6.2        |       |
| Range                       | 0–28                | 0–37             |       |

BC indicates breast cancer; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; MRM, modified radical mastectomy; BCT, breast-conserving therapy; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; AC, doxorubicin, and cyclophosphamide; TAC, docetaxel (taxotere), doxorubicin, and cyclophosphamide; SD, standard deviation.

\*  $P \leq .05$  is significant with nominal data tested using the chi-square test and ordinal data tested using the Fisher exact test.

† Between-group differences were tested by univariate analysis of variance with  $P \leq .05$  considered statistically significant.

‡ See Paskett 2007.<sup>14</sup>



**FIGURE 2.** (A and B) Standardized position for Perometer upper extremity measurement.

**TABLE 3**  
Time to Lymphedema Diagnosis, Intervention, and Follow-up

| Variable                       | LE group only |       |
|--------------------------------|---------------|-------|
|                                | Mean ± SD     | Range |
| Time to diagnosis of LE, mo*   | 6.9 ± 4.3     | 1–18  |
| Duration of intervention, wk   | 4.4 ± 2.9     | 2–12  |
| Postintervention follow-up, mo | 4.8 ± 4.1     | 2–24  |

LE indicates lymphedema; SD, standard deviation.

\* Onset of intervention.

**Statistical Analysis**

Statistical analyses were performed using SPSS software (version 15.0; SPSS Inc., Chicago, Ill). A repeated-measure 2 (LG vs CG) × 3 (baseline, onset of intervention, and follow-up) analysis of variance (ANOVA) tested whether the means of the dependent variables (affected limb volume and percent limb

**TABLE 4**  
Comparison of Upper Limb Volume Changes (in mL and %) Between the Control and Lymphedema Groups at Baseline, Onset of Intervention, and Follow-up

| Variable              | Control group: Mean $\pm$ SD |                |               | Lymphedema group: Mean $\pm$ SD |              |               | P     |
|-----------------------|------------------------------|----------------|---------------|---------------------------------|--------------|---------------|-------|
|                       | UL volume, mL                | Change, mL     | Change, %     | UL volume, mL                   | Change, mL   | Change, %     |       |
| Unaffected UL volume  |                              |                |               |                                 |              |               |       |
| Baseline              | 1253 $\pm$ 295               |                |               | 1315 $\pm$ 344                  |              |               | .375  |
| Onset of intervention | 1255 $\pm$ 304               | 2 $\pm$ 96     | 0.2 $\pm$ 7.2 | 1328 $\pm$ 355                  | 13 $\pm$ 76  | 1.1 $\pm$ 6.7 |       |
| Follow-up             | 1252 $\pm$ 294               | -1.3 $\pm$ 112 | 0.2 $\pm$ 8.7 | 1341 $\pm$ 351                  | 26 $\pm$ 83  | 2.2 $\pm$ 7.3 |       |
| Affected UL volume    |                              |                |               |                                 |              |               |       |
| Baseline              | 1256 $\pm$ 291               |                |               | 1331 $\pm$ 347                  |              |               | .005* |
| Onset of intervention | 1259 $\pm$ 288               | 2.7 $\pm$ 89   | 0.5 $\pm$ 6.6 | 1414 $\pm$ 378                  | 83 $\pm$ 119 | 6.5 $\pm$ 9.9 |       |
| Follow-up             | 1258 $\pm$ 279               | 2.3 $\pm$ 103  | 0.7 $\pm$ 7.9 | 1377 $\pm$ 341                  | 46 $\pm$ 103 | 4.1 $\pm$ 8.8 |       |

UL indicates upper limb; SD indicates standard deviation; UL, upper limb.

\*  $P < .05$  is significant upper limb volume for between group, baseline-affected, and baseline-unaffected upper limb volume tested by repeated-measures multivariate analysis of variance.

volume change) were significantly different ( $P \leq .05$ ) over time for the LG compared with the CG. We also calculated a relative risk for LE (Table 2), which we defined according to Paskett et al, to identify the risk ( $P < .05$ ) of developing LE based on the number of lymph nodes removed.<sup>14</sup>

## RESULTS

Table 3 outlines the time trajectory of the onset, intervention, and follow-up for the LG. Table 4 compares UL volume changes (in milliliters and percents) between the LG and the CG. Univariate ANOVAs indicated that the 2 groups did not differ significantly at baseline, ( $F_{1,84} = 1.187$ ;  $P = .279$ ). The average time from baseline (preoperative) to diagnosis of subclinical LE was 6.9 months, during which time the LG exhibited a statistically significant increase ( $P < .001$ ) in the volume of their affected limb. The LG and CG limb volume changes over time are exhibited in Figure 3. Changes in volume over time differed significantly between the LG and the CG (Wilks  $\lambda$ ,  $F_{3,82} = 4.608$ ;  $P = .005$  for group\*time interaction) with a mean ( $\pm$ SD) increase in limb volume of 83 mL ( $\pm$ 119 mL) or 6.5% ( $\pm$ 9.9%) in the LG compared with 2.7 mL ( $\pm$ 89 mL) or 0.5% ( $\pm$ 6.6%) increase in the CG.

The LG had significantly higher UL volume than the CG when the compression intervention was introduced ( $F = 4.596$ ;  $P = .035$ ). The average duration of the compression garment intervention was 4.4 weeks. During the follow-up period after the intervention (mean, 4.8 months) a mean ( $\pm$ SD) limb volume decrease of 46 mL ( $\pm$ 103 mL) or 4.1% ( $\pm$ 8.8%) was noted in the LG with activity-related garment wear only (as described above) compared

with 2.3 mL ( $\pm$ 103 mL) or 0.7% ( $\pm$ 7.9%) decrease in the CG ( $F = 3.131$ ;  $P = .080$ ).

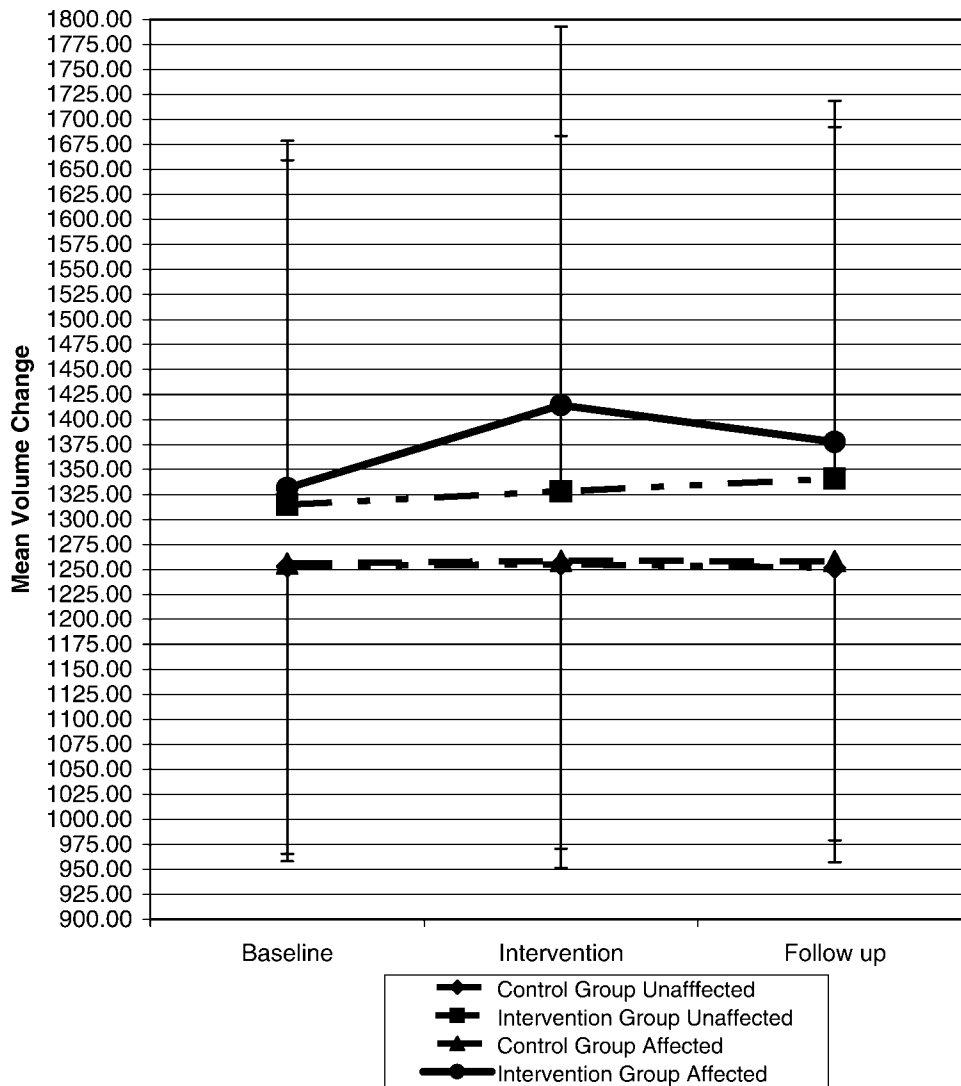
Although the body mass index (BMI) increased over time for both the CG and the LG, the difference was not significant between groups (Table 1). The LG exhibited a higher BMI at baseline and at follow-up, consistent with reports that correlate increased BMI with the onset of LE.<sup>9,11</sup>

Using Paskett's risk calculation, the LG demonstrated a higher relative risk related to the number of lymph nodes removed. However, that risk did not differ statistically from the risk in the CG.

## DISCUSSION

BC morbidity trials highlight the need for preoperative measurement and prospective surveillance to identify impairments.<sup>9,31,42,43</sup> Early detection and management of LE is an integral part of a surveillance program.<sup>12,32,44,45</sup> However, inconsistent and inaccurate LE measurement techniques, along with a lack of standard diagnostic criteria, have prevented a surveillance model from becoming an accepted standard of care.<sup>34,46,47</sup> Recommendations for diagnostic standardization include using reliable and sensitive measurement tools to detect volume change, identifying a threshold value of volume change for the diagnosis of LE, and obtaining preoperative volume measurements.<sup>20,24,31,34,48,49</sup>

The Perometer is a sensitive and standardized device that uses infrared optoelectronic technology to detect and quantify limb volume changes.<sup>22,29,31</sup> Goltner et al reported that changes in interstitial tissue congestion up to 150 mL may occur before limb swelling is visible, and they quantified this volume change by using optoelectronic perometry.<sup>50</sup> Those authors hypothesized, and we concur, that subclini-



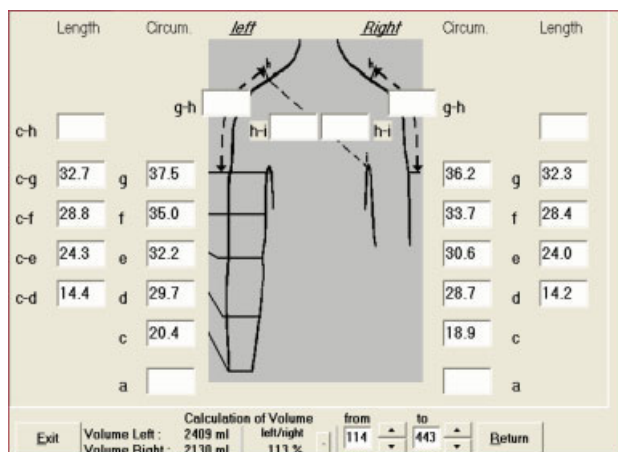
**FIGURE 3.** Mean volume change over time in the affected limb versus the unaffected limb. Error bars are  $\pm 1$  standard deviation.

cal interstitial congestion is the basis for patient-reported sensory changes in the limb and is a precursor to the onset of LE. Similarly, we observed that subclinical congestion is detectable in the limb and that, when adequately managed with a conservative compression intervention, the change is measurable overtime.

Perometer software provides assessment of the entire limb volume and the percentage difference between limbs (Fig. 4) and allows for interlimb comparison over time.<sup>48</sup> Figure 5A,B illustrates limb volume changes at the onset of subclinical LE (accounting for weight gain) for 1 woman's limbs. Although this patient demonstrated increased limb volume bilaterally because of weight gain, the affected left limb volume increased nearly twice the percentage increase of the unaffected right limb.

Neglecting to measure limb volume before BC treatment introduces possible error in accurately diagnosing LE. Pretreatment limb volume measurement accounts for pre-existing normal interlimb variance, which may range from 3% to 10%, depending on arm dominance and activity level.<sup>51</sup> An accurate early diagnosis of LE cannot be made unless pre-morbid limb volume disparity is quantified and regular follow-up is conducted to monitor limb volume change. We demonstrated a statistically significant change in limb volume in our cohort at the threshold of 3%. Without accurate preoperative quantification of normal interlimb variance, this meaningful subclinical volume change will be missed.

Existing classification systems for LE fail to recognize a sensitive diagnostic threshold for subclinical LE. A variety of incompatible grading systems have



**FIGURE 4.** Upper limb volumes and circumferences (Circum.) from the Perometer software.

evolved based on Stillwell's 1969 LE classification system, which defined significant LE as a >10% volume increase compared with the unaffected limb.<sup>52</sup> These derivations include; the Common Terminology Criteria for Adverse Events version 3 (CTCAEv3) (5%-10% volume change), the Late Effects of Normal Tissue/Subjective Objective Management and Analytic Scale (2- to 4-cm girth difference at any point on the limb), the International Society of Lymphology (<20% minimal LE), and the American Physical Therapy Association Guide to Physical Therapy Practice LE grading system (>2.5 cm girth change).<sup>48,53-55</sup> Variability among scales contributes to inconsistent incidence reports of LE and conflicting recommendations for treatment.

Optimal management of LE requires an accurate, early diagnosis using a diagnostic threshold that is sensitive to subclinical tissue changes. Armer et al identify a threshold of 10% volume change as diagnostic for lymphedema. This correlates to approximately 200 mL volume change in the limb and is associated with clinically apparent, symptomatic LE. When applying this criterion, they report a 42% incidence of BC-LE. Francis et al used a threshold of 5% limb volume change to diagnose LE, as outlined in the CTCAEv3 classification system,<sup>7,48</sup> and reported LE rates of 17% in patients who underwent SLNB and 47% in patients who underwent ALND based on preoperative limb measurements. These reports demonstrate that incidence rates of LE are higher than previously anticipated when a sensitive volumetric threshold is used for diagnosis and, thus, offer a more accurate depiction of BC-related LE.

A new classification system is needed to recognize subclinical lymphedema and encourage early intervention to diminish the negative functional, cos-

metic, and psychosocial consequences of LE.<sup>6,56,57</sup> On the basis of our findings, we believe that a more sensitive threshold for diagnosing LE is warranted and can be quantified by using optoelectronic imaging technologies.<sup>36</sup>

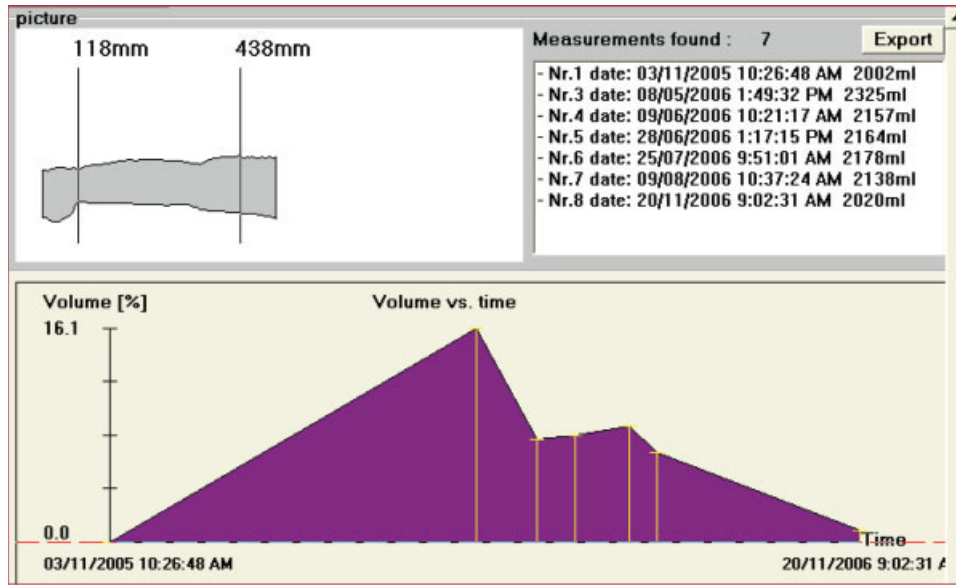
The standard of care for treating and managing clinically apparent LE is well established.<sup>55,58-60</sup> However, to our knowledge there is no standard for the treatment of early-stage, subclinical LE. When the diagnosis of LE is delayed, therapeutic management requires intensive decongestive therapy and life-long maintenance.<sup>61</sup> Components of a decongestive therapy program include skin care, compression bandages, manual lymphatic drainage, garments, and exercise administered over the course of several weeks<sup>62,63</sup> and require life-long maintenance to prevent swelling exacerbations.<sup>64</sup> This is burdensome and expensive. Other methods for managing LE include pneumatic compression devices, surgical debulking, and laser therapy.<sup>55,65,66</sup> Our patients demonstrated a significant decrease in limb volume and sustained volume maintenance using the compression garments over a short duration.

We recommend preoperative screening with postoperative follow-up using standardized measurement techniques as the most effective means to diagnose subclinical LE. Preoperative assessment is vital to a surveillance protocol, because it identifies normal interlimb variance, allowing for an accurate assessment of postoperative volume changes consistent with LE. Regular intervals of postoperative follow-up enable early identification of LE and other physical impairments resulting from BC-related treatment.<sup>67</sup> The average time to onset of LE in this cohort was 6.9 months (SD  $\pm$  4.3; range, 1-18 months). Historic work by Petrek et al demonstrated that the highest frequency of onset of LE occurred in the first 3 postoperative years.<sup>68</sup> Those findings support the contention that interval follow-up should continue for the first postoperative year or longer.<sup>7,34,68</sup>

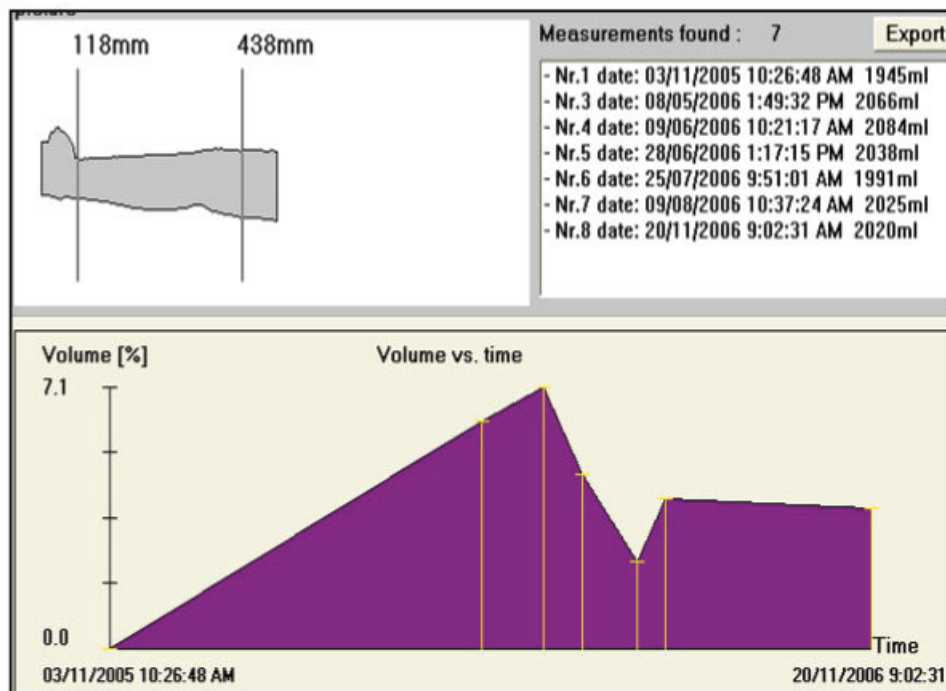
On the basis of this report, we define a 3% volume change from baseline as diagnostic criterion for subclinical LE, requiring conservative intervention. Furthermore, we propose a new grading system for BC-LE that identifies a diagnostic threshold for subclinical LE with recommendations for conservative treatment (Table 5). This system relies on a prospective surveillance model to realize the benefit of early identification and management of BC-LE.

### Limitations

We recognize that this trial was limited because it did not have a randomized-controlled design. In the



A



B

**FIGURE 5.** Bilateral upper limb volumetric changes over time with the (A) left upper limb demonstrating subclinical lymphedema compared with the (B) right upper limb.

context of our morbidity trial, when LE was identified as an impairment, it was managed conservatively with the intervention. The case-control design of this study prevented us from controlling for many of the BC treatment-related side effects that may have contributed to the onset of LE and outcomes identified with the compression trial.

In addition, we recognize that few clinical sites have access to optoelectronic measurement technology. However, in the absence of a Perometer, other assessment tools, including; water displacement, bioelectrical impedance analysis, circumferential girth measurement, and subjective assessment tools, when used in the context of a surveillance program,



**TABLE 5**  
**Proposed Classification of Secondary Lymphedema in Patients With Breast Cancer**

| Signs and symptoms  | Objective measure*  | Management   |
|---|---|--|
| At risk of lymphedema   |   |  |
| Impaired lymph transport because of removal/obliteration of lymphatic nodes and vessels   | Limb volume 0%–3% greater than baseline   | Education for risk reduction; education for signs and symptoms of lymphedema; education for risk reduction   |
| Grade 1: Subclinical lymphedema   |   |  |
| Subclinical swelling is not clinically/visually evident but is measurable objectively; subjective reports of limb heaviness, aching, and numbness; protein-rich fluid   | Limb volume 3%–5% greater than baseline   | Elastic sleeve (off the shelf or custom fit), 20–30 mm Hg with daily wear until swelling subsides  |
| Grade 2: Mild lymphedema  |   |  |
| Clinically/visually evident swelling on inspection with obscuration of anatomic architecture; reported limb heaviness, aching, swelling, and numbness; accumulation of protein-rich fluid; swelling subsides with limb elevation; pitting may occur             | Limb volume 5%–8% greater than baseline   | Education to prevent progression; elastic sleeve (off the shelf or custom fit), 20–30 mm Hg; regular ongoing wear; decongestive therapy if not responsive to sleeve wear |
| Grade 3: Moderate lymphedema  |   |  |
| Visually apparent deviation from normal anatomic contour; limb elevation alone rarely reduces tissue swelling, because tissue fibrosis is present; late in Level 3, pitting becomes increasingly difficult because of proliferative fibrosis                    | Change >8% from baseline limb volume  | Complete decongestive therapy; manual lymph drainage; compression bandaging; exercise and skin care; compression garments; education for self-care                       |
| Grade 4: Severe lymphedema  |   |  |
| Obliteration of skin folds; obvious deviation from normal anatomic contour; late in Level 4, lymphorrhea; lymphostatic elephantiasis in which pitting is absent because of marked tissue fibrosis and skin changes, such as hyperkeratosis and warty overgrowth | Change >8% from baseline limb volume; interfering with activities of daily living | Complete decongestive therapy  |
| Grade 5: End-stage  |   |  |
| Progression to malignancy (ie, lymphangiosarcoma)   | Interfering with activities of daily living                                       | Surgical/medical intervention  |
| Grade 6   |   |  |
| Death   |   |  |

\* Measured by perometry.

may prove efficacious in diagnosing subclinical LE. Further research is warranted to validate those tools in the context of a surveillance trial.

### Implications for Practice

Preoperative baseline measurement is vital to successfully diagnosing subclinical LE. However, currently, physical therapists in clinical practice rely on an impairment-based model for diagnosing and treating LE. This paradigm is inadequate if a subclinical diagnosis is to be made. A shift in the current practice pattern in favor of a surveillance model is necessary and indicated based on the results presented here. In the absence of a surveillance program, the earliest diagnosis of LE will be missed.

In conclusion, preoperative assessment in the context of a prospective surveillance model enables the early detection and management of subclinical LE. An early intervention protocol with 20- to 30-mm Hg compression garments, as outlined in this report, significantly reduces the affected limb volume to near baseline measures and prevents progression to

a more advanced stage of LE for at least the first year postoperatively. Further research is warranted to confirm the long-term clinical and cost effectiveness of this surveillance model compared with a traditional impairment-based model in treating BC-LE.

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