ABSTRACT

Breast cancer survivors are at life-time risk of developing lymphedema (LE). Quantification of LE has been problematic as the criteria used to identify lymphedema use various methods to assess changes in the volume of the affected limb. In part because of difficulties and variability in measurement and diagnosis, the reported incidence of LE varies greatly among women treated with surgery and radiation for breast cancer. The goal of this research was to describe the trends for LE occurrence over three points in time (12, 30, and 60 months) among breast cancer survivors using four diagnostic criteria based on three measurement techniques. Participants were enrolled following diagnosis of breast cancer but before surgery. Baseline limb volume and symptom assessment data were obtained. Participants were followed every 3 months for 12 months, then every 6 months thereafter for a total of 60 months. Limb volume changes (LVC) in both limbs were measured using three techniques: objectively by (a) circumferences at 4 cm intervals and (b) perometry and subjectively by (c) symptom experience via interview. Four diagnostic criteria for LE most often reported in the literature were used: (i) 2 cm circumferential change; (ii) 200 mL perometry LVC; (iii) 10% perometry LVC; and (iv) signs and symptoms (SS) report of limb heaviness and swelling, either ‘now’ or ‘in the past year’ (diagnostic criteria i-iii define increases/differences in limb volume from baseline and/or between the affected and non-affected limb). Standard survival analysis methods were applied to identify when the criteria corresponding to LE were met. Trends in LE occurrence are reported for preliminary analysis of data from 236 participants collected at 6-, 12-, 18-, 24-, 30-, and 60-months post-op. At 60 months post-treatment, LE incidence using the four criteria ranged from 43% to 94%, with 2 cm associated with the highest frequency for lymphedema occurrence and SS the lowest. Sixty-month trends are compared to earlier trends at 12- and 30-months, per criterion. These preliminary findings provide additional evidence that breast cancer survivors are at risk for developing LE beyond the first year following treatment. Cases of lymphedema continue to emerge through 60-months post-breast cancer surgery. This 60-month analysis supports the previous 12- and 30-month analyses in finding the 2 cm criteria to be the most liberal definition of LE. The self-report of heaviness and swelling, along with 10% LVC, represent the most conservative definitions (41% and 45%, respectively). Furthermore, the variety of criteria used to identify LE, along with the absence of baseline (pre-treatment) measurements, likely contribute to the wide range of LE incidence rates reported in the literature.

Keywords: breast cancer, secondary lymphedema, diagnostic criteria (for lymphedema), lymphedema occurrence, survival analysis (for lymphedema)
Nearly 200,000 American women are newly affected by breast cancer each year and it is the most common type of women’s cancer in the U.S., accounting for 27% of all cancers (1). Breast cancer comprises the most common cancer for women (outside of skin cancer) in developed parts of the world (2). Worldwide, more than a million women are newly diagnosed with breast cancer every year, accounting for one tenth of all new cancers and nearly one-quarter (23%) of all female cancer cases (2). In addition, almost 2.5 million breast cancer survivors are living in the U.S. (1), and the five-year survival rate in Europe is 76% (3). Of those affected by breast cancer, it is conservatively estimated that up to 40% will develop lymphedema (LE), depending on criteria applied. However, all survivors are at risk for developing LE over their lifetime (4,5), and the number of survivors affected and potentially affected by secondary LE is staggering, comprising potentially 1 to 5 million people.

Lymphedema is the accumulation of protein-rich fluid in the interstitial spaces of the affected body part due to a blockage or malfunction in the lymph system. This edema is different from post-op swelling which may occur immediately after surgery. LE swelling may cause discomfort and sometimes disability; additionally, it can lead to cellulitis and lymphangitis, predisposing the patient to systemic and sometimes life-threatening infection. The physical and psychological aspects of the condition greatly impact the daily lives of LE patients (6-10). Indeed, research has shown even minimal limb volume increase affects quality of life (10). An increasing number of studies report on risk factors related to the development of secondary LE, including body weight (11), and type of surgery, body weight, infection, and injury (12). Co-morbidities of elevated BMI, orthopedic issues, cardiac conditions requiring medication usage, and cancer staging requiring hormone blocker usage were also found more often in those with LE (13).

Recent scientific literature reports that anywhere from 5 to 60 percent (14) or 6 to 62.5 percent (15) of the breast cancer population meets the criteria for LE. Medical literature, however, suggests a more conservative occurrence, 15 to 20 percent of the breast cancer population (16). A common estimate is that 20 to 40 percent of breast cancer survivors develop LE (7,17-21), and the rate does not significantly vary between Caucasians and African-Americans (22). The discrepancies among the reported percentages stem from difficulties in measurement, diagnosis, and follow-up (14,15,21,23-27) as well as the lack of pre-operative baseline comparison or adjustment for changes in body mass index (BMI).

Traditionally, finding 2 or more cm difference in limb girth at some anatomic point between the affected and non-affected limbs warranted clinical diagnosis of LE (25-28). However, other methods are also commonly used. A 200 ml limb volume difference or a 10 percent limb volume change (LVC) from baseline and/or between the affected and non-affected limb are both documented methods of LE diagnosis (25-27,29). Self-reported signs and symptoms are also identified as predictive of LE (25-27,30). Recently, a novel BMI-adjusted criterion was used to assess LE occurrence (31).

The reported incidence of LE fluctuates greatly among each participant group at risk for LE. It has been found that often breast cancer patients do not recall being made aware of the risk of LE post-op (32,33). This lack of information may cause them to take longer to recognize and report possible symptoms of LE. Likewise, some survivors may not report symptoms because they may not know what LE is or how to detect it (32) or they were unaware of swelling (34). Other survivors are well-aware of their risk and detect LE via self-assessment. However, overall a lack of sufficient knowledge about LE and its effects contributes to variance in survivors’ reported incidence of LE. Health care providers do not typically report data on LE occurrence to a central data bank so
epidemiological evidence of LE occurrence is fragmented.

While numerous studies have reported LE incidence during the first 12 months following breast cancer treatment, little is known regarding long-term LE occurrence. Very few studies have examined LE incidence past one year post-surgery, and many that have are retrospective or cross-sectional, not prospective, in nature. In fact, in one analysis of existing literature, the authors found the study with the shortest follow-up (12 months) reported the lowest LE incidence (14). Likewise, the study with the longest follow-up (11 years) reported the highest incidence (14). It is also reported that chart-review of medical diagnosis frequently understates the true incidence of LE (35), a finding corroborated in our current research (unpublished data).

AIMS

The current study aimed to compare three measurement techniques using four diagnostic criteria to quantify LE occurrence up to 60 months post breast cancer surgery. Trends for LE occurrence were examined over three points in time (12, 30, and 60 months). This study is unique in its prospective design, examining LE prevalence through 5 years with baseline data collection occurring before and immediately following surgery. The preliminary findings will add new insight into late-onset lymphedema emergence and the rationale for the duration and measurement approach for optimal observation of LE incidence.

METHODS

The study was designed to use prospective, repeated-measures on data collected on 236 female participants newly-diagnosed with breast cancer. Participant recruitment and data collection took place at a Midwestern university-affiliated state cancer center. The participants were consented, enrolled, and assessed at pre-diagnosis, post-surgery, every 3 months for 12 months, then every 6 months thereafter for a total of 60 months.

Two objective measurement techniques were used at each visit to quantify limb volume characteristics: circumferential measurement and infra-red perometry. (A) Traditional anthropometric measurements recorded limb girth every four cm on each arm using a non-stretch, flexible tape measure. (B) Infra-red perometry (Perometer 350S, Juzo, Cuyahoga Falls, OH) was used to record three-dimensional images of each limb, which were the basis for limb volume calculations. Both upper limbs were measured at each time point for comparison, with the mean of three repeated measures used in the analyses. A detailed description of these techniques has been previously published (25-27).

In addition to the two objective measures, one subjective assessment of LE symptoms was administered each visit through a nurse interview using the LE and Breast Cancer Questionnaire (LBCQ) as a guide. The LBCQ consists of 57 questions examining 19 signs and symptoms drawn from the literature and clinical observation and has been validated previously (30). Based on these published findings, self-report of heaviness or swelling ‘now’ or ‘in the past year,’ was included as one definition for LE.

From those measurements, four criteria for identifying LE were used: (i) 2 cm circumferential change at any measured anatomic location; (ii) 200 mL perometry limb volume change (LVC) in the affected arm; (iii) 10% perometry LVC in the affected arm; and (iv) report of limb heaviness and swelling, either ‘now’ or ‘in the past year.’ The objective-based criteria for identifying LE (items i-iii) were based on change from baseline measurements and/or versus contralateral unaffected limb.

Certain participants met the definitions for LE before surgery at the baseline measurement for one or more of the four the criteria used here. Data from those participants were retained in the study but were not
included in the analysis for that particular criterion, resulting in different numbers of participants for a given criterion. A subject who met the definition at one time point was considered to have met the definition at all subsequent time points.

Sample Description

At enrollment in the study, the mean age of participants was 57 years old (range 30 to 89). The treatment characteristics of study participants varied greatly. The majority of the participants, 48 percent, had a mastectomy, 39 percent had a lumpectomy, and 11 percent had both surgical treatments. Sixty percent underwent chemotherapy and 51 percent underwent radiation treatment. Forty-three percent of participants had sentinel lymph node biopsy (SLNB) treatment, and 30 percent underwent axillary lymph node dissection (ALND). Eleven percent underwent both SLNB and ALND treatments while 16 percent had neither treatment. All of these treatment characteristics illustrate the diverse yet representative treatment of the study sample.

Survival Analysis

The Lifetest procedure in SAS v9 (SAS Institute Inc., Cary, NC, USA) was used to estimate the survival distributions under each of the definitions of LE using the product-limit or Kaplan-Meier method. Survival analysis allows one to estimate the probability of distribution of time to a specified event. Specifically, the survival curve gives the probability that the event of interest will occur later than a given time. The event of interest in this analysis is the diagnosis of LE. At time 0 (baseline), the probability is 1.00 (or 100%) that no one has met the criteria for diagnosis. Time was measured from initial breast cancer treatment (surgery) to the first diagnosis of LE. Kaplan-Meier estimates of the survival curves were obtained separately for each of the four definitions of LE and are displayed in Fig. 1.
TABLE I
Occurrence Rates of Lymphedema Using Four Diagnostic Criteria

<table>
<thead>
<tr>
<th>Identifying Criteria</th>
<th>6 months (n=178)</th>
<th>12 months (n=178)</th>
<th>18 months (n=178)</th>
<th>24 months (n=178)</th>
<th>30 months (n=178)</th>
<th>36 months (n=178)</th>
<th>48 months (n=178)</th>
<th>60 months (n=178)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 cm</td>
<td>44 (37-51)</td>
<td>66 (59-75)</td>
<td>75 (72-85)</td>
<td>81 (75-87)</td>
<td>87 (81-92)</td>
<td>88 (82-93)</td>
<td>92 (86-96)</td>
<td>94 (87-98)</td>
</tr>
<tr>
<td>10% LVC</td>
<td>200 mL LVC</td>
<td>24 (19-31)</td>
<td>47 (33-47)</td>
<td>56 (41-57)</td>
<td>65 (49-64)</td>
<td>66 (58-73)</td>
<td>74 (59-74)</td>
<td>83 (66-82)</td>
</tr>
<tr>
<td>n=193</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>10% LVC</td>
<td></td>
<td>11 (7-11)</td>
<td>29 (17-29)</td>
<td>36 (21-35)</td>
<td>40 (30-44)</td>
<td>43 (33-48)</td>
<td>48 (36-51)</td>
<td>55 (40-57)</td>
</tr>
<tr>
<td>n=193</td>
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For any subject for whom the LE diagnosis was met, the actual time is not known precisely since limb volume was measured every 3 months for the first year and then every 6 months to 60 months, and not every day. When present, we know LE occurred since the previous measurements were taken but we do not know precisely when it emerged. Further, although subjects were scheduled for measurement visits at 3 or 6 month intervals, the actual time between visits varied (27).

Limitations

Only data from subjects with pre-op baseline measurements were used in this analysis. Also, immediate post surgery data, which may provide insight to the earliest possible onset of LE, was excluded from analysis due to potential confounding results from post surgery swelling. Thus, the immediate post-op visit data were omitted for all four survival analyses to avoid mistakenly identifying post-op swelling as LE. Some subjects met the definition of lymphedema with comparisons made only to the ipsilateral limb at baseline and not to the contralateral limb at a particular time point. Although this may not appear to take into account changes in body mass, we have previously shown in this cohort that the comparisons to either the ipsilateral or contralateral limb are not significantly different (10). In addition, preliminary analysis using BMI-adjusted values have not affected the trends in the slope of the curve (manuscript in progress). We also considered a subject who met the definition of lymphedema at one time point to meet this definition at all subsequent time points. This may increase the reporting of lymphedema but it reflects current clinical care. It also protects against misleading conclusions from subjects who undergo treatments that reduce the size of their limb and therefore would no longer meet the definition of lymphedema at subsequent time points.

RESULTS

The 2 cm identifying criterion was the most liberal of the four methods examined here, resulting in the highest estimation of LE at the end of the 30 months (87%) and at 60 months (94%). The 200 mL LVC criteria was the second most likely to identify LE at the
end of 30 months (65%) and at 60 months (83%). Meanwhile, 10% LVC and SS were the most conservative of the criteria, identifying LE in 50% and 43% of the participants at 60 months, respectively. The lymphedema incidence rates for each method over time (each six-month interval from baseline to sixty-months) are presented in Table 1. In addition, the survival analysis is displayed in Fig. 1 for all four criteria at 60 months. Figs. 2 to 5 display the survival analyses for preliminary exploration of trends at 12 and 30 months alongside the 60-month analysis reported here. Each of the four criteria is separately displayed. These sequential analyses performed as larger numbers of survivors were enrolled and followed over time provide increased confidence in the trends seen.

When examined over smaller time frames, the overall trends continued. At any 6-month point of time during the study, the 2 cm criteria identified participants with LE at the highest frequency. Similarly, 200 mL LVC was the second most likely to identify LE at any point in the study. However, while 10% LVC and SS had similar occurrence rates at 30 months, they had somewhat different rates of LE emergence over that time period. SS was more likely to identify LE in the first 12 months (32%), then slowed (36% at 30 months and 43% at 60 months). In contrast, 10% LVC was slower to identify LE (22%) in the first 12 months, but relatively doubled the rate of identifying LE thereafter (40% at month 30 and 55% at month 60).

DISCUSSION

Previous work in our laboratory has shown that identification of LE in the first year post-surgery for breast cancer varies greatly depending on the four commonly-used criteria for defining LE (26). These findings were further corroborated in the 30-month analysis (27). The present study expands on these findings by measuring LE occurrence through five years, one of the only bodies of work to prospectively measure LE occurrence for that length of time. As with the 12- and 30-month findings, LE incidence varied greatly depending on the criteria used.

**Fig. 2.** Survival analysis for 2 cm criteria to identify LE based on three different points of time.
Nearly all participants (94%) met the criteria for LE based on the 2 cm method, by far the highest incidence rate in this analysis. In contrast, SS identified the fewest participants (43%). This wide range of occurrence rates (51%) mirrors the high and low range of occurrence rates at 12 months (66% to 22% using 2 cm and 10% LVC, respectively). This finding represents a common situation, since in the absence of a “gold standard” to diagnosis LE there exists a wide range of criteria used by nurses, therapists, physicians, and researchers. This analysis provides evidence that the discrepancies widely noted...
in the literature regarding the identification of LE are due, in part, to the variety of criteria used.

A unique aspect of the design of this study is the use of pre-surgery measurements as baseline data. The majority of the literature available is based on LE occurrence using post-treatment data as the comparison criteria. By using pre-surgery measurements, we were able to identify those participants who met the criteria for, but did not have, lymphedema at baseline. Those participants were not included for further analysis for that particular criterion, eliminating a confounding factor for later LE identification. Using this method, up to 23% of the participants at baseline were identified to meet one of the criteria for LE before treatment due to reasons other than LE (i.e. limb volume differences due to arm dominance). It is the objective measurements (2 cm, 10% LVC, 200 mL LVC) that were the criteria more frequently met (11-21%), while the subjective criterion (SS) was met at pre-surgery much less frequently (7%). The lack of pre-surgery measurements in other studies likely results in erroneous (under-) estimation of LE, and contributes to the wide-ranging discrepancies in LE occurrence rates across the literature. These findings document the importance of pre-treatment anthropometric and symptom data collection.

These preliminary findings provide additional evidence that breast cancer survivors are at a long-term risk for developing LE. Indeed, our findings show that LE emergence, regardless of the method used for estimation, continued to increase past the first year post-treatment. From month 12 to month 30, LE identification increased by an additional 4-25%, and from months 30-60, LE incidence increased by 7-18%, depending on the criterion used. This increase that occurs past the first 30 months underscores the need for long-term surveillance measurement of limb volume and patient signs and symptoms in breast cancer survivors by healthcare professionals.

The preliminary results of this 60-month analysis of LE occurrence provide unique insight into one aspect of breast cancer survivorship. Future research in our program of study will continue to examine LE incidence up to seven years post-breast cancer.
treatment. In addition, a prospective longitudinal risk-reduction intervention for the treatment and management of LE is currently underway. Thirdly, a psychosocial analysis of the impact of breast cancer, an equally neglected area of LE research, is ongoing. Finally, a pilot study examining genetic predisposition for development of secondary LE among breast cancer survivors is underway. These and other work now underway hold promise in increasing our understanding of lymphedema risk factors and emergence following breast cancer treatment.

**CONCLUSIONS**

Confirmation of the 12- and 30-month LE trends at 60 months increase our confidence in the findings. These preliminary findings provide additional evidence that breast cancer survivors are at a risk for developing LE beyond the first year following treatment. This 60-month analysis supports the previous 12- and 30-month analyses in finding the 2 cm criteria as the most liberal definition of LE. The self-report of heaviness and swelling, along with 10% LVC, represent the most conservative definitions (43% and 55%, respectively) at 60 months. Furthermore, these analyses demonstrate that the range of criteria used to identify LE, along with the lack of pre-treatment measurements, are likely responsible for the wide range of lymphedema rates reported in the literature.

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