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Scientific paper

Can a practicing surgeon detect early lymphedema reliably?

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Abstract

Background: Lymphedema may be identified by simpler circumference changes as compared with changes in limb volume.
Methods: Ninety breast cancer patients were prospectively enrolled in an academic trial, and seven upper extremity circumferences were measured quarterly for 3 years. A 10% volume increase or greater than 1 cm increase in arm circumference identified lymphedema with verification by a lymphedema specialist. Sensitivity and specificity of several different criteria for detecting lymphedema were compared using the academic trial as the standard.
Results: Thirty-nine cases of lymphedema were identified by the academic trial. Using a 10% increase in circumference at two sites as the criterion, half the lymphedema cases were detected (sensitivity 37%). When using a 10% increase in circumference at any site, 74.4% of cases were detected (sensitivity 49%). Detection by a 5% increase in circumference at any site was 91% sensitive.
Conclusions: An increase of 5% in circumference measurements identified the most potential lymphedema cases compared with an academic trial.

Keywords: Lymphedema; Measurements; Circumference

Halsted described lymphedema of the upper extremity after treatment of breast cancer by mastectomy in the early 1920s [1]. It continues to be of significant lifelong concern even with modern treatment of breast cancer. The incidence of lymphedema has been reported from 6% to 30% [2]. Early and reliable diagnosis continues to be challenging because multiple methods of detection are reported that are difficult to compare. The delay in identification of lymphedema contributes to the negative psychosocial impact already imposed by the potential physical limitations, discomfort, and disfigurement that result from the condition.

There are various methods reported for the detection of lymphedema including water displacement measurement of arm volume, tissue tonometry, and radiographic means such as magnetic resonance imaging (MRI) and computed tomography (CT). However, more commonly, circumferential measurements are used to detect lymphedema. As of yet, however, there are no well-established guidelines for diagnosis of lymphedema using circumferential measurements and no consensus on what measurement change constitutes lymphedema [3]. In a review of the literature by Petrek and Heelan [2], the definition of lymphedema ranged from greater than 2 cm change to greater than 10 cm change. There are reports citing that a greater than 2 cm difference from baseline (preoperative) measurements identifies lymphedema [4,5]. Generally, two or more circumferential measurements are taken along the arm, including at bony landmarks, to evaluate for lymphedema [5,6].

In a prospective trial from the American College of Surgeons Oncology Group (ACOSOG) [7], lymphedema is described as a 2 cm or greater increase over the baseline measurement or greater than 10% increase in circumference

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of the ipsilateral arm. In addition, for the purpose of the ACOSOG protocol, participating members are instructed to take the measurements 10 cm proximal and distal to the lateral epicondyle.

In order to verify and compare various circumference change criteria for lymphedema detection, a group of lymphedema cases were identified by volumetric determinations prospectively collected on breast cancer patients in an academic trial that included examination by a lymphedema specialist. A 10% increase in limb volume was accepted as lymphedema [8,9]. In addition, any change in circumference greater than 1 cm led to examination and measurement by a lymphedema specialist, identifying additional lymphedema cases. Then measurements in the lymphedema cases identified in the academic trial were compared with other definitions of lymphedema that used fewer sites for detection, and various changes in circumference in order to determine specificity and sensitivity of lymphedema detection.

Methods

After approval by the Human Investigation Committee at Wayne State University and human subjects subcommittee of the DoD (DAMD 17-00-1-0495), patients from the Alexander J. Walt Comprehensive Breast Center at Karmanos Cancer Institute were enrolled prior to surgery, and after signing the approved study consent form. Participants were 18 years old or older, male or female, with newly diagnosed, resectable breast cancer. Eligible subjects were scheduled to undergo mastectomy or lumpectomy with lymph node sampling, dissection, or sentinel node biopsy, or breast conservation therapy followed by radiation therapy. Exclusion criteria included previous axillary surgery or radiation, planned mastectomy without axillary surgery or radiation therapy, inability to provide consent, or no plans to follow up at any of the Karmanos facilities after surgery. Demographic information was collected by questionnaire, which included ethnicity, education level, and income. The type of surgery, breast cancer stage, occurrence of chemotherapy and radiation therapy was recorded during the study.

From June 1999 through December 2002, 107 subjects were enrolled and evaluated for lymphedema after surgical treatment of breast cancer. Of 107 subjects, 90 subjects were evaluable. The reasons for nonevaluable subjects were as follows: subjects did not want to continue in the study (10), did not meet study entry criteria upon review (5), or did not undergo axillary surgery or radiation therapy as planned (2). Measurements were taken preoperatively of bilateral arms. The circumferential measurements were taken across the palm of the hand, at the wrist, and at 10 cm intervals proximal to the wrist, and at the elbow. The volume was then calculated based on the total volume of a series of frusta. A frustum, a cone with the top cut off so the upper surface is parallel to the base, is felt to be a more accurate representation of the upper extremity [7,8,10,11]. Measurements and volume calculations were taken quarterly for up to 3 years. Quarterly limb volumes were compared with preoperative values on the ipsilateral side. In the event that a patient had a change in weight of 10 pounds or greater (gain or loss), then measurements were repeated and volumes calculated creating a new baseline. Percent change from preoperative volumes were calculated quarterly using the following equation: volume % change = (current volume − preoperative volume/preoperative volume) × 100 [9]. A 10% increase in volume as compared with preoperative measures was considered to be lymphedema after verification by a lymphedema specialist. In addition, anyone with a circumference measurement increase of greater than 1 cm was also referred to the lymphedema specialist for additional measurements and examination. Not all of these were judged to have lymphedema, but this route identified some additional cases (38.5%).

For comparison, the criterion of a 10% change and 5% change in circumferential measurement was applied to the sites proximal and distal to the elbow. This was done to evaluate the effectiveness of the two-site method to diagnose lymphedema as compared with the sites measured for the academic trial. Then 10% change and a 5% change in circumference at any of the measured sites along the limb were calculated. Additionally, measures greater than 2 cm were also identified. The lymphedema specialist evaluated all potential cases of lymphedema identified by these comparison methods in order to determine true positive and true negative cases. The time of diagnosis of lymphedema was determined as months after the date of surgery. The sensitivity and specificity of each of the methods using circumference changes were determined in comparison to the lymphedema cases confirmed in the academic trial. The timing of the diagnosis of lymphedema was one of the factors used in determining sensitivity and specificity. If the differences in the timing of diagnosis were within 3 months, they were coded as an agreement. SAS version 8.2 was used for all statistical analyses.

Results

The patients eligible for inclusion in the study were African-American (30%), Caucasian (51.1%), Hispanic (3.3%), Arab/Chaldean (2.2%), Asian (2.2%), Native American (3.3%), and other (6.7%; Table 1). One subject did not indicate race (1.1%). Overall, the average age of the patients enrolled was 53.7 years, and all were women, although men were eligible to enroll as well. The evaluable subjects had breast cancer stages from 0 through IV. Forty-five of the patients (50%) had mastectomy with axillary surgery, 38 (42.2%) had lumpectomy with axillary surgery, and the remaining 7 (7.8%) had lumpectomy with radiation therapy. In addition, half of the patients had radiation therapy.

The patients were followed up in the trial for a mean of

Table 1
Patient characteristics

	With lymphedema	Without lymphedema
Number	38*	52
Mean age (yrs ± SD)	54.8 ± 13.4	54.4 ± 10.3
Race		
African American	14	13
Caucasian	16	30
Hispanic	3	0
Arab/Chaldean	1	1
Asian	0	2
Native American	0	3
Other	4	2
Unknown	0	1
Breast cancer stage		
0	3	6
I	7	17
IIA	11	11
IIB	5	14
IIIA	8	1
IIIB	3	2
IV	1	1
Chemotherapy	16	15
Radiation therapy	16	27
Employment status		
Working	15	28
Not working	10	7
Retired	10	8
Not answered	3	9
Highest education level		
Less than high school	4	1
High School/GED	21	28
Associate degree	0	0
Bachelor degree	8	9
Masters degree	1	4
Doctorate/professional school	1	1
Not available	3	9
Annual income		
<$5,000	3	4
$5,001–$15,000	6	4
$15,001–$30,000	5	5
$30,001–$50,000	3	2
$50,001–$75,000	3	8
>$75,000	10	13
Not available	8	16

* One patient had bilateral disease.

13 ± 7.9 months (range 3 to 36), with enrollment occurring throughout. Thirty-eight (38) patients (with 39 limbs affected) of the 90 evaluable patients (42.2%) were found to have lymphedema based on the academic trial standards of 10% increase in baseline volume or greater than 1 cm change at 1 of the 7 measured sites with verification by the lymphedema expert. One patient had bilateral disease. The mean age of patients with lymphedema was 54.8 years. Thirty-two of the 39 diagnoses (82.1%) of lymphedema were made within the first year (acute lymphedema). Most persisted past 1 year (86.7%). The average time until diagnosis of lymphedema was 7.6 months and ranged from 3 to 28 months (Table 2). There was no difference in incidence of lymphedema based upon type of surgical procedure.

Table 2
Lymphedema detection in academic trial by type of surgery*

	Type of breast cancer surgery			
	Mastectomy with axillary surgery (n = 45)	Lumpectomy with axillary surgery and RT (n = 38)	Lumpectomy and RT (n = 7)	All (n = 90)
With lymphedema	19	18	2	39‡
Acute LE†	13	18	2	33
Mean time to LE diagnosis (months)	8 ± 6	7 ± 6	6.5 ± 0.7	7.6 ± 5.8

* Academic trial LE criteria: 10% or greater volume change or 1 cm or greater circumference change at any site, all verified by LE specialist.

† Acute LE was lymphedema diagnosed within the first year after surgery.

‡ One patient had bilateral disease.

RT = radiation therapy; LE = lymphedema.

There were not enough cases of sentinel lymph node biopsy ([SLNB] 13) to compare these lymphedema criteria at this time. However, 5 of 13 were diagnosed with lymphedema in the academic trial after SNLB.

Based on one of the ACOSOG criteria for diagnosis of lymphedema, 10% change in circumference for measurements 10 cm above and below the elbow, 20 patients (37% sensitivity, 92% specificity) were identified. The average interval until diagnosis was 11.7 months (Table 3). When a 10% change in circumference was applied to any of the measurements along the limb, 29 patients (49% sensitivity, 81% specificity) were identified. The average interval until diagnosis was 10.7 months (Table 4).

Determining a greater than 2 cm change in circumference above and below the elbow identified 28 cases (59% sensitivity, 85% specificity) which overlapped with the cases identified by 10% circumference increase in the same sites (Table 5). Diagnosis of lymphedema occurred at 9.3 months on average. When all measured sites were examined for a greater than 2 cm change, then 32 cases were identified (70% sensitivity, 76% specificity; Table 5). The diagnosis occurred at 8.6 months on average.

In order to increase sensitivity, 5% changes in circum-

Table 3
Comparison of LE detection with the academic trial using 10% and 5% circumference change above and below the elbow

	10% change around elbow	5% change around elbow
Potential LE cases	18	45
Mean time to LE diagnosis (months)	11.7 ± 6.3	8.3 ± 5.9
Sensitivity	37%	80%
Specificity	92%	71%

LE = lymphedema.

Table 4
Comparison with the academic trial of LE detection using 10% and 5% circumference change at any site

	10% change at any site	5% change at any site
Potential LE cases	28	62*
Mean time to LE diagnosis (months)	10.7 ± 6.1	7 ± 5
Sensitivity	49%	91%
Specificity	81%	46%

* One patient had bilateral surgeries and was positive bilaterally.
LE = lymphedema.

ference were determined around the elbow (Table 3), and at all measured sites (Table 4). With a 5% circumference change around the elbow, there were 36 cases identified at a mean of 8.3 months (80% sensitivity, 71% specificity; Table 3). However, when 5% circumference change was determined for any measured site, then all 39 lymphedema cases from the academic trial were identified at 7.5 months (91% sensitivity, 46% specificity; Table 5).

Comments

Most patients do not have lymphedema after surgery or radiation therapy. However, for the approximately 30% of postsurgical/postradiation patients in whom the condition develops, it can be life altering and affect their quality of life. Interestingly, it can start within the first year after surgery. Some cases resolve within that year, others persist. Still others occur at some interval after the first year. There are several treatment modalities available for therapy. However, a delay in diagnosis delays therapy. Earlier treatment can prevent acute lymphedema from becoming more advanced and chronic, even if it does not resolve after 1 year. When it is left untreated, chronic lymphedema can progress to chronic inflammation, fibrosis, swelling, and increased risk of cellulitis [12]. Therefore, early identification of potential lymphedema remains a goal for surgical practices.

Table 5
Comparison with the academic trial of LE detection using >2 cm circumference change at any site and specifically above and below the elbow

	>2 cm around the elbow	>2 cm at any site
Potential LE cases	30	39
Mean time to LE diagnosis (months)	9.3 ± 6.2	8.6 ± 5.9
Sensitivity	59%	70%
Specificity	85%	76%

* One patient had bilateral disease.
LE = lymphedema.

The diagnosis is more complex in patients who experience a feeling of heaviness, swelling, or pain, in the absence of corroborating volume or circumferential changes. These patients may be considered to have lymphedema by subjective complaints and require evaluation a by lymphedema specialist as well [13]. The subjective complaints often times precede the ability to clinically document lymphedema [9]. The physical changes that accompany the condition create difficulty with tasks associated with jobs, households, and even personal care, especially in severe cases [14]. The psychological impact can be tremendous resulting in sexual dysfunction, depression, and feelings of isolation.

Modern day surgical practices in breast surgery are aimed at reducing post surgical and treatment morbidity. With the advent of SNLB, it has been reported that arm swelling and subjective complaints are decreased in comparison with traditional axillary lymph node dissection (ALND) [15–17]. Sener et al [17] reported 6.9% incidence of lymphedema in patients undergoing SLNB followed by obligatory ALND. The incidence of lymphedema decreased to 3% with SNLB alone (lymphedema was characterized by a minimum 20% volume change in that particular study). Although the data are promising, the number of lymphedema cases was falsely low due to the determination of a greater than 20% circumference increase at sites 10 cm above and below the elbow. This is predicted to increase the false negative rate for lymphedema detection. Therefore, future studies examining the occurrence of lymphedema in cases with SLNB require standardized criteria for identifying potential cases.

Although there are generally accepted criteria to diagnose lymphedema, there are no universally applied methods to diagnose potential lymphedema, thereby complicating interpretation of literature. This also has serious implications for surgical practice in making a presumptive diagnosis and referral to a lymphedema specialist. While a lymphedema specialist may apply multiple complex measurements and other clinical evaluations in arriving at the confirmation of lymphedema, surgeons may need simpler screening criteria that would reliably detect lymphedema in order to refer for consultation. For example, some authors have used or referred to a method of two measurements (one above and one below the elbow) with a 2 cm increase in circumference for diagnosis of lymphedema [2,4,15,18], When data from the subjects in this study was evaluated by this criterion, we found that 28 of the 39 (71.8%) cases diagnosed with lymphedema would also have been diagnosed by this method (Table 5). When the 2 cm increase was applied to any site, the true positive diagnosis rate was 82.1%, missing 17.9% of the cases.

When ACOSOG criteria for lymphedema were applied to the measurement data (10% increase in circumference around elbow), 48.7% of the documented lymphedema cases would have been missed as compared with evaluating sites along the arm (Table 3). Ten cases (25.6%) would have been missed based on the ACOSOG criteria of 10% cir-

cumferential change if applied to any site. In addition, the academic trial identified patients with lymphedema 3 months earlier on average in comparison to ACOSOG criteria. It should be noted, however, that if the ACOSOG criteria of 10% change over baseline measurement was lowered to 5%, all of the patients identified by the academic trial would have been positively diagnosed with lymphedema by that standard (Tables 3 and 4). On average, patients would have been diagnosed 3.7 months earlier if this criterion were utilized instead of 10% and 0.6 month earlier than using a 10% volume change.

In addition, we used a greater than 1 cm change in circumference at any site as a trigger for referral to the lymphedema specialist who would further evaluate for lymphedema [3,19,20]. Thirty-seven of 39 lymphedema cases had a greater than 1 cm change. We feel that this is a reliable indicator of lymphedema. However, although the sensitivity was 76% for this approach, the specificity was only 39%. This may lead to a greater number of referrals to the lymphedema specialist than would have the diagnosis. With confirmation of the diagnosis, lymphedema therapy could begin.

In conclusion, methods of lymphedema diagnosis that are readily available, inexpensive, quantifiable, and easily reproduced are ideal for evaluation of patient in a surgical practice [6]. The academic trial utilizing frequent measurements and volumetric determinations identified lymphedema in 43.3% of the total patients evaluated, which is higher than the general incidence of lymphedema reported in the literature [2]. The methodology is also more complex than would be practical in a surgical practice. However, simpler determination of circumference change at multiple sites along the affected limb may identify potential cases for referral, leading to earlier treatment and lessen the psychosocial and physical impact. By using a 5%, rather than 10% change in circumference or using a greater than 1 cm change in measurement at sites along the length of the arm, reliable detection of probable lymphedema in a clinical setting can be accomplished without complicated volume determination. The later can be utilized by lymphedema specialists along with other complex evaluations.

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