LYMPHATIC RESEARCH AND BIOLOGY
Volume 14, Number 1, 2016

DOI: 10.1089/lrb.2015.0001

Ultrasound and Clinical Measures for Lymphedema

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Abstract

Background: Treatment for breast cancer has increased patient survivorship exponentially over the past few decades. With increased survivorship, more women are living with the longstanding effects of breast cancer treatment, such as lymphedema. Patients, health care providers, and payers depend on practical and efficient clinical measures to accurately diagnose and monitor disease progression or regression. However, current clinical measures do not include objective measures that assess lymphedetamous tissue accurately. This study compared current measures to a novel use of ultrasound (US) imaging to quantify tissue texture.
Methods and Results: Seventeen women diagnosed with lymphedema completed self-report questionnaires and then were tested twice by two lymphedema physical therapists who measured edema, fibrosis, and limb volume differences. One therapist measured subjects' limbs using US imaging and derived measures of entropy and average pixel intensity. Volume measures were consistent between therapists ($p < 0.01$) but palpation was not ($0.01 < p < 0.72$). Therapists' measures correlated better to subjects' self-report of edema ($0.01 < p > 0.32$) as compared to fibrosis ($0.23 < p > 0.90$). US measures were reliable (Cronbachs's $\alpha = 0.7$ and 0.91 for entropy and API, respectively). Entropy measures demonstrated significant differences between subjects' involved versus uninvolved forearms ($p = 0.03$).
Conclusions: Therapists were not consistent with each other when rating edema or fibrosis; however, they were consistent when measuring limb volume differences. US measures (entropy) demonstrated a significant difference between involved and uninvolved. US imaging, as a tool to quantify subcutaneous tissues, holds promise to be a safe, mobile, and effective method to measure lymphedema tissue texture.

Introduction

Treatment for breast cancer has increased patient survivorship exponentially over the past few decades.[1] With increased survivorship, more women are living with the longstanding effects of breast cancer treatment such as lymphedema. Lymphedema is a chronic swelling condition that can be a result of damage or injury to the lymphatic system, including lymph nodes and lymphatic vessels.[2–5] Damage to the lymphatic transport system results in an overload of lymph fluid that accumulates in the subcutaneous space, causing distortion in limb shape, increased limb weight, decreased limb function, difficulty with clothing fit, increased infection risk, decreased quality of life, and interference with body appearance and/or acceptance.[2,5–7]

Patients, health care providers, and third party payers depend on practical, efficient, and useful tests that can be performed in a clinical setting in order to accurately measure, diagnose, and manage lymphedema. Accurate measures are also necessary to monitor progression or regression of the disease, as well as treatment effects. In the clinical setting, physical therapists (PTs) are healthcare providers who often treat lymphedema and are likely to be involved in diagnosis, treatment, and monitoring of this condition.

The examination of a patient with lymphedema includes a patient's history, patient self-report or perception of symptoms, limb volume measurement, and observation and palpation of skin integrity to assess for edema and fibrosis. Patient questionnaires such as the Lymphedema Symptom, Intensity and Distress Scale (LSIDS)[8] and the Vermont Lymphedema Network Body Map (VLNBM)[9] are utilized to gather information regarding patient perception of symptoms such as fibrosis and edema.

In the clinical setting, the most objective measure of lymphedema is limb volume. Clinicians indirectly measure limb volume by using circumferential measures, taken at specific segments along the length of the arm, and then later converting these measures to total limb volume by using the

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truncated cone or frustrum method.[10,11] Although circumferential measurement of limb volume is reported to be a reliable measurement,[10] it is limited to measures of limb shape and size.

In addition to limb shape and size, changes in subcutaneous tissue are also an important consideration because these subcutaneous changes may affect treatment options, risk of infection, and long-term outcomes. The subcutaneous tissue texture changes can include edema and fibrosis (a sequellae of pooling or long-term edema). Excessive protein-rich lymph fluid that accumulates in the subcutaneous space signals a trigger for increased fibroblastic activity,[2,4] causing a hardening of the tissue, or fibrosis.

Currently, changes in subcutaneous tissues are not quantified with a limb volume measurement. Instead, to assess tissue texture changes, clinicians, such as (PTs), qualitatively judge the amount and quality of edema and fibrosis when they palpate the patient's tissue in the affected area. In addition, clinicians rely on the patient's perception of hardening of the tissue. Therefore, an objective measure to quantify subcutaneous tissue is desirable, given that a number of changes occur in the subcutaneous space in the presence of lymphedema. Furthermore, there are no studies that examine the reliability of clinician palpation of edema and fibrosis, nor are there studies that compare palpation by the clinician to other lymphedema measurement tools.

Ultrasound (US) imaging may be a potential tool to view, assess, and quantify subcutaneous tissue in lymphedetamous limbs. US imaging studies have primarily measured depth of tissue,[12–15] but not tissue texture. However, a pilot study in 2005 used US imaging texture analysis on a subject with breast cancer-related lymphedema.[16] Texture analysis of US images was used to derive the variables entropy and average pixel intensity (API).[16] Entropy is a measure of randomness within the US image that reflects how organized or disorganized the tissue is. API is a measure of brightness within the US image; brighter areas within the tissue correlate to higher echogenicity of the tissue.[17] Echogenicity is a measure of the tissue's ability to reflect an echo from the ultrasound wave and higher echogenicity indicates that the tissue has higher density, suggestive of more connective tissue.

Thus, both entropy and API have the potential to quantify subcutaneous tissues with respect to tissue organization and/or tissue density. Recent studies reported that patients with lymphedema have increased or altered echogenicity in the subcutaneous tissue of their affected limbs; however, the authors did not quantify the echogencity.[18,19]

Thus, there are no reports on: 1) the correlation between palpation by clinicians and patients' subjective self-report or other clinical tools; 2) the reliability of US use in a clinical setting; or 3) the quantification of subcutaneous tissue changes.[18,19] In addition, there is a lack of studies that report on the reliability of palpation by clinicians with subjective self-report or other clinical tools, the reliability of US use in a clinical setting, or the quantification of subcutaneous tissue changes.[18,19]

Therefore, we sought to examine if: 1) clinical assessments performed by PT clinicians and the patient's self-report of arm lymphedema are reliable and correlated with each other; 2) measures of lymphedema derived from US images (API and entropy) of the arm are reliable and correlated with PT clinical assessment and patient self-report of arm lymphedema; and 3) US imaging measures differ between the subjects' involved and uninvolved arms.

Materials and Methods

Subjects

This study was a longitudinal design with two time points for data collection (Fig. 1). To recruit subjects for this study, we posted flyers at local cancer centers and physical therapy clinics and sent letters to patients whom we had seen in the last 5 years in two of our out-patient physical therapy clinics that specialize in lymphedema treatment. Potential participants who responded to a letter or flyer were screened by telephone to determine their eligibility.

Inclusion criteria were women, aged 21 or older, who had undergone unilateral breast cancer treatment that may have included mastectomy, lumpectomy, axillary lymph node dissection, and/or radiation therapy and had confirmed lymphedema diagnosis by a physician. Potential participants were excluded from the study if they had either previous breast cancer treatment or unexplained edema in the uninvolved arm. None of the participants were undergoing intensive lymphedema treatment.

This study was approved by the Institutional Review Board at the University of Vermont (study ID: CHRMS: M11-242) in accordance with their Federal wide Assurance with the US Department of Health and Human Service, Office of Human Research Protections. The authors attest that the research was also undertaken in compliance with the Helsinki Declaration, revised 2008. All subjects provided written, informed consent, and the rights of each subject were protected.

PT clinicians

Clinical measures included subject self-report and measures of lymphedema (edema and fibrosis) taken independently by each clinician. Each clinician was a PT who had greater than 10 years of experience in treating patients with lymphedema, and both were certified in complete decongestive therapy through the Lymphedema Association of North America. The PTs were blinded to the results of each other's assessment.

Session One

Subject self-report measures. After signing a consent form, subjects completed a demographic questionnaire, the Lymphedema Intensity and Distress Scale (LSIDS)[8] and the Vermont Lymphedema Network Body Map (VLNBM)[9] (see Fig. 2 and Fig. 3, respectively). The LSIDS lists 36 symptoms, each of which is rated by the patient from 1 to 10 for intensity and 1 to 10 for distress, where 1 is rated as slight and 10 is severe. The VLNBM is a diagram of a human body, divided into anterior and posterior sections of the face, limb, and torso. Subjects indicated where they were having symptoms of edema and or fibrosis by marking on the respective section on the VLNBM diagram. While the VLBM was a general map of the full body, this study only used the arms and torso sections of the map since interest was focused there.

Clinical measures. The PT clinicians independently assessed both the involved and uninvolved extremity of each subject using measures consistent with clinical practice as described below.

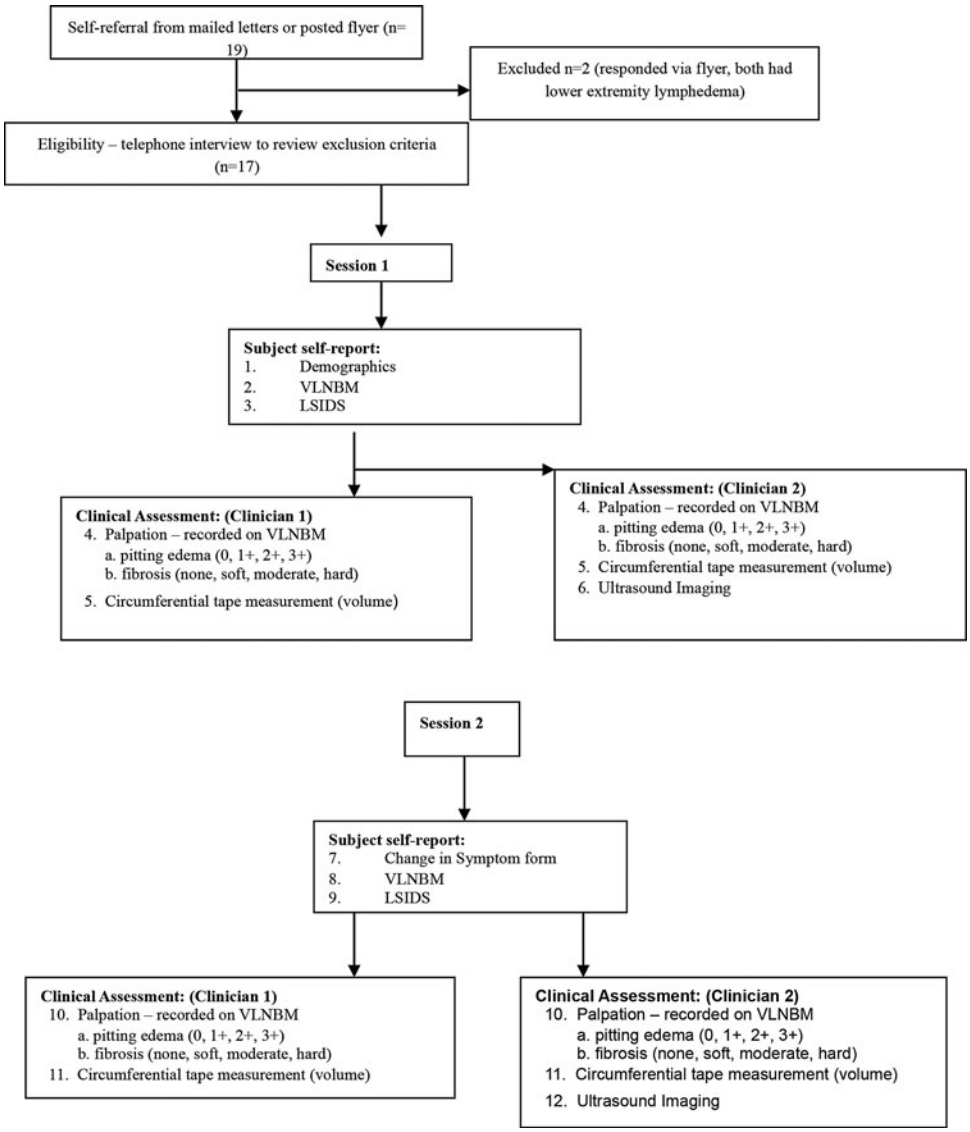

FIG. 1. Study flow.

Palpation assessment for edema and fibrosis. While subjects were sitting, each PT palpated the subject's involved and uninvolved extremity to determine the degree of pitting edema, or increased subcutaneous fluid congestion. To identify pitting edema, the PT applied firm digital pressure into the subject's skin for 5 seconds. If the skin tissue did not rebound and an indentation remained after the finger pressure was removed, the PT judged that pitting edema was present. The PTs scored tissue rebound as 0, 1+, 2+, or 3+. If tissue did not indent and instead immediately rebounded to its previous position, the PT recorded a zero. If a fingerprint remained in the tissue, the clinician recorded a 1+, and if the tissue indented deeper than a finger width, she recorded a 2+. If marked indentation lasted several seconds, the PT recorded a 3+.[20] The PTs recorded pitting edema scores for each arm segment on the VLNBM.

Each PT also palpated each extremity to rate fibrosis, or tissue hardening under the skin. The PTs rated fibrosis as follows: 0, if she judged the tissue was normal; she recorded a '1' if she judged the tissue was soft or boggy, yet the skin was still mobile, a '2'; moderately fibrotic or firm and more difficult to lift the skin, a '3'; and if she judged the tissue as hard, without skin mobility.[4] Each PT recorded fibrotic scores for each arm segment on the VLNBM.

Circumferential measures to assess upper extremity volume. Each PT recorded the circumferential measurements of the subjects' upper extremities while the subjects rested in a supine position. Starting at the ulnar styloid process, the PT measured and recorded circumferential measures every 4 cm along the extremity up to the axilla.[21] Hand volume was not considered and thus not included in the calculation of limb volume. These measures were later converted to volume using the truncated cone formula.[21]

Ultrasound imaging. The primary investigator (KJ, PT2) also obtained US images (Sonosite M-Turbo ultrasound machine with a 15 MHz linear transducer) at two sites on all subjects' involved and uninvolved upper extremities: (1) on the anterior forearm at a point two-thirds the distance proximally from the most distal wrist crease to the midpoint in the ante-cubital fossa; and (2) on the lateral elbow, one half the distance between the mid-cubital fossa and the lateral epicondyle (Fig. 2). The two points were chosen based on

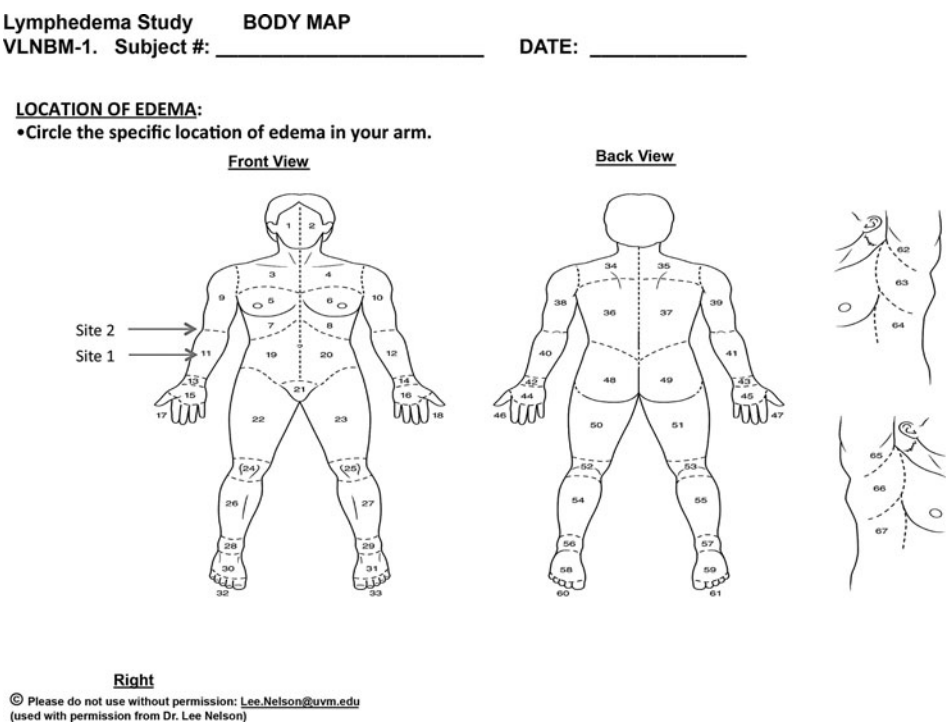

FIG. 2. Vermont Lymphedema Network Bodymap (VLNBM).

previous ultrasound studies.[16,19,30] However, the lateral elbow point is much less studied and the PT clinicians included the lateral elbow because this area is believed to be a common area for fibrosis and it is a consistent circumferential measurement point.

PT2 took five US images at each site and analyzed the images using Matlab ([b]The MathWorks, Inc., Natick, MA). On each US image, eleven square, horizontal regions of interest (ROI)[16] were created at the top of the image to capture information in the superficial tissue layers up to a depth of 4 mm. Each ROI

Lymphedema Symptom Intensity and Distress Survey-Arm Version 2.0

For each symptom below circle yes or no to indicate whether you have had this symptom **DURING THE PAST WEEK.**
If you circle yes, please rate how intense this symptom was using the 1 to 10 point scale.
Also rate how distressed you were by this symptom using the 1 to 10 point scale.

Symptom	Yes/No	Intensity	Distress
1. Heaviness in your arm	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
2.Tightness in your arm	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
3. Burning pain in your arm	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
4. Burning pain in your chest	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
5. Stabbing pain in your arm	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
6.Cramping pain in your arm	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
7. Pain in your arm	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
8. Warmth in your arm	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
9. Coldness in your arm	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
10. Numbness in your arm	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
11. Achiness in your am	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
12. Swelling in your arm	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
13. Hardness in your arm	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
14. Tingling in your arm	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
15. Pins and needles in your arm	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe
16. Difficulty moving arm side to side	Yes No	Slight 1 2 3 4 5 6 7 8 9 10 Severe	Slight 1 2 3 4 5 6 7 8 9 10 Severe

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FIG. 3. Lymphedema Symptom Intensity Distress Survey (LSIDS).

was a 42 pixel square, measuring 4×4 mm. We chose 4 mm based on a previous study.[16] Five images multiplied by 11 ROIs results in 55 measures for each site. To determine reliability, the means across the 55 measures for each site were derived for both average pixel intensity (API) and entropy.

Session Two

Subjects returned for Session Two, 1 to 4 weeks later and completed a ''Change in Symptoms'' questionnaire to report if any symptoms increased or decreased since Session One. The questionnaire also included questions about exposure to inflammatory risk factors such as burns, cuts, heat, intense activity, etc. Subjects completed the LSIDS and VLNBM again to record their symptoms. Each PT repeated assessments as in Session One (Fig. 1).

Statistical analysis

Utilizing pilot data from US images taken from patients diagnosed with lymphedema, a power calculation was performed and a sample size of 14 subjects was determined to be sufficient to detect differences in API and entropy between involved and uninvolved arms within subjects with an 80% power and 5% Type I error. We sought to recruit 20 subjects in the event that subjects were unable to attend the second session.

Associations between clinical assessments made by the two PTs, between PTs and subject's reports and limb volumes were determined by calculating Pearson and Spearman correlation coefficients. Subjects' perceptions of symptoms were compared between forms and visits using a kappa statistic. US measures (API and entropy) were compared with PTs' assessments and with subjects' perceptions of pitting edema and fibrosis using Spearman's rho, while Pearson's was used to correlate limb volumes between PTs and limb volume differences to US measures.

The reliability of US images was analyzed using Cronbach's alpha. A Cronbach's α measure greater than or equal to 0.7 is considered acceptable and those greater than or equal to 0.9 are considered excellent.[22] Mixed model analysis of variance models were used to compare the US measures (API and entropy) between involved and uninvolved arms, whereas a one-way analysis of variance (ANOVA) was used to compare the mean of 55 ROIs for entropy and API to volume differences. *P* values of less than or equal to 5% ($p \leq 0.05$) were regarded as statistically significant. Statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC, USA)

Results

We recruited 17 women with unilateral lymphedema as a result of breast cancer treatment and all subjects had been diagnosed with lymphedema by their healthcare provider. Subjects were on average aged 64 years (range: 48–87) and varied in the duration of lymphedema diagnosis (range: 2 months–14 years). Almost half (53%) of the women wore a day compression sleeve and 59% wore a night compression unit. See Table 1 for other subjects' demographics and characteristics.

Table 1. Subject Characteristics

Characteristics	*Number of subjects (except where noted)*
Age (mean and range in years)	64.1 (48–87)
BMI (mean and range) (kg/m^2)	29.4 (21.6–48.0)
Right hand dominant	16
Left hand dominant	1
Right side involved	7
Left side involved	10
Lumpectomy	8
Partial mastectomy	1
Mastectomy	8
No. nodes removed (mean and range)	14 (3–22)
Sentinel node biopsy	
Yes	7
No	7
Not sure	3
Chemotherapy	
Yes	12
No	5
Radiation treatment	
Yes	14
No	3
Diagnosis of lymphedema since completing cancer treatment (years)	5 years (2 mos–14 yrs)
Completes self-lymphatic drainage	
Yes	15
No	2
Has used compression bandaging	
Yes	14
Currently bandaging	4
No	3
Uses a day compression garment	
Yes	9
No	8
Uses a night compression garment	
Yes	10
No	7
Has had complete decongestive therapy	
Yes	14
No	1
Not sure	2

Correlation of PTs' clinical assessments

Comparisons of pitting edema and fibrosis ratings between PTs. The two PTs were more consistent with fibrosis assessments than they were with edema ratings. When rating the posterior aspects of the upper and lower arm, PT1 and PT2 were highly correlated for judging edema and fibrosis (Spearman's rho = 0.35–0.54; $0.01 < p < 0.05$ and Spearman's rho = 0.37–0.52, $0.01 < p < 0.03$, respectively). The PT's ratings of fibrosis correlated well for the anterior lower arm (Spearman's rho = 0.51; $p < 0.01$). However, the PTs did not demonstrate agreement when rating the anterior upper or anterior lower arm for edema (Spearman's rho = 0.28 and 0.29, $p = 0.12$ and 0.11) or when rating the anterior upper arm for fibrosis (Spearman's rho = 0.06; $p = 0.72$).

Circumference and volume measures. Both PTs demonstrated agreement when measuring circumference at the mid-forearm and elbow (Pearson's r = 0.95–0.97; $p < 0.01$) and when measuring total limb volume difference between involved and uninvolved extremities (Pearson's r = 0.95;

Table 2. Comparison of Lymphedema Diagnostic Criteria by Combining the 17 Subjects Across Two Sessions ($n = 34$)

Threshold criteria for determining the presence of lymphedema using limb volume difference	*PT1 Number of times the subjects met threshold*	*PT2 Number of times the subjects met threshold*	*Number of times PT1 and PT2 agreed*
Minimal detectable change (150 mL)[33]	21	21	20 (59%)
>100 mL (Minimal clinical important difference)[57]	21	23	21 (62%)
≥10% limb volume difference	17	17	17 (50%)
≥5% limb volume difference	21	22	20 (59%)
≥3% limb volume difference	26	24	24 (71%)
Number of times subjects did not meet ≥3% limb volume difference.	7*	10	7 (19%)

Seventeen subjects tested twice, $N = 34$; *1 missing data point for PT 1.

$p < 0.01$). In addition, each PT demonstrated a high correlation between sessions when measuring subjects' limb circumference at the mid-forearm and elbow (Pearson's r = 0.96–0.98; $p < 0.01$) and when measuring total limb volume differences between the involved and uninvolved extremities (Pearson's r = 0.96–0.98; $p < 0.01$).

We also compared limb volume differences between the two PT's calculations in light of the numerous published definitions of lymphedema.[23–28] A minimal detectable change (MDC) was set at 150 mL.[10] Out of 17 subjects tested twice ($n = 34$), the two PTs agreed 20/34 times (59%) that subjects had greater than 150 mL of limb volume difference (Table 2). Using a minimal volume difference of 100 mL to define lymphedema,[2], the two PTs agreed that 21/34 (62%) subjects actually had lymphedema. Other definitions of lymphedema include a minimum limb volume difference of ≥3%, 5%, or 10% difference.[24–28] If the definition of lymphedema were a minimum 5% difference in volume, the two PT's agreed that 20/34 (59%) of the subjects had lymphedema. If the definition was set at a 10% minimum, 16/34 (47%) of the subjects had lymphedema.

Subjects' perception of lymphedema

Lymphedema symptoms between sessions. Comparing the VLNBM results between Sessions One and Two, subjects demonstrated substantial agreement when rating their edema for the anterior lower arm ($k = 0.63$) and fibrosis for the anterior upper and lower arm ($k = 0.82$ and 0.64, respectively). However, subjects did not demonstrate sufficient agreement when rating edema of the anterior upper arm or the entire posterior arm, nor did they show agreement when rating fibrosis for the entire posterior arm. In addition, subjects did not demonstrate significant agreement between sessions when rating their edema and fibrosis symptoms using the LSIDS ($k = 0.23$ and 0.17, respectively). However, nine of seventeen subjects (53%) reported that their symptoms had changed between sessions (time between sessions ranged from 1–4 weeks). Five subjects reported that their symptoms decreased and four perceived that their symptoms had increased.

Comparison of subjects' symptoms between questionnaires. When comparing subjects' perception of their fibrosis and edema using the LSIDS versus the VLNBM, subjects demonstrated substantial agreement when rating fibrosis ($k = 0.65$) and only fair agreement when rating edema ($k = 0.27$) in their arms.

PT assessment (VLNBM) versus subject rating (LSIDS) of edema and fibrosis. We selected two items from the LSIDS questionnaire (''Swelling in your arm'' and ''Hardness in your arm'') to examine the correlation of the subjects' perception of edema to ratings of edema based on the PT's palpation of edema. Subjects who circled 'yes' for either item proceeded to rate the intensity of their edema on a scale from one (slight) to 10 (severe). PT2 was consistent with the subjects' rating of edema in both the upper and lower arm (Spearman's rho = 0.37–0.42; $0.01 < p < 0.03$) (Table 3). However, PT1's edema rating correlated with the subjects' for the anterior lower arm (Spearman's rho = 0.40, $p = 0.02$) and posterior lower arm (Spearman's rho = 0.48, $p = 0.01$), but not the anterior upper arm or posterior upper arm. Correlations between the PTs' ratings of fibrosis of the upper or lower arm did not correlate well with subjects' rating of ''hardness'' in their arm (Table 3).

Ultrasound analysis

Reliability. PT2 took five ultrasound (US) images at two different sites on each subjects' involved and uninvolved

Table 3. PT Assessment (VLNBM) versus Subject Rating (LSIDS) of Edema and Fibrosis

	Spearman's rho	P *value*
PT1/Subject Edema		
Anterior upper arm	0.31	0.08
Anterior lower arm	0.40	**0.02**
Posterior upper arm	0.18	0.32
Posterior lower arm	0.48	**0.01**
PT2 /Subject Edema		
Anterior upper arm	0.42	**0.01**
Anterior lower arm	0.37	**0.03**
Posterior upper arm	0.38	**0.03**
Posterior lower arm	0.38	**0.03**
PT1 /Subject Fibrosis		
Anterior upper arm	0.02	0.90
Anterior lower arm	0.09	0.60
Posterior upper arm	0.04	0.84
Posterior lower arm	0.15	0.41
PT2 /Subject Fibrosis		
Anterior upper arm	0.06	0.75
Anterior lower arm	0.03	0.86
Posterior upper arm	0.04	0.81
Posterior lower arm	0.21	0.23

arms during Session One and again during Session Two. When using entropy and API derived from the US image as continuous variables of measurement, PT2 demonstrated good reliability across the five trials (Cronbachs's $\alpha = 0.7$ and 0.91 for entropy and API, respectively).

Comparison of US and PT2's clinical assessment of edema and fibrosis. Ultrasound variables taken by PT2 were compared to her palpation assessments of edema and fibrosis from the VLNBM. There was not a significant correlation between ultrasound measures (API or entropy) at the anterior lower arm compared to PT2's assessment of edema and fibrosis (Spearman's rho = –0.25–0.18; $0.16 < p < 0.88$) At the lateral elbow, which spans the posterior upper and lower arm portions indicated on the VLNBM, PT2's assessment demonstrated significant correlations between API and fibrosis on the posterior upper arm (Spearman's rho = 0.45; $p < 0.01$) and posterior lower arm (Spearman's rho = 0.41; $p = 0.02$). In addition, palpation of edema compared to entropy demonstrated significant correlation in the posterior lower arm (Spearman's rho = –0.39; $p = 0.02$).

Comparison of US and limb volume measures. Ultrasound measures were compared to limb volume differences that were taken by PT2. There was not a correlation between US measures for either API (Pearson's r = 0.09; $p = 0.62$) or entropy (Pearson's r = –0.14; $p = 0.45$) in relation to volume differences.

Comparison of US measures and self-report. The ultrasound variables (API and entropy) were compared to the subjects' self-report (LSIDS) for edema and fibrosis. US measures of entropy correlated well with subjective report of edema ratings at the lateral elbow (Spearman's rho = –0.35; $p = 0.05$). However, there was not a significant correlation with either edema or fibrosis at the forearm (Spearman's rho = –0.09–0.12; $0.57 < p < 0.97$).

Comparison of US measures between involved and uninvolved limbs. We used an ANOVA to examine the ultrasound variables (API and entropy) between the involved and uninvolved extremities. Mean entropy at the forearm, demonstrated a significant difference between involved [mean = 6.09; CI(5.98–6.21)] and uninvolved sides (mean = 6.17; CI(6.05–6.28)], $p = 0.03$) (Table 4). However, entropy was not significantly different at the lateral elbow ($p > 0.05$) between involved and uninvolved sides and API did not reach statistical significance at either site.

Discussion

Our study examined current clinical measures of lymphedema between two experienced PTs, as well as a novel measure utilizing US imaging. US imaging was also compared to clinical assessments, as well as to subject perception of lymphedema symptoms. We found that subjective measures such as palpation and subject perception were not consistent, whereas circumferential tape measures used to calculate limb volume were consistent between sessions and clinicians. Our analysis comparing US images to clinical assessment of fibrosis demonstrated good correlation for API at the lateral elbow. In addition US imaging compared to clinical assessment of edema demonstrated good correlation for entropy on the posterior lower arm. Finally, we found that US imaging is reliable for measuring mean entropy between involved and uninvolved limbs at the anterior forearm.

PT assessments compared to subject perception of arm lymphedema

Palpation. Palpation is used routinely in the clinic to judge lymphedetamous tissue. Although there are grades (1+, 2+, 3+) and terms (soft, moderate, hard, brawny) commonly used, the literature lacks operational definitions to support these subjective tests. We attempted to study how well these tests agreed between two experienced PTs.

Our results indicate that two experienced PT's rating of fibrosis and edema have varied agreement depending on anatomical location. The PTs agreed when judging edema of the posterior arm but not the anterior arm. Fibrosis ratings were more consistent on the anterior lower arm and along the entire length of the posterior aspect of the arm; however, the PTs did not reach agreement rating fibrosis along the anterior upper arm. It is unclear why the PTs did not agree on ratings of edema and fibrosis on the anterior upper arm.

Other studies that attempt to quantify subcutaneous characteristics also use the anterior forearm. For example, studies using tonometry and US imaging test the anterior forearm, likely due to convenience because the anterior forearm is a relatively level surface on which an external device such as an ultrasound head or tonometry plunger could be applied.[29,30] In another study that tested reliability between two examiners who recorded US images at two different sites on the arm, the authors reported excellent results at the anterior forearm versus fair to good of the upper anterior arm.[30] Similar to our study, Kim et al.[30] had more consistent results testing the anterior forearm versus the upper anterior arm; however, our PTs also demonstrated consistency along the length of the posterior arm which other studies have not tested.

Volume. In our study, the two PTs consistently measured limb volumes using a circumferential measurement technique. There is extensive agreement in the literature that indicates circumferential measurement is reliable and valid,[10,11,31,32] as

Table 4. Ultrasound API and Entropy Measures (Mixed Model Repeated Measures Analysis of Variance)

	Mean Entropy (95% CI)	P *value*	*Mean API (95% CI)*	P *value*
Anterior forearm				
Involved	6.09 (5.98–6.21)	**0.03**	49.02 (46.07–51.96)	0.93
Uninvolved	6.17 (6.05–6.28)		49.08 (46.13–52.03)	
Lateral elbow				
Involved	6.07 (5.98–6.17)	0.64	50.39 (48.38–52.40)	0.23
Uninvolved	6.09 (6.00–6.18)		49.32 (47.31–51.33)	

well as easy to perform in the clinic. Our study supports that circumferential tape measures are a consistent measure of limb volume.

Although limb volume is a routine measure for lymphedema diagnosis as well as a measure of treatment outcome, authors still do not agree on a consistent threshold for volume differences between involved and uninvolved limbs in order to make a diagnosis of lymphedema. When we considered the various threshold levels between involved vs. uninvolved limbs (≥3%, 5%, 10%, >200 mL, >2 cm, >5 cm, etc.[24,26,33–35]) that are used to define lymphedema, we found that the percent agreement varied between the two PTs about the presence of lymphedema. In addition, diagnostic definitions solely based on volume fail to identify subjects who may have had extensive treatment and who were regularly using compression garments. The use of compression garments in our participants was reflected in the fact that some individuals presented with less limb volume in their involved extremity compared to their uninvolved extremity. These data support the argument that volume should not be the only objective measure of lymphedema.

Subject self-report. Studies indicate that patients' perceptions, as opposed to any diagnostic test, are the best indicators of lymphedema symptoms,[36,37] particularly for acute lymphedema. Given that our study included participants with both acute and chronic lymphedema (diagnosed by a physician), we acknowledge that subjects may change their perception of severity once they have accepted and lived with their lymphedema diagnosis for a long period of time. Consequently, some subjects with chronic lymphedema in our cohort may have under reported their lymphedema symptoms and thus appeared to disagree with the PTs' ratings.

In contrast, in a study of women with chronic lymphedema, the authors compared physical measures to self-report and found higher agreement between the physical measures versus moderate agreement with self-report.[25] Future studies could include larger cohorts that are subgrouped based on lymphedema chronicity and assessed separately.

In addition, studies investigating acute lymphedema considered the arm as a whole rather than individual arm segments, as we did in our study. When asked to interpret isolated segments of the arm, subjects may perceive symptoms differently when regarding their arm as a whole. We speculate that the subjects were better rating their anterior arm, as this area might be easier for the subjects to see and therefore self-assess.

Ultrasound imaging: Reliability and correlation with PT2s clinical assessments and subject self-report

Our study showed that one PT could consistently take US images that were reliable for both API and entropy at two different sites (the lateral elbow and anterior forearm). In another US study in 2005, ten US images (converted to API and entropy) were taken at the lateral elbow of one subject who had a bilateral mastectomy and lymphedema of one limb.[16] The authors reported minimal variation between images, with entropy having less variation, suggesting that US as a potential clinical tool when using entropy as an outcome measure.

We compared PT2's ratings of edema and fibrosis to her recordings of the US variables (API and entropy). Although there was not a correlation at the anterior forearm, the lateral elbow demonstrated correlation between API and PT2's ratings of fibrosis. It is unclear why there was not a correlation at the anterior forearm; however, as previously stated, the two PTs were less consistent rating the anterior forearm for edema in this study compared to the posterior arm.

Ultrasound measures between involved and uninvolved limbs

Using API and entropy, we found a significant difference in mean entropy between involved and uninvolved extremities on the anterior forearm. Mean entropy was lower on the involved arms compared to the uninvolved arms. In contrast, Ashikaga et al. (1995)[16] measured the lateral elbow of one subject and found that mean entropy tended to be higher on the involved versus the uninvolved side. A major difference existed between the subject studied by Ashikaga et al. (1995) and our subjects in that the subject studied by Ashikaga et al. (1995) had a bilateral mastectomy whereas our subjects did not have any previous surgery on the uninvolved side. We question if the subject in Ashikaga's (1995) study had a true 'control,' or a true uninvolved side. In addition, our subjects were a mixed cohort of acute and chronic (2 months to 14 years) cases of lymphedema, versus Ashikaga's subject, who had chronic lymphedema.

US measures may be capturing valuable differences in the subcutaneous layer of lymphedetamous tissue that clinicians are unable to identify. Entropy of the anterior forearm was found to be statistically different between involved and uninvolved limbs; however, our PTs did not consistently agree on edema assessments at this location. US imaging may be a valuable tool for identifying changes in tissue at the subdermal level. However, future studies are needed to continue to evaluate this potential tool and studies should be repeated on cohorts who have different degrees of lymphedema with regard to severity and chronicity in order to elucidate further the usefulness of US measures in evaluating and managing this condition, such as: (1) subjects who have undergone breast cancer treatment, yet not diagnosed with lymphedema, (2) subjects with acute early onset edema, and (3) subjects with chronic lymphedema.

In addition, future studies are recommended to include anatomical markers for US measures that correspond with current palpation sites, such as those included in this study, yet ideally would include other sites such as in the hand and the posterior aspect of the upper arm (i.e., triceps.muscle area).

Limitations

Our study was limited by a small sample size ($n = 17$) that had a large range in time since lymphedema diagnosis (2 months to 14 years). Subjects with longer standing lymphedema are expected to have different tissue changes, may perceive/accept their edema differently, and may each have different long-term care of their lymphedema with a variety of compression options (which are expected to affect both edema and fibrosis). About half of our subjects wore compression garments regularly. These variations may have skewed our results because the use of compression garments are believed to affect tissues, although there are no studies to support this widely held clinical assumption. Therefore, it is recommended that subjects wearing regular compression

garments be tested as a separate group. We recommend that future studies examine acute and chronic lymphedema subjects separately if the interest is to quantify tissue texture.

Another limitation to our study was the placement of the US transducer at the lateral forearm (site 2). We chose this site because it had been previously studied. However, the lateral forearm was a difficult site to match with the VLNBM questionnaire because the lateral elbow spanned two segments of VLNBM diagram. Thus, it was unclear if clinical assessments of the lateral elbow were recorded under the 'anterior' or 'posterior' portion of the diagram on the VLNBM. Consequently, comparing US results to clinical assessments at the lateral elbow may not have been as accurate.

Last, our study examined US images to a depth of 4 mm, which primarily includes the dermis and superficial subcutaneous tissue. After viewing multiple images, particularly from subjects who had variable levels of edema (acute to chronic), we believe that analyzing US images to a deeper tissue level (up to 8 mm) may have provided more valuable information about subcutaneous tissue. However, depth is a difficult threshold to define as changes in depth will identify different structures for different degrees of edema.

An individual with high volume edema may have subcutaneous edema and fibrosis up to 8 mm deep. On the contrary, acute edema measured up to 8 mm may include subfascial structures, or even superficial skeletal muscle. Therefore, future US imaging studies that examine deeper tissue layers should consider grouping subjects by limb volume, progression of disease, and/or severity.

Conclusions

Our findings indicate that subjects are consistent when rating the anterior aspect of their arms and that PTs are consistent in rating the posterior aspect of the subjects' arms. When comparing US measures (entropy and API), we found that entropy measured on the anterior forearm was significantly different between involved and uninvolved extremities. Thus, US imaging has promise as a clinical tool for quantifying lymphedema.

Acknowledgments

Thank you to the University of Vermont, Department of Rehabilitation and Movement Science, for providing the ultrasound machine used in this study.

Author Disclosure Statement

No competing financial interests exist.

References

1. Breast Cancer Facts and Figures, 2011–2012. *American Cancer Society* 2011; http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-030975.pdf. Accessed November, 2014.
2. Casley-Smith JR, Boris M, Weindorf S, Lasinski B. Treatment for lymphedema of the arm—The Casley-Smith method: A noninvasive method produces continued reduction. Cancer 1998;83:2843–2860.
3. Hinrichs CS, Watroba NL, Rezaishiraz H, et al. Lymphedema secondary to postmastectomy radiation: Incidence and risk factors. Ann Surg Oncol 2004;11:573–580.
4. Foldi M, Foldi E, Kubik S, eds. *Textbook of Lymphology,* first ed. Munich: Deutsche Bibliothek; 2003.
5. Lawenda BD, Mondry TE, Johnstone PA. Lymphedema: A primer on the identification and management of a chronic condition in oncologic treatment. CA Cancer J Clin 2009;59:8–24.
6. Hayes SC, Johansson K, Stout NL, et al. Upper-body morbidity after breast cancer: Incidence and evidence for evaluation, prevention, and management within a prospective surveillance model of care. Cancer 2012;118:2237–2249.
7. Harris SR, Hugi MR, Olivotto IA, Levine M. Clinical practice guidelines for the care and treatment of breast cancer: 11. Lymphedema. CMAJ 2001;164:191–199.
8. Ridner SH. Developement of the lymphedema symptoms intensity and distress scale arm. J Clin Oncol 2010;28:7.
9. Nelson L. *Vermont Lymphedema Network Body Map*. 1999.
10. Taylor R, Jayasinghe UW, Koelmeyer L, Ung O, Boyages J. Reliability and validity of arm volume measurements for assessment of lymphedema. Phys Ther 2006;86:205–214.
11. Deltombe T, Jamart J, Recloux S, et al. Reliability and limits of agreement of circumferential, water displacement, and optoelectronic volumetry in the measurement of upper limb lymphedema. Lymphology 2007;40:26–34.
12. Balzarini A, Milella M, Civelli E, Sigari C, De Conno F. Ultrasonography of arm edema after axillary dissection for breast cancer: A preliminary study. Lymphology 2001;34:152–155.
13. Gniadecka M. Localization of dermal edema in lipodermatosclerosis, lymphedema, and cardiac insufficiency. High-frequency ultrasound examination of intradermal echogenicity. J Am Acad Dermatol 1996;35:37–41.
14. Doldi SB, Lattuada E, Zappa MA, Pieri G, Favara A, Micheletto G. Ultrasonography of extremity lymphedema. Lymphology 1992;25:129–133.
15. Mellor RH, Bush NL, Stanton AW, Bamber JC, Levick JR, Mortimer PS. Dual-frequency ultrasound examination of skin and subcutis thickness in breast cancer-related lymphedema. Breast J 2004;10:496–503.
16. Ashikaga T, Burns D, O'Brien P, Schaberg KB, Huston D. Texture analysis of post breast cancer lymphedema ultrasound images obtained using a portable device—A pilot study. Lymphat Res Biol 2005;3:147–155.
17. Bianchi S, Martinoli C. *Ultrasound of the Musculoskeletal System: Diagnostic Imaging*. New York: Springer; 2007.
18. Devoogdt N, Pans S, De Groef A, Geraerts I, Christiaens MR, Neven P, Vergote I, Van Kampen M. Postoperative evolution of thickness and echogenicity of cutis and subcutis of patients with and without breast cancer-related lymphedema. Lymphat Res Biol 2014;12:23–31.
19. Tassenoy A, De Mey J, De Ridder F, Van Schuerbeeck P, Vanderhasselt T, Lamote J, Lievens P. Postmastectomy lymphoedema: Different patterns of fluid distribution visualized by ultrasound imaging compared with magnetic resonance imaging. Physiotherapy 2011;97:234–243.
20. Sussman C, Bates-Jensen B., eds. Wound Care: *A Collaborative Practice Manual for Health Professionals.* 3rd ed. Philadelphia: Lippincott Williams and Wilkins; 2007.
21. Sitzia J. Volume measurement in lymphoedema treatment: Examination of formulae. Eur J Cancer Care (Engl) 1995;4:11–16.
22. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–174.
23. Liljegren G, Holmberg L. Arm morbidity after sector resection and axillary dissection with or without postoperative

radiotherapy in breast cancer stage I. Results from a randomised trial. Uppsala-Orebro Breast Cancer Study Group. Eur J Cancer 1997;33:193–199.
24. Stout NL, Pfalzer LA, Levy E, et al. Segmental limb volume change as a predictor of the onset of lymphedema in women with early breast cancer. PM R 2011;3:1098–1105.
25. Czerniec SA, Ward LC, Refshauge KM, et al. Assessment of breast cancer-related arm lymphedema—Comparison of physical measurement methods and self-report. Cancer Invest 2010;28:54–62.
26. Stanton AW, Badger C, Sitzia J. Non-invasive assessment of the lymphedematous limb. Lymphology 2000;33:122–135.
27. Armer JM, Stewart BR. A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. Lymphat Res Biol 2005;3:208–217.
28. Hayes S, Cornish B, Newman B. Comparison of methods to diagnose lymphoedema among breast cancer survivors: 6-month follow-up. Breast Cancer Res Treat 2005;89:221–226.
29. Chen YW, Tsai HJ, Hung HC, Tsauo JY. Reliability study of measurements for lymphedema in breast cancer patients. Am J Phys Med Rehabil 2008;87:33–38.
30. Kim W, Chung SG, Kim TW, Seo KS. Measurement of soft tissue compliance with pressure using ultrasonography. Lymphology 2008;41:167–177.
31. Karges JR, Mark BE, Stikeleather SJ, Worrell TW. Concurrent validity of upper-extremity volume estimates: Comparison of calculated volume derived from girth measurements and water displacement volume. Phys Ther 2003;83:134–145.
32. Mayrovitz HN, Sims N, Macdonald J. Assessment of limb volume by manual and automated methods in patients with limb edema or lymphedema. Adv Skin Wound Care 2000; 13:272–276.
33. Armer JM. The problem of post-breast cancer lymphedema: Impact and measurement issues. Cancer Invest 2005;23: 76–83.
34. Cheville AL, McGarvey CL, Petrek JA, Russo SA, Thiadens SR, Taylor ME. The grading of lymphedema in oncology clinical trials. Semin Radiat Oncol 2003;13:214–225.
35. McLaughlin SA, Wright MJ, Morris KT, et al. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: Objective measurements. J Clin Oncol 2008;26:5213–5219.
36. Armer JM, Radina ME, Porock D, Culbertson SD. Predicting breast cancer-related lymphedema using self-reported symptoms. Nurs Res 2003;52:370–379.
37. Norman SA, Localio AR, Potashnik SL, et al. Lymphedema in breast cancer survivors: Incidence, degree, time course, treatment, and symptoms. J Clin Oncol 2009;27:390–397.

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