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Original Article

Is ultrasound a useful tool for supporting lymphedema diagnosis or monitoring the effectiveness of complex decongestive therapy in patients with breast cancer-related lymphedema?

Ozan Volkan Yurdakul, Teoman Aydin

Bezmialem Vakıf University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Istanbul, Turkey

Abstract

Aim: To determine whether ultrasound is a useful tool for supporting the diagnosis of lymphedema and/or monitoring the effectiveness of complex decongestive therapy in patients with breast cancer-related lymphedema (BCRL).

Materials and Methods: We studied both arms of 21 BCRL patients (one affected, one not-affected as a control). Patients underwent 30 sessions of complex decongestive therapy and bandaging (5 days/week, 45 min/day). The skin was marked at 0, 10, 20, and 35 cm between the volar wrist and acromioclavicular joint and between the dorsal wrist and posterolateral margin of the acromion before treatment and on the last day of treatment. Volume of the arm (Vtotal) was calculated by circumferential measurements with dermal and subcutaneous tissue thickness and compliance measurements. We summed thicknesses as "UStotal" and averaged compliances to determine "Compliance" values. The change of values on the affected side were compared to the unaffected side. We examined correlations between Vtotal, (standard method), UStotal, and Compliance.

Results: Change of Vtotal ($p = 0.004$) and UStotal ($p = 0.045$) with treatment were different between the affected and unaffected arm. Compliance did not change in affected side with treatment. When the correlation between Vtotal, UStotal, and Compliance are performed, before treatment, after treatment, and the change with treatment values were correlated between Vtotal and UStotal ($r = 0.626, 0.604, 0.459$ respectively), no correlation was found between Vtotal and Compliance.

Conclusion: In these patients, UStotal can be used to support the diagnosis of BCRL and/or monitor treatment in this population. UStotal/body mass index of ≥0.41 mm/kg/m^2 can aid the diagnosis of BCRL with 81% sensitivity, 90.5% specificity, and 0.823 area under the curve (AUC). However, compliance does not seem an appropriate measurement for diagnosis and/or treatment monitoring.

Keywords: Lymphedema; ultrasound; decongestive treatment; arm volume.

INTRODUCTION

Breast cancer-related lymphedema (BCRL) is a type of secondary lymphedema caused by surgical resection of axillary lymph nodes, fibrosis induced by radiation during treatment, obstruction of lymphatics by metastatic tumor, or infection (1). The estimated prevalence of BCRL is reported to be 25% (2). Complex decongestive therapy is considered the most effective conservative therapy, and it comprises manual lymphatic drainage, non-elastic bandage compression therapy, exercise, and skin care (3). Decongestive therapy is considered to exert force on the interstitial fluids and proteins inside lymphatics thereby shifting them toward lymphatic vessels (4).

Various methods have been described to diagnose lymphedema and monitor treatment success in upper extremity lymphedema. Measuring the affected extremity total volume with upper extremity circumference measurements using measurement tapes, water displacement volumetry, and infrared optoelectronic volumetry have been suggested for this purpose previously (5, 6). Among these, volume displacement and circumferential limb measures have been accepted as gold standards for measuring changes in limb volume (7). Arm circumferential measurements are valid and reliable

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Corresponding Author: Ozan Volkan Yurdakul, Bezmialem Vakıf University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Istanbul, Turkey, **E-mail:** yurdakul_ozan@yahoo.com

measurements of limb volume and appear to be much more efficient in the clinical settings (8). Additionally, clinical severity of lymphedema is usually graded according to International Society of Lymphology (ISL) staging as follows: Stage 1, early accumulation of fluid that subsides with limb elevation; Stage 2, tissue swelling that is not reduced by limb elevation alone, pitting usually occurs; and Stage 3, lymphostatic elephantiasis in which pitting can be absent with skin changes (9). However, ISL staging usually does not reflect the distribution and progression of the disease, and, thus, more precise measurements for delineating disease status are warranted (10).

Increased skin and subcutaneous tissue thickness is a typical feature of lymphedema (11). Ultrasound can visualize the thickening of subcutaneous, epifascial, and subfascial compartments and accumulation of interstitial fluid (12). For this reason, ultrasound is widely deployed as a non-invasive and inexpensive screening method to diagnose lymphedema and monitor its treatment of. Recent literature has focused mainly on the use of ultrasonography to aid in diagnosis (11, 13, 14). However, only few studies have investigated ultrasound measurements as a tool to monitor treatment (15, 16). Therefore, the present study aimed to determine whether ultrasound can be used as a useful tool for supporting diagnosis and/or monitoring the treatment of patients with BCRL of the arm.

MATERIAL and METHODS

Study design and patient enrollment

This cross-sectional trial included 21 female patients with unilateral BCRL who were admitted to our tertiary outpatient clinic between March 2018 and March 2019. The unaffected limb of the patients was set as the control arm. The study was performed in accordance with the Declaration of Helsinki–Ethical Principles for Medical Research Involving Human Subject, and approval was obtained from the Institutional Ethics Committee (No: 2018-5/45). All patients provided their written informed consent before participating in the study. The inclusion criteria were as follows: 1) undergone breast cancer surgery, 2) a 2-cm difference in circumferential measurement at the same level between the affected and unaffected arm, and/or having a diagnosis of lymphedema with lymphoscintigraphy. The exclusion criteria included 1) bilateral lymphedema and 2) body mass index (BMI) of >35 kg/m^2.

Because there are no studies similar to the present study, effect sizes were calculated based on data after preliminary analysis with 15 patients in each group. A minimum of 21 patients was considered to be sufficient for each group (for Volume total [Vtotal]), with an effect size of 0.831, 80% power and 0.05 level of significance.

Complete Decongestive therapy procedure

All patients were treated by an experienced physiotherapist 45 minutes once a day, 5 days/week for a total of 30 sessions. In each session, the physiotherapist perfomed manual lymphatic drainage (MLD) techniques including stationary circles, scooping, pumping, and rotary techniques as well as tissue softening techniques such as kneading and the skin fold technique as described by Földi *et al.* (17). After MLD, multi-layer bandaging (finger gauze bandaging, tubular stockinet, soft padding bandage, foam pads, and short-stretch bandage layers) was performed until the next session. Home exercises promoting lymphatic flow were programed by the same physiotherapist. The same measurements were obtained both for the affected and unaffected (control) arms before and after treatment.

Circumferential measurements

The patient's arm was laid in the supine position, with both arms on the bed. To determine the measurement sites on patient's arms, a measurement tape was placed between midpoint of the volar wrist crease and acromioclavicular joint anteriorly and between midpoint of the dorsal wrist (between styloid processes) and posterolateral margin of the acromion posteriorly by a physician. Assuming the wrist as the "0" point, the distance of 10, 20, 30 and 35 cm from 0 point were marked by tape measurement both anteriorly and posteriorly, forming four truncated cones for bilateral measurement. The last segment was constructed as 5 cm not to exceed the maximal length of arm in women. Circumferential measurements were performed by measuring the circumference of each arm between relevant sites. Arm volumes of both affected and unaffected sides were calculated from these circumferential measurements. The volume of each of the four arm segments were calculated using the formula for a truncated cone as follows (18):

$$V = h(C_1^2 + C_1C_2 + C_2^2) / 12\pi$$

Where V is the volume of segment, C_1 and C_2 are the circumferences at end segments, and h is the distance between two measurements sites. The sum of all four segments was calculated as total volume (Vtotal) of that limb.

Ultrasonography measurements

Ultrasonography was performed by a certified physiatrist using a 7–13 MHz linear array probe with a calibrated device (LOGIQ P5, GE Healthcare, Chicago, IL, USA) immediately after performing circumferential measurements. The same points used for circumferential measurements were used for the ultrasonography procedure. The midpoint of the marks between the sides of the measuring tape, which was previously marked, was considered to be the ultrasound measuring site. The probe was placed perpendicularly to the upper limb axis both in anterior and posterior arms to the points where circumferential measurements were performed. Enough amount of gel was placed on the measurement site to avoid compression of the probe. A line was drawn by selecting the software system of the ultrasound between upper border of the dermis and the echogenic border of the muscular fascia. The same measurement was performed twice with no compression and maximal

compression (e.g., Figure 1). Maximal compression was defined as the point where thickness of the soft tissue could no longer be reduced with additional compression (19). The thicknesses acquired with no compression from ten points of each limb were summed to obtain total ultrasound thickness (UStotal) for each limb. Additionally, resistance to compression (Compliance) measurements was calculated as follows (19):

(Thickness with no compression - thickness with maximal compression)/ Thickness with no compression.

After obtaining a compliance value for each ten points, the mean values were calculated for the mean compliance of that arm. The difference of measurements before and after treatment were calculated by subtracting the value after treatment from the value before treatment. The difference values are represented as $Vtotal_{dif}$, $UStotal_{dif}$, and $Compliance_{dif}$.

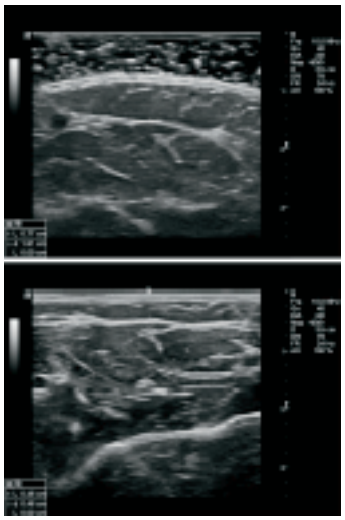

Figure 1. An example of the measurement of soft tissue thickness (dotted lines) without compression (a) and with compression (b) on ventral aspect of 10 cm.

Statistical Analysis

IBM SPSS Statistics v21.0 statistical software (Armonk, NY, USA) was used to perform all statistical analyzes. The Shapiro–Wilk test was used to test variable distribution. Descriptive statistics were indicated as "mean ± standard deviation" and "median, minimum – maximum" for quantitative variables; and "frequency and percentage [n (%)]" for categorical variables. The Mann-Whitney U test was used to compare two groups with non-normal distributed variables. The Spearman's rank correlation analysis was used to assess correlations between non-normal distributing variables. The relations were interpreted as highly correlated when r was ≥ 0.60, moderately correlated when r was between 0.30 and 0.60, and weakly correlated when r was ≤ 0.30 (20). Receiver operating characteristic (ROC) curve analysis was performed to detect the cutoff values for UStotal and UStotal/BMI, and data were presented as area under the curve (AUC), 95% confidence intervals (CI), sensitivity, and specificity values. Relevant cutoff values were calculated according to the Youden's index. A p value of < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

We studied 42 upper limbs (21 affected, 21 unaffected) of BCRL patients. The mean age was 52.4±12.4 years, mean BMI was 23.7±5.5 kg/m^2, and symptom duration was 30.7±45.2 months. Six (29%) patients' right arm and 15 (71%) patients' left arm was affected, while 11 (52%) patients underwent partial mastectomy and 10 (48%) patients underwent modified radical mastectomy.

The affected arms' Vtotal, UStotal, and compliance values were 2393.63±797.16 mm^3, 13.04±3.46 mm, and 0.37±0.07 before the treatment and 2268.55 ± 715.46 mm^3, 12.68±2.93 mm, 0.37±0.08 after the treatment, respectively. The unaffected arms' Vtotal, UStotal, and compliance measurements were 2200.29±471.83 mm^3, 10.81±2.24 mm, and 0.39 ± 0.07 before the treatment and 2325.26±614.54 mm^3, 10.76±2.24 mm, and 0.45±0.07 after treatment, respectively. Table 1 presents the demographic and clinical characteristics of the study population.

Between group comparisons of measurements

Table 2 presents the comparison of measurements between the affected and unaffected arms. There was a significant difference between the affected and unaffected limb in terms of the pre- and post-treatment difference in Vtotal (p =0.004), UStotal (p =0.045), and compliance (p=0.003).

Correlation between circumferential and ultrasonographic measurements

There was a positive and strong correlation between Vtotal and UStotal (r =0.626, p =0.002), but there was no significant correlation between Vtotal and Compliance measurements (p =0.989) before treatment. Additionally, after the treatment, Vtotal showed a strong positive correlation with UStotal (r=0.604, p=0.004) but no significant correlation with Compliance (p=0.134). Regarding the difference in measurements before and after the treatment, $Vtotal_{dif}$ showed a positive, moderate correlation with $UStotal_{dif}$ (r=0.459, p=0.047) but no significant correlation with $Compliance_{dif}$ (p=0.788). Correlations between measurement parameters in affected limbs are presented in Table 3.

Diagnostic performance of ultrasonographic measurements

The results of the ROC analysis determined that a cutoff value of ≥11.17 mm for UStotal determines BCRL with a sensitivity of 71.4%, specificity of 71.4%, and an AUC of 0.739 (CI = 0.588–0.889). UStotal/BMI of ≥0.41 mm/kg/m^2 distinguishes limbs with BCRL from normal limbs with 81% sensitivity, 90.5% specificity, and 0.823 AUC (CI = 0.683–0.964). The obtained ROC curve is presented in Figure 2.

Table 1. Demographic and clinical characteristics of the study population

		Mean ± SD/ n (%)	Median (Min–Max)
Age (years)		52.38 ± 12.38	47 (38 – 75)
Height (m)		1.59 ± 0.07	1.59 (1.46 – 1.75)
Weight (kg)		72.81 ± 13.72	74 (50 – 100)
BMI (kg/m^2)		23.72 ± 5.48	27.58 (20.44 – 40.06)
Symptom duration (months)		30.67 ± 45.2	12 (1 – 192)
Affected side	Right	6 (29%)	
	Left	15 (71%)	
Surgical procedure	PM	11 (52%)	
	MRM	10 (48%)	
ISL staging BT	Stage 1	10 (48%)	
	Stage 2	8 (38%)	
	Stage 3	3 (14%)	
ISL staging AT	Stage 1	13 (62%)	
	Stage 2	6 (29%)	
	Stage 3	2 (9%)	
Affected side			
Vtotal BT (mm^3)		2393.63 ± 797.16	2073.54 (1383.79 – 4499.16)
Vtotal AT (mm^3)		2268.55 ± 715.46	2090.43 (1503.1 – 4398.62)
UStotal BT (mm)		13.04 ± 3.46	12.41 (8.95 – 21.15)
UStotal AT (mm)		12.68 ± 2.93	11.73 (9.05 – 18.89)
Compliance BT		0.37 ± 0.07	0.39 (0.19 – 0.48)
Compliance AT		0.37 ± 0.08	0.39 (0.17 – 0.47)
Unaffected side			
Vtotal BT (mm^3)		2200.29 ± 471.83	2197.53 (1280.46 – 3321.26)
Vtotal AT (mm^3)		2325.26 ± 614.54	2152.07 (1452.38 – 3685.13)
UStotal BT (mm)		10.81 ± 2.24	10.35 (6.92 – 14.14)
UStotal AT (mm)		10.76 ± 2.24	11.17 (7.14 – 15.3)
Compliance BT		0.39 ± 0.07	0.39 (0.27 – 0.5)
Compliance AT		0.45 ± 0.07	0.46 (0.3 – 0.56)

BMI: body mass index, PM: partial mastectomy, MRM: modified radical mastectomy, ISL: International Society of Lymphology, V: volume, US: ultrasound, BT: before treatment, AT: after treatment.

Table 2. Comparison of measurements between affected and unaffected limbs

	Affected limb Mean ± SD Median (Min–Max)	Unaffected limb Mean ± SD Median (Min–Max)	P
Vtotal$_{dif}$ (mm^3)	−125.08 ± 318.71	124.97 ± 333.93	0.004*
	−100.54 (−100.54 to 478.78)	64.56 (−106.69 to 80.24)	
UStotal$_{dif}$ (mm)	−0.36 ± 1.39	0.39 ± 0.87	0.045*
	−0.09 (−3 to 1.73)	0.55 (−1.53 to 1.89)	
Compliance$_{dif}$	0.0 ± 0.06	0.05 ± 0.05	0.003*
	−0.01 (−0.01 to 0.13)	0.05 (−0.02 to 0.16)	

* The Mann–Whitney U Test
V: volume, US: ultrasound, dif: difference

Table 3. Correlations between measurement parameters in affected limb.

		r	p
	UStotal BT (mm)	0.626	0.002*
Vtotal BT (mm^3)	Compliance BT	−0.003	0.989
	UStotal AT (mm)	0.604	0.004*
Vtotal AT (mm^3)	Compliance AT	−0.338	0.134
	$UStotal_{dif}$ (mm)	0.459	0.047*
$Vtotal_{dif}$ (mm^3)	$Compliance_{dif}$	0.062	0.788

* Spearman's rank correlation analysis
V: volume, US: ultrasound, dif: difference, BT: before treatment, AT: after treatment.

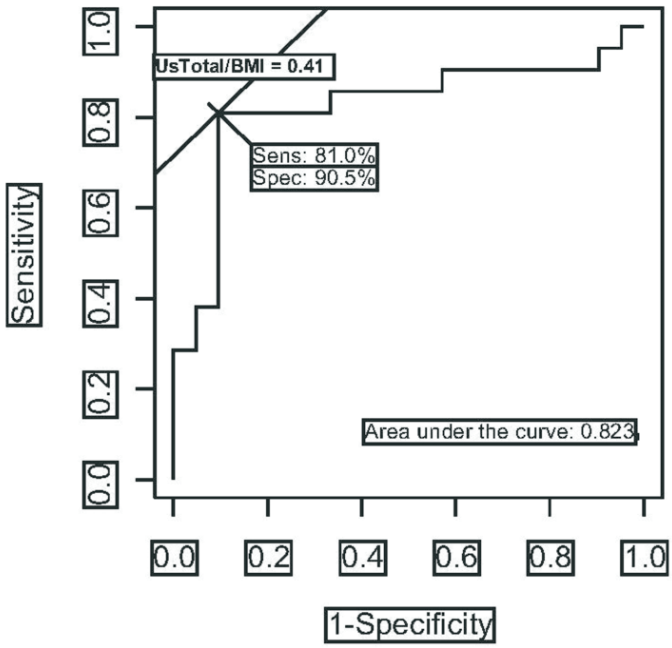

Figure 2. Receiver operating characteristic (ROC) curve obtained for UStotal/BMI.

DISCUSSION

Volume of extremities can be measured by volumetry or circumferential measurements using a measuring tape to help diagnose and assess the course of lymphedema (13). Arm circumferential measurement is practical in the clinical setting; therefore, it is the most popular method to assess limb volume in BCRL (8). Some authors have reported ultrasonography measures of skin and subcutaneous tissue thickness (SCT) in patients with BCRL (11, 13, 14). Additionally, some studies suggest that the compliance of the subcutaneous soft tissues are affected with lymphedema (13). In this manner, the aim of our study was to determine whether ultrasound measures of dermal and SCT and compliance can be used to aid to diagnose and/or monitor treatment in patients with BCRL.

In a previous study, Lee *et al.* (15) investigated how SCT and compliance measurements via ultrasonography changed with complex decongestive therapy over 2 weeks. They measured the circumference, soft tissue thickness, and compliance at three points on the ventral aspect of the affected limb. They demonstrated that after treatment, soft tissue thickness decreased at all three points as assessed by circumferential measurements on the elbow, and at 10 cm proximal points by measurement of soft tissue thickness. However, compliance measurements did not change significantly at any site. They concluded that ultrasound may be a useful indicator of treatment efficacy. Our study demonstrated that a decrease in Vtotal, UStotal was greater in the affected limb compared to the unaffected limb after the treatment. Consistent with previous work, compliance measurement did not change in affected limb; however, there was a slight increase in unaffected arm. However, different from the aforementioned study, our study involved both the dorsal and ventral aspect of the arms. Considering that lymphedema does not affect the ventral aspect of the extremity alone, the dorsal aspect also should be evaluated. Additionally, we investigated how total arm volume as calculated by circumferential measurements and the sum of ultrasonographic measurements at certain sites were correlated, and found that UStotal measurement was positively correlated with limb volume before treatment and after 6 weeks of treatment. Furthermore, we demonstrated that UStotal is positively correlated to the change in extremity volume, suggesting that this can be used to also monitor treatment effectiveness.

Previous work by Lim *et al.* (13) showed that compliance of the affected limb was lower than the unaffected side. With treatment, we expected an increase in the compliance of the affected limb. Interestingly, while there was an increase in compliance in the unaffected arm, there was no change in the affected arm. Additionally, there was no correlation between the circumferential volumetric measurement and ultrasonographic compliance measurement before and after treatment. We interpreted this to mean that compliance cannot be used to monitor the effectiveness of treatment, and also it is possible that there are reliability problems with compliance measurements. Fibrosis of the soft tissues alter the physiological characteristics, including compliance (15), which can also be influenced by the stage of the disease.

Suehiro *et al.* (21) investigated how SCT changed in the affected arm compared to the unaffected arm at five points (medial upper arm, lateral upper arm, medial forearm, lateral forearm, dorsum of the hand) in BCRL patients. Similar to our findings, they showed an increased SCT, but did not seek whether this measurement could monitor

effectiveness of the treatment. Rather than offering a formula for the whole arm for diagnosis, they compared the same sites between the two arms. In our study, we aimed to determine a cutoff value for ultrasonographic measurements performed for diagnosing BCRL. When we analyzed the correlation between UStotal, which is a measure of SCT, in unaffected limb and weight and BMI, we found that instead of weight, BMI was the most determinant factor affecting the UStotal measurement ($r = 0.705$, $p < 0.001$ for BMI; $r = 0.631$, $p = 0.002$ for weight). On this basis, we analyzed both UStotal and UStotal/BMI for determining the diagnosis of BCRL. We found that UStotal of ≥11.17 mm determines BCRL with a sensitivity of 71.4%, specificity of 71.4%, and AUC of 0.739, which are low for a diagnostic test. However, UStotal/BMI of ≥0.41 mm/kg/m^2 distinguishes limbs with BCRL from normal limbs with 81% sensitivity, 90.5% specificity, and an AUC of 0.823, which represents a good discrimination power.

Another study examined how complex decongestive treatment affects leg volume and subcutaneous thickness (16), concluding that leg volume can increase in a certain number of patients despite treatment. Furthermore, the study demonstrated that subcutaneous thickness in the medial thigh region is strongly correlated with circumferential measurements (16). In the current study, we determined volume and ultrasonographic measurements changes with treatment in the upper extremity, finding a significant correlation between volume and UStotal measurement before and after treatment.

There are some limitations of our study. First, our study has a relatively small sample size. Moreover, although circumferential measurements are reliable and are the most practical measurement method for evaluating arm volume, it cannot provide a precise arm volume. We examined the effectiveness of ultrasonographic measurements for monitoring the treatment on the basis of the correlation among circumferential measurements. The results would be different with precise limb volumes obtained by volumetry.

CONCLUSION

Our study demonstrated that the sum of dermal and SCTs at ten suggested points (UStotal) was greater than the same measurement of the affected side, as well as circumferential measurements. Additionally, our UStotal measurement was well-correlated with Vtotal as acquired by circumferential measurement before and after treatment. Although ultrasonography measurements of compliance were significantly lower in the affected limb compared to the unaffected limb, it did not change with treatment and did not significantly correlate with Vtotal. UStotal measurement can help practitioners to support and confirm the diagnosis of lymphedema and monitor the effectiveness of the treatment via ultrasonography. UStotal/BMI of ≥0.41 mm/kg/m^2 can determine BCRL with 81% sensitivity, 90.5% specificity, and 0.823 AUC. We do not recommend compliance measurements for diagnosing or monitoring lymphedema. Further studies with larger sample sizes are required to assess the reliability of these measurements and further modify our suggested UStotal measurement methods.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles according to the Declaration of Helsinki

Ozan Volkan Yurdakul ORCID:0000-0003-4567-8133
Teoman Aydin ORCID:0000-0002-0902-6771

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