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DIAGNOSTIC ACCURACY OF INTERLIMB DIFFERENCES OF ULTRASONOGRAPHIC SUBCUTANEOUS TISSUE THICKNESS MEASUREMENTS IN BREAST CANCER-RELATED ARM LYMPHEDEMA

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ABSTRACT

Use of ultrasound as an assessment technique for lymphedema has been increasing with measurement of subcutaneous tissue thickness used for both assessment and treatment outcome. Reliability of ultrasound examination of the thickness of the skin and subcutaneous tissue have been studied. However, interlimb differences of ultrasonographic subcutaneous tissue thickness have not been explored. This study aimed to establish diagnostic accuracy of interlimb differences of ultrasonographic subcutaneous tissue thickness measurements in breast cancer-related arm lymphedema. We compared the truncated cone method by using circumference measurements and interlimb differences of ultrasonographic subcutaneous tissue thickness measurements to evaluate the diagnostic accuracy of interlimb differences of ultrasonographic subcutaneous tissue thickness measurements. Sensitivity, specificity, receiver-operating characteristic (ROC) curve, and area under the curve (AUC) were used. Analysis of ROC curves yielded area under the curve (AUC) of 0.804 (p=0.002). ROC analysis identified 0.17cm as the cut-point for differentiating between tissue with and without lymphedema resulting in a sensitivity of 79.3% and specificity of 69.2%.

Keywords: assessment, breast cancer, diagnosis, lymphedema, measurement, ultrasound

Breast cancer-related arm lymphedema is a potential sequela from treatment of breast cancer. It may occur in almost 40% of the patients who have undergone breast cancer surgery or radiation therapy (1). Clinically, the diagnosis of lymphedema is based mainly on patient history and self-report of symptoms, visual inspection and skin palpation, and the determination of volume differences between both limbs. Volume can be measured in several ways. Volumetry using water displacement is considered the gold standard (2,3). Water displacement and circumference measurement are used in clinical practice and are accurate and reliable methods of volumetry (4). The most common criterion for lymphedema diagnosis is a volume difference of 200 mL (5). Sander et al demonstrated that volume measurements using truncated cone yielded volumes closest to water displacement and had high intra- and inter-observer reliability (6). The ICC value for both intrarater and interrater reliability was detected as 0.99 (4). However, volume measurements are not only influenced by fluid changes, but also by compositional changes of muscle mass, bone, or fat. Also, water displacement is too cumbersome and messy to be used in routine clinical practice (e.g., practical limits such as the size of the limb, measuring areas near the root of the limb, and hygiene issues) (7,8). Evaluation of the effectiveness of treatments for lymphedema requires an accurate, easy-to-use method for the detection of lymphedema (9).

Ultrasound is an easily feasible noninvasive technique which is widely used in rehabilitation settings (10). Measurement of subcutaneous tissue thickness via ultrasound can be less time consuming than volume measurements with water displacement and circumference measurements. Measurement of subcutaneous tissue thickness has been used for both assessment and treatment outcome (11-14). Recently reliability of ultrasound examination of the thickness of the skin and subcutaneous tissue were studied by Han et al (15). However, the diagnostic accuracy of this method has not been investigated before. Early identification of breast cancer-related lymphedema is critical to start treatment earlier. Consequently, reliability and diagnostic accuracy of the assessment techniques of lymphedema is crucial to evaluate both severity at the time of diagnosis, and later effectiveness of treatment. This study aimed to establish diagnostic accuracy of interlimb differences of ultrasonographic subcutaneous tissue thickness measurements in breast cancer-related arm lymphedema.

METHODS

Forty-three patients with breast cancer-related lymphedema who were admitted to Special Outpatients Clinics of Lymphedema Management and Follow-Up of the Department of Physical Medicine and Rehabilitation, Marmara University School of Medicine between April 2018 and July 2018 participated in this prospective cross-sectional study. The study was approved by the Research Ethics Board of the Marmara University School of Medicine. It was registered on the Clinical Trials Registry (registration number NCT03676127). Informed and written consent was obtained from all patients. Inclusion criteria were: (1) patients with post-mastectomy lymphedema aged 18 and above; (2) patients with unilateral breast cancer who underwent breast surgery and at least one axillar lymphadenectomy; and (3) patients with stable lymphedema for at least 3 months (no lymphedema-related infection requiring antibiotics within the past three months, no complex decongestive therapy within the past three months, no recorded 10% change in volume or circumference of the affected arm in the last three months). Exclusion criteria were: (1) bilateral lymphedema; (2) patients with a blurred border of papillary dermis and dermo-hypodermal junction; (3) having other malignant diseases; (4) current episodes of cancer or metastases; and (5) with preoperative upper extremity disability.

Sample Size Estimation

Sample size estimation was performed using the GPower V.3.1.7 (University of Kiel, Kiel, Germany). The sample size was calculated on the basis of the previously reported the mean difference in subcutaneous tissue thickness in the study conducted Suehiro et al (11). Power analysis using a power of 95% and a significance of p=0.05 showed that 28 patients had to be recruited when the mean expected value of subcutaneous tissue thickness in patients with lymphedema was 1.3mm with a standard deviation of 0.5 and the mean expected value in the patients without lymphedema was 0.8mm with a standard deviation of 0.2.

Outcome Assessments

Patient characteristics

Demographic data, lymphedema duration, surgery type, and clinical lymphedema stage of the patients were collected. The first researcher recorded patient characteristics, performed volume measurements and obtained ultrasound images of the affected and unaffected sides. The second researcher measured subcutaneous tissue thickness without knowing patient characteristics.

Volume measurements

The circumferential upper limb measurements were carried out with the arm abducted at 30° and started at the level of the carpometacarpal joint then following every 5 cm proximal to this point along both limbs. A computer program (limb volumes professional version 5.0) was used to convert these values into limb volumes in milliliters. The difference in volume of affected and unaffected sides was defined as edema (volume difference). The criterion for lymphedema diagnosis is volume difference of 200 ml (5). The dominant arm of a person has shown to be 3.3% ± 3% (mean ± SD) larger than the non-dominant arm, and >5% difference is unlikely to be produced by dominance alone (16-19). The edema volumes of patients were assessed considering arm dominance.

Ultrasonographic measurement

The subjects were placed supine on an examination table with the forearm supinated and relaxed. Ultrasound gel was applied liberally to the skin and the probe placed transversely on the arm. The subcutaneous tissue thickness was measured from the medial forearm in the affected and unaffected extremities with Esaote Mylab ultrasound machine with a 6-18 MHz linear array probe. The probe was held in axial position in medial forearm over the flexor carpi radialis muscle. The depth of image captured was set at 2 cm. The scanning site was chosen as medial forearm because Suehiro et al found that the differences in lymphedema grades between the affected and unaffected arms were most evident in the medial forearm, and ultrasonographic severity grade in medial forearm represents extracellular fluid status in the entire arm *(Fig. 1)* (11,20). All images were obtained between 11:00 AM and 12:00 AM to avoid the effect of diurnal variation in skin water

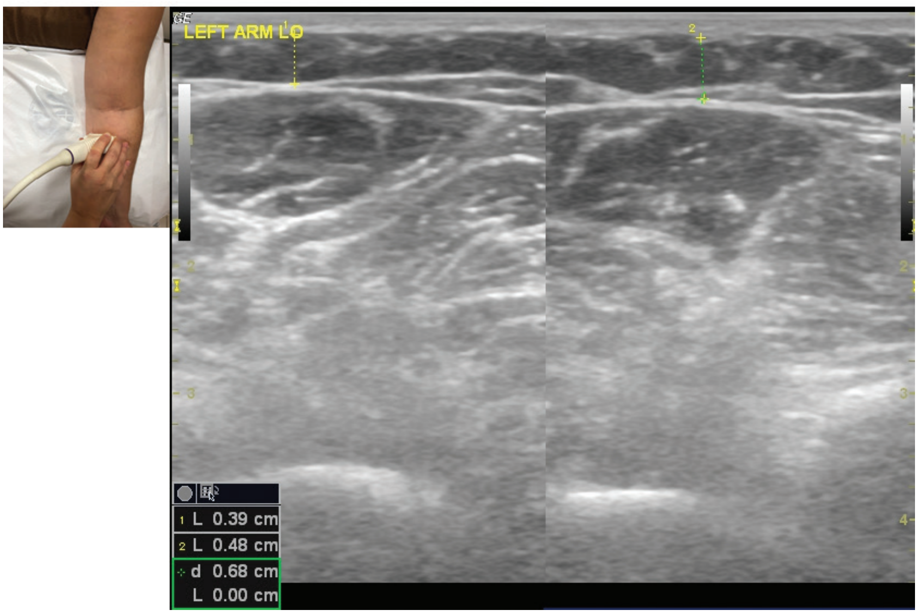

Fig. 1. Image depicting collection of ultrasonographic data from a patient (left) and measurement of subcutaneous tissue thickness (right).

content on subcutaneous tissue thickness and ultrasound echogenicity (21). Subcutaneous thickness was defined as the distance between the posterior echogenic border of the dermis and the anterior echogenic border of the deep muscular fascia (11). On the images captured on the medial forearm, thickness of subcutaneous tissue was measured by using console measurement tools on the ultrasound unit.

Statistical Analysis

Statistical analyses were performed using IBM SPSS for Windows version 20.0 software (IBM Corp., Armonk, NY, USA). Analysis of the characteristics of patients was performed using descriptive studies. Independent samples t-test was used to compare the ultrasonographic measurement of subcutaneous tissue thickness according to the volume. Spearman's rank correlation was used to test the relationship between ISL clinical stage and interlimb differences of ultrasonographic subcutaneous tissue thickness measurements. The capacity of interlimb differences of ultrasonographic subcutaneous tissue thickness measurements in predicting the presence of lymphedema was analyzed using Receiver Operating Characteristic (ROC) curve analysis. When a significant cut-off value was observed, the sensitivity, specificity were determined. While evaluating the area under the curve, a 5% type-1 error level was used to accept a statistically significant predictive value of the test variables.

RESULTS

Figure 2 depicts the flow diagram for recruitment and selected patient characteristics are presented in *Table 1*. Significant interlimb differences were found regarding ultrasonographic measurement of subcutaneous tissue thickness according to the volume (volume <200ml versus volume >200ml) (*Table 2*). Lymphedema stage and interlimb differences of ultrasonographic subcutaneous tissue thickness measurements were moderately correlated (r=0.6, p=0.0001). There was a strong correlation between interlimb volume differences and interlimb differences of ultrasonographic subcutaneous tissue thickness measurements (r=0.74, p=0.0001). The ROC curve is displayed in *Fig. 3*. Analysis of ROC curves yielded area under the curve (AUC) of 0.804 (p=0.002) when the reference standard method for lymphedema was defined by volume differences calculated from circumferential measurements by using truncated cone method (absence of lymphedema volume <200ml and presence of lymphedema volume >200ml) (*Table 3*). ROC analysis identified 0.17cm as the cut-point for differentiating between tissue with and without lymphedema, with a sensitivity of 79.3% and specificity of 69.2% (*Table 4*).

DISCUSSION

The incidence of lymphedema increases with the increasing number of women undergoing treatments for breast cancer. Objective and accurate methods for assessing lymphedema are needed. The use of ultrasound as an assessment technique for lymphedema is becoming increasingly widespread. Volumetric and circumferential measurements are widely used methods for the detection and follow-up evaluation of lymphedema (22). Sequential circumference measurements along designated measure points are commonly used in clinical practice. Limb volumes can be calculated or estimated by using truncated cone formula. In the present study, we intended to compare the truncated cone method by using circumference measurements and interlimb differences of ultrasonographic subcutaneous tissue thickness measurements to evaluate the diagnostic accuracy of interlimb differences of ultrasonographic subcutaneous tissue thickness measurements in breast cancer-related arm lymphedema. We chose volume differences calculated from circumferential measurements by using truncated cone method as a reference standard because it is both an accurate and easy-to-use method for the detection of lymphedema. The utility of ultrasound measurement

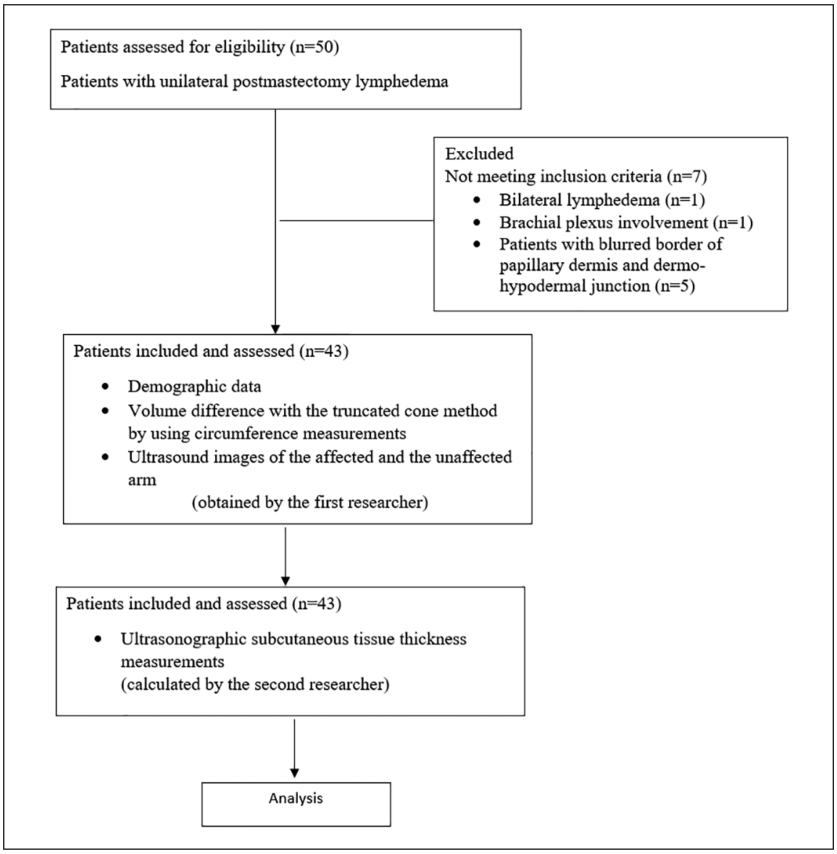

Fig. 2. Flow diagram of the study recruitment.

TABLE 1
Patient Characteristics

Age (years; mean±SD)	50.84±8.67
BMI (kg/m^2; mean±SD)	29.26±5.03
ISL lymphedema clinical stage (median (minimum-maximum))	2 (0-3)
Duration of lymphedema (months; mean±SD)	34.02±28.98
Affected side	
Right	21 (48.8%)
Left	22 (51.2%)
Dominant side	
Right	41 (95.3%)
Left	2 (4.7%)
Surgery type	
Mastectomy	33 (76.7%)
Breast conserving surgery	10 (23.3%)
Subcutaneous tissue thickness at affected arm (cm)	0.77±0.35
Subcutaneous tissue thickness at unaffected arm (cm)	0.45±0.17
Interlimb differences of ultrasonographic subcutaneous tissue thickness measurements in breast cancer related arm lymphedema (cm)	0.32±0.29

BMI=Body mass index; ISL=The International Society of Lymphology

TABLE 2
Differences Between Groups in Terms of Ultrasonographic Measurement of Subcutaneous Tissue Thickness

	Volume difference <200ml	Volume difference >200ml	p value
Ultrasonographic measurement of subcutaneous tissue thickness (cm)	0.12±0.1	0.36±0.3	0.02

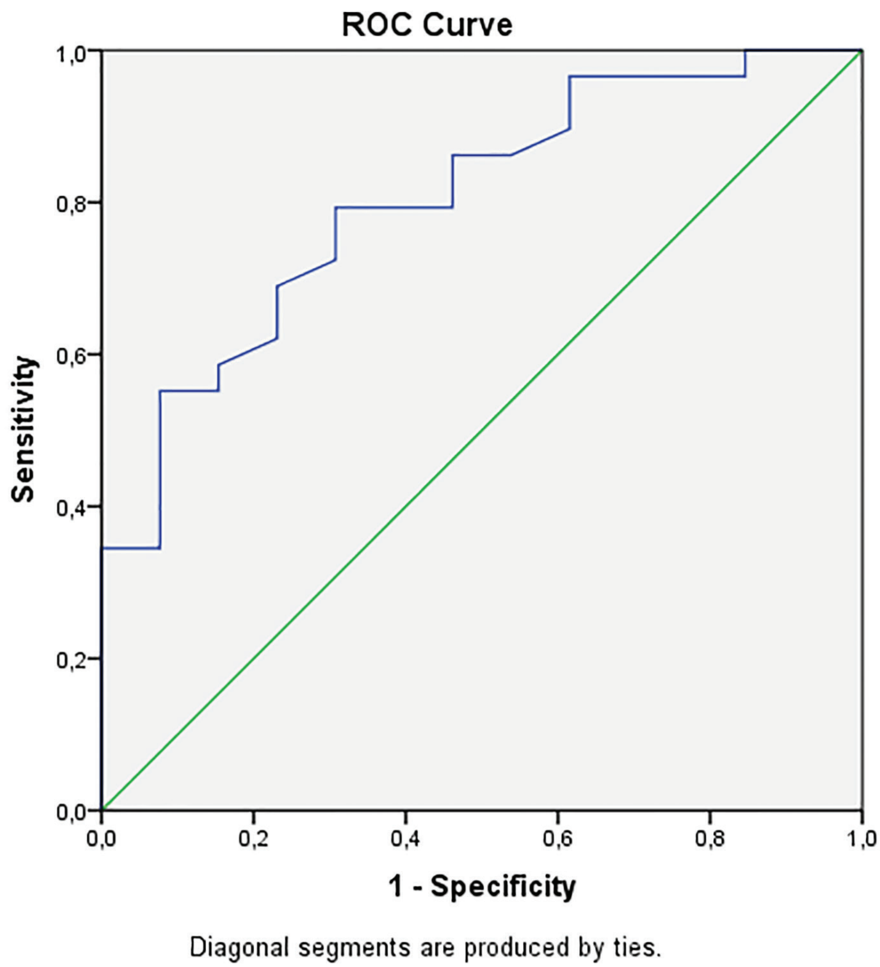

Fig. 3. ROC curve of arm volume and of interlimb differences of ultrasonographic subcutaneous tissue thickness measurements

TABLE 3 Area under the Receiver-Operating Characteristics Curve			
	AUC (95% CI)	SE	p
Interlimb differences of ultrasonographic subcutaneous tissue thickness measurements in breast cancer related arm lymphedema	0.804 (0.667-0.941)	0.07	0.002

AUC, area under curve; CI, confidence intervals

of subcutaneous tissue thickness has been previously studied, and the percentage change in subcutis thickness was found to be correlated with the percentage change in edema, and ultrasonographic findings were consistent with measurements of circumferences and limb volumes (22,23). Although ultrasound measurement of subcutaneous tissue thickness has been used in the evaluation of therapy results, the diagnostic accuracy had not been clarified. Ultrasound measurement of subcutaneous tissue thickness can be less time consuming than circumferential measurements and water displacement method. This is of practical utility to many physicians. The interlimb difference of 0.17cm was identified as the cut-point for differentiating between tissue with and without lymphedema, with a sensitivity of 79.3% and specificity of 69.2%. Our findings of AUC of 0.804 support the use of between side difference in subcutaneous tissue thickness in the assessment of breast cancer-related arm lymphedema. We found that the sensitivity of this cut-off value was higher than its specificity. High sensitivity is clearly important where the test is used to identify a serious but treatable disease (24). Since detecting and treating lymphedema earlier is crucial, it is essential to use a test with high sensitivity when assessing the presence of lymphedema (25).

In this study, lymphedema stage and interlimb volume differences were correlated with interlimb differences of ultrasonographic subcutaneous tissue thickness measurements. In agreement with our findings, Mellor et al found that skin thickness was found to be correlated with increased severity of lymphedema as measured by using perometer (21). In another study, Choi et al investigated the correlations between bioimpedance, circumferential, and ultrasonographic measurement of the interlimb difference of subcutaneous thickness (26). They measured subcutis thickness with and without applying pressure. They detected impedance ratios were correlated with interlimb subcutis thickness without pressure. Although the correlation analysis was significant, correlation coefficient (0.623) revealed a week correlation. Tassenoy et al reported significant differences between the affected and unaffected arms of patients with postmastectomy lymphedema in terms of dermal and subcutaneous thickness in their study comparing ultrasonographic images with those obtained using magnetic resonance imaging to explain the nature of morphologic changes (27).

Previously, two studies evaluated the reliability of skin and subcutaneous thickness for the diagnosis and evaluation of the lymphedema (15,28). One of the reliability studies assessed skin and subcutaneous thickness without pressure while the other assessed skin and subcutaneous thickness in the upper extremity with or without pressure (15,28). Ultrasonographic measurements of skin and subcutaneous thickness were also used as treatment outcomes (22,23). However, none of the studies assessed diagnostic accuracy. To the best of our knowledge, this is the first study evaluating the diagnostic accuracy of interlimb differences of ultrasonographic dermal thickness measurements in breast cancer-related arm lymphedema. The

TABLE 4
Diagnostic Accuracy of Interlimb Differences of Ultrasonographic Subcutaneous Tissue Thickness Measurements (CM) in Breast Cancer Related Arm Lymphedema

Value	Sensitivity	1 - Specificity
-1.0100	1.000	1.000
-.0100	1.000	.923
-.0050	1.000	.846
.0050	.966	.846
.0200	.966	.769
.0400	.966	.692
.0500	.966	.615
.0650	.931	.615
.0900	.897	.615
.1050	.862	.538
.1150	.862	.462
.1350	.793	.462
.1550	.793	.385
.1700	.793	.308
.1900	.759	.308
.2000	.724	.308
.2050	.690	.231
.2400	.621	.231
.2700	.621	.231
.2750	.586	.154
.2900	.552	.154
.3100	.552	.077
.3200	.552	.077
.3650	.483	.077
.4200	.448	.077
.4350	.379	.077
.4450	.345	.077
.4850	.345	.000
.5500	.310	.000
.6100	.276	.000
.6550	.241	.000
.6750	.207	.000
.7150	.172	.000
.7900	.138	.000
.9000	.103	.000
1.0000	.069	.000
1.0650	.034	.000
2.1000	.000	.000

Note. In ROC analysis, we pegged either sensitivity or specificity to preset values of 0.65 - 0.9 and estimated 0.17 as the variable of interest.

study has several limitations. When assessing diagnostic accuracy, gold standard techniques should be utilized. The gold standard for the measurement of limb swelling is the water displacement method (3). In the clinical environment, the two accepted gold standards for measuring limb volume change are water displacement volumetry and circumferential limb measures. Most of the health professionals interested in lymphedema use circumferential measurements in clinical practice since it is more feasible than water displacement. Since we intended to compare the truncated cone method by using circumference measurements and interlimb differences of ultrasonographic subcutaneous tissue thickness measurements to evaluate the diagnostic accuracy of interlimb differences of ultrasonographic subcutaneous tissue thickness measurements in breast cancer-related arm lymphedema, we used truncated cone method. Further studies evaluating the diagnostic accuracy with both water displacement and truncated cone method should be conducted to draw conclusions on the diagnostic accuracy of interlimb differences of ultrasonographic subcutaneous tissue thickness measurements.

The most common criterion for lymphedema diagnosis is a volume difference of >200 ml (5). However, according to the results of the study conducted by Ancukiewicz et al, this absolute change in arm size of 200 ml may not be accurately generalized to populations with different distributions of patient body size (25). They found that temporal variation in the absolute volume of the unaffected arm correlated with body size while relative volume change is independent of body mass index (25). Further studies comparing the diagnostic accuracy of ultrasonographic measurement of subcutaneous tissue thickness, absolute and relative change in volume can be helpful for more accurate detection of lymphedema.

Neither interlimb differences of ultrasonographic subcutaneous tissue thickness nor volume measurements reflect tissue changes related to lymphedema. Subcutaneous echogenicity (SEG) grade and subcutaneous echo-free space (SEFS) grade invented by Suehiro et al by using via B-mode ultrasonography allow semi-quantitation of nonspecific subcutaneous tissue inflammation and fluid accumulation (29). Increase in SEG is attributed to increased cell density and increased collagen content in the tissue, and it is considered to indicate the presence of ongoing or previous inflammation in the area. SEFS represents the fluid accumulated in the spaces between superficial fasciae, which is freely mobile in the spaces. Devoogdt et al investigated the postoperative evolution of thickness and echogenicity of cutis and subcutis with ultrasonography for one year after axillary dissection for breast cancer (14). They measured thickness of cutis and subcutis via ultrasound and arm volumes by using truncated cone method before, and 1, 6, and 12 months after axillary dissection for primary breast cancer. They also qualitatively assessed the echogenicity of cutis and subcutis and rated as disturbed and not disturbed. They calculated sensitivity based on the proportion of some patients with lymphedema and disturbed ultrasonographic image to all patients with lymphedema. Specificity was calculated based on the ratio, which was estimated based on the number of patients without lymphedema and non-disturbed ultrasonographic image and all patients without lymphedema. For most ultrasonographic measurements, sensitivity was low and ranged between 10% and 43%. Only for disturbed echogenicity of the cutis at the wrist and increased thickness of the subcutis at the ventral lower arm and triceps was sensitivity found to be higher (100%, 67%, and 67%, respectively). In contrast to the findings of the present study, specificity was detected remarkably higher and ranged between 59% and 100%. However, the area under the curve and cut off value for interlimb differences of subcutis were not studied. The researchers mentioned that there is no cut-off value for the changed thickness of cutis and subcutis. The thickness of cutis was considered as increased when the difference of thickness between affected and healthy side was more than 0.3mm and the difference of thickness was more than 20% (14).

In conclusion, using ultrasonography, a relatively fast and reproducible method, the presence of lymphedema can be detected with a reasonable sensitivity but low specificity in patients with breast cancer-related lymphedema. Future research investigating the usefulness of SEG and SEFS grades as an adjunctive to interlimb differences of ultrasonographic subcutaneous tissue thickness in the evaluation of breast cancer-related lymphedema is required.

CONFLICT OF INTEREST AND DISCLOSURE

All authors declare no competing financial interests exist.

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