REVIEW ARTICLE

ISSN 2508-190X

CLL 2(2):36-42, 2017

www.kslymph.or.kr

Quantitative Ultrasonographic Evaluation of Lymphedema

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There are several techniques to measure the state of the lymphedema. One of the most popular methods is using ultrasonography with consideration of the structure of the affected area. Thus the purpose of this article was to compare the clinical usefulness of the ultrasonographic techniques in measurement of lymphedema. The general measurement techniques of the lymphedema using ultrasonography were illustrated. The soft tissue thickness measurement of the lymphedema is most commonly performed using ultrasonography. The other method is measuring the lymphedema in two dimensional aspect. To increase the reliability and measure the hardness, compliance measurement of the lymphedema is suggested. Lastly, elastography technique was suggested to measure the hardness of the lymphedema. Ultrasonographic measurement has the advantages of fast, safe, costless, and repeatable. With more studies regarding cut off value and guidelines, it could strongly be recommended as a measurement tool of lymphedema in clinical settings.

Key Words: Lymphedema · Cancere patients · Ultrasonographic measurement · Structural measurement · Reliability

INTRODUCTION

Lymphedema is the swelling, typically of subcutaneous tissues, as a result of obstruction of lymphatic vessels or lymph nodes, with the accumulation of lymph in the affected region [1-4]. It usually occurs by disturbance of the lymphatic circulation and is most commonly reported following breast radiation therapy [5]. In general, chemotherapy with taxane or supraclavicular radiation therapy, at doses higher than 40 Gy, may lead to a significant increase in breast volume due to tissue reactions with an edema [6]. Although breast irradiation itself does not initiate cutaneous edema, unless other predisposing or aggravating factors are present, it does cause sclerosis of the skin, late post-radiation therapy, and tissue fibrosis, which may obstruct lymph flow and slow down regeneration and formation of new lymph vessels. Lymph node irradiation in the breast area may decrease filter function and inhibit the normal lymphatic proliferative response to inflammatory stimuli. Consequently, swelling and fibrosis increase as the disease progresses [3].

Several techniques have been proposed to measure the status of the lymphedema by considering the inner structures of the affected area. These methods use ultrasonography, magnetic resonance imaging (MRI), computed tomography (CT), elastography, and bioelectrical impedance spectroscopy [7]. There are several advantages of these techniques. First, they allow detecting the real amount or volume of the lymph tissue from its surrounding healthy tissue. Theoretically, these methods can objectively differentiate between pathologic tissue and normal tissue. Second, these methods can detect the texture of the pathologic tissue, as well as the volume. In this context, impedance and elastography could help to define the stage of the lymphedema, by measuring the fibrotic status that is filled with fluid collection or becoming fibrotic (soft, compliant). Also, ultrasonography, MRI, and CT can demonstrate the histologic changes in the tissue [7,8]. These techniques can screen for various musculoskeletal diseases that occur after breast cancer surgery, measure the thickness of the cutaneous, epifascial, and subfascial tissue compartments, and establish the softness of the tissue. Nonetheless, these techniques re-

▸ Received: October 23, 2017, ▸ Accepted: October 31, 2017

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quire considerable time, are expensive, demand specific expertise and sometimes generate unwanted radiation exposure. Although ultrasonography is safe and is not a radiation hazard, it is regarded as a relatively subjective and variable assessment. For these reasons, in spite of their advantages, MRI, CT and ultrasonography are not commonly performed in clinical settings.

Conversely, some techniques do not consider the inner structure, such as the length, width or volume dimensions. Evaluation of lymphedema has most commonly been focused on the size and volume of the affected arm. One of the most popular means of evaluating lymphedema in clinics is the circumference measurement of the affected limb using a measuring tape, and the volume is calculated by volumetry using water displacement or three-dimensional (3D) optoelectronic estimation [9]. However, these measurements do not show the structural changes (e.g., fibrosis, hardness) in subcutaneous tissues. Also, despite the simplicity of these techniques, errors during analysis could occur. For instance, excessive tape-measure pressure on the tissue, inaccurate marked points, and improper measuring angle relative to the limb axis could arise [4]. Moreover, although volumetry can rapidly measure the 3D volume of the affected limb without radiation hazard, it does not establish the real ratio and state of the lymphedema [10]. Therefore, a method that considers the inner structure of the tissue without radiation hazard is needed to determine lymphedema.

MAIN

The General Measurement Techniques of Lymphedema using Ultrasonography

Ultrasonographic measurement has been suggested as the most appropriate approach to determine lymphedema in clinical settings [1,3,5]. Theoretically, it could measure the subcutaneous thickness of the lymphedema with no radiation hazard. There are several advantages of the ultrasonographic measurement method. It is inexpensive, easily accessible, and demonstrates histological changes. It can also measure the thickness of cutaneous, epifascial, and subfascial tissues, detect the fluid collection or fibrosis (softness, compliance), and measure the softness of the tissue. Due to its advantages, ultrasonography can screen various musculoskeletal diseases that occur after breast cancer operation. However, this method has a few limitations: is a relatively subjective tool and there is a risk that the clinical findings could be influenced, by different maximal compression power performed by each examiner [4,11].

The general ultrasonographic measurement technique for determining the soft tissue thickness of an arm is shown in Fig. 1. The skin thickness is identified as the distance between two thin echogenic lines bordering a hypoechoic dermis, as detailed in previous studies. This increase in skin thickness is caused by increased extravascular-extracellular leakage space in the (hypo)dermis and extensive cellular fibrosis, characterized by the loss of a consistent pattern in extracellular structures.

The definition of lymphedema soft tissue thickness is the summation of skin and subcutaneous tissue thickness on ultrasonography [11]. If the thickness of the skin is over 2 mm, with increased echogenicity, then disturbance or poor visibility of the deeper echogenic line and interstitial fluid accumulation occur [5]. The International Society of Lymphology consensus document classifies the severity of lymphedema by stages (0-III) [13]. Ultrasonographic measurement can detect lymphedema when the severity is stage II or above because stage I lymphedema is difficult to differentiate from arm edema of other causes [3].

Adjusting the B-mode gain on the high-frequency ultrasound images, particularly when evaluating subcutaneous echogenicity, is suggested so that the subepidermal low echogenic band (SELEB) unambiguously appears black, or otherwise normal subcutaneous fat in parts of the body other than the arms appear black [1,3]. In this way, the skin thickness is defined as the distance between the posterior echogenic border of the epider-

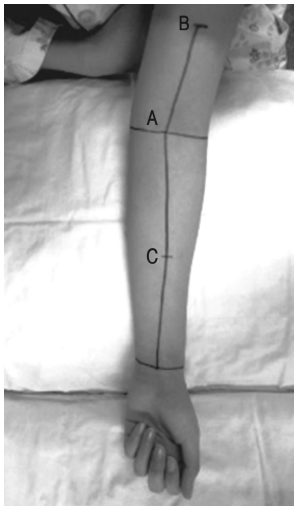


Fig. 1. Ultrasonographic measurement of the soft tissue thickness [2]. The thickness of the soft tissue is measured at 10 cm above and below the elbow crease, by ultrasonography. A, B, and C refer to the elbow crease, and 10 cm above and below the elbow crease, respectively.

mal entrance echo and the posterior echogenic border of the dermis (because an epidermal entrance echo does not reflect the true thickness of the epidermis). The SELEB is the distance between the anterior and posterior echogenic borders of the SELEB. The subcutaneous tissue is termed the distance between the posterior echogenic border of the dermis and the anterior echogenic border of the deep muscular fascia [1]. Thus, the subcutaneous echogenicity is graded as follows [1]:

- Grade 0: No or little increase in echogenicity in the subcutaneous layer. Horizontal or obliquely oriented echogenic lines caused by connective tissue bundles are distinctly observed.
- Grade 1: Diffuse and monotonous increases in echogenicity in the subcutaneous layer. Echogenic lines are unclear but identifiable.
- Grade 2: Diffuse increases in echogenicity. Echogenic lines are not identifiable.

Also, the subcutaneous echo-free space (SEFS) is graded as detailed below [17].

- Grade 0: No SEFS.
- Grade 1: Horizontally oriented (<45° to the skin) SEFS only.
- Grade 2: Presence of vertically oriented (≥45° to the skin) SEFS bridging the horizontally oriented SEFSs.

I. Soft tissue thickness measurement using ultrasonography

The soft tissue thickness measurement technique was reported by Suehiro et al. [3]. The measurement sites are at 10 cm above and below the elbow crease (AE and BE, respectively), in the medial and lateral upper arm, and medial and lateral forearm, and on the dorsum of the hand (Fig. 2).

- Medial upper arm (MUA): from the medial side of the upper arm to the biceps brachii muscle;
- Lateral upper arm (LUA): from the lateral side of the upper arm to the biceps brachii muscle;
- Medial forearm (MFA): from the medial side of the forearm to the brachioradialis muscle;
- Lateral forearm (LFA): from the lateral side of the forearm to the brachioradialis muscle; and
- Dorsum of the hand (DH): on the first dorsal interosseous muscle of the hand.

According to Suehiro et al. [3], however, the borders of these structures were irregular and were not always located parallel to the epidermal surface. Therefore, the distances were measured at three points (right, middle, and left) of each acquired image and the averaged value calculated. Otherwise, the mean value at the center area could be used for rapid measurement. The proportion of the increase in the thickness of each structure in the arm with lymphedema was then calculated using the following formula.

Increase ratio=(thickness in the lymphedema side-thickness in the normal side)/thickness in the normal side.

Although this approach proved relatively fast and simple, it only determines the focal measurement sites, namely, the two locations in the upper and lower arm, respectively, and, hence, the whole volume of the lymphedema could not be suggested. In addition, no pressure should be applied to the transducer during the procedure, because this can introduce measurement error.

II. The two-dimensional (2D) measurement method by ultrasonography

A volume measurement procedure using ultrasonography has been considered, to overcome the limitations of the soft tissue thickness measurement technique. Given that the real 3D volume of the lymphedema cannot be measured in clinical settings, precise measurement of the 2D cross-sectional area (CSA) could be more

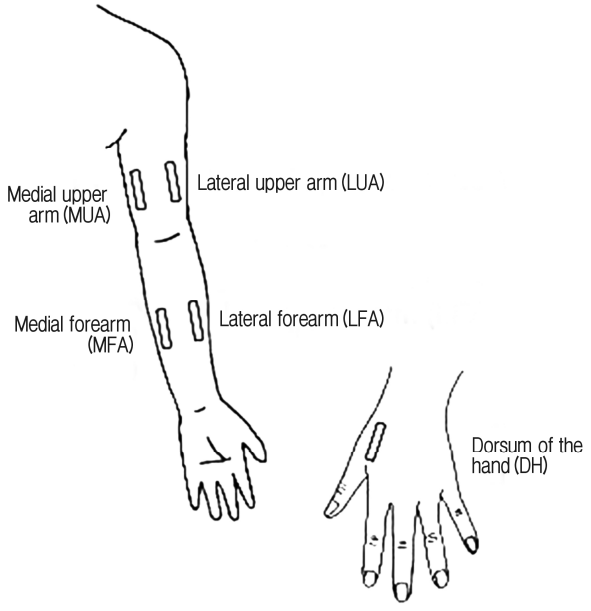


Fig. 2. Sites of measurement for lymphedema thickness determination using ultrasonography on the arm [3].

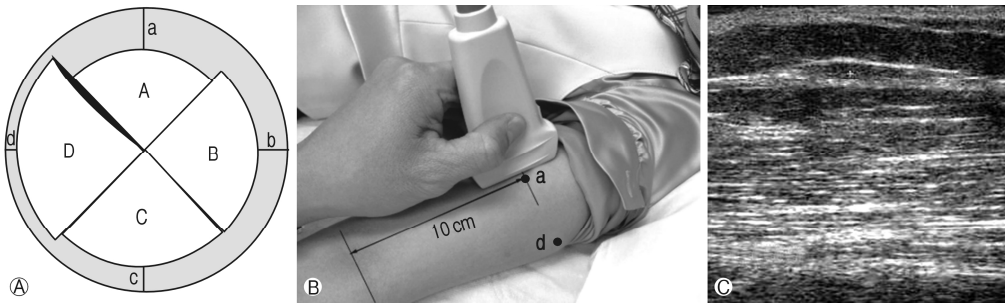


Fig. 3. Estimation of the three-dimensional volume of the lymphedema by two-dimensio- nal measurement method of the cross-sectional area using ultrasonography [12]. (**A**) The shaded area represents the lymphedema. r=soft tissue thickness measured at four different points. A, B, C, and D denote the quarters of the imaginary cross-sectional area of the limb. The skin thickness was recorded at 10 cm above and below the elbow crease at four sites. Both arms of each patient were examined by two independent practitioners. (**B**) a, b, c, and d denote the thickness of the soft tissue in the superior (a), medial (b), inferior (c), and late- ral (d) directions. (**C**) Soft tissue thickness was measured from the skin to the outer margin of the fascia. The patient performed a dynamic muscle test under the examiner's instruc- tion, allowing differentiation of the muscle layer.

suitable than simple soft tissue thickness measurement. Using CT, ultrasonography or MRI, estimation of the 3D volume by precise determination of the CSA has been proposed by Hwang et al.[10]. Unlike CT and MRI, the CSA of the lymphedema cannot be measured without radiation hazard using ultrasonography, due to the depth limitation of the method. Therefore, the authors advocated the measurement of the soft tissue thickness at four different sites, creating an imaginary CSA (Fig. 3).

By measuring the subcutaneous tissue thickness and the circumference of both arms, the CSA of the lymphedema could be calculated [12]:

$$\Delta \text{CSA (cross-sectional area of the soft tissue)}$$
$$= \Delta \text{total cross-sectional area of the limb-(A+B+C+ D)}$$
$$= \pi r\text{-}1/4\ (\pi\ (r\text{-}a)^2+\pi\ (r\text{-}b)^2+\pi\ (r\text{-}c)^2+(r\text{-}d)^2)$$
$$= \mathbf{Y/4\ (a+b+c+d)-\pi/4\ (a^2+b^2+c2+d^2)}$$

The approach was applied to a study of 20 female participants, and the ratio of the lymphedema compared to the normal side was acquired [12] (Table 1).

The right side is the lesion side and the ratios of the lymphedema, circumference, cross-sectional area (CSA) and the compliance, are shown in the shaded areas, respectively. AE and BE refer to 10 cm above and below the elbow crease, respectively. Compliance is the difference in soft tissue thickness with and without compression divided by the soft tissue thickness without compression.

Table 1. The ratio of the lymphedema compared to the normal side

	Left			Right		
Circumference	AE	10 cm	22.2	AE	10 cm	23.7
	BE	10 cm	19.8	BE	10 cm	21.4
Sonographic	AE	a	0.43	AE	a	0.55
Measurement		b	0.96		b	1.08
		c	0.76		c	1.04
		d	1.15		d	1.32
	BE	a	0.47	BE	a	0.59
		b	0.43		b	0.45
		c	0.30		c	0.25
		d	0.35		d	0.34
CSA	AE		15.95	AE		20.27
	BE		7.18	BE		8.15
Ratio	AE		1	AE		1.27
	BE		1	BE		1.13

AE: above elbow, BE: below elbow, CSA: cross sectional area. a, b, c, d stands for superior, medial, inferior and lateral side of each limb.

Clinical Evidence of the 2D Measurement Method Using Ultrasonography

In the same study, Hwang et al. assessed the reliability of the proposed technique [12]. There was a strong in-

tra-rater reliability (α=0.961) and a moderate inter-rater reliability (α=0.747) for the measurements at all soft tissue locations. Regarding the measurement site, there was no significant difference in reliability between the AE and BE for intra-rater analysis. Furthermore, there was a poor reliability between the amount of tissue in the CSA and simple circumference measurement, and a moderate correlation with volumetry.

Hence, in spite of its advantages, several limitations of the 2D method technique could be highlighted. First, this technique is a subjective measurement method, and thus, the reliability may be variable, depending on the pressure applied to the transducer and measuring tape by the examiner. Theoretically, the reliability is highest when the same examiner performs measures on the same patient. Second, a relatively long time is required to achieve precise measurements compared to simple circumference measurement by measuring tape or volumetry. Consequently, it might not be the preferred option in a clinical setting. Third, due to its depth limitation, ultrasonography has a limited application, particularly to regional swelling areas, joint areas or severely thickened tissue. Fourth, the landmarks of the measuring point should be same. Otherwise, technical measurement bias can result. Finally, as this method is estimating the lymphedema by measuring the CSA, the result is likely to differ from the actual 3D lymphedema value. Nevertheless, this 2D measurement sonographic technique is safe, precise and straightforward, and could be commonly used to measure lymphedema using ultrasonography.

III. The compliance measurement technique

The compliance measurement procedure was first introduced by Kim et al. in 2008 [4]. As the lymphedema develops, its volume and hardness increase. Thus, this method was established to study the hardness or fibrotic changes in the lymphedema, using ultrasonography. The reliability of the measurement was not compared to ultrasonography, due to the limitation of the latter. However, the authors attempted to increase the method consistency by maximally pressing the soft tissue with a probe and then comparing the difference with the original tissue depth [4]. This 'reliability' varies, however, depending on the fibrotic change in the tissue. In this sense, the technique is testing the reliability to assess the thickness, with or without pressure, by measuring the soft tissue thickness with a probe.

As part of this procedure, the soft tissue thickness was measured once again while applying maximal compression, which was defined as compression with the pressure at which additional compression did not produce a notable decrease in the thickness of the soft tissue. The 'compliance' was calculated from the difference in soft tissue thickness, with and without compression, divided by the soft tissue thickness without compression:

There are several drawbacks of the compliance measurement technique. First, as there is no absolute, objective, measurement method of soft tissue by ultrasonography, this process does not accurately reflect the real volume or characteristics of the lymphedema. Second, the maximal pressure applied could be influenced by the sonographer. Third, the application is limited to round, narrow, and joint spaces. Fourth, the anatomical landmarks should be the same whenever it is measured. Fifth, as the compliance consists of the summation of its inner structures including soft tissue, muscle, and fascia, it is not possible to exclusively predict the real compliance of the lymphedema. Hence, this technique could be more meaningful when combined with other procedures.

IV. Measurement of the lymphedema using elastography

Elastography has gradually emerged as among the most widely used and applied approaches for measuring lymphedema [5]. In this method, the tissue displacement (or strain) is monitored during repeated compression and decompression of the affected tissue, with the transducer. The strain is lower in hard tissue compared to soft tissue. Although several sonoelasticity techniques have been investigated, static elastography is the most commonly performed technique. Static elastography obtains the ultrasonographic signals from an axial imaging plane before and after a slight compression of the tissue. The pre- and post-compression frames are processed to generate images of local strain as an elasticity color map, termed an elastogram [5], Information about the hardness can be obtained by comparing the pre- and post-compression images, using a cross-correlation technique to determine the amount of displacement of each B-mode image pixel (Fig. 4). Moreover, the quantitative comparison of a strain or elasticity ratio between tissues with different elasticity can be achieved [5], as described in more detail below. Additionally, a modified approach to calculating the 2D strain, was presented by Yang et al., in which the pre- and post-compression (deformation) B-mode image sequences were registered using an intensity-based non-rigid registration algorithm (INRA) [14]. The *in vitro* results of the palm are shown in Fig. 4 [14].

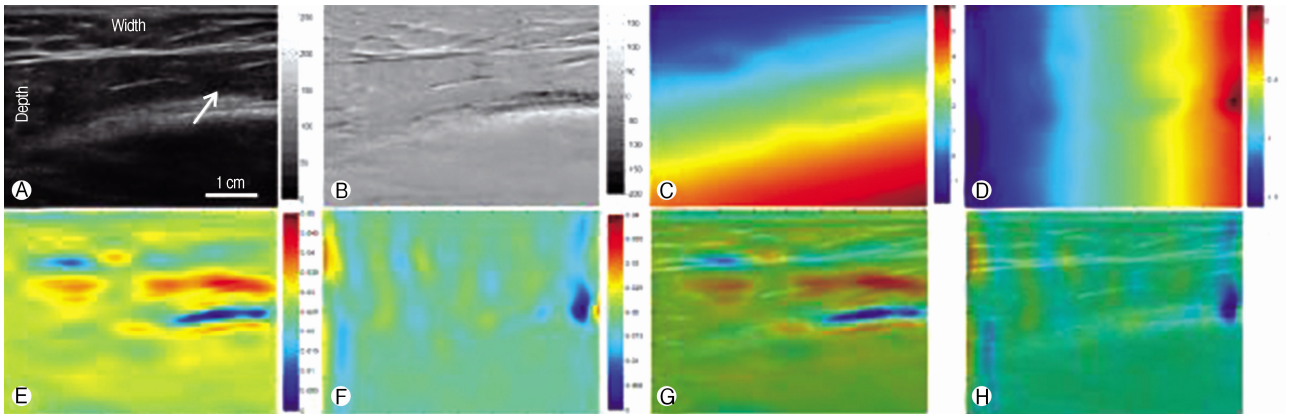


Fig. 4. *In vivo* results of the palm. (**A**) Pre-compression B-mode image of the palm, (**B**) B- mode intensity difference between pre- and post-compression, (**C**) Axial displacement, (**D**) Lateral displacement, (**E**) Axial strain images from an intensity-based non-rigid registration algorithm (INRA) method, (**F**) Lateral strain image from INRA method, (**G**) Axial fusion image of the B-mode and strain images, and (**H**) Lateral fusion image of the B-mode and strain images.

Sonoelastography is a noninvasive, cost-effective, safe and widely-accessible technique that could provide more information than simple soft tissue thickness measurement. For instance, Adriaenssens et al. undertook ultrasonography measurements following high-frequency ultrasound B-mode scans in breast cancer patients, to evaluate the tissue elasticity as a means of visualizing fluid retention, following breast conserving surgery and radiotherapy [5]. A 12-MHz linear probe was positioned on the breast (quadrant), and an elastogram generated, displaying a strain color scale image and strain graph. Regions of interest were placed on the color scale image for comparative analysis.

The interstitial fluid accumulation in the breast increased the tissue strain values. Thus, the mean absolute elastography ratio of the subcutis significantly increased in the operated breast after radiotherapy relative to the baseline measurement. However, although the absolute elasticity ratio of the subcutis increased in the different quadrants examined, there was no significant change in the mean absolute elasticity ratio of the subcutis of the four quadrants. The correlation between the elasticity ratio of the subcutis and the other breast edema criteria depended on the visibility of the echogenic line. Also, there was no clear elasticity criteria or cut-off value to diagnose the lymphedema.

V. Histologic evaluation by ultrasonography

Ultrasonography for histological investigation was introduced by Fumiere et al. [7] in 2007, for accurate delineation of the tissue alterations in chronic lymphedema. The authors observed that normal subcutaneous septa appeared as hyperechogenic lines in ultrasonography (hyposignal lines in MRI), while hyperechogenic subcutis in ultrasonography could be attributed to interlobular and intralobular water accumulation and/or to interlobular and intralobular fibrosis. Doldi et al. [11] reported that ultrasound features of lymphedema included structural changes (mild hyperechogenic dermis, hypoechogenic subcutaneous layer and reflective streaks, hyperechogenicy of the muscle compartment) and volumetric changes (slight increase in the thickness of the dermis, an increase in the subcutaneous layer, an increase, decrease or no change in the muscle mass). Ronka et al. [15] evaluated the deeper echogenic line of the skin, skin thickness, and interstitial fluid as markers for subcutaneous edema in breast cancer patients at 1-year post-surgery. Van der Veen et al. [16] documented a significant increase in hyperechogenic subcutaneous tissue on the fascial side and, overall, a higher echogenicity of the edematous arm than the non-edematous side, by ultrasound imaging of two female cadavers with unilateral breast amputation. The presence of the interstitial fluid accumulation was assessed in ultrasound B-mode scans, as hypoechoic fluid infiltration (dark bands) between the fat lobules.

CONCLUSION

Several conclusions can be suggested, regarding the usefulness of ultrasonography for measuring lymphe-

dema. First, can the thickness of soft tissue be measured objectively with ultrasonography? As ultrasonography is a subjective measurement method, varied results could be obtained, due to examiner influence, anatomic variation (applying point of the probe within the screen, same arm position of the subjects), and variable pressure application. However, the measurement variability could be reduced significantly when the measurement guidelines are controlled. Second, is ultrasonography efficient compared to other measurement methods? The cost of ultrasonography is relatively inexpensive, and it is easily accessible compared to other techniques. In addition, it can demonstrate histological changes, screen for various musculoskeletal diseases, and correctly observe the real volume of the structure. Ultrasonography has similar advantages to CT or MRI, as it is safe, rapid, repeatable and able to perform a dynamic evaluation. Thus, ultrasonography could be suggested as a first and best method to safely and reliably measure lymphedema. Further study should be undertaken to specify the cut-off value or criteria of lymphedema, to generalize the ultrasonographic measurement methods in clinical settings.

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