OPEN

PRS GLOBAL OPEN

ORIGINAL ARTICLE
Reconstructive

Effectiveness of Vascularized Lymph Node Transfer for Extremity Lymphedema Using Volumetric and Circumferential Differences

Olivia A. Ho, MD*
Sung-Yu Chu, MD†
Yen-Ling Huang, MD†
Wen-Hui Chen, MD†
Chia-Yu Lin, MSc*
Ming-Huei Cheng, MD, MBA*

Background: Circumferential difference of lymphedematous limbs at designated anatomic distances has been the primary mode for measuring lymphedematous extremities. Computed tomography (CT) imaging produces accurate, consistent, hygienic volume measurements and a direct limb representation. This study compares these 2 main modalities and assesses their correlation.
Methods: CT and circumferential difference measurements, costs, and correlation of patient limbs that received vascularized lymph node transfer were compared.
Results: Mean circumferential difference by tape measurement pre- and postoperatively was 31.4% ± 19.1% and 17.4% ± 8.8% for upper limbs and 43.2% ± 16.1% and 22.4% ± 12% for the lower limbs, respectively. Mean CT volumetric difference pre- and postoperatively were 36.1 ± 4.1% and 27.2 ± 2.8% for the upper limb and 46.2 ± 3.2% and 33.2 ± 2.1% for the lower limbs, respectively. CT volume measurements significantly correlated with their respective circumferential difference with Pearson correlation coefficient of $r = +0.7$, which was statistically significant ($P = 0.03$), indicating a strong positive correlation between circumferential difference and actual limb volume changes as determined by CT imaging. Circumferential differences are more cost effective than CT volume assessments in the domains of measurement frequency ($P = 0.03$), fee ($P < 0.01$), time ($P = 0.03$), total cost per year ($P < 0.01$), and cost/minute ($P = 0.03$).
Conclusions: Standardized circumferential differences that are currently used are comparable to unbiased CT volumetric measurements and can be used as a reliable, reproducible, minimally invasive, low cost, and accurate method of measuring the lymphedematous limbs. *(Plast Reconstr Surg Glob Open 2019;7:e2003; doi: 10.1097/GOX.0000000000002003; Published online 13 February 2019.)*

INTRODUCTION

Lymphedema is a debilitating condition characterized by progressive indolent swelling in soft tissues.[1,2] Primary lymphedema is idiopathic, while secondary lymphedema is most often a result of infection, cancer ablation, lymph node removal, and radiation therapy. Secondary lymphedema is one of the most devastating sequelae of cancer care, second only to cancer recurrence. In breast cancer patients, there is strong evidence that factors such as axillary lymph node dissection, a greater number of lymph nodes dissected, mastectomy, and high body mass index (BMI) increase the risk of lymphedema in these patients, while moderate evidence supports a role for radiation and chemotherapy.[3–10] However, the magnitude of the increased risk is difficult to compare across studies because of the different approaches to measuring lymphedema and the variable lengths of follow-up. At present, there is no definitive treatment for lymphedema. Mainstay treatment options include complex decongestive therapy, compressive garments, liposuction, lymphovenous anastomosis (LVA), and vascularized lymph node transfer (VLNT).[1,2,11,12] Various types of lymph node transfers have been described

*From the *Division of Reconstructive Microsurgery, Department of Plastic and Reconstructive Surgery, Chang Gung Memorial Hospital, Chang Gung University, College of Medicine, Taoyuan, Taiwan; and †Department of Medical Imaging and Interventional Radiology, Chang Gung Memorial Hospital, Chang Gung University, College of Medicine, Taoyuan, Taiwan.*

Received for publication September 8, 2018; accepted September 14, 2018.

DOI: 10.1097/GOX.0000000000002003

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by the authors.*

including submental, groin, supraclavicular areas, thoracodorsal axis, and omentum donor sites.[13–18]

The measurement of the excess interstitial fluid in lymphedematous limbs is a developing science. Outcomes following both conservative nonsurgical and surgical treatments have focused on objective measurements, with limb circumferential difference being the predominant benchmark used for comparative evaluations. Limb circumferential difference using anatomical landmarks has been demonstrated to be reliable and reproducible.[1,2,11,12,15–17]

Despite the consistency and ease of this method of measurement for clinicians and patients to perform, there has been criticism that circumferential difference may not provide an accurate volumetric assessment of the limb. Multiple alternative methods have been proposed including the water displacement method (water plethysmography), inverse water displacement, limb circumferential difference, perometry (infrared beams to measure the limb outline), bioimpedance spectroscopy (measuring tissue resistance to an electrical current to determine extracellular fluid volume), skin fold calipers, 3-D photography, and radiographic measurements [computed tomography (CT), magnetic resonance imaging, ultrasound].[1,14,19–36] However, these methods are also subject to criticism. Even the proposed gold standard, water displacement, has its limitations such as reproducibility, hygiene concerns variability (eg, water temperature), and limited access to equipment.[1,14]

Using CT imaging to differentiate between lymphedema, cellulitis, and generalized edema is a well-known technique.[37] Lymphedema features on CT include evidence of skin thickening, honeycombing (ie, thickened interstitial tissues in the subcutaneous layer that cross each other and appear as polygonally shaped fat attenuation with peripheral septa-like structures composed of fluid or fibrous tissue) and the presence of fat lobules that are taller than they are wide.[38] The use of radiographic imaging provides a standardized and reproducible way of measuring volume. CT can accurately measure the volume of edema using a cross-sectional area of the region of interest to observe changes in the tissue properties.[39,40] CT imaging provides a direct 3-D representation of the patient's limb. As such, CT scans are essentially one of the least subjective methods for determining limb volume measurements. In comparing CT volumetric measurements with the current method of circumferential difference that is employed routinely in clinical practice, their comparison and correlation can be assessed.

METHODS

This study was approved by the Research Ethics Board from the Chang Gung Memorial Hospital IRB#201700312B0. This was a retrospective review of prospectively gathered data from patients with lymphedema. The inclusion criteria were any patient diagnosed with grade I to IV lymphedema at our institution from January 2013 to May 2016, who had undergone VLNT and completed CT scans both preoperatively and 12 months postoperatively. Patients had both upper and lower limb lymphedema. All patients received conservative treatments involving compression therapy and lymphatic massage before receiving VLNT surgery. Patients who had bilateral limbs affected by lymphedema were still included since both limbs were not the same circumference or volume.

For the purposes of this study, to standardize a section of the limb for volume measurements (and for comparison with the volume measurements obtained from CT imaging), the circumferential difference was measured at 10 cm above and 10 cm below the elbow for upper limb lymphedema. To compare with circumferential difference, the lower limb lymphedema measurements used were 15 cm above the knee and 10 cm above the ankle. For consistency, these circumferential differences were taken every month by the same clinical coordinator (C.Y.L.) at each follow-up appointment (Fig. 1). Circumferential differences of the affected and unaffected upper and lower limbs were determined and recorded in centimeters. The circumferential difference was defined as the circumference of the lesion limb (a) minus the circumference of the healthy limb (c) divided by the circumference of the healthy limb (c), in other words, [circumferential differentiation = (a – c)/c].[1]

CT Volumetric Measurement

A standardized CT scanning protocol was used by the Radiology Department at Chang Gung Memorial Hospital. The CT imaging was performed with a 320-row, single-source, single focal spot MDCT scanner (Aquilion One Dynamic Volume CT; Toshiba Medical System, Tochigiken, Japan), without contrast material. The entire upper or lower extremity was scanned using a craniocaudal scanning direction in the supine position. The upper limbs were pronated with the palm facing downward and the lower limb in a neutral position with toes pointing up. The examined field is from the umbilicus to the toes for the lower limb scan, and from the shoulder to the fingertips for the upper limb. For each examination, images were obtained from the raw data by using the following parameter setting: 10-mm-thickness sections, 0.5-second rotation time, 65 pitch, automatic exposure control, and 100 kVp for the lower limb and 120 kVp for the upper limb scan. The CT-based volume measurement was performed with a manually placed region of interest and a computer-aided Hounsfield unit (HU) selection. Volume of the upper limbs was calculated from the axillary crease to the wrist. For the lower limbs, volume was calculated from the perineum to the ankle. Each image was transferred to an image archive and stored in a Digital Imaging and Communications in Medicine format for later analysis. Preoperative and 12-month postoperative CT scans were obtained for each subject. The volume measurements from the same standardized area as the circumferential difference (ie, 10 cm above and below the elbow for upper extremities; 15 cm above the knee and 10 cm above the ankle for lower extremities) were calculated from the CT imaging (Fig. 1). All CT scans were directly read and/or reviewed for final interpretation by a single radiologist (S.Y.C.) at our institution for consistency.

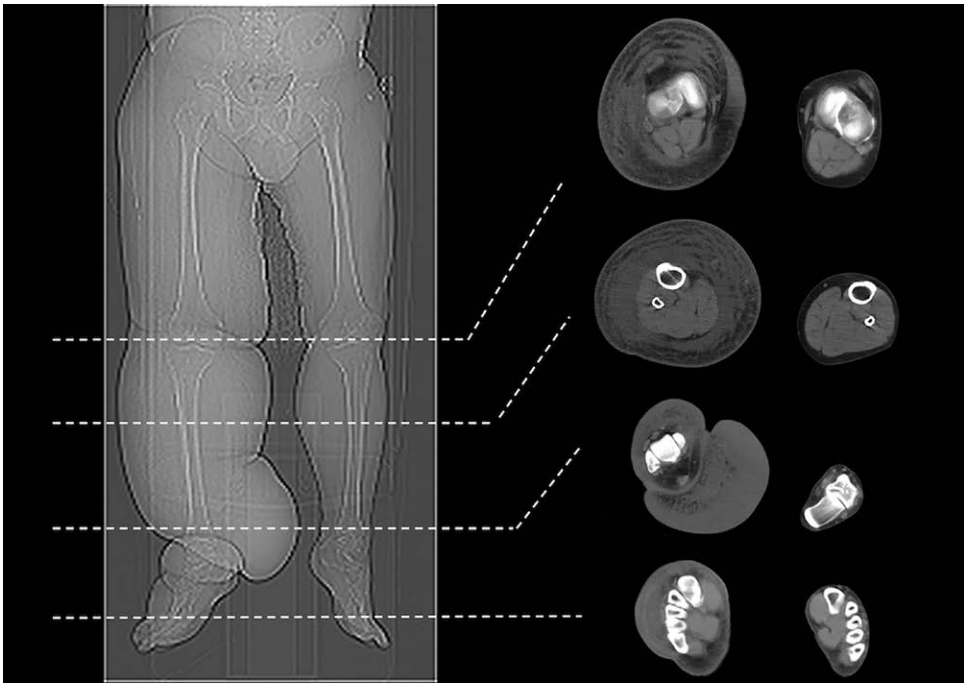

Fig. 1. Patient with lower limb lymphedema with circumferential measurements and their respective CT volume assessment.

The upper extremity lymphedema group was assessed separately from the lower extremity group. The improvement of circumferential difference by tape measure was compared with the volumetric difference by CT. Preoperative measurements of the 2 modalities were compared. Then, postoperative measurements of the 2 modalities were compared.

Cost of circumferential difference and the cost of obtaining CT scans and volumetric measurements were determined. A comparison of the 2 methods of lymphedematous limb measurements was made to determine the cost per minute of time used and the total cost per year.

Statistical Analysis

The data were summarized in counts, percentages, and means ± SD for continuous variables. Categorical variables were obtained for lymphedema grades. Subjects were then assessed with both upper and lower limbs together and then assessed in only upper and only lower limb lymphedema groups. The Kruskal-Wallis test was used for rank-based nonparametric data. The Pearson correlation coefficient was used to determine linear dependence in comparing measuring modalities. All statistical analyses were performed using SPSS 17.0 statistical software (SPSS, Inc., Chicago, Ill.).

RESULTS

Patient Demographics

Seventy-six patients were included in this study with a mean age of 50.1 years and an average BMI of 25 (Table 1). Thirty patients had upper extremity lymphedema, and 46 had lower extremity lymphedema. All patients had secondary lymphedema. Six patients had bilateral lower limb lymphedema. The average circumferential difference and CT volumetric difference were determined (Table 2).

None of the cases of upper or lower limb lymphedema were grade I. The most common severity grade was grade III (upper limbs: 15/30 = 50%, lower limbs: 24/53 = 45%). The second most common severity grade was grade II (upper limbs: 12/30 = 40%, lower limbs: 21/53 = 40%). Grade IV, the most severe grade, was the least common for both upper and lower lymphedema limbs (upper limbs: 3/30 = 10%, lower limbs: 8/53 = 15%; Table 1). The mean duration of lymphedema symptoms was 41.1 ± 32 months for upper limb patients and 80.7 ± 106.4 months for lower limb patients. The occurrence of cellulitis preoperatively was more common in the lower limb group with an average of 9.4 ± 7.5 times per year compared with 4.3 ± 4.6 times per year for patients with upper limb lymphedema. Conservative treatments were used on average for 20.6 ± 22.9 months for upper limb patients and 32.1 ± 31.1 months for lower limb patients. The mean follow-up was 68.4 ± 31.1 months for upper limb patients and 31.8 ± 29.7 months for lower limb patients.

Upper Extremity Lymphedema Group

Preoperative mean circumferential difference (see the formula in the methods section) above the elbow (AE) was 32.3 ± 21% and below the elbow (BE) was 30.4 ± 18.1% (Table 2). The average of the AE and BE values was 31.4% ± 19.1%. For the preoperative upper limb lymphedema group (Table 2), volume difference by CT was 36.1 ± 4.1% (Table 2).

Table 1. Demographics and Disease Characteristics of Patients Having Undergone VLNT and Pre- and Postoperative CT Imaging

	Patient Number N (%)	Limb Number N (%)	Age Mean ± SD (y/o)	BMI Mean ± SD (kg/m²)	Cheng's Lymphedema Grade	Symptom Duration (mo) Mean ± SD	Conservative Treatment Duration (mo) Mean ± SD	Cellulitis Occurrence (Times/Year)		Follow-up (mo) Mean ± SD
								Preoperative Mean ± SD	Postoperative Mean ± SD	
Upper limb	30 (39.5)	30 (36.6)	61.0±13.7	24.6±5.7	I: 0 II: 12 III: 15 IV: 3	41.1±32	20.6±22.9	4.3±4.6	0.5±0.8	68.4±31.1
Lower limb	46 (60.5)	52 (63.4)	45.3±17.2	25.4±3.4	I: 0 II: 21 III: 24 IV: 8	80.7±106.4	32.1±31.1	9.4±7.5	0.4±0.8	31.8±29.7
Total, n (%)	76 (100)	82 (100)	53.2±15.5	25±4.6	I: 0 II: 33 III: 39 IV: 11	60.9±69.2	26.4±27	6.9±6.1	0.5±0.8	50.1±30.4
P	0.03*	0.04*	0.03*	0.06	0.03*	0.03*	0.03*	0.04*	0.7	0.03*

Seventy-six patients included, 70 with unilateral limb lymphedema and 6 with bilateral lower limb lymphedema.
*Kruskal-Wallis test.

At a follow-up of 68.4 ± 31.1 months, mean circumferential difference AE was 20% ± 9.3% and BE was 15.3% ± 8.3%. The average of the AE and BE values was 17.4% ± 8.8%. For the postoperative upper limb lymphedema group (Table 2), volume difference by CT was 27.2 ± 2.8% (for the diseased limbs).

For the upper limb group, pre- and postmeasurements using the 2 modalities were compared to determine the degree of improvement after VLNT surgery (Table 2). When comparing the pre- and postoperative mean reduction of circumferential difference by tape measure, it showed an improvement after VLNT surgery of 12.3% ± 11.7% for AE and 15.1% ± 9.8% for BE, with a mean of 13.7% ± 10.6%. A comparison of the pre- and postoperative mean volumetric difference by CT revealed an improvement after VLNT surgery of 25.2 ± 7.8%.

Lower Extremity Lymphedema Group

For the preoperative lower limb lymphedema group (Table 2), volume difference by CT was 46.2 ± 3.2%. Mean circumferential difference for above the knee (AK) was 49% ± 20.4% and above the ankle (AA) was 38% ± 12.4%. The average of the AK and AA values was 43.2% ± 16.1%.

For the postoperative lower limb lymphedema group (Table 2), volumetric difference by CT was 33.2 ± 2.1%. The mean circumferential difference AK was 25.3% ± 12.3% and AA was 20.3% ± 12.3%. The average circumferential difference of the AK and AA values was 22.4 ± 12.

For the lower limb group, pre- and postmeasurements using the 2 modalities were compared to determine the degree of improvement after VLNT surgery (Table 2). A comparison of the pre- and postoperative mean volumetric reduction difference by CT showed an improvement after VLNT surgery of 28.1 ± 2.1%. When comparing the pre- and postoperative mean improvement of circumferential difference by tape measure, improvement after VLNT surgery was 23.7% ± 8.1% for AK and 17.7% ± 0.1% for AA, with a mean of 20.4% ± 4.1%.

Comparison of Circumferential Difference Versus CT Volume Measurement

There was a significant correlation between the circumferential difference and their respective CT scan volumes ($P = 0.03$) with a Pearson correlation coefficient of $r = +0.7$ for the upper and lower limb assessments when assessed together (Tables 3). A Pearson correlation coefficient of $r = +0.7$ indicated a positive linear relationship between circumferential difference and CT volume. High absolute value of the correlation between 0.60 and 0.79 indicates a strong effect size.

The cost of each method was determined and converted to United States dollars (Table 4). Circumferential difference cost $2.50 per section and included the price of materials such as the measuring tape and the cost of employing clinical personnel. The cost of a CT volume measurement was $100 per visit and included the cost of obtaining the CT image, radiologist reporting, radiology assistant service, and image reconstruction fee. There was a significant difference in the cost between the 2 methods ($P < 0.01$).

The duration of time needed to perform the limb measurements with measuring tape was 3 minutes, whereas the duration of time for a CT scan investigation was 15 minutes, which was statistically significant ($P = 0.03$). However, pre- and postoperative visits for tape measurements were more frequent (8 times per year) compared with those for CT volume measurements (2 times per year; $P = 0.03$).

Yearly cost for the tape measurement method was significantly less than that for CT assessment ($20 versus $200, $P < 0.01$). Cost per minute of time used to conduct each measurement was also significantly less for the tape measurement than the CT methods ($0.83/min versus $6.67/minute, $P = 0.03$). Clearly, prices will vary in different countries and at different institutions, and the estimated cost of each method will depend on the type of health insurance available in the absence of a national health insurance system.

Table 2. Comparison Between Tape Circumferential Difference and CT Volumetric Difference

Lesion Side	Patient Number N (%)	Limb Number N (%)	Mean Circumferential Difference by Tape Measurement						Improvement of circumferential Difference Mean ± SD			Mean Volumetric Difference by CT		Improvement of Volumetric Difference Mean ± SD/(cm³)
			Preoperative Mean ± SD			Postoperative Mean ± SD						Preoperative	Postoperative	
			AE or AK (%)	BE or AA (%)	Mean (%)	AE or AK (%)	BE or AA (%)	Mean (%)	AE or AK (%)	BE or AA (%)	Mean (%)	Mean ± SD/%	Mean ± SD/%	
Upper limb	30 (39)	30 (36.6)	32.3±21	30.4±18.1	31.4±19.1	20±9.3	15.3±8.3	17.4±8.8	12.3±11.7	15.1±9.8	36.1±4.1	36.1±4.1 (from AE to BE)	27.2±2.8 (from AE to BE)	8.9±0.7 (from AE to BE)
Lower limb	46 (60)	52 (63.4)	49±20.4	38±12.4	43.2±16.1	25.3±12.3	20.3±12.3	22.4±12	23.7±8.1	17.7±0.1	20.4±4.1	46.2±3.2 (from AK to AA)	33.2±2.1 (from AK to AA)	13±1.1 (from AK to AA)
Total	76 (100)	82 (100)	40.7±20	34.2±15.3	37.1±17.6	22.7±10.8	17.8±10.3	19.1±10.2	18±9.9	16.4±5.0	17.2±7	41.2±2.4	30.2±2.8	11±0.4
P	0.03*	0.04*	Upper limb: preoperative tape measurements versus CT volume: r = 0.7, *P* = 0.03* Lower limb: preoperative tape measurements versus CT volume: r = 0.7, *P* = 0.03* measurements versus CT volume: r = 0.7, *P* = 0.03*									Upper limb: preoperative tape measurements versus CT volume: r = 0.7, *P* = 0.03*; postoperative tape Lower limb: preoperative tape measurements versus CT volume: r = 0.7, *P* = 0.03*; postoperative tape		

The volumetric difference is defined as the volume of the lesion limb (d) minus the volume of the healthy limb (e) divided by the volume of the healthy limb (e), in other words [volumetric difference = (d – e)/e].
Seventy-six patients included, 70 with unilateral limb lymphedema and 6 with bilateral lower limb lymphedema. The circumferential difference is defined as the circumference of the lesion limb (a) minus the circumference of the healthy limb (c) divided by the circumference of the healthy limb (c), in other words [circumferential difference = (a – c)/c].
Preoperative upper limb lymphedema group, mean volume by CT was 7900.5 ± 3698.2 cm^3 (cubic centimeter). Postoperative upper limb lymphedema group, volume difference by CT was 5908.5 ± 1203.2 cm^3 (cubic centimeter).
Preoperative lower limb lymphedema group, volume difference by CT was 14098.4 ± 3894.2 cm^3 (cubic centimeter). Postoperative lower limb lymphedema group, volume difference by CT was 10094 ± 3582.3 cm^3 (cubic centimeter).
"* indicates p ≤ 0.05 and statistically significant"

DISCUSSION

Despite the consistent results and significant improvement in limb swelling that have been demonstrated to occur after lymphedema microsurgery, circumferential difference was sometimes criticized for not providing an accurate assessment of volume. This study demonstrates that circumferential differences taken at standardized locations using the ankle, knee, and elbow as anatomical reference points are very reliable and consistent with the volumetric measurements obtained with CT imaging. More importantly, these circumferential differences can be performed at any clinic visit, pre- and postoperatively, and provide an opportunity for medical personnel and patients to engage in fruitful and productive dialogue.

Currently, there is no single perfect method for measuring lymphedema of the extremities that is uniformly employed by all clinicians and surgeons.[34] Since the various treatment approaches to lymphedema are still evolving, having a simple, easy, reliable and reproducible measurement tool not only allows clinicians to track the progress in their own patients but also establishes a standardized metric such that different surgeons and centers globally can compare assessments and therapeutic results. The most common objective outcome measurement of lymphedema treatment includes circumferential difference, volumetric limb measurements, and episodes of cellulitis. While there are benefits to radiologic imaging measurements, these are slow to perform, relatively expensive, and can expose the patient to unnecessary radiation.[41] Circumferential differences can be performed multiple times during the same day, have essentially no risk to the patient, are not time consuming, and do not require expensive equipment. Furthermore, they are highly reproducible and do not require complex training to perform. The ability to accurately and reliably measure the degree of swelling of lymphedematous limbs allows clinicians to assess whether there is worsening or improvement of the condition before, during or after a conservative or surgical intervention. The absence of a need for specialized equipment means that patients can even perform the measurements themselves at home, tracking their progress between clinic visits.

To advance the growing field of lymphedema management and to pursue meaningful outcomes, there needs to be a consensus regarding methods of measurements. This will facilitate further research not only into the effects of noninvasive approaches to measurement but also cost-effectiveness, long-term patient's function, well-being, and quality of life.[42–44]

Some of these areas have already been studied, such as quality of life and the impact of the lymphedema condition on affected patients.[43] Given the significant impact of lymphedema on patients' day to day function, quality of life measures in lymphedema have been an important area of study in the literature.[43,45,46] Patients with upper and lower limb lymphedema were shown to have improvements in all domains of health-related quality life and overall quality of life.[43,45] The

Table 3. Comparison between Limb Circumferential Measurements and CT Volumetric Measurements Using Pearson Correlation Coefficient in 76 Consecutive Patients with Upper and Lower Limb Lymphedema

Measurements				Tape Measurement		CT Volumetric Measurement	
				Preoperative Circumferential	Postoperative Circumferential	Preoperative Total Volume	Postoperative Total Volume
Tape measurements	Preoperative	Circumferential	Pearson Correlation coefficient	1			
	Postoperative	Circumferential	Pearson Correlation coefficient	0.6; $P = 0.6$	1		
CT volume	Preoperative	Total volume	Pearson Correlation coefficient	0.7; $P = 0.03$*	0.7; $P = 0.03$*	1	
	Postoperative	Total volume	Pearson Correlation coefficient	0.7; $P = 0.03$*	0.7; $P = 0.03$*	0.5; $P = 0.06$	1

"* indicates $p \leq 0.05$ and statistically significant"

Table 4. Cost and Time Comparisons of Circumferential and CT Volumetric Measurements

Cost	Circumferential Measurement	CT Volumetric Assessment	*P*
Measurement frequency (per year)	8 times	2 times	0.03*
Fee (USD)	$2.50*	$100†	<0.01*
Duration of time taken during measurement (min)	3	15‡	0.03*
Total cost per year	$20	$200	<0.01*
Cost per minute	$0.83	$6.67	0.03*

*Includes material cost of measuring tape and hired clinical personnel fee.
†Includes cost of obtaining the CT imaging, radiologist reporting fee, radiology assistant fee, image reconstruction cost.
‡Plus processing.

Lymphedema Quality of Life (LYMQoL) is a condition-specific instrument that can be used to track changes in quality of life throughout an upper- or lower-limb lymphedema treatment.[43] Specifically, patient-reported outcomes demonstrated improvement in the domains of function, body appearance, symptom, and mood after VLNT.[43] Patients who had health-related quality of life improvement also had limb circumference reduction.

However, the lack of consensus regarding a standard measurement for diagnosing and tracking progress following treatment for lymphedema is an impediment to researchers and clinicians. A standardized method of measurement would provide a common language that would facilitate discussions and meaningful comparisons of results obtained across multiple centers.

CONCLUSIONS

CT volumetric measurement correlated strongly with circumferential difference in lymphedematous limbs. Circumferential difference is a reliable, reproducible, minimally invasive, accurate, time-efficient, and cost-effective method of documenting upper and lower limb lymphedema swelling pre- and postoperatively and during long-term follow-up. Both CT volumetric difference and circumferential difference confirmed the effectiveness of VLNT postoperatively.

Ming-Huei Cheng, MD, MBA, FACS
Division of Reconstructive Microsurgery
Department of Plastic and Reconstructive Surgery
Chang Gung Memorial Hospital
College of Medicine, Chang Gung University
5 Fu-Hsing Street, Kueishan
Taoyuan 333, Taiwan
E-mail: minghuei@cgmh.org.tw

REFERENCES

1. Cheng MH, Chang DW, Patel KM. *Principles and Practice of Lymphedema Surgery*. New York, N.Y.: Elsevier; 2015.
2. Ito R, Zelken J, Yang CY, et al. Proposed pathway and mechanism of vascularized lymph node flaps. *Gynecol Oncol*. 2016;141:182–188.
3. Basta MN, Fox JP, Kanchwala SK, et al. Complicated breast cancer-related lymphedema: evaluating health care resource utilization and associated costs of management. *Am J Surg*. 2016;211:133–141.
4. DiSipio T, Rye S, Newman B, et al. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *Lancet Oncol*. 2013;14:500–515.
5. Kocak Z, Overgaard J. Risk factors of arm lymphedema in breast cancer patients. *Acta Oncol*. 2000;39:389–392.
6. Mitra D, Catalano PJ, Cimbak N, et al. The risk of lymphedema after postoperative radiation therapy in endometrial cancer. *J Gynecol Oncol*. 2016;27:e4.
7. Norman SA, Localio AR, Kallan MJ, et al. Risk factors for lymphedema after breast cancer treatment. *Cancer Epidemiol Biomarkers Prev*. 2010;19:2734–2746.
8. Paskett ED, Naughton MJ, McCoy TP, et al. The epidemiology of arm and hand swelling in premenopausal breast cancer survivors. *Cancer Epidemiol Biomarkers Prev*. 2007;16:775–782.
9. Yen TW, Fan X, Sparapani R, et al. A contemporary, population-based study of lymphedema risk factors in older women with breast cancer. *Ann Surg Oncol*. 2009;16:979–988.
10. Warren LE, Miller CL, Horick N, et al. The impact of radiation therapy on the risk of lymphedema after treatment for breast cancer: a prospective cohort study. *Int J Radiat Oncol Biol Phys*. 2014;88:565–571.
11. Lin CH, Ali R, Chen SC, et al. Vascularized groin lymph node transfer using the wrist as a recipient site for management of postmastectomy upper extremity lymphedema. *Plast Reconstr Surg*. 2009;123:1265–1275.
12. Patel KM, Lin CY, Cheng MH. From theory to evidence: long-term evaluation of the mechanism of action and flap integration of distal vascularized lymph node transfers. *J Reconstr Microsurg*. 2015;31:26–30.
13. Allen RJ Jr, Cheng MH. Lymphedema surgery: patient selection and an overview of surgical techniques. *J Surg Oncol*. 2016;113:923–931.

14. Baumeister BGH, Chang DW, Neligan PC. Lymphatic reconstruction of the extremities. In Chang J, Neligan PC, eds. *Plastic Surgery*, Vol. 6. NY: Elsevier Health Sciences; 2012.
15. Cheng MH, Chen SC, Henry SL, et al. Vascularized groin lymph node flap transfer for postmastectomy upper limb lymphedema: flap anatomy, recipient sites, and outcomes. *Plast Reconstr Surg.* 2013;131:1286–1298.
16. Cheng MH, Huang JJ, Huang JJ, et al. A novel approach to the treatment of lower extremity lymphedema by transferring a vascularized submental lymph node flap to the ankle. *Gynecol Oncol.* 2012;126:93–98.
17. Cheng MH, Huang JJ, Wu CW, et al. The mechanism of vascularized lymph node transfer for lymphedema: natural lymphaticovenous drainage. *Plast Reconstr Surg.* 2014;133:192e–198e.
18. Ramsey K, Lymphoedema PM. In Farhadieh RD, Bulstrode NW, Cugno S, eds. *Plastic and Reconstructive Surgery: Approaches and Techniques.* NJ: Wiley-Blackwell; 2015.
19. Bagheri S, Ohlin K, Olsson G, et al. Tissue tonometry before and after liposuction of arm lymphedema following breast cancer. *Lymphat Res Biol.* 2005;3:66–80.
20. Bloomquist K, Hayes S, Adamsen L, et al. A randomized crossover trial to detect differences in arm volume after low- and heavy-load resistance exercise among patients receiving adjuvant chemotherapy for breast cancer at risk for arm lymphedema: study protocol. *BMC Cancer.* 2016;16:517.
21. Chen YW, Tsai HJ, Hung HC, et al. Reliability study of measurements for lymphedema in breast cancer patients. *Am J Phys Med Rehabil.* 2008;87:33–38.
22. Chromy A, Zalud L, Dobsak P, et al. Limb volume measurements: comparison of accuracy and decisive parameters of the most used present methods. *Springerplus.* 2015;4:707.
23. Cornish B. Bioimpedance analysis: scientific background. *Lymphat Res Biol.* 2006;4:47–50.
24. Czerniec SA, Ward LC, Lee MJ, et al. Segmental measurement of breast cancer-related arm lymphoedema using perometry and bioimpedance spectroscopy. *Support Care Cancer.* 2011;19:703–710.
25. Dylke ES, Schembri GP, Bailey DL, et al. Diagnosis of upper limb lymphedema: development of an evidence-based approach. *Acta Oncol.* 2016;55:1477–1483.
26. Hidding JT, Viehoff PB, Beurskens CH, et al. Measurement properties of instruments for measuring of lymphedema: systematic review. *Phys Ther.* 2016;96:1965–1981.
27. Moseley A, Piller N, Carati C. Combined opto-electronic perometry and bioimpedance to measure objectively the effectiveness of a new treatment intervention for chronic secondary leg lymphedema. *Lymphology.* 2002;35:136–143.
28. Ng M, Munnoch A. Clinimetrics of volume measurement in upper limb LE. *J Lympho.* 2015;5:62–67.
29. Stanton AW, Badger C, Sitzia J. Non-invasive assessment of the lymphedematous limb. *Lymphology.* 2000;33:122–135.
30. Stanton AW, Northfield JW, Holroyd B, et al. Validation of an optoelectronic limb volumeter (Perometer). *Lymphology.* 1997;30:77–97.
31. Taylor R, Jayasinghe UW, Koelmeyer L, et al. Reliability and validity of arm volume measurements for assessment of lymphedema. *Phys Ther.* 2006;86:205–214.
32. Tierney S, Aslam M, Rennie K, et al. Infrared optoelectronic volumetry, the ideal way to measure limb volume. *Eur J Vasc Endovasc Surg.* 1996;12:412–417.
33. Ward LC. Bioelectrical impedance analysis: proven utility in lymphedema risk assessment and therapeutic monitoring. *Lymphat Res Biol.* 2006;4:51–56.
34. Yamamoto N, Yamamoto T, Hayashi N, et al. Arm volumetry versus upper extremity lymphedema index: validity of upper extremity lymphedema index for body-type corrected arm volume evaluation. *Ann Plast Surg.* 2016;76:697–699.
35. Yamamoto T, Yamamoto N, Hara H, et al. Upper extremity lymphedema index: a simple method for severity evaluation of upper extremity lymphedema. *Ann Plast Surg.* 2013;70:47–49.
36. Yamamoto T, Matsuda N, Doi K, et al. The earliest finding of indocyanine green lymphography in asymptomatic limbs of lower extremity lymphedema patients secondary to cancer treatment: the modified dermal backflow stage and concept of subclinical lymphedema. *Plast Reconstr Surg.* 2011;128:314e–321e.
37. Shin SU, Lee W, Park EA, et al. Comparison of characteristic CT findings of lymphedema, cellulitis, and generalized edema in lower leg swelling. *Int J Cardiovasc Imaging.* 2013;29:135–143.
38. Hadjis NS, Carr DH, Banks L, et al. The role of CT in the diagnosis of primary lymphedema of the lower limb. *AJR Am J Roentgenol.* 1985;144:361–364.
39. Martin CJ. Radiation dosimetry for diagnostic medical exposures. *Radiat Prot Dosimetry.* 2008;128:389–412.
40. Monnin-Delhom ED, Gallix BP, Achard C, et al. High resolution unenhanced computed tomography in patients with swollen legs. *Lymphology.* 2002;35:121–128.
41. Wilkins EG, Lowery JC, Smith DJ Jr. Outcomes research: a primer for plastic surgeons. *Ann Plast Surg.* 1996;37:1–11.
42. Morgan PA, Franks PJ, Moffatt CJ. Health-related quality of life with lymphoedema: a review of the literature. *Int Wound J.* 2005;2:47–62.
43. Patel KM, Lin CY, Cheng MH. A prospective evaluation of lymphedema-specific quality-of-life outcomes following vascularized lymph node transfer. *Ann Surg Oncol.* 2015;22:2424–2430.
44. Thoma A, Jansen L, Sprague S. Outcomes in microsurgery. *Plast Reconstr Surg.* 2009;124:e303–e312.
45. Keeley V, Crooks S, Locke J, et al. A quality of life measure for limb lymphedema (LYMQOL). *J Lymphoedema.* 2010;5:26–37.
46. Taghian NR, Miller CL, Jammallo LS, et al. Lymphedema following breast cancer treatment and impact on quality of life: a review. *Crit Rev Oncol Hematol.* 2014;92:227–234.