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Three-dimensional laser scanning as a reliable and reproducible diagnostic tool in breast cancer related lymphedema rehabilitation: a proof-of-principle study

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Abstract. – OBJECTIVE: In this study, we aimed to assess the reproducibility and reliability of a three-dimensional laser scanner (3DLS) in measuring the upper limb volume of BRCL women undergoing a 2-week complete decongestive therapy (CDT).

PATIENTS AND METHODS: 3DLS and CM were used to measure the upper limb volume in a cohort of BCRL women before (T0) and after (T1) a 2-week CDT. We evaluated: a) correlation between 3DLS and CM at both time points; b) level of agreement and the consistency of the different measurements at both time points; c) correlation between the inter-rater operator analysis in terms of total limb volume differences before and after rehabilitative treatment of both circumferential method and laser scanning 3D in breast cancer related lymphedema patients.

RESULTS: Taken together, 43 BCRL women (age 51.1 ± 5.4 years) were included. Both 3DLS and CM showed a significant inter and intra-operator correlation in the arm volume measurement at both time-points (T0: r^2=0.99, *p*<0.0001; T1: r^2=0.99, *p*<0.0001). 3DLS showed a strong correlation with CM (r^2=0.99, *p*<0.0001) in terms of volume measurement and provided greater intra-operator correlation (r^2=0.92 *vs.* 0.62) in detecting volume variations after the treatment (T1-T0).

CONCLUSIONS: 3DLS confirmed to be highly sensitive, cheap and easy-to-use in the evaluation of the upper limb volume in BCRL women before and after a rehabilitative treatment. These findings suggest that augmented reality technologies might be very useful in oncological rehabilitation.

Key Words:
Lymphedema, Breast cancer, Breast cancer lymphedema, Rehabilitation, Upper limb, 3D laser scanner, Complete decongestive therapy.

Introduction

Breast cancer (BC) survivorship has been continuously increasing for the last years due to the improvement in its diagnosis and treatment[1-3]. Given the growing number of BC long-term survivors, an efficient multidisciplinary approach is beneficial in the clinical management of several complications that survivors might experience[4-7].

Breast cancer related lymphedema (BCRL) is a common and detrimental treatment-related consequence that involves up to 25% of BC survivors[7]. This condition can arise up to 11 years after surgery[8,9]. BCRL is characterized by the interstitial accumulation of fluid in the upper extremity after surgery and/or radiations, with subsequent

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negative impact in both health-related quality of life (HRQoL) and sanitary costs[2,7-12]. Early detection of BCRL is the prerequisite for an optimal treatment.

A key phase in the diagnosis and follow-up of BCRL patients is represented by the accurate arm volume assessment. For this task, several approaches have been proposed over the last few years, including water displacement (WD)[13-15], circumferential method (CM)[15-17], and three-dimensional laser scanner (3DLS)[18-20]. WD has been traditionally viewed as the "gold standard" procedure to assess the upper limb volume[13-15]. Regrettably, its use in real-life clinical practice is complex, time-consuming, and not recommended in a substantial proportion of patients, such as those with skin lesions[21,22]. The CM is based on the assumption that the truncated cone solid is a proxy of the arm shape, requiring the measurement of specific circumferences across the arm to infer its volume[23]. Although several studies questioned the sensitivity of CM due to the gibbousness of the upper limbs in BCRL patients[16,18,22-27], this method is still adopted in the clinical practice in many centers. In particular, this method is troubled by the remarkable degree of heterogeneity in the constellation of locally developed measuring protocols[23].

Recently, 3DLS-based methods have emerged as promising tools for the arm volume measurement[18-20]. These devices, allowing the real-time digital reconstruction of three-dimensional objects, have been originally implemented in the setting of orthopedic conditions, showing great performances in terms of accuracy, non-invasiveness, and cost-effectiveness[28]. Accurateness and reproducibility of 3DLS and WD have previously been compared[19], showing that the former is not inferior to the latter for the upper limb volume measurement[18,19]. Indeed, 3DLS is capable of detecting extremely small variations of volume including the presence and reduction of gibbousness and swelling (e.g., as a consequence of bandages, press therapy, manual lymph drainage)[29]. These characteristics might give information on the treatment efficacy in order to improve the currently available rehabilitation programs[18]. Recently, our group showed that 3DLS might be incorporated into the clinical workup of BCRL to allow for a precise, reproducible, reliable, and cheap diagnosis[20]. However, up to date, to the best of our knowledge, there are no studies assessing the reproducibility and reliability of 3DLS in quantifying the volume reduction of the upper limb after a complete decongestive therapy (CDT) in BCRL patients.

In this proof-of-principle study, we sought to characterize the reproducibility and reliability of a 3DLS compared to CM in upper limb volume measurement in BCRL women undergoing 2-week rehabilitation treatment.

Patients and Methods

Participants

We recruited women referred to Outpatient Service for the Oncological Rehabilitation of the Physical and Rehabilitative Medicine Unity of the University Hospital in Novara, Italy from January to June 2019. Inclusion criteria were the following: a) adult women (aged >18 years); b) BC survivors; c) diagnosis of BCRL Stage II-III; d) breast surgery performed by at least 6 months; e) absence of skin lesions at upper limb level; f) absence of trauma and/or other conditions able to modify arm structure and volume. We excluded patients with: a) cardiovascular comorbidities; b) vascular pathologies involving upper limb; c) anemia ([Hb] <9 g/dl); d) severe thrombocytopenia (<100,000 platelets/mm^3); e) history of bleeding; f) central nervous system lymphomas; g) metastases of any kind and/or concomitant brain tumors; h) being unable to sign informed consent. The study was approved by the Institutional Review Board. Participants were properly informed about the aims of the research, testing procedures, personal data treatment, and the possibility of withdrawal at any time. Written informed consent was obtained from each subject before taking part in the experiment and all the procedures were conducted according to the principles of the Declaration of Helsinki.

Study Design

All patients underwent a 2-week CDT, consisting of 5 sessions per week for a total of 10 sessions. Each session included skincare, manual lymphatic drainage, and multi-layer inelastic lymphoedema bandaging, and exercise therapy. The upper limb volumes of all study participants were assessed at the baseline (T0) and at the end of the 2-week CDT (T1) by CM and 3DLS. Both examinations were performed twice by two physical therapists with more than 20 years of experience in lymphedema disorder treatments, for a total of four measurements for each subject (mean values of the two CM and 3DLS evaluations were used for statistical analysis). The study flow chart is represented in Figure 1.

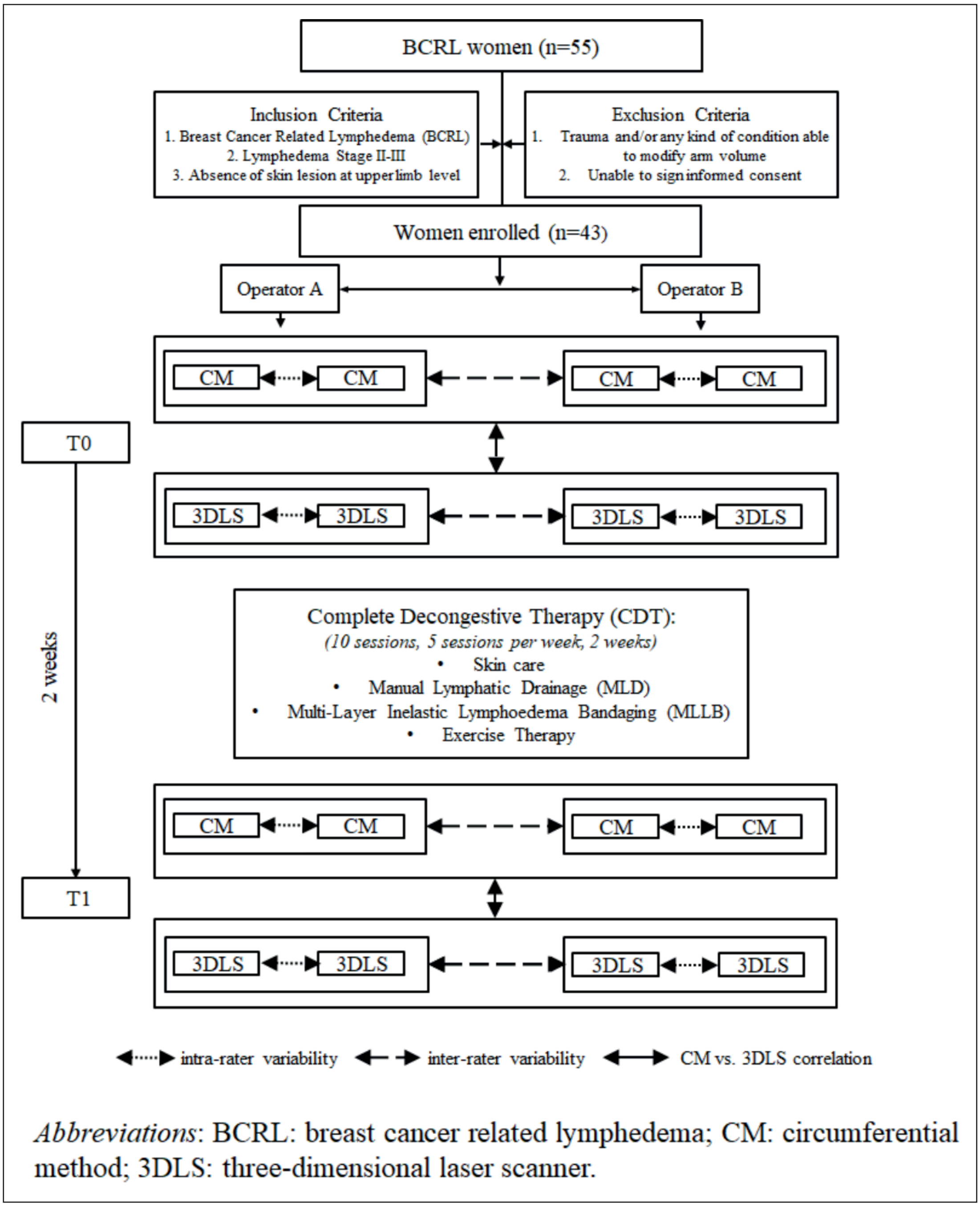

Figure 1. Study flow chart.

Outcomes

CM

CM consisted of measuring through tape with 1 mm of sensitivity upper limb circumferences of participants. They had to be in an upright sitting position with the arm on a table, shoulders in neutral rotation and flexion of 45°, and forearms at maximum supination, as described for lymphedema patients[30]. All the measurements were made in correspondence of markers made on the skin from wrist to deltoid muscle level, with 5 cm intervals (Figure 2a), as previously described in several studies[16,23]. Subsequently, the marker points were deleted from the skin surface after each measurement to not influence the operator.

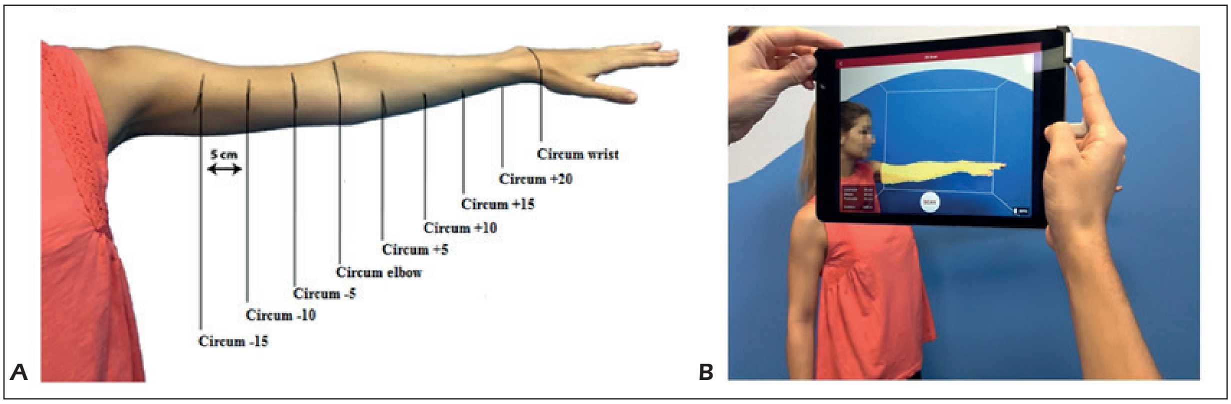

Figure 2. A, Marker points on upper limb. **B**, The three-dimensional laser scanner using a common tablet.

The arm volume was calculated using the following frustum formula[31]:

$$V = h * \frac{C'^2 + C'C'' + C''^2}{12\pi}$$

3DLS

A portable 3DLS system, the Structure Sensor (Occipital, Inc©, Boulder, CO, USA), was applicated on a common tablet (Figure 2b) and used to evaluate the upper limb volumes. All data were saved and processed using the software Captevia Rodin4D, Version 3.3.3.1 (Rodin SAS©, Merignac, France). To guarantee the proper accuracy during the scanning phase, it was necessary to ensure that subjects could maintain a stable position for the entire measurement duration. All 3DLS scans were performed with the subject standing and with the whole arm fully extended and pronated fixed at 90° of shoulder flexion position. In order to ensure a proper scanning, 3DLS was placed in proximity to the subject at the maximum distance of 1 meter in a fixed position on the stand where the hand was held up. After scanning, data were saved on a laptop and volume was obtained offline through the CAD-CAM Rodin4D, version 10.0.77.0 (Rodin SAS©, Merignac, France).

Statistical Analysis

Statistical analysis was performed using the GraphPad 6 package, version 6.0 (GraphPad Software, Inc©, San Diego, CA, USA). Intra-rater volume measurement differences have been evaluated using Wilcoxon test and inter-rater volume differences by the Mann–Whitney U-test, at both time-points. Inter and intra-rater correlation were evaluated with Pearson's correlation (r^2) and the relationship between volumes measured with CM and 3DLS were analyzed using linear regression, at both time-points. Bland-Altman plot was performed to assess the level of agreement and the consistency of the two measurements at both time-points. Furthermore, the correlation between the inter-rater operator analysis in terms of total limb volume differences after rehabilitative treatment of both techniques was assessed using linear regression. A type I error (alpha) level of 0.05 was chosen.

Results

We included 43 BCRL women, mean aged 51.1 ± 5.4 years, with a mean body mass index of 24.2 ± 2.5 kg/m^2. Both CM and 3DLS showed a high intra-operator reproducibility rate with a mean r^2=0.99 for both techniques. All results of the inter-operator analysis of 3DLS and CM regarding every single volume, forearm, arm, and total arm showed no differences at any evaluated volume (Tables I and II).

Both 3DLS and CM showed a highly significant inter-operator correlation in upper limb volume measurement (T0: r^2=0.99, p<0.0001; T1: r^2=0.99, p<0.0001) (as showed by Tables I and II) regarding every single volume without any statistically significant difference between the two raters as confirmed by the Mann-Whitney U test.

3DLS mean volumes showed a strong correlation with CM in total arm volume measurement at both time points (T0: r^2=0.99, p<0.0001; T1: r^2=0.99, p<0.0001), as evidenced by Figure 3a.

Table I. Intra- and inter-operator analysis of laser scanning 3D at the baseline (T0) and after 2-week treatment (T1).

	T0 (n=43)								
	Intra-operator analysis						Inter-operator analysis		
	Operator A			Operator B			Operator A	Operator B	
	1st measure	2nd measure	r^2	1st measure	2nd measure	r^2	Mean	Mean	r^2
V1 (dm^3)	0.09 ± 0.06	0.09 ± 0.06	0.99	0.09 ± 0.06	0.09 ± 0.06	0.99	0.09 ± 0.06	0.09 ± 0.06	0.99
V2 (dm^3)	0.20 ± 0.09	0.20 ± 0.09	0.99	0.20 ± 0.09	0.20 ± 0.09	0.99	0.20 ± 0.09	0.20 ± 0.09	0.99
V3 (dm^3)	0.28 ± 0.11	0.28 ± 0.11	0.99	0.28 ± 0.11	0.28 ± 0.11	0.99	0.28 ± 0.11	0.28 ± 0.11	0.99
V4 (dm^3)	0.34 ± 0.11	0.34 ± 0.11	0.99	0.34 ± 0.11	0.34 ± 0.11	0.99	0.34 ± 0.11	0.34 ± 0.11	0.99
V5 (dm^3)	0.36 ± 0.12	0.36 ± 0.12	0.99	0.36 ± 0.12	0.36 ± 0.12	0.99	0.36 ± 0.12	0.36 ± 0.12	0.99
V6 (dm^3)	0.37 ± 0.11	0.37 ± 0.11	0.99	0.37 ± 0.11	0.37 ± 0.11	0.99	0.37 ± 0.11	0.37 ± 0.11	0.99
V7 (dm^3)	0.44 ± 0.12	0.44 ± 0.12	0.99	0.44 ± 0.12	0.44 ± 0.12	0.99	0.44 ± 0.12	0.44 ± 0.12	0.99
V8 (dm^3)	0.46 ± 0.15	0.46 ± 0.15	0.99	0.46 ± 0.15	0.46 ± 0.15	0.99	0.46 ± 0.15	0.46 ± 0.15	0.99
V forearm (dm^3)	1.32 ± 0.44	1.32 ± 0.44	0.99	1.32 ± 0.45	1.32 ± 0.45	0.99	1.32 ± 0.45	1.32 ± 0.45	0.99
V arm (dm^3)	1.26 ± 0.37	1.26 ± 0.37	0.99	1.27 ± 0.37	1.27 ± 0.37	0.99	1.27 ± 0.37	1.27 ± 0.37	0.99
V tot (dm^3)	2.58 ± 0.79	2.58 ± 0.79	0.99	2.59 ± 0.79	2.59 ± 0.79	0.99	2.59 ± 0.79	2.59 ± 0.79	0.99
	T1 (n=43)								
	Intra-operator analysis						Inter-operator analysis		
	Operator A			Operator B			Operator A	Operator B	
	1st measure	2nd measure	r^2	1st measure	2nd measure	r^2	Mean	Mean	r^2
V1 (dm^3)	0.08 ± 0.06	0.08 ± 0.06	0.99	0.08 ± 0.06	0.08 ± 0.06	0.99	0.08 ± 0.06	0.08 ± 0.06	0.99
V2 (dm^3)	0.20 ± 0.09	0.20 ± 0.09	0.99	0.20 ± 0.08	0.20 ± 0.09	0.99	0.20 ± 0.09	0.20 ± 0.08	0.99
V3 (dm^3)	0.27 ± 0.09	0.27 ± 0.09	0.99	0.27 ± 0.09	0.27 ± 0.09	0.99	0.27 ± 0.09	0.27 ± 0.09	0.99
V4 (dm^3)	0.33 ± 0.10	0.33 ± 0.10	0.99	0.34 ± 0.11	0.34 ± 0.10	0.99	0.33 ± 0.10	0.34 ± 0.11	0.99
V5 (dm^3)	0.35 ± 0.10	0.35 ± 0.10	0.99	0.35 ± 0.10	0.35 ± 0.10	0.99	0.35 ± 0.10	0.35 ± 0.10	0.99
V6 (dm^3)	0.36 ± 0.11	0.35 ± 0.11	0.99	0.36 ± 0.11	0.36 ± 0.11	0.99	0.36 ± 0.11	0.36 ± 0.11	0.99
V7 (dm^3)	0.43 ± 0.13	0.43 ± 0.13	0.99	0.43 ± 0.13	0.43 ± 0.13	0.99	0.43 ± 0.13	0.43 ± 0.13	0.99
V8 (dm^3)	0.45 ± 0.15	0.45 ± 0.15	0.99	0.45 ± 0.15	0.45 ± 0.15	0.99	0.45 ± 0.15	0.45 ± 0.15	0.99
V forearm (dm^3)	1.23 ± 0.40	1.23 ± 0.40	0.99	1.24 ± 0.40	1.24 ± 0.40	0.99	1.23 ± 0.40	1.24 ± 0.40	0.99
V arm (dm^3)	1.24 ± 0.36	1.24 ± 0.36	0.99	1.24 ± 0.36	1.24 ± 0.36	0.99	1.24 ± 0.36	1.24 ± 0.36	0.99
V tot (dm^3)	2.47 ± 0.73	2.47 ± 0.73	0.99	2.48 ± 0.73	2.48 ± 0.73	0.99	2.47 ± 0.73	2.48 ± 0.73	0.99

Data are expressed as means ± standard deviations. Statistical analysis performed was Pearson correlation coefficient.

Table II. Intra- and inter-operator analysis of circumferential method at the baseline (T0) and after 2-week treatment (T1).

	T0 (n=43)								
	Intra-operator analysis						Inter-operator analysis		
	Operator A			Operator B			Operator A	Operator B	
	1st measure	2nd measure	r^2	1st measure	2nd measure	r^2	Mean	Mean	r^2
V1 (dm^3)	0.14 ± 0.05	0.14 ± 0.05	0.99	0.14 ± 0.05	0.14 ± 0.05	0.99	0.14 ± 0.05	0.14 ± 0.05	0.98
V2 (dm^3)	0.22 ± 0.09	0.22 ± 0.09	0.99	0.22 ± 0.09	0.22 ± 0.09	0.99	0.22 ± 0.09	0.22 ± 0.09	0.99
V3 (dm^3)	0.28 ± 0.10	0.28 ± 0.10	0.99	0.28 ± 0.10	0.28 ± 0.10	0.99	0.28 ± 0.10	0.28 ± 0.10	0.99
V4 (dm^3)	0.34 ± 0.10	0.34 ± 0.10	0.99	0.34 ± 0.10	0.34 ± 0.10	0.99	0.34 ± 0.10	0.34 ± 0.10	0.99
V5 (dm^3)	0.36 ± 0.12	0.36 ± 0.12	0.99	0.36 ± 0.12	0.36 ± 0.12	0.99	0.36 ± 0.12	0.36 ± 0.12	0.99
V6 (dm^3)	0.37 ± 0.11	0.37 ± 0.11	0.99	0.37 ± 0.11	0.37 ± 0.11	0.99	0.37 ± 0.11	0.37 ± 0.11	0.99
V7 (dm^3)	0.44 ± 0.12	0.44 ± 0.12	0.99	0.44 ± 0.12	0.44 ± 0.12	0.99	0.44 ± 0.12	0.44 ± 0.12	0.99
V8 (dm^3)	0.48 ± 0.15	0.48 ± 0.15	0.99	0.48 ± 0.16	0.48 ± 0.16	0.99	0.48 ± 0.16	0.48 ± 0.16	0.99
V forearm (dm^3)	1.30 ± 0.41	1.30 ± 0.41	0.99	1.31 ± 0.41	1.31 ± 0.41	0.99	1.31 ± 0.41	1.31 ± 0.41	0.99
V arm (dm^3)	1.29 ± 0.38	1.29 ± 0.38	0.99	1.30 ± 0.38	1.30 ± 0.38	0.99	1.30 ± 0.38	1.30 ± 0.38	0.99
V tot (dm^3)	2.60 ± 0.77	2.60 ± 0.77	0.99	2.61 ± 0.76	2.61 ± 0.76	0.99	2.61 ± 0.76	2.61 ± 0.76	0.99
	T1 (n=43)								
	Intra-operator analysis						Inter-operator analysis		
	Operator A			Operator B			Operator A	Operator B	
	1st measure	2nd measure	r^2	1st measure	2nd measure	r^2	Mean	Mean	r^2
V1 (dm^3)	0.14 ± 0.05	0.14 ± 0.05	0.99	0.14 ± 0.05	0.14 ± 0.05	0.99	0.14 ± 0.05	0.14 ± 0.05	0.99
V2 (dm^3)	0.20 ± 0.09	0.20 ± 0.09	0.99	0.20 ± 0.09	0.20 ± 0.09	0.99	0.20 ± 0.09	0.20 ± 0.09	0.99
V3 (dm^3)	0.27 ± 0.10	0.27 ± 0.09	0.99	0.26 ±0.10	0.27 ±0.10	0.99	0.26 ± 0.11	0.27 ±0.10	0.99
V4 (dm^3)	0.34 ± 0.11	0.34 ± 0.11	0.99	0.34 ± 0.10	0.34 ± 0.11	0.99	0.34 ± 0.11	0.34 ± 0.11	0.99
V5 (dm^3)	0.35 ± 0.10	0.35 ± 0.10	0.99	0.35 ± 0.10	0.35 ± 0.10	0.99	0.35 ± 0.10	0.35 ± 0.10	0.99
V6 (dm^3)	0.37 ± 0.11	0.37 ± 0.11	0.99	0.37 ± 0.11	0.37 ± 0.11	0.99	0.37 ± 0.11	0.37 ± 0.11	0.99
V7 (dm^3)	0.43 ± 0.13	0.44 ± 0.13	0.99	0.43 ± 0.12	0.43 ± 0.13	0.99	0.43 ± 0.13	0.43 ± 0.12	0.99
V8 (dm^3)	0.46 ± 0.15	0.46 ± 0.15	0.99	0.46 ±0.13	0.46 ±0.13	0.99	0.46 ± 0.15	0.46 ±0.13	0.99
V forearm (dm^3)	1.30 ± 0.45	1.30 ± 0.44	0.99	1.30 ± 0.45	1.30 ± 0.45	0.99	1.30 ± 0.45	1.30 ± 0.45	0.99
V arm (dm^3)	1.26 ± 0.39	1.26 ± 0.38	0.99	1.27 ± 0.37	1.26 ± 0.37	0.99	1.26 ± 0.39	1.27 ± 0.37	0.99
V tot (dm^3)	2.56 ± 0.80	2.57 ± 0.80	0.99	2.56 ± 0.79	2.56 ± 0.79	0.99	2.56 ± 0.80	2.56 ± 0.79	0.99

Data are expressed as means ± standard deviations. Statistical analysis performed was Pearson correlation coefficient.

The strong correlation between 3DLS and CM has been also confirmed by the Bland-Altman plot (Figure 3b); this plot has been widely used to compare two measurement techniques focusing on the same parameter, based on the assumption that a strong correlation could not be synonymous of a strong agreement. Furthermore, we found significant ($p<0.0001$) correlations in the inter-operator analysis in terms of total limb volumes differences after the 2-week CDT (T1-T0) for both techniques. It was interesting to notice that 3DLS correlation was higher than CM ($r^2 = 0.85$ *vs.* $r^2 = 0.64$) (Figure 3c for further details).

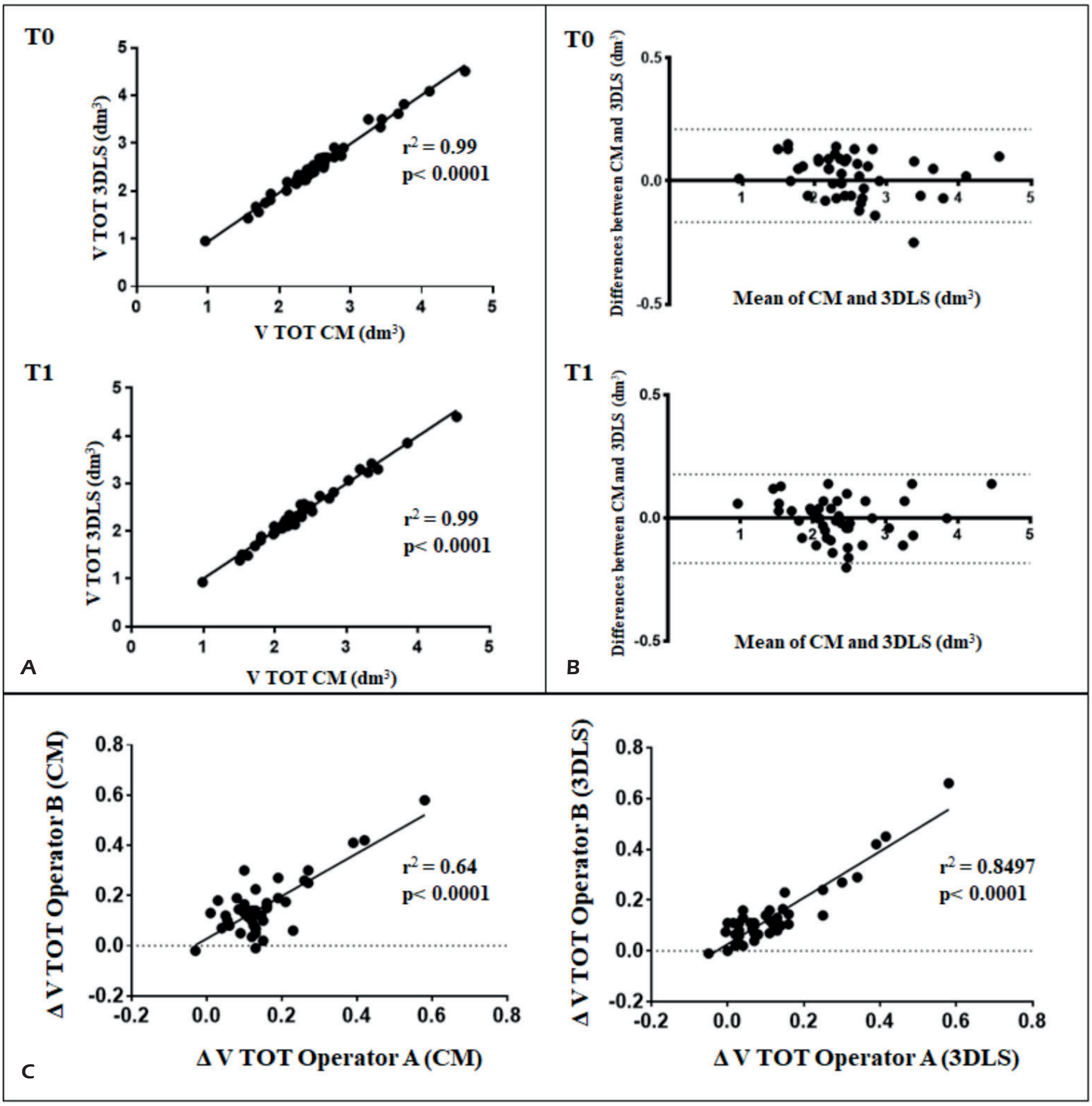

Figure 3. ***A***, Correlation between three-dimensional laser scanning (3DLS) and circumferential method (CM) at both timepoints; ***B***, Bland-Altman plot showing the level of agreement and the consistency of the two measurements at both timepoints; ***C***, Correlation between the inter-rater operator analysis in terms of total limb volume differences after rehabilitative treatment of both CM and 3DLS techniques.

Discussion

BCRL, despite being not lethal *per se*, is strongly detrimental for the HRQoL of BC survivors with a negative impact on sanitary costs, making necessary an early management[2,7,8,10-12]. Thus, it is mandatory to use an accurate and reliable tool for limb volume measurement, for both an adequate diagnosis and to monitor modifications induced by rehabilitation in these patients. 3DLS has already been proved to be a useful tool for measuring the upper limb volume[18-20] In the present study, we demonstrated for the first time its reproducibility and reliability also in assessing the differences after a specific CDT treatment in a cohort of BCRL women.

Several studies addressed arm volume measurement in lymphedema patients and different techniques have been investigated and compared[13-15,17,18,22-26]. Up to date, WD is actually considered the gold standard in arm volume measurement for both clinical and research purposes[13-15]. However, its main limitation is the inability to highlight and measure swelling and gibbousness of the arm, crucial for both patients and physicians in high stage lymphedema. Indeed, WD is not routinely used in the clinical setting for both practical and technical limitations like the presence of skin lesion, extremely common in these patients. The most widely used method in clinical practice is still the CM, although it might be subject to errors due to the use of an approximated formula for the volume calculation (frustum formula). These errors could be mainly related to the high intra-operator variability, operator experience and, in case of high stage lymphedema, to irregular limb shape (i.e., gibbousness).

3DLS has been showed to be a promising technique for quick volume measurement and it has been already compared to WD[19] and CM[18,20] for upper limb volume measurement in healthy subjects. Firstly, McKinnon et al[19] performed a pilot study comparing 3DLS to WD in terms of a series of regularly shaped objects of known volume, a set of irregularly shaped objects of unknown volume, and the volume of the arms of 10 human volunteers. They showed a mean difference between WD volume and 3DLS volume of 151.7±189.5 ml, and the coefficient of reproducibility of WD was 450.8 ml, whereas for 3DLS it was 174 ml. Similar results were recently obtained by Preu et al[33] comparing a 3DLS device to WD for upper limb volume measurement in BCRL patients. They showed no significant difference in upper limb volume quantification between the two methods in BCRL patients ($p = 0.807$); moreover, 3DLS had a high intra-rater reliability (Intraclass Correlation Coefficient = 0.999) compared to WD, with intriguing implications for its clinical implementation in routine BCRL diagnosis and rehabilitative treatment. However, the authors underlined the high costs of the 3DLS device, the effort in arm reference points detection and acquisition combined with time-consuming software elaboration.

Recently, Cau et al[18] have compared 3DLS to CM in 12 healthy subjects, showing a high intra- and inter-operator reliability and a satisfactory level of agreement for both techniques; however, the 3DLS device appeared to be a more accurate volume instrument, taking into account the significant difference of volumes. Thus, in 2020, in a pilot study performed by our group[20], we compared the use of a portable 3DLS device to CM on 30 healthy subjects and 30 BCRL patients; we showed that 3DLS not only had a higher correlation but also was significantly quicker (total time including acquisition and digital processing: 202±27 sec *vs*. 293±17 sec; $p<0.0001$) in evaluating the upper limb volume in both groups.

Taking into account the previous works in literature, in the present proof-of-principle study, we demonstrated for the first time the reproducibility and reliability of a portable 3DLS device compared to CM in measuring upper limb volumes in a cohort of BCRL women before and after the rehabilitation treatment, assessing the improvement obtained through the CDT. These findings are intriguing considering the relative quickness, accuracy, and reproducibility of the 3DLS; moreover, these data suggest a relatively fast learning curve of this device, at least comparable to CM.

Taken together, all these points might suggest crucial implications for the implementation of portable 3DLS techniques in different real practice clinical settings (i.e., outpatient or home care) and for the potential reduction of health sanitary costs in terms of both personnel and procedures costs.

However, this study has several limitations: firstly, the small sample size, although comparable and slightly higher than similar studies published in the literature about this topic; secondly, 3DLS was not compared to WD, considered as the gold standard for limb volume measurement, because we have chosen the CM, the most widely used technique in order to obtain data with direct implications in clinical practice.

In this proof-of-principle study, we confirmed that the 3DLS technique is a highly sensitive, reproducible, and easy-to-use method in evaluating the upper limb volume in BCRL women. Moreover, to the best of our knowledge, this is the first study that demonstrated the reproducibility and reliability of a 3DLS device also in detecting volumetric differences in the upper limb after a specific rehabilitation treatment in a cohort of BCRL patients. Therefore, this method might have positive implications for lymphedema management in the clinical practice, considering the key role of augmented reality technologies in BCRL clinical workup.

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Conflict of Interests

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References

1) Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.
2) Iorio GC, Franco P, Gallio E, Martini S, Arcadipane F, Bartoncini S, Rondi N, Giglioli FR, Ala A, Airoldi M, Donadio M, De Sanctis C, Castellano I, Ricardi U. Volumetric modulated arc therapy (VMAT) to deliver nodal irradiation in breast cancer patients. Med Oncol 2017; 35: 1.
3) Franco P, Iorio GC, Bartoncini S, Airoldi M, De Sanctis C, Castellano I, Ricardi U. De-escalation of breast radiotherapy after conserving surgery in low-risk early breast cancer patients. Med Oncol 2018; 5: 62.
4) Elder EE, Brandberg Y, Björklund T, Rylander R, Lagergren J, Jurell G, Wickman M, Sandelin K. Quality of life and patient satisfaction in breast cancer patients after immediate breast reconstruction: a prospective study. Breast 2005; 14: 201-208.
5) Losco L, Cigna E. Aesthetic refinements in C-V flap: raising a perfect cylinder. Aesthet Surg J 2018; 17: NP26-NP28.
6) de Sire A, Invernizzi M, Lippi L, Cisari C, Özçakar L, Franchignoni F. Blurred lines between axillary web syndrome and Mondor's disease after breast cancer surgery: a case report. Ann Phys Rehabil Med 2019 May 20. pii: S1877-0657(19)30063-6. doi: 10.1016/j.rehab.2019.04.007. [Epub ahead of print].
7) Michelotti A, Invernizzi M, Lopez G, Lorenzini D, Nesa F, De Sire A, Fusco N. Tackling the diversity of breast cancer related lymphedema: perspectives on diagnosis, risk assessment, and clinical management. Breast 2019; 44: 15-23.
8) Invernizzi M, Michelotti A, Noale M, Lopez G, Runza L, Giroda M, Despini L, Blundo C, Maggi S, Gambini D, Fusco N. Breast cancer systemic treatments and upper limb lymphedema: a risk-assessment platform encompassing tumor-specific pathological features reveals the potential role of trastuzumab. J Clin Med 2019; 24: pii: E138.
9) Invernizzi M, Corti C, Lopez G, Michelotti A, Despini L, Gambini D, Lorenzini D, Guerini-Rocco E, Maggi S, Noale M, Fusco N. Lymphovascular invasion and extranodal tumour extension are risk indicators of breast cancer related lymphoedema: an observational retrospective study with long-term follow-up. BMC Cancer 2018; 18: 935.
10) DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 2013; 14: 500-515.
11) Invernizzi M, Lopez G, Michelotti A, Venetis K, Sajjadi E, De Mattos-Arruda L, Ghidini M, Runza L, de Sire A, Boldorini R, Fusco N. Integrating Biological Advances Into the Clinical Management of Breast Cancer Related Lymphedema. Front. Oncol. 2020; 10:422. DOI: 10.3389/fonc.2020.00422.
12) Stout NL, Weiss R, Feldman JL, Stewart BR, Armer JM, Cormier JN, Shih YC. A systematic review of care delivery models and economic analyses in lymphedema: health policy impact (2004-2011). Lymphology 2013; 46: 27-41.
13) Damstra RJ, Glazenburg EJ, Hop WC. Validation of the inverse water volumetry method: a new gold standard for arm volume measurements. Breast Cancer Res Treat 2006; 99: 267-273.
14) Mayrovitz HN, Sims N, Hill CJ, Hernandez T, Greenshner A, Diep H. Hand volume estimates based on a geometric algorithm in comparison to water displacement. Lymphology 2006; 39: 95-103.
15) Meijer RS, Rietman JS, Geertzen JH, Bosmans JC, Dijkstra PU. Validity and intra- and interobserver reliability of an indirect volume measurements in patients with upper extremity lymphedema. Lymphology 2004; 37: 127-133.
16) Mayrovitz HN, Sims N, Macdonald J. Assessment of limb volume by manual and automated methods in patients with limb edema or lymphedema. Adv Skin Wound Care 2000; 6: 272-276.
17) Cheifetz O, Haley L; Breast cancer action management of secondary lymphedema related to breast cancer. Can Fam Physician 2010; 56: 1277-1284.
18) Cau N, Galli M, Cimolin V, Aranci M, Caraceni A, Balzarini A. Comparative study between circum-

ferential method and laser scanner 3D method for the evaluation of arm volume in healthy subjects. J Vasc Surg Venous Lymphat Disord 2016; 4: 64-72.

19) McKinnon JG, Wong V, Temple WJ, Galbraith C, Ferry P, Clynch GS, Clynch C. Measurement of limb volume: laser scanning versus volume displacement. J Surg Oncol 2007; 96: 381-388.

20) Invernizzi M, Runza L, De Sire A, Lippi L, Blundo C, Gambini D, Boldorini R, Ferrero S, Fusco N. Integrating augmented reality tools in breast cancer related lymphedema prognostication and diagnosis. J Vis Exp 2020; 156: e60093.

21) Ng M, Munnoch A. Clinimetrics of volume measurement in upper limb LE. J Lymphoedema 2010; 5: 62-67.

22) Karges JR, Mark BE, Stikeleather SJ, Worrell TW. Concurrent validity of upper-extremity volume estimates: comparison of calculated volume derived from girth measurements and water displacement volume. Phys Ther 2003; 83: 134-145.

23) Deltombe T, Jamart J, Recloux S, Legrand C, Vandenbroeck N, Theys S, Hanson P. Reliability and limits of agreement of circumferential, water displacement, and optoelectronic volumetry in the measurement of upper limb lymphedema. Lymphology 2007; 40: 26-34.

24) Maihafer GC, Llewellyn MA, Pillar WJ Jr, Scott KL, Marino DM, Bond RM. A comparison of the figure-of-eight method and water volumetry in measurement of hand and wrist size. J Hand Ther 2003; 16: 5-10.

25) Gjorup C, Zerahn B, Hendel HW. Assessment of volume measurement of breast cancer-related lymphedema by three methods: circumference measurement, water displacement, and dual energy X-ray absorptiometry. Lymphat Res Biol 2010; 8: 111-119.

26) Sander AP, Hajer NM, Hemenway K, Miller AC. Upper-extremity volume measurements in women with lymphedema: a comparison of measurements obtained via water displacement with geometrically determined volume. Phys Ther 2002; 82: 1201-1212.

27) Tewari N, Gill PG, Bochner MA, Kollias J. Comparison of volume displacement versus circumferential arm measurements for lymphoedema: implications for the SNAC trial. ANZ J Surg 2008; 78: 889-893.

28) Harrison JA, Nixon MA, Fright WR, Snape L. Use of hand-held laser scanning in the assessment of facial swelling: a preliminary study. Br J Oral Maxillofac Surg 2004; 42: 8-17.

29) Mestre S, Veye F, Perez-Martin A, Behar T, Triboulet J, Berron N, Demattei C, Quéré I. Validation of lower limb segmental volumetry with hand-held, self-positioning three-dimensional laser scanner against water displacement. J Vasc Surg Venous Lymphat Disord 2014; 2: 39-45.

30) Torres Lacomba M, Yuste Sánchez MJ, Zapico Goñi A, Prieto Merino D, Mayoral del Moral O, Cerezo Téllez E, Minayo Mogollón E. Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: randomised, single blinded, clinical trial. BMJ 2010; 340: b5396.

31) Sitzia J. Volume measurement in lymphoedema treatment: examination of formulae. Eur J Cancer Care 1995; 4: 11-16.

32) Preuss M, Killaars R, Piatkowski de Grzymala A, Binnebösel M, Neumann U. Validity and reliability of three-dimensional imaging for measuring breast cancer-related lymphedema in the upper limb: a cross-sectional study. Lymphat Res Biol 2018 Oct 3. doi: 10.1089/lrb.2017.0076. [Epub ahead of print].