Analysis of different lymphedema assessment tools in women with breast cancer after mastectomy.

Rocío Abalo-Núñez[1,2], Iria Da Cuña-Carrera[1,2], Alejandra Alonso-Calvete[1,3], Eva Mª. Lantarón-Caeiro[1,2], Mercedes Soto-González[1,2].

[1] *Faculty of Physiotherapy. University of Vigo. Pontevedra. Spain.*

[2] *Clinical Physiotherapy Group. Galicia Sur Health Research Institute (IIS Galicia Sur) SERGAS, Vigo, Spain.*

[3] *REMOSS Research Group. University of Vigo. Pontevedra. Spain.*

Correspondence: Alejandra Alonso-Calvete. Faculty of Physiotherapy. University of Vigo. Campus A Xunqueira s/n, 36005, Pontevedra. Spain. alejalonso@uvigo.es
+34986801750

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Abstract

Background: Lymphedema is a common complication after mastectomy in women with breast cancer. Several methods have been described to assess and diagnose lymphedema, being one of the most studied the perimeter and ultrasonography. However, the reliability of these methods and the correlation between them are still controversial. The aim of this study was to analyse the reliability ofcytometry and ultrasound imaging in the assessment of lymphedema in women with breast cancer after mastectomy and to study the correlation between them.

Methods and Results: A cross-sectional study was conducted in 29 women with mastectomy after breast cancer. Lymphedema in the arm was measured both with cytometry and ultrasonography. Reliability was calculated with intraclass correlation coefficient. The correlation between the two methods was carried out with the Pearson Correlation Coefficient. Both cytometry (M1: α=0.999, ICC=0.996; M2=: α=0.998, ICC=0.994) and ultrasonography (M1: α=0.992, ICC=0.976; M2=: α=0.991, ICC=0.973) are reliable methods to assess lymphedema in the arm. No significant correlations were found between them ($p > 0.05$).

Conclusions: Cytometry and ultrasonography appear to be adequate for the measurement of oedema in women with breast cancer after mastectomy. However, for an accurate measurement of lymphedema, these measurements should not be used interchangeably.

Keywords: Ultrasound imaging; Manual lymphatic drainage, Breast cancer, Lymphedema

Condensed abstract

The aim of this study was to analyse the reliability of perimeter and ultrasound imaging in the assessment of lymphedema in women with breast cancer after mastectomy and to study the correlation between them. A cross-sectional study was conducted in 29 women with mastectomy after breast cancer. Lymphedema in the arm was measured both with cytometry and ultrasonography and both methods appeared to be adequate for the measurement of oedema in women with breast cancer after mastectomy.

Introduction

Lymphedema is a common complication following breast cancer surgery [1]. It is characterized by persistent tissue swelling due to an abnormal accumulation of lymph in the tissues [1] affecting about 15% to 30% of patients [2,3]. Lymphedema has been shown to have a significant negative physical and psychological impact on patients who suffer from it, affecting arms, hands, fingers, wrists, elbows, shoulders, neck, breast, chest, or any combination of these areas [4]. Consequently, prior studies have reported an urgent need to implement effective methods to treat and/or prevent lymphedema, as well as to have reliable methods for its diagnosis and measurement [2,3].

One of the most used methods to evaluate lymphedema in women after mastectomy and to determine the size of the affected limb are perimeter measurements, assessed with a tape measure [5]. This technique has been shown as one of the most efficient and widely used methods in clinical practice to evaluate lymphedema [6]. Moreover, prior research has

64 also reported that self-measurements of the perimeter by patients is reliable and valid
65 when assessing lymphedema [6].
66 On the other hand, other authors such as Taylor et al. [7] have studied volume measurements
67 as a tool to asses lymphedema. These volumes could be calculated with formulas, using
68 valid and precise anatomical references [7] or through displacements in the volume of water
69 [8]. In this sense, both techniques have been described as reliable and closely related, but
70 do not measure the same amount of oedema, therefore, they should not be used
71 interchangeably [8].
72 Nevertheless, recent studies have reported that measurements of perimeter of volume
73 have several disadvantages, such as not recognizing small oedemas or not providing
74 information on their stage [9]. Similarly, other research has suggested that the assessment
75 of limb size alone does not provide a complete clinical picture or help predict response to
76 treatment [10]. In fact, lymphedema is often not diagnosed until the patients themselves
77 notice subtle signs of swelling, such as the inability to wear rings or watches, or symptoms
78 such as discomfort, heaviness or tightness in the limb [1].
79 For these reasons, the need has arisen to develop new techniques which consider the
80 mechanical or physical properties of tissues to evaluate lymphedema, such as
81 lymphogammagraphy, bioimpedance, fluoroscopy, MRI, or ultrasound. Specifically, the
82 use of ultrasound imaging has increased in clinical practice and has been demonstrated as
83 a useful method with the ability to reveal physiological changes in the tissues [10,11].
84 Previous studies have also informed that the difference in dermal thickness is an easy and
85 inexpensive measure to quantify lymphedema and correlates with treatment parameters
86 and patient-reported impacts on quality of life [12]. This method allows visualization of
87 tissues and detection of changes in tissue density and structure, providing useful clinical
88 information. Nevertheless, imaging options appear not to be always available to therapists

and are rarely used in research or clinical practice with women with breast cancer after mastectomy. Thus, scientific evidence support that more research is required to determine the reliability, sensitivity and specificity of ultrasound imaging in the assessment of lymphedema [10,11].

Therefore, the aim of this study was to analyze the reliability of two methods for assessing lymphedema: cytometry and ultrasound imaging in women with breast cancer after mastectomy and to study the correlation between them.

Methods

Design

A crossover study was conducted in order to analyze the reliability of two methods for measuring oedema: cytometry and ultrasonography. Both techniques have reported high reliability in previous studies and have been demonstrated as adequate methods for measuring oedema in the arm [13–15]. A secondary aim was to compare both techniques and analyze whether they can be used interchangeably.

This investigation was carried out during March and April 2021. The Declaration of Helsinki was followed, and the protocol of the study was approved by the Institutional Ethics Committee of the University of Vigo (reference number: 205-2021-3). All participants received information about the study and voluntarily signed a written informed consent form.

Participants

Thirty-four women with lymphedema after breast cancer were initially recruited and 29 met the inclusion criteria. Inclusion criteria were: I) Women included in the lymphedema treatment maintenance program through the Galician Lymphedema Association; II)

Women with secondary unilateral lymphedema (stage 2 according to International Society of lymphology) [16] after breast cancer surgery. Exclusion criteria were I) Women undergoing chemotherapy or radiotherapy treatment; II) Severe systemic or neurological disease.

Sample size was calculated with the software G*Power (version 3.1.1). The study of Tambour et al. [17] was selected. The variable selected was "circumference of the arm" comparing affected vs unaffected arm (179.2 ± 4.93 vs 154.4 ± 2.46; effect size = 0,63). Considering a power of 0.9 and an alpha error of 0.05, an estimated sample size of 23 subjects was calculated, as a minimum to report consistent results. To account for a potential 30% loss to follow-up, a total of 29 participants was deemed necessary to ensure adequate power for the analysis.

All participants were equally randomized to the group 1 and group 2 by a person who was not involved in either the assessments or the intervention. Simple randomization using tables of random numbers with allocation reason 1:1. Hidden allocation was used.

Procedures

In order to measure the amount of oedema in the upper limb, two different techniques were selected: cytometry and ultrasound. Both methods were used in the same arm and measurements were randomly conducted in the same day, to avoid changes in the oedema. According to previous research [18] two locations were selected in the arm: 10 cm under the lateral epicondyle (M1) and 10 cm above the lateral epicondyle (M2). In both points, 3 measurements were carried out and the mean value was used to report the amount of oedema.

Regarding the performance of the measurements, women were lying in supine position with the arm resting. First, the measurement points (M1 and M2) were marked and then the oedema was randomly measured with cytometry or ultrasonography.

For cytometry, the diameter was measured with a thin and flexible plastic tape, running through the entire diameter of the arm without applying pressure [13,14]. For ultrasonography, the thickness of the subcutaneous tissue was measured with an ultrasound scanner (GE Logic-e 4-12 MHZ, 39mm lineal transducer; B mode). The probe was placed perpendicular to the ventral axis of the upper limb [19] and sufficient ultrasound gel was applied to obtain a correct image without pressing on the tissues. The thickness of the subcutaneous tissue was obtained calculating the distance from the upper limit of the skin/subcutaneous tissue to the lower limit of the muscle fascia [15]. All measurements were carried out by a physical therapist with knowledge and training in both cytometry and musculoskeletal ultrasound imaging, who was also trained in measuring subcutaneous tissues.

Statistical analyses

All statistical analyses were conducted with the Software SPSS for Macintosh (version 25.0, Chicago, IL, USA). The normality of the data was analyzed both graphically and with the Shapiro–Wilk test. The reliability measurements were calculated with Cronbach Alpha and the intraclass correlation coefficient (ICC). According to previous studies, an ICC $\geq$ 0.7 indicated satisfactory reliability, $\geq$0.75 good reliability, and $\geq$0.9 excellent reliability [20]. For the Cronbach Alpha, values between 0.7 and 0.9 are described as adequate and values > 0.9 are excellent [21]. The comparisons between both methods of measurement were conducted with the Pearson Correlation Coefficient (r). These correlations were classified as weak ($0.1 < r < 0.3$), moderate ($0.4 < r < 0.6$), strong ($0.7 < r < 0.9$) and perfect ($r = 1$) [22]. Student's t-test for related samples was performed to

analyze the differences between measurements with cytometry and ultrasonography. For all analyses, the significance value was set at $p<0.05$.

Results

In the measurements of the oedema in the arm, an excellent reliability has been demonstrated both with cytometry (M1: $\alpha=0.999$, ICC=0.996; M2=: $\alpha=0.998$, ICC=0.994) and with ultrasonography (M1: $\alpha=0.992$, ICC=0.976; M2=: $\alpha=0.991$, ICC=0.973).

Comparing the measurements with both techniques, a moderate correlation has been reported between cytometry and ultrasonography in M1 ($r=0.46$; $p=0.014$), with significant differences between both techniques in M1 ($p<0.001$) (Figure 1). In M2 no significant correlation has been found between cytometry and ultrasonography ($r=0.349$; $p=0.068$), and significant differences between both techniques have been reported ($p=0.01$) (Figure 2).

[Figures 1 and 2 near here]

Discussion

The aim of this research was to analyze the reliability ofcytometry and ultrasound imaging for measuring lymphedema in women with breast cancer after mastectomy. In addition, the correlation between these two methods has also been analyzed.

The main results of this study suggest that measurements of the perimeter with cytometry and measurements with ultrasonography have demonstrated an excellent reliability in the assessment of lymphedema in both points (M1 and M2). Regarding the cytometry, previous similar research agree with these results [5], considering this method as reliable and universal for diagnosis and assessment of lymphedema and finding an excellent inter-rater reliability of circumferential measurements and calculated volumes of arm measurements [7]. About ultrasonography, the results found in this investigation also agree with findings in the study of Mellor et al. [23], which concluded that the measurement of

190 the dermic thickness with this method is useful especially in the diagnosis of
191 lymphedema.
192 Over the years, different methods of diagnosis and assessment of lymphedema have been
193 described. Some of them have been widely used due to their ease of use and low cost,
194 such as perimeter measurements, indirect volume or water displacement [24] but others have
195 been less analyzed due to their complexity and the lack of access, such as bioimpedance
196 [25] or MRI [26].
197 Considering the results of this study and prior research analyzing the reliability of
198 cytometry and ultrasonography in the measurement of oedema, it is suggested that both
199 techniques appear to be the most adequate to assess lymphedema and could be used
200 interchangeably [7]. The decision of selecting one or another method may be conditioned
201 by the knowledge and expertise of the evaluators, the availability of the methods or the
202 previous measurements conducted. Cytometry provides perimeter measurements which
203 are more easily analyzed, even being able to do it themselves, but it does not consider the
204 subcutaneous tissues [27]. Previous research in this topic suggested that cytometry appears
205 to be more adequate for late stages of lymphedema, where constant revaluation is
206 necessary [28], but in patients with early stages of lymphedema cytometry may fail to detect
207 profound early stage changes in the subcutaneous tissues that ultrasound does [11] and,
208 moreover, mistakes in the measurements have been reported in terms of the pressure of
209 the tape [29], the anatomical references selected or an inadequate angle in relation to the
210 longitudinal axis of the limb [30,31] and a low specificity (over 73%) [32]. To minimize the
211 impact of these factors, a previous study [33] suggested to perform several measurements
212 and calculate the mean value of them, as conducted in this research.
213 On the other hand, ultrasonography has recently arisen as an excellent method for
214 assessment and diagnosis of lymphedema, due to its great objectivity in the measurement

of the subcutaneous tissues and dermic thickness [34]. Ultrasonography has been described as a safe, mobile and effective tool to measure lymphedema tissue texture, differentiating it from deeper structures [35]. However, some considerations have been pointed out, including the measurement only in one area of the limb [35] and the possible effect of the pressure of the probe, which might modify the thickness of the tissue [15]. Specifically, regarding the pressure exerted during the evaluation, it is important to place the probe perpendicular to the ventral axis of the upper limb and to apply sufficient ultrasound gel to obtain a correct image without pressing on the tissues [15]. Finally, measurements of dermic thickness with ultrasonography have to be performed by an expert evaluator, with training in ultrasonography in order to decrease the risk of mistakes [15].

Therefore, both cytometry and ultrasonography appear to be valid and reliable methods to assess lymphedema. The use of one ofthese methods or another will depend on the stage of lymphedema, the training of the evaluator, the availability of the tools or the information required [27,28,35].

Regarding the correlation between both techniques, findings in this study suggest that no significant and relevant correlations have been found between cytometry and ultrasonography in any area (points M1 and M2). These results do not agree with Uzkeser et al. [13] who found a significant positive correlation between cytometry and ultrasonography. However, this study conducted measurements only in women with lymphedemas greater than 2 cm, whereas in our sample we included women with all types of lymphedemas. Additionally, Erdinc et al. [36] investigated the diagnostic contribution of ultrasonography in unilateral lymphedema in comparison with perimeter measurements and observed that both techniques had a moderate correlation in the anterior quadrants and a strong and positive correlation in the dorsal quadrants of the affected limb. Whereas, in the unaffected limb, a strong positive correlation was identified in all quadrants,

suggesting that the measurement area may influence the correlation, probably due to tissue differences in the body areas. At this respect, previous studies also demonstrated that the oedema and the fat are not distributed equally throughout the tissues [37], so the point of measurement is of great relevance, and especially in early diagnosis, when the oedema is not evident and research in this topic recommends performing the evaluation 30 cm proximal to the styloid, as the area that can best predict the risk of lymphedema [38]. Consequently, the correlation between cytometry and ultrasonography in the measurement of lymphedema appears to be controversial and, although these methods are adequate for assessing lymphedema, it is not recommended to use them interchangeably.

Limitations

This study presents several limitations which have to be considered. First, women were not asked whether they were taken any medication, especially those indicated to control the oedema [39]. Second, women were not measured before the onset of the oedema, so the authors are not able to compare the arm with lymphedema with their previous condition, and all the comparisons have been conducted with the healthy arm [40]. However, the differences between arms in terms of weight changes, dominance or activity have been described so these comparisons have to be read carefully [41].

Conclusions

Both cytometry and ultrasonography appear to be reliable methods to measure lymphedema in the arm of women with breast cancer after mastectomy.

However, for an accurate measurement of lymphedema, these measurements should not be used interchangeably.

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FIGURE LEGENDS

Figure 1. Comparison of the amount of oedema measured with cytometry and ultrasonography (US) in M1

Figure 2. Comparison of the amount of oedema measured with cytometry and ultrasonography (US) in M2.