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Local Tissue Water Variations in Women at Risk of Developing Arm Lymphedema Following Breast Cancer Treatment—A Retrospective Study

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Abstract

Background: Early diagnosis and treatment of breast cancer-related arm lymphedema (BCRAL) is essential to prevent progression. Local tissue water (LTW) can be assessed using the tissue dielectric constant (TDC), enabling detection before an increase of arm volume occurs. However, knowledge of the variation of LTW during cancer treatment and appropriate LTW thresholds for early detection of BCRAL is limited. The aim of this study was to examine differences in LTW between the arms, assess changes in LTW in each arm during adjuvant treatment, and calculate theoretical inter-arm thresholds for BCRAL.
Method and Results: This retrospective cohort study included 120 women treated with axillary lymph node dissection and radiotherapy. At 4–6 weeks post-surgery, LTW was significantly higher in the contralateral upper arm and the forearm at the lateral site compared to the ipsilateral arm. At 3–4 months post-radiotherapy, LTW remained higher in the contralateral upper arm at the lateral site and the forearm at the medial site. LTW decreased at the medial site of the ipsilateral upper arm and at the ventral site of the contralateral upper arm. Potential TDC ratio thresholds to detect BCRAL, including 3 SD, were calculated as 1.40 in the upper arm and 1.30 in the forearm.
Conclusion: At both follow-ups, LTW was higher in the contralateral arm at specific sites compared to the ipsilateral arm and decreased at specific sites in both arms during oncological treatment. The calculated TDC thresholds may improve detection of BCRAL and enhance the interpretation of lymphedema status during oncological treatment.

Keywords: local tissue water, tissue dielectric constant, breast cancer, axillary lymph node dissection, oncological treatment, radiotherapy

Introduction

Breast cancer-related arm lymphedema (BCRAL) is primarily caused by axillary surgery and radiotherapy. Additional risk factors include mastectomy, tumor stage, older age, high body mass index, and chemotherapy.[1–4] The incidence of BCRAL varies depending on follow-up time, diagnostic criteria, and threshold definitions. The standard use of sentinel lymph node biopsy (SLNB) has significantly reduced the prevalence of BCRAL from 23,6% following surgery with axillary lymph node dissection (ALND) to 4.9% with SLNB 2 years after surgery.[5] However, despite a decreased number of women developing BCRAL, more individuals are living longer with the consequences of treatments due to improved therapies and survival.

Early diagnosis and treatment are essential[6–10] both for reducing the number of women who develop chronic lymphedema and for mitigating its impact on health-related quality of life.[11–13] Conventionally, an increase in arm volume has been the gold standard for diagnosing arm lymphedema. However, in mild BCRAL, the lymphedema may be present only locally[14,15] and begins with dermal backflow in the

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subcutaneous tissue. Early impairment of superficial lymphatic transport has been identified as a risk factor for the development of clinical BCRAL.[1] Local tissue water (LTW) in the skin and subcutaneous tissue can be assessed using the tissue dielectric constant (TDC), enabling detection before an increase of fluid in the arm volume occurs.[16] In patients with mild BCRAL who have undergone ALND and radiotherapy, both of which are associated with higher risk of BCRAL, the highest values in of LTW in the arm have been found in the cutaneous tissue on the medial side of the upper arm and forearm.[16] Current thresholds of LTW for early diagnosis of BCRAL are based on preoperative values obtained from measurement points at the ventral site in the upper arm and forearm.[17] Notably, in that study, the majority of participants had undergone SLNB (55%) or had not received any radiotherapy (22%), both of which are associated with a lower risk of BCRAL.[17]

Previous research indicates that the LTW in the arm on the operated side is not affected by breast cancer prior to surgery.[18] However, there is limited knowledge about how LTW in the arms changes after surgery and during cancer treatment. Given this, it is important to establish the variation of LTW in both the ipsilateral and contralateral arm, and at multiple measurement sites after ALND and during adjuvant cancer treatment. Increased knowledge of the LTW variation of the arms in women who have undergone ALND and are undergoing adjuvant treatment can aid in improving the early diagnosis of BCRAL and provide a basis for the interpretation of LTW measurements of the arms of women with BCRAL.

Thus, the aim of this study was to examine differences in LTW between the ipsilateral and contralateral arms, assess changes in LTW in each arm during adjuvant treatment, and calculate theoretical inter-arm thresholds for BCRAL in women who underwent ALND and radiotherapy.

Materials and Methods

Study design

A retrospective cohort study. The article is written according to the STROBE.[19]

Subjects

A total of 120 women treated for node-positive breast cancer with ALND and radiotherapy, but with no diagnosed BCRAL, were examined as part of a routine follow-up program at the Physiotherapy Cancer Unit, Department of Occupational Therapy and Physiotherapy, Karolinska University Hospital, between 2014 and 2020. The women were assessed and measured by three experienced physiotherapists/lymphedema therapists at follow-up 4–6 weeks after surgery (T1) and at 3–4 months after completing radiotherapy (T2). These time points have been identified as appropriate for detecting arm lymphedema in a previous study.[20] Women who attended only one of the two follow-ups were excluded. Additional exclusion criteria included contralateral cancer, recurrent cancer, or concurrent diseases that could interfere with the measurements of lymphedema, such as infection or deep vein thrombosis.

Those who were diagnosed with mild BCRAL were also excluded, as they were included in a randomized controlled trial (RCT).[6] In that RCT, mild BCRAL was defined as palpation of increased skin and subcutaneous thickness combined with an arm volume increase of more than 5% compared to the contralateral arm and/or a TDC threshold of 1.45 in the upper arm and 1.30 in the forearm.

Ethical approval

The study was completed in accordance with the Declaration of Helsinki as revised in 2013 and approved by the Regional Ethical Board, D number: 2023-06832-01.

Data collection

Data regarding LTW, age, surgical method (breast-conserving surgery or mastectomy), and oncological treatment (chemotherapy regime, radiotherapy, endocrine therapy, HER 2-targeted therapy) were extracted from medical records. Also, the occurrence of bilateral cancer, recurrence, and comorbidities was collected.

LTW in the skin and upper subcutis of both arms was assessed using the MoistureMeterD Compact (MMDC) (Delfin Technologies Ltd, Finland). A low-intensity 300 MHz signal is emitted from the probe in contact with the skin, allowing for the calculation of the TDC value. The TDC values are directly related to the water content in the tissue. In this study, a probe with an effective penetration depth of 2.5 mm was utilized, which corresponds to a maximum of 78.5% pure water content. The TDC ratios obtained with our MMDC are comparable to those reported with the MMDC device that corresponds to a maximum of 100% pure water content.[21] According to Mayrovitz et al., the TDC method is reliable with an intraclass correlation coefficient value of 0.77, a standard error of measurement of 0.03 reflecting high precision, and a minimal detectable change of 0.08.[22] In the present study, measurements were taken once,[23] while participants were seated with their arms relaxed, at three locations for each upper arm and forearm bilaterally. These three locations are described as the medial, ventral, and lateral sites. For the upper arm, measurements were taken at 5 cm proximally to the antecubital fossa, and for the forearm, at 5 cm distal to the antecubital fossa (Fig. 1). In cases of peripherally inserted central catheter (picc-line) in the upper arm, only the medial and lateral sites were measured. The designation ipsilateral arm is referring to the same side of the breast cancer operation, and contralateral arm is referring to the non-operated side.

Statistical analysis

Descriptive statistics were presented as mean ± SD for continuous data and as number and proportion (%) for categorical data. The TDC data were not normally distributed and were presented as median (min-max). In order to compare with other studies, the mean ± SD was also presented. Differences in LTW between the ipsilateral and contralateral arm were calculated with the Wilcoxon signed rank test. Limb dominance was not considered in our analysis of the differences between the arms, as it has been shown to have no effect on TDC values or ratios.[24] Differences in LTW for each arm between the examination 4–6 weeks (T1) and 3–4 months after completion of radiotherapy (T2) were calculated with Wilcoxon signed-rank test. When calculating theoretical lymphedema inter-arm thresholds, the mean TDC ratio +3 SD

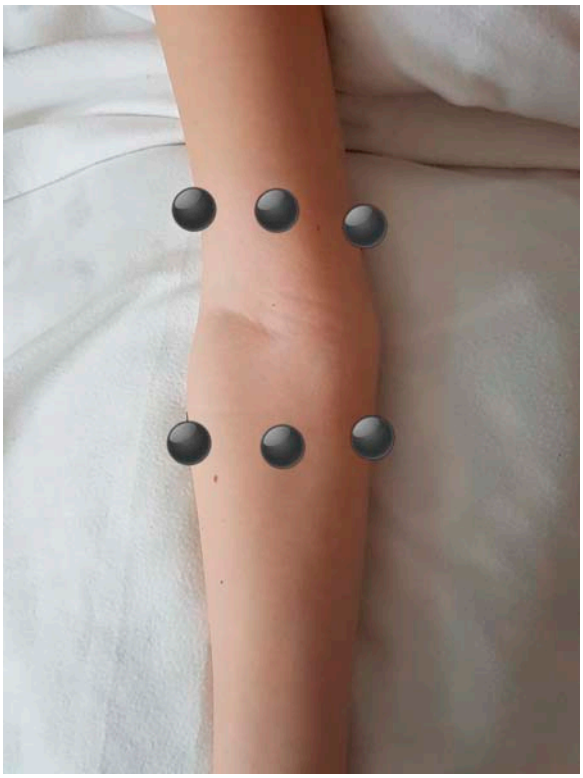

FIG. 1. Local tissue water was measured in both arms lateral, ventral and medial, 5 cm proximal and distal to the antecubital fossa.

was used. The analyses were carried out in IBM SPSS Statistics 29, and a significance level of $p < 0.05$ (two-tailed) was chosen.

Table 1. Participants and Treatment Characteristics ($N = 120$)

Age in years, mean (SD)	54.8 (14.0)
Surgery	
Surgery, mastectomy and ALND, *n* (%)	35 (29)
Surgery, reconstruction and ALND, *n* (%)	18 (15)
Surgery, breast conserving and ALND, *n* (%)	67 (56)
Number of lymph nodes removed, mean (SD)	12.2 (5.5)
Number of lymph nodes with metastasis, mean (SD)[a]	2.1 (3.2)
Operated side, *n* right/left	61/59
Oncological treatment	
Radiotherapy, *n* yes (%)	120 (100)
Breast/chest wall and regional lymph nodes	107 (89)
Breast/chest wall only	11 (9)
Only regional lymph nodes	1 (1)
Missing	1 (1)
Chemotherapy, *n* yes/no (%)	110 (92)/9 (7)
Missing	1 (1)
Preoperative	44 (37)
Preoperative and postoperative	43 (36)
Postoperative	23 (19)
Missing	2 (2)
Endocrine therapy, *n* yes/no (%)	88 (73)/31 (26)
Missing	1 (1)
HER 2 targeted therapy, *n* yes/no (%)	32 (27)/88 (73)

[a]Patients receiving preoperative chemotherapy may have had positive lymph nodes with fibrosis at the pathological analysis which then was calculated as lymph nodes with no metastasis.
ALND, axillary lymph node dissection.

Results

A total of 283 women who underwent ALND and radiotherapy were invited for follow-up visits 4–6 weeks after surgery (T1) and 3–4 months after completion of radiotherapy (T2). Of these, 163 women were excluded based on the following criteria: attending at fewer than two visits ($N = 113$), bilateral cancer ($N = 11$), rheumatoid arthritis ($N = 3$), malignant melanoma ($N = 1$), deep vein thrombosis ($N = 4$), infection in the picc-line ($N = 2$) or breast ($N = 3$), and hematoma in the breast ($N = 1$). Also, women with recurrent breast cancer ($N = 24$) or death ($N = 1$) within 1 year of the last measurement were excluded. Data of LTW and oncological treatment for the remaining 120 women were analyzed. The mean age of the included women was 54.8 ± 14.0 years. All women underwent breast surgery with ALND and received adjuvant radiotherapy, with 56% having breast-conserving surgery and 44% mastectomy. Additionally, 92% of the women received chemotherapy, with 73% having received preoperative chemotherapy at T1 and 55% receiving postoperative chemotherapy at T2 (Table 1).

Differences in LTW between the arms

Examination 4–6 weeks after surgery (T1). At T1, the LTW was statistically significantly higher in the contralateral upper arm and forearm at the lateral site compared to the ipsilateral arm. The median TDC value at the lateral site of the ipsilateral upper arm was 27.0 (range: 18–36), while the corresponding value on the contralateral arm was 28.0 (range: 19–38), ($p = 0.009$). The median TDC value at the lateral side of the ipsilateral forearm was 29.0 (range:15–40) compared to 28.5 (range: 20–46) on the contralateral arm, ($p = 0.037$) (Table 2).

Examination 3–4 months after finishing radiotherapy (T2). At T2, LTW was significantly higher in the contralateral upper arm in the lateral site and in the medial site of the forearm compared to the ipsilateral arm. The median TDC value at the lateral site of the ipsilateral upper arm was 27 (range:19–34), whereas the contralateral upper arm had a median value of 28 (range: 21–41), ($p < 0.001$). Additionally, the median TDC at the medial site of the ipsilateral forearm was 25.5 (range: 20–35), compared to 26.0 (range: 20–35) on the contralateral arm ($p = 0.032$) (Table 2).

Changes in LTW during oncological treatment

There was a significant decrease in LTW at the medial site of the ipsilateral upper arm at the ventral site of the contralateral upper arm from T1 to T2. The median TDC value at the medial site of the ipsilateral upper arm was 23.0 (range 16–37) at T1 and 23.0 (range 18–35) at T2 ($p = 0.030$). At

Table 2. Local Tissue Water Assessed by Tissue Dielectric Constant (TDC) in the Arms of Breast Cancer Survivors Without Lymphedema 3–4 Weeks After Surgery (T1) and 3–4 Months After Completed Radiotherapy (T2), ($N = 120$)

Testing site	*T1 absolute TDC value ipsilateral arm (IA)*	*T1 absolute TDC value contralateral arm (CA)*	*Difference between arms at T1* p *value**	*T2 absolute TDC value ipsilateral arm (IA)*	*T2 absolute TDC value contralateral arm (CA)*	*Difference between arms at T2* p *value**	*Difference between follow-ups T1-T2* p *value**
Upper arm[a]							
Medial	***N* = 120**	***N* = 113**		***N* = 120**	***N* = 120**		
median (min-max)	23.0 (16–37)	24.0 (16–32)	0.564	23.0 (18–35)	23.0 (17–32)	0.071	IA: 0.030*
mean (SD)	23.4 (3.9)	23.3 (3.3)		22.7 (3.1)	23.0 (2.9)		CA:0.546
Ventral	***N* = 118**	***N* = 103**		***N* = 120**	***N* = 120**		
median (min-max)	25.0 (19–47)	26.0 (20–34)	0.074	25.0 (19–39)	25.0 (19–35)	0.346	IA: 0.608
mean (SD)	25.5 (4.2)	26.0 (3.1)		25.3 (3.6)	25.5 (3.4)		CA: 0.003*
Lateral	***N* = 118**	***N* = 117**		***N* = 120**	***N* = 120**		
median (min-max)	27.0 (18–36)	28.0 (19–38)	0.009*	27.0 (19–34)	28.0 (21–41)	<0.001*	IA: 0.870
mean (SD)	26.9 (3.6)	27.5 (3.5)		27.0 (3.2)	27.8 (3.5)		CA: 0.667
Forearm[a]							
Medial	***N* = 120**	***N* = 120**		***N* = 120**	***N* = 120**		
median (min-max)	26.0 (20–34)	26.0 (20–35)	0.148	25.5 (20–35)	26.0 (20–35)	0.032*	IA: 0.631
mean (SD)	26.1 (3.6)	26.3 (3.4)		25.9 (3.2)	26.3 (3.0)		CA: 0.927
Ventral	***N* = 118**	***N* = 118**		***N* = 120**	***N* = 120**		
median (min-max)	26.0 (19–38)	25.0 (20–36)	0.495	25.0 (18–43)	26.0 (20–35)	0.809	IA: 0.314
mean (SD)	26.0 (3.8)	26.1 (3.5)		26.4 (3.8)	26.3 (3.3)		CA: 0.530
Lateral	***N* = 118**	***N* = 118**		***N* = 119**	***N* = 120**		
median (min-max)	29.0 (15–40)	28.5 (20–46)	0.037*	28.0 (19–39)	29.0 (20–37)	0.061	IA: 0.101
mean (SD)	28.3 (3.9)	28.7 (3.9)		28.1 (3.6)	28.4 (3.6)		CA: 0.171

[a]Measured 5 cm from the antecubital fossa.
*Significance level $p \leq 0.05$ calculated with Wilcoxon signed rank test.
IA, ipsilateral arm; CA, contralateral arm.

the ventral site of the contralateral upper arm, the median TDC value decreased from 26.0 (range: 20–34) at T1 to 25.0 (range: 19–35) at T2 ($p = 0.003$) (Table 2).

Calculated TDC ratio thresholds for detecting mild BCRAL

The calculated TDC ratio thresholds, including +3 SD for the upper arm at T1, ranged between 1.22 and 1.41 and at T2 between 1.19 and 1.30 depending on measuring site. In the forearm, the TDC ratio thresholds at T1 ranged between 1.23 and 1.30 and at T2 between 1.23 and 1.33 (Table 3). The highest TDC ratio was in the upper arm medial at T1 (Table 3).

Discussion

In this study, we measured LTW at multiple sites on both arms of women with breast cancer during their oncological treatment. Our results demonstrate that, 4–6 weeks post-surgery, LTW was significantly higher in the contralateral upper arm and forearm at the lateral site. Similarly, 3–4 months post-radiotherapy, LTW was higher in the contralateral upper arm at the lateral site and in the forearm at the medial site. After completion of chemotherapy and radiotherapy, a significant decrease in LTW was observed at the medial site of the ipsilateral arm and at the ventral site of the contralateral upper arm. Potential TDC ratio thresholds to detect early BCRAL, including three standard deviations, were calculated to 1.40 in the upper arm and 1.30 in the forearm.

The higher LTW in the contralateral upper arm and forearm at some of the measuring sites compared to the ipsilateral arm both 3–4 weeks after surgery and 3–4 months after completing radiotherapy was somewhat surprising. These findings suggest that LTW in the contralateral arm may be affected by repeated blood sampling, the presence of a peripheral inserted catheter, or the effects of chemotherapy. Interestingly, there was no significant difference in LTW at the ventral site of the contralateral upper arm, which might be expected if blood sampling was the cause. Our result might be explained by the greater amount of missing data for those who had a peripheral inserted catheter at the ventral upper arm during the examination. It is also possible that some women restore the lymphatic flow without signs of dermal backflow, which may explain the absence of increased LTW in the ipsilateral arm. Suami et al. reported that lymphatic fluid might be carried through either by regenerated lymphatic vessels, the lateral pathway, or dermal backflow.[25] Koelmeyer et al. observed that the ipsilateral axilla was the most frequent compensatory drainage region (74.9%), followed by the clavicular (41.8%) and parasternal regions (11.3%) after surgery with ALND.[26] Furthermore, in cases of axillary web syndrome, recanalization of the thrombus appears to occur, eventually restoring lymphatic flow within 3 months after surgery.[27] Interestingly, our findings contrast with previous research. Mayrovitz et al. compared both arms in 30 healthy women and 30 women with breast cancer prior to surgery and found no significant difference in LTW between the arms, either in healthy women or those

Table 3. Calculated Tissue Dielectric Constant (TDC) Ratio and Inter-Arms TDC Ratio Thresholds on the Arms of Breast Cancer Survivors without Lymphedema 3–4 Weeks after Surgery (T1) and 3–4 Months after Completed Radiotherapy (T2), (N = 120)

Testing site	*TDC ratio*[b] *at T1*	*Calculated TDC ratio thresholds at T1*[c]	*TDC ratio*[b] *at T2*	*Calculated TDC ratio thresholds at T2*[c]
Upper arm[a]				
Medial				
mean (SD)	1.02 (0.13)	1.41	0.99 (0.10)	1.29
Ventral				
mean (SD)	0.99 (0.11)	1.32	1.00 (0.10)	1.30
Lateral				
mean (SD)	0.98 (0.08)	1.22	0.98 (0.07)	1.19
Forearm[a]				
Medial				
mean (SD)	0.99 (0.08)	1.23	0.99 (0.08)	1.23
Ventral				
mean (SD)	1.00 (0.10)	1.30	1.0 (0.11)	1.33
Lateral				
mean (SD)	0.99 (0.09)	1.26	0.99 (0.10)	1.29

[a]Measured 5 cm from the antecubital fossa.
[b]TDC ratio = Absolute TDC value ipsilateral arm/contralateral arm.
[c]Including +3 standard deviations. Thresholds are the ratios which if exceeded represent a high likelihood of arm lymphedema.

with breast cancer.[18] That study concluded that breast cancer did not affect LTW in the ipsilateral or contralateral arm prior to surgery. However, the extent of the axillary surgery was unclear, the measurements were limited to the forearm at the ventral site, and the cohort was small.[18] Similarly, Mazor et al., examined 112 breast cancer survivors with an average of 6.9 years after the cancer diagnosis and found no difference in LTW between the ipsilateral and contralateral arm.[14] The majority of women in that study underwent SLNB (83%), only 53% had radiotherapy, and measurements were limited to the ventral site of the forearm and upper arm.[14] The difference between our findings and those of earlier studies could be explained by the fact that all women in our study underwent ALND and radiotherapy, and the time points for the examinations varied.

When comparing LTW at the ventral site of the forearm 4–6 weeks post-surgery in our study (ipsilateral arm/contralateral arm: 26.0/26.1), with a study of 80 women with breast cancer pre-surgery[28] (ipsilateral arm/contralateral arm: 24.8/24.9), the absolute TDC values in our study were higher. However, the TDC ratio was comparable between the two studies (1.00) in our study versus (0.998) in the study by Mayrovitz et al.[28] The higher absolute LTW observed in our study may be attributed to the smaller proportion of ALND in the study by Mayrovitz et al. or the potential impact of oncological treatment. In our study, 100% had surgery with ALND, and 73% of the women were treated with preoperative chemotherapy, which could have an impact on LTW. Previous studies have reported chemotherapy, including taxanes[1,2,4] and treatment with HER-2[2] as risk factors for developing BCRAL. Future research is therefore needed to investigate the impact of LTW on different chemotherapy regimes and HER-2 treatment. To reduce the possible impact of oncological treatment, calculating the TDC ratio between the arms is crucial for more accurate comparisons.

Furthermore, in the present study, the highest TDC ratio and a significant decrease in LTW were observed at the medial site on the upper arm. These findings are consistent with previous research showing that the highest TDC ratios were identified at the medial sites of the upper arm and forearm at the time of diagnosis of mild BCRAL.[16] The decrease in LTW may be attributed to the natural restoration of lymphatic vessels and the fluid transport through alternative pathways, as described by Suami et al.[25] These findings confirm that the medial site is the most appropriate location for measuring or screening for BCRAL.

Regarding calculations of thresholds, the most conservative method is by adding 3 standard deviations of measured arm TDC ratios, which would encompass 99.7% of the patients. Applying this method to all measured sites, we revealed potential TDC ratio thresholds of 1.40 in the upper arm and 1.30 in the forearm to detect mild BCRAL. These thresholds are slightly lower than the previous suggested TDC ratio thresholds of 1.45 in the upper arm and 1.30 in the forearm.[17] Additionally, a threshold of 1.20 for both the upper arm and forearm has been suggested in another study.[28] However, this threshold value seems to be too low according to our results. In clinical practice when examining at-risk patients, it is important to also palpate and to measure volume, as not all patients exhibit increased LTW in the skin and subcutaneous tissue.[16]

Strengths and limitations. A strength of the present study was limited missing data despite its retrospective design. However, 40% of the women were excluded due to attending fewer than two visits. During the time of data collection, women were not consistently scheduled for the follow-up visit 3–4 months after completing radiotherapy. Nevertheless, we opted to analyze only the women who attended both visits, and we consider that this exclusion has not affected the validity of our results. Our results showed significant differences in LTW between both arms and that LTW decreased in specific sites during oncological treatment. However, the differences are small, and therefore the clinical implementation is unclear. The new thresholds calculated in our study should be interpreted with caution.

During the same time period when participants were included in the present study, there was concurrent inclusion in another study,[6] involving women diagnosed with mild BCRAL. In that study, one of the three inclusion criteria was a TDC ratio above 1.45 in the upper arm and/or 1.30 in the forearm. However, the diagnosis of BCRAL required both palpation of increased skin and subcutis thickness and/or relative volume exceeding 5%. In our study, some women had a positive palpation but fell below the before mentioned thresholds, while others exceeded the thresholds without a positive palpation. It would have been impossible to investigate appropriate thresholds for mild BCRAL without utilizing TDC measurements, as this method identifies approximately 45% of the patients with mild BCRAL.[16]

Conclusion

Our findings showed that LTW was higher in the contralateral arm at specific sites compared to the ipsilateral arm. Furthermore, LTW decreased at specific sites in both arms during oncological treatment. These results suggest that a deeper understanding of LTW variations, along with the calculated thresholds, could play a crucial role in the early detection of BCRAL and enhance the interpretation of lymphedema status during oncological treatment.

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Authors' Contributions

K.B.: Conceptualization, data curation, formal analysis, writing—original draft, writing—review and editing. C.G., L.N.-W., and H.S: review and editing. K.J.: Conceptualization, funding acquisition, writing—review and editing. All authors read and have approved the final article.

Author Disclosure Statement

No competing financial interests exist.

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