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COMPARISON OF PEROMETRY-BASED VOLUMETRIC ARM MEASUREMENTS AND BIOIMPEDANCE SPECTROSCOPY FOR EARLY IDENTIFICATION OF LYMPHEDEMA IN A PROSPECTIVELY-SCREENED COHORT OF BREAST CANCER PATIENTS

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ABSTRACT

Breast cancer-related lymphedema (BCRL) affects more than one in five women treated for breast cancer, and women remain at lifelong risk. Screening for BCRL is recommended by several national and international organizations for women at risk of BCRL, and multiple methods of objective screening measurement exist. The goal of this study was to compare the use of perometry and bioimpedance spectroscopy (BIS) for early identification of BCRL in a cohort of 138 prospectively-screened patients. At each screening visit, a patient's relative volume change (RVC) from perometer measurements and change in L-Dex from baseline (ΔL-Dex) using BIS was calculated. There was a negligible correlation between RVC and ΔL-Dex (r=0.195). Multiple thresholds of BCRL were examined: RVC ≥5% and ≥10% as well as and ΔL-Dex ≥6.5 and ≥10. While some patients developed an elevated RVC and ΔL-Dex, many demonstrated elevations in only one threshold category. Moreover, the majority of patients with RVC ≥5%, ΔL-Dex ≥6.5, or ΔL-Dex ≥10 regressed to non-elevated measurements without intervention. These findings suggest a role for combining multiple screening methods for early identification of BCRL; furthermore, BCRL diagnosis must incorporate patient symptoms and clinical evaluation with objective measurements obtained from techniques such as perometry and bioimpedance spectroscopy.

Keywords: Breast cancer-related lymphedema, bioimpedance spectroscopy, perometry, lymphedema screening, prospective trial, breast cancer

Breast cancer-related lymphedema (BCRL) is a chronic, progressive condition that affects more than one in five women treated for breast cancer (1). It is characterized by an abnormal accumulation of lymphatic fluid in the affected extremity, causing both microscopic changes in the tissue and visible changes in extremity size due to persistent edema (2). Patients experience a myriad of symptoms in the affected limb, including tightness, heaviness, fullness, pain, and impaired limb function (3,4). Moreover, patients with BCRL are at an increased risk of developing infections such as cellulitis (5,6).

Historically, BCRL was treated with an impairment-based model wherein patients were diagnosed and treated for BCRL only after presenting with significant visible

swelling. In recent years, the management of lymphedema in at-risk patients has shifted away from this model and towards a screening-based approach, in which patients are prospectively screened for BCRL throughout breast cancer treatment and follow-up. Screening is currently recommend-ed for patients treated for breast cancer by several large organizations, including the National Lymphedema Network, International Society of Lymphology, American Society of Breast Surgeons, and the National Comprehensive Cancer Network (7-10).

Successful screening programs utilize objective limb measurements, patient symptomatology, and clinical evaluation to determine whether a patient requires referral to a Certified Lymphedema Therapist (CLT) for treatment. Objective measurements aim to detect lymphatic fluid retention in the upper extremity by measuring changes in overall volume or fluid content of the affected limb. Perometry represents one method for identifying change in overall limb volume, whereas bioimpedance spectroscopy (BIS) measures changes in tissue impedance reflecting extracellular fluid content of the affected limb.

When using volumetric measurements, lymphedema is typically defined as ≥10% increase in arm volume compared to preoperative baseline without similar changes in the contralateral arm (11). The Relative Volume Change (RVC) equation, which accounts for preoperative asymmetry and postoperative changes in the ipsilateral and contralateral arm, can be used to calculate arm volume changes for patients undergoing unilateral breast surgery (12). Changes in arm volume can be determined in a myriad of ways, including: water displacement, infrared perometry, and circumferential tape measurements converted to volume. Specifically, perometry is an optoelectronic technique that uses infrared light to calculate whole arm volume and has been shown to be reliable, valid, and sensitive for detecting subclinical lymphedema (13-17).

In contrast to volumetric measurements, BIS measures extracellular fluid in an extremity by assessing the resistance to flow of a low-level electrical current. Using this data, a Lymphedema Index (or L-Dex) score is calculated, which compares impedance to flow in the affected and unaffected limb (18). Scores more than 10 units above a preoperative baseline measurement are considered indicative of early BCRL (19), but recent literature suggests that scores greater than 7.1 and 6.5 units above baseline may better indicate lymphedema and subclinical lymphedema, respectively (20,21).

While BRCL diagnosis should incorporate factors other than objective measurements such as patient symptomatology and clinical evaluation, it is important to understand the relationship between volumetric and BIS measurements as they assess different characteristics of the arm. Both are used in screening and treatment as well as in research settings; an institution's objective measurement of choice largely depends on financial resources, clinical space, and workflow. Previous literature has sought to assess different methods of lymphedema assessment and thresholds; however, many of these studies carry significant limitations, and further evidence is required. Armer et al compared four different diagnostic criteria for lymphedema using both perometry and circumferential techniques to calculate limb volume, and they found that a limb volume change of 10% was the most conservative of the four definitions whereas a difference in arm circumference of two centimeters was the most liberal definition (11). Since the time of this publication, significant strides have been made in terms of axillary staging and radiation and these results no longer reflect the population currently treated for breast cancer. Stout et al sought to demonstrate whether a screening program starting at preoperative baseline utilizing perometry is effective in prevention of lymphedema, and they found that significant decreases in arm volume obtained through compression sleeve use at an RVC of 3% were maintained. However, this study lacked a control group, and therefore the role of screening and early intervention using a 3% threshold remains unclear (16). More recently, Ridner et al's

interim analysis of the PREVENT trial compares BCRL progression rates using limb volume measurements calculated from girth measures and BIS in a cohort of 508 patients screened for BCRL using either tape measure or BIS. The authors concluded that post-treatment surveillance with BIS reduced BCRL progression (defined as necessitating complete decongestive therapy) by approximately 10%, and they recommended screening for BCRL using BIS (22). However, the reduction in BCRL progression with BIS was not statistically significant. There was no control group (i.e. patients who did not receive treatment), and the authors utilized one primary endpoint of BCRL despite their aim to compare measurement tools which are not interchangeable. Finally, Bundred et al's 2020 study compared lymphedema screening with both perometry and BIS in 1100 patients accrued to the PLACE trial. They found that 24-month BCRL incidence using BIS (L-Dex ≥10) was twice that using relative arm volume increase (RAVI) >10% criterion (45.2% vs 22.5% respectively). 24.5% of patients required compression sleeves. The authors concluded that RAVI >10% was more concordant with clinical sleeve application than BIS criteria and is the best diagnostic tool for BCRL (23). This study aims to add to the literature base by comparing L-Dex values measured via BIS and RVCs measured by perometry in a current cohort of women prospectively screened for BCRL beginning at preoperative baseline in a well-established BCRL screening program.

MATERIALS AND METHODS

Study Design and Setting

Since 2005, the Lymphedema Research Program at Massachusetts General Hospital has screened for BCRL in patients treated for breast cancer as part of our Lymphedema Screening Program, approved by the Partners Human Research Committee (Institutional Review Board 2008P000540). This screening trial is an ongoing program that identifies women with BCRL by using objective measurements and patient-reported outcome measures, provides access to early treatment, and generates evidence-based research to improve lymphedema diagnosis and treatment. Relevant clinical data are collected in conjunction with patient measurements and symptoms in a large, prospectively-maintained database.

In 2011, we initiated a clinical trial within the Lymphedema Screening Program to investigate BIS measurements in addition to perometry in screening for BCRL, with a goal of accruing 270 patients who underwent unilateral breast surgery (NCT01544335). At preoperative baseline, patients were consented, measured with perometry and BIS, and given a baseline symptoms assessment. Patients were evaluated using perometry, BIS, and a symptoms assessment at their regularly scheduled oncology follow-up visits (every 3-12 months) with a goal of screening for at least five years after their definitive breast cancer surgery. Patients were referred for lymphedema evaluation with a CLT if RVC was ≥10%, if the patient reported significant symptoms, and/or if focal swelling was present per institutional standard of care. Accrual for the trial was completed in August 2018.

Inclusion criteria included: being older than 18 years of age, with histologically or cytologically confirmed invasive or in-situ carcinoma of the breast, and undergoing unilateral breast surgery with axillary surgery (either sentinel lymph node biopsy or axillary dissection). Exclusion criteria included: metastatic disease, history of primary lymphedema, previous surgery or radiation to the upper body, or contraindications to bioimpedance spectroscopy (bilateral breast and/or axillary surgery, cardiac implants, pregnancy).

From the originally accrued cohort of 270 patients, 191 met eligibility requirements (*Fig. 1*). Patients were unenrolled from the trial at the time of postoperative screening visit if they underwent bilateral breast surgery (n=65) or withdrew consent (n=14). Of these 191 patients, 53 patients who were removed as they were either lost to follow up (n=27), deceased during the course of the study (n=4), progressed to metastatic breast cancer (n=3),

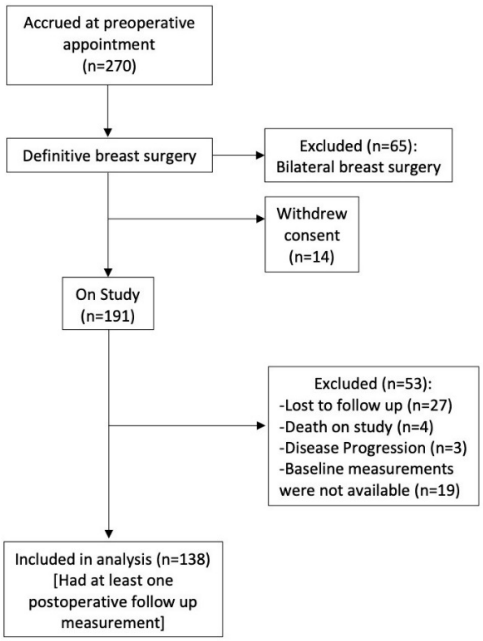

Fig. 1: Patient Accrual, Enrollment, and Inclusion. Patients were accrued for the study at their initial multidisciplinary breast cancer diagnosis appointments which was before treatment decisions were finalized including type of surgery and location of adjuvant treatment. Patients were only included in this cohort if they have received unilateral surgery and had at least one follow up measurement (n=138). Lymphedema outcomes (Table 2) were assessed in the 114 patients who had at least one follow up measurement more than three months after surgery.

or lacked baseline measurements with either device (n=19). The final cohort consisted of 138 patients who had at least one postoperative follow-up measurement by the time of analysis.

Measurement Techniques and Definition of BCRL

All patients underwent bilateral arm volume measurements via the Perometer, which uses the PeroPlus 2000 software (Perosystem Messgeräte GmbH, Wuppertal, Germany), according to our previously published screening protocol (24). In brief, patients sat on a chair perpendicular to the Perometer with the upper extremity abducted at 90°, and with the fingers and thumb adducted such that the hand lies flat. Three consecutive measurements were obtained for each arm, and the median of the three values was calculated and incorporated into the RVC equation: RVC = [(A2U1/(U2A1) - 1] X 100%, where A1 and A2 are the ipsilateral arm volumes at preoperative (baseline) and postoperative assessments, respectively, and U_1 and U_2 are the contralateral arm volumes at preoperative and postoperative assessments, respectively (12).

BIS measurements were obtained using a U400 device (Impedimed Limited, Brisbane, Australia), following established guidelines (19). In brief, the skin was prepared with alcohol before electrode attachment and measurements were taken with the patient laying in a supine position for at least three minutes prior, with the arms adducted at the sides. Cole plots were assessed for quality, and the resulting L-Dex values were recorded and used to calculate a change from preoperative baseline (ΔL-Dex).

For the purpose of this analysis, thresholds for BCRL were defined as RVC ≥5%, RVC ≥10%, ΔL-Dex ≥6.5, and ΔL-Dex ≥10 units from preoperative baseline. Per our institution's standard of care, patients with an RVC ≥10% were referred to a CLT for BCRL evaluation.

Statistical Analyses

Patient, tumor, and treatment information was collected using medical record review and was stored in a database using REDCap 7.0.14 (Vanderbilt University, Tennessee). Patient age, body mass index (BMI), number of excised lymph nodes, and months of follow-up were included in the analysis as continuous variables. Other variables such as breast and axillary surgeries, regional lymph node radiation (RLNR), and chemotherapy types were dichotomized. Median and range values were reported for continuous variables. The correlation between RVC and ΔL-Dex values was plotted, and the correlation strength was assessed using the Pearson correlation coeffi-

TABLE 1
Demographics and Treatment-Related Characteristics (n=138)

	Median/Number (Range/Percent)
Age	53.7 (27.2-75.0)
BMI	26.1 (16.1-43.9)
Surgery	
Mastectomy +/- reconstruction	26 (18.8%)
Lumpectomy	112 (81.2%)
Nodal Surgery	
ALND	32 (23.2%)
SLNB	100 (72.5%)
None	6 (4.3%)
Total lymph nodes sampled	2 (0-31)
RLNR	43 (31.2%)
Neoadjuvant chemotherapy +/- adjuvant chemotherapy	24 (17.4%)
Adjuvant chemotherapy alone	37 (26.8%)
Follow-up (months since surgery)	24.4 (0.3-79.8)
Follow-Up Measurements	3 (1-10)

Body mass index (BMI), axillary lymph node dissection (ALND), sentinel lymph node biopsy (SLNB), regional lymph node radiation (RLNR)

cient, r. All statistical analyses were conducted using R Version 1.2.1335 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

RESULTS

The final cohort consists of 138 patients with a total of 442 follow-up measurements. Demographic and treatment-related characteristics of the patient cohort are depicted in *Table 1*. The median age was 53.7 years with a median BMI of 26.1 kg/m^2. In terms of breast cancer treatment, 81.2% of patients under-went a lumpectomy, 18.8% underwent a mastectomy with or without reconstruction, 72.5% received sentinel lymph node biopsy (SLNB) for axillary staging, 23.2% received axillary lymph node dissection (ALND), and 31.2% received RLNR. The median number of follow-up measurements was three (range: 1-10 months), and the median time to last follow-up was 24.4 months postoperatively.

As described above, thresholds for BCRL were defined as RVC ≥5%, RVC ≥10%, ΔL-Dex ≥6.5, and ΔL-Dex ≥10 units. Table 2 demonstrates BCRL outcomes according to threshold and the overlap between RVC and BIS thresholds. Note that this table includes the 114 patients who had at least one follow-up measurement at least three months post-surgery. Of the 25 patients who had a RVC ≥5%, 11 had a ΔL-Dex ≥6.5 units, with 9 of these patients having a ΔL-Dex ≥10 units. Of the 5 patients who had a RVC ≥10%, 3 had a ΔL-Dex ≥6.5 units, with 2 of these patients having a ΔL-Dex ≥10 units. Of the 37 patients who had a ΔL-Dex ≥6.5 units, 11 had a RVC ≥5%, 3 of whom had a RVC ≥10%. Finally, of the 27 patients who had a ΔL-Dex ≥10 units, 9 had a RVC ≥5%, 3 of whom had a RVC ≥10%. When comparing all follow-up measurements for the entire cohort (n=442), including those measurements taken within the first three months after surgery, there was negligible correlation between RVC and ΔL-Dex score from baseline (r=0.195) (*Fig. 2*).

Tables 3 and 4 demonstrate the number of patients who met a BCRL threshold based on ΔL-Dex (*Table 3*) or RVC (*Table 4*) and

subsequently experienced regression to below the threshold without treatment. Of the 24 patients who had a ΔL-Dex ≥6.5 units at least 3 months postoperatively, 22 patients regressed with a median time to regression of 23.8 months (range: 0.8-39.2 months), 18 (81.8%) of whom did not receive lymphedema treatment. For those who regressed without treatment, the median time of first ΔL-Dex ≥6.5 units was 7.7 (range: 3.3-28) months after surgery. Similarly, of the 16 patients who had a ΔL-Dex ≥10 units at least 3 months postoperatively, 14 patients regressed with a median time to regression of 18.3 months (range: 2.2-39.2 months), 10 (71.4%) of whom did not receive treatment. For those who regressed without treatment, the median time of first ΔL-Dex ≥10 units was 8.3 (range: 3.3-28) months after surgery. Of the 17 patients who had a RVC ≥5% at least 3 months postoperatively, 13 patients regressed with a median time to regression of 6.2 months

TABLE 2
Lymphedema Outcomes for Patients Based on Various Definitions and Thresholds

	ΔL-Dex ≥ 6.5 (n=37)	ΔL-Dex < 6.5 (n=77)
RVC ≥ 5% (n=25)	11	14
RVC < 5% (n=89)	26	63
	ΔL-Dex ≥ 6.5 (n=37)	**ΔL-Dex < 6.5 (n=77)**
RVC ≥ 10% (n=5)	3	2
RVC < 10% (n=109)	34	75
	ΔL-Dex ≥ 10 (n=27)	**ΔL-Dex < 10 (n=87)**
RVC ≥5% (n=25)	9	16
RVC < 5% (n=89)	18	71
	ΔL-Dex ≥ 10 (n=27)	**ΔL-Dex < 10 (87)**
RVC ≥10% (n=5)	3	2
RVC < 10% (n=109)	24	85

Relative volume change (RVC), change in L-Dex from preoperative baseline (ΔL-Dex); Patients were excluded if they did not have at least one measurement more than three months after surgery (n=114)

TABLE 3
Reduction of Elevated ΔL-Dex in Patients

	ΔL-Dex ≥6.5 more than 3 months post-surgery	ΔL-Dex ≥10 more than 3 months post-surgery
Total patients	37	27
Patients who have at least one measurement after initial elevated measurement	24	16
Patients who regressed to ΔL-Dex <6.5	22/24 (91.7%)	14/16 (87.5%)
Without treatment	18/22 (81.8%)	10/14 (71.4%)
With treatment	4/22 (18.2%)	4/14 (28.6%)

Change in L-Dex from preoperative baseline (ΔL-Dex)

TABLE 4 Reduction of Elevated RVCs in Patients	
	RVC ≥5% more than 3 months post-surgery
Total patients	25
Patients who have at least one measurement after initial elevated measurement	17
Patients who regressed to RVC <5%	13/17 (76.5%)
Without treatment	7/13 (53.8%)
With treatment	6/13 (46.2%)

(range: 0.7-24.4 months), 7 (53.8%) of whom did not receive lymphedema treatment. For those who regressed without treatment, the median time of first RVC ≥5% was 17.4 (4.4 - 56.0) months after surgery. Per institutional standard of care, all patients who meet a RVC ≥10% threshold are referred for CLT evaluation, thereby preventing a similar analysis for these patients.

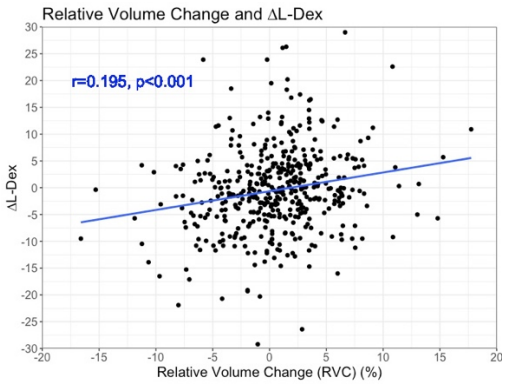

Fig. 2: Correlation between Relative Volume Change and Change in L-Dex Units from preoperative baseline measurements. All 442 follow-up measurements are included in this analysis.

DISCUSSION

Given recent recommendations by major academic organizations to implement lymphedema screening as standard of care (7-10), it is imperative to understand how different methods of objective measurement and respective BCRL treatment thresholds compare. Few studies to date examining modes of measurement for BCRL screening and diagnosis incorporate preoperative baseline measurements and long-term follow up in a cohort reflecting up-to-date breast cancer treatment protocols. This study aims to contribute to the body of evidence examining thresholds for BCRL treatment by examining outcomes in a cohort of patients who were prospectively screened with perometry, a volumetric-based method, and BIS, an impedance-based method which measures change in extracellular fluid content.

As demonstrated in *Fig. 2*, there was negligible correlation (r=0.195) between RVC and ΔL-Dex when assessing all measurements (n=442). This is in contrast with previous literature which has demonstrated a positive correlation between assessments obtained using perometry and BIS measures (25-27). A recent publication from Coroneos et al demonstrated a significant correlation between L-Dex ratio and limb volume ratio in 26 patients with lymphedema, 21 of whom had upper extremity lymphedema from breast cancer treatment and five of whom had lower extremity lymphedema (25). However, the study compared L-Dex ratio to limb volume ratio, neither of which take into account a preoperative baseline measurement. Incorporating preoperative baseline for both volumetric and BIS measurements is critical as it has been shown that patients have natural asymmetry between arms and abnormal L-Dex values at preoperative baseline (21,26,28,29). A 2015 analysis of 612 patients by Bundred et al

examined the correlation between relative limb volume change and L-Dex values compared to preoperative baseline measurements (26). This study found modest correlations between limb volume change and L-Dex values at three and six months follow-up. However, unlike the current study, they utilized a high-risk cohort of patients who underwent ALND, and they did not evaluate for correlation past six months. Longitudinal results are needed before definitive conclusions about the correlation between RVC and ΔL-Dex can be made, given that BCRL diagnosis can occur months to years after breast cancer surgery.

For the purpose of the current analysis, several BCRL thresholds were utilized based on previous definitions in the literature. Regardless of which method of measurement or BCRL threshold was used, the overall incidence of BCRL in our cohort was low. This is likely due to the inherent low-risk nature of our patient cohort, in which the majority of patients (72.5%) underwent SLNB and only 31.2% received RLNR. When BCRL thresholds other than RVC ≥10% were used, a significantly higher percentage of patients than expected met a BCRL threshold (based on the majority undergoing SLNB rather than ALND). Specifically, RVC ≥5% (25/138, 18.1%) and ΔL-Dex of ≥6.5 (37/138, 26.8%) or ≥10 units (27/138, 19.6%), identified a significantly higher percentage of the cohort as having lymphedema than one would expect, given that the majority of patients underwent SLNB. The meta-analysis by DiSipio, which analyzed 72 different studies reporting lymphedema incidence based on different objective methods, including both perometry and BIS, found that the combined incidence of BCRL in patients who underwent SLNB was 5.6% (95% CI: 6.1-7.9) (1). The incidence of lymphedema as defined by RVC ≥10% (5/138, 3.6%) in this study most closely aligned with the expected incidence of BCRL in a low-risk cohort such as ours; however, it should be noted that lymphedema incidence varies depending on the threshold used for diagnosis. Bundred and colleagues' recent publication demonstrated comparable results to ours such that thresholds including RVC>5%, ΔL-Dex >7.5 and ΔL-Dex>10 resulted in higher BCRL rates than would be expected in such a cohort: the incidence of BCRL at 24 months defined by RVC ≥5%, RVC >10%, ΔL-Dex >7.5, and ΔL-Dex ≥10 was 51.4%, 22.4 %, 57.6%, and 45.2%, respectively. This finding was in comparison to a 24.5% incidence of lymphedema as defined by treatment with use of upper extremity sleeves, demonstrating that use of RVC >10% most closely concurred with clinical lymphedema diagnosis (23). Altogether, the findings from these studies demon-strates the significant variation in number of patients who meet various BCRL thresholds based on method of assessment and threshold used.

In our study, while there was some overlap in the patients who met BCRL thresholds using ΔL-Dex or RVC, there were also a number of patients who met a BCRL threshold based on only one method of assessment. Interestingly, the majority of patients in our study who met a BCRL threshold other than RVC ≥10% regressed to below the respective threshold without intervention as determined by chart review. This draws into question the decision to use early thresholds such as RVC ≥5% or ΔL-Dex >7.5 as diagnostic to institute treatment. Future research should determine who is at greatest risk for progression of BCRL and therefore which patients will benefit from early intervention. Due to the limited sample size, we could not analyze the timing of onset of elevated measurements and the timing of regression for these groups of patients. Nonetheless, these findings suggest that single time-point measurements may not be sufficient to diagnose BCRL in the absence of clinically evident swelling or patient-reported symptoms, especially in patients who are at a lower risk for BCRL such as the majority of our cohort. This consideration emphasizes an important point about both methods of objective measurement (the Perometer and BIS): they are screening tools that alone are not diagnostic for BCRL, as neither method evaluates lymphatic function directly. Elevated measurements from either device

using any objectively measured threshold should be used to refer patients for a clinical evaluation by a CLT or similarly qualified individual, who will then be able to incorporate physical examination, patient symptoms, and medical history to accurately diagnose BCRL. In addition, our findings, in combination with those from Bundred et al, suggest that BCRL thresholds of RVC ≥5% and ΔL-Dex of ≥6.5 or ≥10 units may over-identify patients (28). This concerns further supports the potential utility of multiple objective measures, in conjunction with symptoms assessments and physical exams, in screening programs to accurately identify patients with BCRL.

This study is not without its limitations. Namely, the low number of patients who developed BCRL as defined by any of the objective measurement thresholds limited the statistical analyses, and as such more longitudinal data is needed to draw definitive conclusions. In addition to the current trial, our program is also conducting a larger study comparing perometry and BIS using the new ImpediMed SOZO device. This longitudinal study will expand on the results of the current study by including patients who were diagnosed with bilateral breast cancer and underwent bilateral breast surgery as the new SOZO technology allows for bilateral arm L-Dex calculations.

Our study clearly demonstrates the need for more longitudinal data examining RVC obtained via perometry and ΔL-Dex obtained using BIS as objective measures for identifying early BCRL within a screening program. Importantly, similar to Bundred et al (23), we found that use of RVC and ΔL-Dex and their respective BCRL thresholds identified different patients with BCRL. This finding suggests that use of multiple methods for screening may be beneficial in identifying patients for further evaluation by CLTs. Moreover, the fact that a majority of patients who met a BCRL threshold and regressed without intervention suggests that more research is needed to clarify who is at risk for progression and therefore would benefit from early intervention with a CLT. No matter the objective tool of choice, patients treated for breast cancer should be screened for BCRL beginning with preoperative measurements and continuing throughout their follow-up, incorporating objective measurements, symptoms assessments, and clinical examination.

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DISCLOSURES

Alphonse Taghian is on the Scientific Advisory Board of Puretech Health and a previous consultant in VisionRT. AGT has been loaned equipment from ImpediMed for use in investigator-initiated clinical trials. Cheryl Brunelle is on the Scientific Advisory Board of Puretech Health. The remaining authors declare no competing financial interests exist.

CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

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