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Measuring Breast Cancer-Related Lymphedema

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Abstract: Breast cancer-related lymphedema (BCRL) presents as swelling in the arm, hand, trunk, or breast at varying times after completion of breast cancer treatment. The reported incidence of BCRL varies widely in part due to its dependence on the type and extent of the treatment, pre-treatment risk factors, and the criteria used to define its presence. Central to this issue are the various quantitative measures that are used to specify lymphedema thresholds for its detection and tracking over time and during treatment. The goal of this chapter is to discuss these issues and the methods available for the non-invasive quantitative assessment of BCRL. Operational principles, advantages and limitations of the various methods, their clinical history of use, and effectiveness are discussed. Covered methods include those used to assess and monitor lymphedema-related changes in tissue water at any anatomical site and also methods used to assess changes only in limbs.

Keywords: breast cancer-related lymphedema; dielectric constant; measuring lymphedema; impedance; limb volume

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INTRODUCTION

Breast cancer-related lymphedema (BCRL) has a variable reported incidence that depends on the objective criteria used and, on the type and extent of a patient's treatment (1–5). When BCRL occurs, it manifests itself as increased fluid anywhere in the at-risk arm (6–8) or thorax (9, 10) or other areas. Most portable and readily accessible noninvasive methods that assess its presence and extent are restricted to those that measure arm size change or the difference between at-risk arm and contralateral arms. These methods include manual (11–13) and automated (8, 14–16) circumference and volume measurements, arm fluid changes assessed by electrical impedance (17–19), and volume changes assessed by water displacement measurements (WDM). These are discussed after a brief description of BCRL incidence, and the factors affecting it. Subsequently, a fully portable measurement method, used to assess localized lymphedema at any anatomical site via tissue dielectric constant measurements (20–24) is described. Other non-invasive methods, including photographic and scanning methods (25–27), magnetic resonance imaging (28, 29), and ultrasound (30–32) are also briefly discussed.

BCRL INCIDENCE

BCRL presents as swelling in the arm, hand, trunk, or breast after breast cancer treatment that, among other more serious outcomes, causes discomfort, distress, disability and anxiety (33). Factors that influence the incidence of BCRL depend on tumor stage, body mass index, axillary lymph node dissection (ALND), number of nodes dissected, axillary radiation, surgery type (34), and the diagnostic criteria used.

BCRL incidence is about 20% at one year and 40% at ten years post-treatment (35–37). Thus, at least one in five female breast cancer survivors will develop BCRL. According to a meta-analysis (36), BCRL incidence was 10.3% between 3–6 months post-surgery, 13.8% between 6–12 months, 18.9% between 12–24 months, 18.6% between 24–60 months, and 15.6% beyond 60 months. BCRL is more prevalent in stage III and stage IV breast cancer since more nodes are generally removed (38, 39). A 15-year prospective study found that 24% of early (stage I and II) and 35.3% of advanced (stage III and IV) breast cancer patients were diagnosed with BCRL (39). Increased body mass index is another important risk factor for BCRL, with obese patients being almost twice as likely to develop BCRL (36, 38, 40, 41).

When comparing the two main surgical treatment options, mastectomy and lumpectomy, breast cancer survivors who had a mastectomy are more likely to get BCRL (38) with incidence reported as 24–49% among mastectomy survivors, and 4–28% among lumpectomy survivors (42). Survivors who had lymph node dissection, with or without axillary radiation, had an increased risk for BCRL (38, 39, 43). BCRL among survivors who had both ALND and radiation was 41%, and in those who did not have radiation, it was 17% (43). BCRL also occurs following sentinel lymph node biopsy (SLNB) without ALND (36, 44). BCRL incidence in breast cancer survivors who had only SLNB was 11.5% but was 39.7% in those with both

SLNB and ALND (44). Increased incidence of BCRL is greater with ALND (36, 45, 46) and with more nodes removed. Removing 1–5 nodes was not a significant risk factor for BCRL whereas BCRL was 5-times more likely if 6–15 nodes were removed, and 10-times more likely if 16 or more nodes were removed (47).

ARM VOLUMES BASED ON MANUAL CIRCUMFERENCE MEASUREMENTS

The circumference of the non-compressed and relaxed arm is measured with a tape-measure that is optimally pulled with a constant tension using a spring-loaded calibrated tape measure at all measured sites (Figure 1). Practical measurement issues include the number of circumferential measurements to be made, their longitudinal separation, the volume calculation model, and how the volumes or circumferences are optimally used to assess initial lymphedema status and its subsequent change due to either time or therapy.

Measurement Details and Volume Calculations

The preceding measurement issues have been investigated in healthy and lymphedematous arms. Casley-Smith was among the first to systematically study these issues (48). An approach was to calculate segment volumes (V_S) between two circumferences ($c_{1,2}$) separated by a distance L using a truncated cone model as $V_S = L/(12p) \times [c_1^2 + c_1 c_2 + c_2^2)$. The formula was used in 150 unilateral BCRL patients with circumferences measured at mid-hand, narrowest part of the wrist, and at 10 cm intervals starting from the middle fingertip. By summing segment

Figure 1. Illustrating arm circumference measurement with a tape measure. The arm circumference is pictured being measured with a tape measure that is equipped with a tension gauge so that measurements at multiple arm sites are made with uniform tension. If two longitudinal separated sites have their circumferences measured the volume of the limb between these segments can be reliably calculated using geometric formulas.

volumes, arm volumes of interest were determined. Percentage edema volume (%EV) was calculated as the volume difference between affected and contralateral arms divided by contralateral arm volume. The %EV determined this way was compared to edema volumes determined via water displacement ($\%EV_W$), considered as the gold-standard. A high correlation between methods was reported (r = 0.925) with a regression equation $\%EV = 1.096\ \%EV_W + 0.007$. These authors suggested that rather than using a truncated-cone model, a summation-of-disks model might be better (49).

Measurements in 15 BCRL patients compared segment lengths of 10-cm vs. about 4-cm in which the 4-cm start was the most distal portion of the wrist and the end at about 45 cm (13). Calculated %EV was similar for both, but shorter segments had a statistically greater %EV that was most evident at greater arm volumes and had better accuracy. The circumference-volume method was also compared to WDM on 14-women with unilateral BCRL using 4-cm segment lengths (12). Small differences in arm volumes were reported depending on method, but inter-arm differentials were highly correlated (r = 0.79). A subsequent reliability and validity study compared the circumference-volume method with WDM on 66 women in which 19 had unilateral BCRL (50). Measured arm length was standardized to start at the wrist (mid-ulnar styloid) and extend to 65% of the distance from olecranon (elbow) to acromion (shoulder tip). Circumferential measurements were made at specified anatomical sites or standardized distances, with four segments used to calculate volume and compared to WDM. Results indicated good correlation between methods but based on limits of agreement, the methods could not reliably be interchanged since calculated volumes were up to 5% greater than WDM values. Based on reliability analyses they concluded that the minimal detectible change in volume that could be used as a clinical threshold representing a real change due to time or treatment was 150 ml.

LIMB VOLUMES FROM AUTOMATED ARM CIRCUMFERENCE MEASUREMENTS

Automation of manual circumference measurements emerged with the arrival of a device commercially known as the Perometer. Its basic operating principle is illustrated in Figure 2.

Measurement Details and Volume Calculations

A sliding frame with imbedded infrared (IR) light sources scans the arm and the "shadow" dimensions D_1 and D_2 are detected and used calculate cross-sectional areas as a constant (k) multiplied by D_1 and D_2. Segment volumes are determined similarly to the manual method with segment volumes summed to produce the arm volume of interest. This method has the advantage of rapidly estimating cross-sectional areas using as low as 0.5 cm segment lengths and an automatic calculation of arm volumes. Disadvantages include device set-up, space requirements, patient positioning, service maintenances and initial cost as compared manual methods.

Initial evaluations on 17 lymphedematous arms indicated an arm volume 6.8 ± 4.3% greater than manual tape-measure values (16). Subsequent tests on

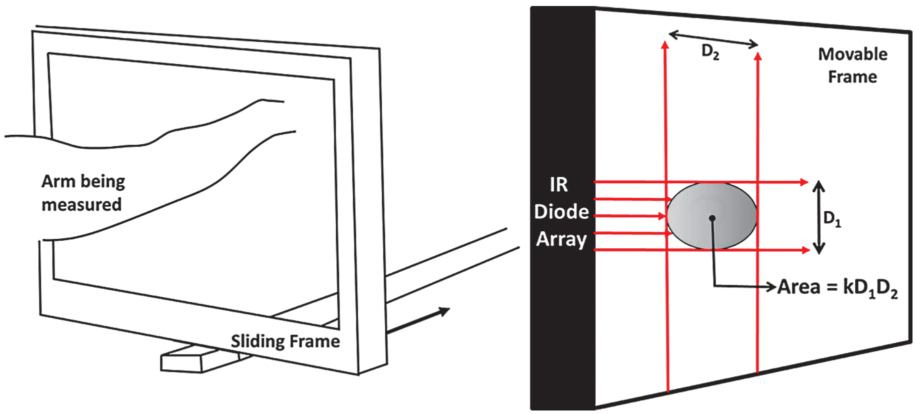

Figure 2. Illustrating automated optoelectronic measurement of arm circumferences. A limb (arm or leg) is placed within a movable frame that contains infrared light sources that illuminate the limb and allow acquisition of limb projected perpendicular dimensions D_1 and D_2. From these measurements the cross-sectional area of the limb slices is calculated for slices of about 2 mm in length. The sum of these slices is used to calculate the limb volume.

37 lymphedematous arms compared automated volumes vs. tape-measure (5-cm intervals) vs. WDM (51). Reproducibility of each method was assessed as satisfactory with inter and intra-class correlation coefficients ranging from 0.937 to 0.997. Repeated measurements by the same rater (intra-rater variation) yielded volume percentage differences of 1.5 ± 1.4% for the Perometer, 2.9 ± 2.9% for WDM and 3.2 ± 4.6% for the tape-measure method. Using perometry to pre-operatively screen 1028 women with unilateral BCRL emphasized the importance of pre-surgical volumes (15). Perometer measurement utility for pre-operative screening and follow-up in large volume centers is supported by findings in which large numbers of patients have been evaluated (8, 15). Perometer usefulness to assess hand volume was evaluated in 20 patients with hand lymphedema and 20 without lymphedema and compared to values determined using WDM (52). It is unclear what calculation method was used but an approximate Perometer volume overestimate of about 7.5% was reported. Other methods to estimate hand volume not requiring sophisticated systems have been reported (53, 54) as well as methods based on bioimpedance spectroscopy (55–57).

BCRL THRESHOLDS BASED ON ARM DIFFERENTIALS OR CHANGES

Beyond clinical assessments and patient symptoms, various quantitative parameters have been developed to help define BCRL presence in its early subclinical stage and later clinical stage. Parameters based on arm metrics were the earliest and remain in use now, but other methods such as bioimpedance and tissue dielectric constant measurements are now also available as discussed later in this chapter.

Metric Thresholds

Most BCRL cases are unilateral, so it is common to compare at-risk arms to contralateral arms with respect to inter-arm differentials. Arm circumferences are measured bilaterally at corresponding anatomical sites and inter-arm circumferences, or inter-arm volumes compared. Untreated BCRL progresses in volume and grade rapidly at first and slowly thereafter (48). Untreated BCRL, quantified as inter-limb volume ratios (V_R), increased by 40.6% in the first year, 12.4% from year one to five, and 4.22% from five to 30 years (58). Problems of BCRL measurements and accurate BCRL incidence assessments were raised by early investigators (59) and parameter values that best reflect BCRL presence were studied by comparing three lymphedema thresholds based on arm metric measurements (60). Arm circumferences were tape-measured at 4-cm intervals and also measured by perometry prior to breast surgery and at 6 and 12-months post-surgery in 110 breast cancer survivors. Incidence was assessed in three ways based on at-risk arms vs. contralateral arms, 2-cm circumference change at any site, and 200 ml volume change and 10% volume change. These thresholds yielded quite different estimated one-year incidence rates of 46%, 24%, and 8%, respectively.

Further study on 236 patients followed for up to 5-years (5) indicated the 2-cm difference predicted a 94% incidence whereas the 10% volume difference criterion predicted a 45% incidence. More recently, 1100 women with breast cancer who had ALND were followed for up to 5-years (8). BCRL thresholds used in this multicenter study were a relative arm volume increase of ≥10% (Perometer determined) and an L-Dex value (8, 14) >10 based on bioimpedance spectroscopy (BIS). By 24 months, 22.8% had BCRL based on volume but 45.6% had it based on L-Dex. Early detection of relative volume increases between 5–10% were strong predictors of BCRL occurring by 36 months. Analyses of the primary study data (61) indicated a median time to develop BCRL was 11.3 months. For women followed to 5 years (n = 156), 31.9% had BCRL as assessed by volume, whereas 77.2% had BCRL according to the 200 ml threshold.

BCRL ASSESSMENTS BASED ON WATER DISPLACEMENT METHODS

WDM is considered by many to be the "gold standard" for volume measurements (50, 62, 63). Insertion of the arm into a water-filled volumeter causes a water volume equal to the inserted arm volume to be displaced and captured as overflow. Although accurate, the method is time-consuming and messy and depends on patient mobility to implement and is not routinely used in clinic. However, it can provide comparisons against which other methods may be assessed and provide reference values against which BCRL thresholds are developed. Absolute arm volume thresholds are most useful if pre-surgery values are not available.

Water Displacement BCRL Thresholds

Using WDM, arm volumes were measured in 112 women (50.6 ± 18.2 years) with a BMI of 24.5 ± 3.9 Kg/m^2 (64). Most were right-handed (n = 100) with right arm volumes about 3% greater than the left. Such handedness differences should be taken into account. Prediction equations extrapolating back to what an arm volume would have been prior to BCRL may be applied based on normative values. For right-handed women, right arm volume (RAV) in terms of left arm volume (LAV) can be expressed as RAV = 0.979 LAV + 96.66 ml. Contrastingly, for LAV of right-handed women the relationship is LAV = 0.991 RAV – 33.3 ml. In each case, a 95% confidence interval was about 148 ml. It was suggested that the equations, together with upper confidence limits, be used for thresholds.

As an example, consider a right-handed woman with a left arm at-risk who has a measured RAV of 3000 ml. Her normal (predicted) LAV is 2940 ml to which is added 148 ml resulting in a 2SD threshold of 3088 ml and an inter-arm ratio of 1.029. Contrastingly, if the right-arm were at-risk with the left arm measured at 3000 ml, the predicted threshold is 3182 ml with an inter-arm ratio of 1.06.

Inter-arm differentials of 200 ml, determined by WDM, were used as a threshold defining sustained BCRL in 85 women 24 months post-surgery (65). Accordingly, 19 (22.4%) had BCRL at 24 months. Contrastingly, based on two inter-arm circumference measurements made at 6 months post-surgery differing by ≥ 2 cm, the calculated probability of sustained BCRL at 24 months was 60%.

BCRL ASSESSMENTS WITH BIOIMPEDANCE SPECTROSCOPY (BIS)

BIS refers to measuring electrical impedance at multiple frequencies. This method is widely used but it has been argued that it is not a proper substitute for volumes or for localized assessments of limb lymphedema and is also not applicable to other body areas (49). Contrastingly, it has been argued that it should be adopted as a gold standard (66). In some quarters it has become common to use a surrogate parameter called the L-Dex (67). There is some controversy whether this parameter and its threshold for BCRL is adequate (68).

BIS Measurement Details

Application of a sinusoidally varying voltage causes a time-varying current that depends on frequency and the current's pathway (Figure 3A). At low frequencies, cell membranes pass little or no current due to the membrane's high electrical capacitance whereas at high frequencies current passes through the cell. As a consequence, the composite pathway may be represented by an equivalent electrical circuit (Figure 3B). The quantities R_e and R_i represent external and internal electrical resistances. These resistance values are inversely related to the amounts of extracellular water (ECW) and intracellular water (ICW) through which the currents flow. Because of the low electrical resistance of body fluids relative to other body components such as fat and connective tissue, the overall measured impedance (Z), which is the ratio of the voltage difference (V) to current (I), is strongly dependent on fluid content. A schematized version of the measurement of arm impedance is shown in Figure 3C in which electrodes are illustrated in accordance with previously evaluated positioning (69).

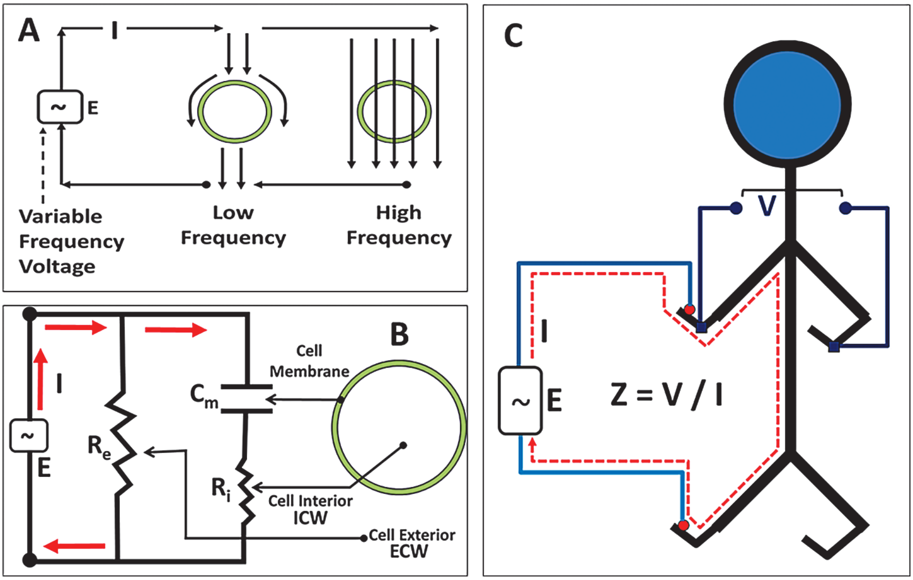

Figure 3. Illustrating basic elements of bioimpedance spectroscopy procedure. A, Applied low frequency currents do not well penetrate cells due to the membrane capacitance whereas high frequency currents do penetrate allowing for an estimate of intra and extracellular water. **B,** An approximate equivalent electrical circuit depicting the various elements of the cellular and extra-cellular current pathways. **C,** Illustrates one configuration of the way in which the excitation and measuring electrodes are applied. The current (I) flows as indicated in the dashed pathway and the voltage difference is measured as V. From these values the arm impedance Z is calculated as the ratio of V/I.

In Figure 3A, the applied voltage (red lines) causes an exciting current to flow (dashed lines). Right arm impedance is determined by the ratio of V (between right and left hands) divided by current (I). In practice, it is possible to separate components attributable to ICW and ECW. In assessing BCRL the concept is that excess arm fluid causes the affected arm to have a reduced impedance vs. a pre-surgery baseline or vs. the contralateral arm. Devices are available for such measurements (Impedimed Ltd, Brisbane, Australia). One version (model SFB7) uses 256 frequencies that range between 3–5 KHz (low frequency) to 1000 KHz (high frequency). Use of multiple frequencies allows extrapolations to evaluate theoretical zero and infinite frequencies based on Cole-Cole plots (70, 71) that describe resistance vs. reactance as a function of frequency (72). These yield estimates of ECW and ICW.

To determine changes only in ECW, which is the dominant fluid change compartment associated with lymphedema, multiple frequencies are much less important and a single frequency of less than 30 KHz (73) may be sufficient. An excellent correlation between single frequency and BIS--determined values was obtained for frequencies ≤ 50 KHz (74). However, whether using single or multiple frequencies, such measurements may not capture the full lymphedema picture because of a non-measured contribution of bound water (75, 76). Some BIS technology is now incorporated in a system allowing BIS measurements while standing.

BCRL Thresholds Based on BIS

Impedance measurements have been used for many years with applications ranging from studying peripheral vasculature (77) to cardiac assessments with impedance cardiography (78). However, its early description in the assessment of lymphedema can be traced to the early-to mid-1990's (79, 80). BCRL thresholds were originally based on inter-limb impedance ratios obtained in healthy persons (dominant/non-dominant) arms, with thresholds defined as inter-arm impedance ratios (contralateral/at-risk) exceeding a mean ratio + 3SD as determined in 60 healthy women (81). The mean and SD of this healthy ratio was 0.964 ± 0.034 that led to a threshold of 1.066. Strictly speaking, this threshold applies to detecting BCRL in women in whom their dominant arm was at-risk. An adjustment to this threshold ratio made for women whose at-risk arm was their non-dominant arm was reported as 1.139 (82). The use of the 3SD threshold is arbitrary but represents a conservative estimate that yields a better sensitivity. This threshold was refined from measurements in 172 healthy women in which dominant/non-dominant impedance ratios were 0.986 ± 0.040 yielding a threshold of 1.106.

BCRL ASSESSMENTS BASED ON TISSUE DIELECTRIC CONSTANT (TDC)

The term tissue dielectric constant (TDC) was coined in 2007 (24) to represent the value of the relative permittivity of skin-to-fat tissue measured in vivo using the open-ended coaxial line method (83–85). To assess edema or lymphedema, it's use is based on the fact that its value strongly depends on tissue water content (86–88). In contrast to lymphedema assessment methods useful only for limbs, TDC measurements are localized and usable to measure skin water or skin-to-fat water at most anatomical sites including breast (20, 89) and trunk (9, 90). Tissue dielectric properties are dependent on their water content and use of the Debye relationship can describe frequency dependence of tissue dielectric properties (91, 92). In this formulation the real part of a complex permittivity (e*) is denoted as e' and its ratio to a vacuum's permittivity (e'/e_0) is relative permittivity (e_r). From a physical perspective, tissue permittivity may be thought of as the electric flux density (D) produced when the tissue experiences an applied electric field (E). In this formulation, the permittivity or TDC may be defined as the ratio of the flux density produced to the electric field causing it (e' = D/E).

TDC Measurement Details

TDC is measured by touching the skin with a probe that has concentric inner and outer electrodes (conductors) that functions as an open-ended coaxial line (Figure 4A-top). The probe inserts a 300 MHz electric field from a battery-operated control box or within the probe itself for a compact version (Figure 4B-bottom). One of the multiprobe types is shown in Figure 4B-top. For both, a time-varying electric field penetrates the tissue (Figure 4A-bottom). For a given frequency, the depth of penetration depends on the probe's radial dimensions (93, 94) with larger diameter probes penetrating deeper (95). Some incident electromagnetic

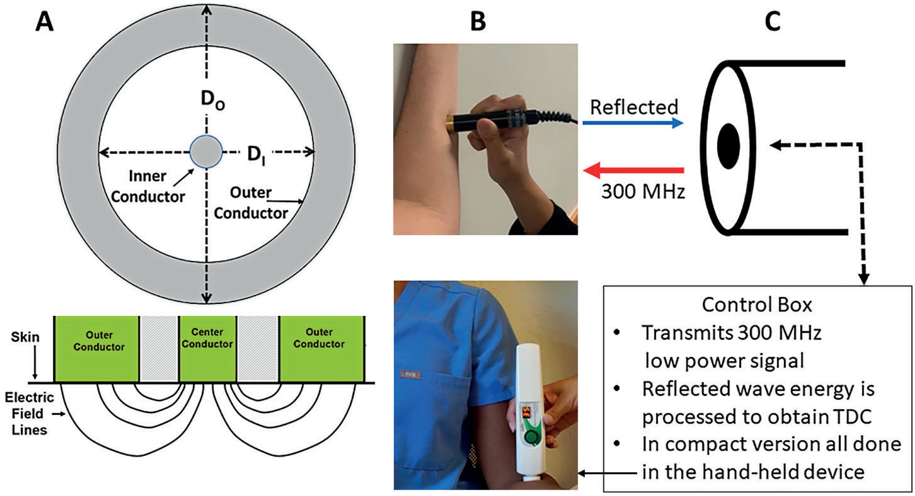

Figure 4. Basic principle and elements of tissue dielectric constant (TDC) measurements of BCRL. A, Cross-section of the TDC measurement probe surface and an illustration of the electric field lines that penetrate the skin. **B,** Illustrates the placement of two different probe systems onto the skin surface. The top probe is connected to a control box that generates the 300 MHz signal and also processes the reflected wave as conceptualized in **C**. The bottom part of **B** shows the compact probe that has all electronics and processing within the hand-held device.

energy is reflected (Figure 4C) and from an analysis of this component, TDC is determined via algorithms based on the physics of the process (85).

Devices are available (Delfin Technologies, Kuopio, Finland) that provide probes for effective measurement depths between 0.5 mm and 5.0 mm (multi-probe system) or fixed depths (compact versions). In some tissues, TDC values depend on measurement depth because of depth-dependent tissue heterogeneity (96, 97). Increased fat with increasing depth tends to lower the TDC value due to low water content of fat (87, 98). Variations in TDC values are also expected based on sex (99–101), age (102, 103), body habitus (104), and at different anatomical sites along the arm (105, 106). These normal biological variations do not importantly impact TDC use as a lymphedema assessment method because of various normalization processes. For unilateral BCRL, inter-arm (107, 108) or inter-trunk (9, 10) or inter-breast (20, 109) ratios are used with the added advantage that specific localized targets can be tracked. The method permits assessing head-and-neck-related lymphedema (110) and lower extremity lymphedema (111, 112) based on individualized inter-site normalizations.

BCRL Thresholds Based on TDC

TDC measurements to a depth of 2.5 mm in 30 healthy pre- and 30 post-menopausal women yielded an inter-arm TDC ratio of 1.040 ± 0.040 vs. 1.640 ± 0.300

in 18 patients with BCRL (24). In that study, no healthy control had an inter-arm ratio as great as 1.200 and no patient had a ratio as low as 1.200. It was suggested that an inter-arm TDC-ratio of 1.200 should be a BCRL threshold-value. Had they used a threshold based on 3SD greater than the mean, it would have been 1.160. Other work supported the 1.200 threshold ratio (113). Inter-arm TDC-ratios were compared between 60 healthy women and 30 patients with unilateral BCRL (114). The healthy group's inter-arm TDC-ratio (dominant/non-dominant) was 1.006 ± 0.085 with a 3SD TDC-threshold-ratio of 1.26. This was initially used to define arm BCRL and were insignificantly affected by patient body mass index, age, measurement depth (96, 108) or hand-dominance (115). Subsequent inter-side measurements made with a compact-type TDC device in 112 breast cancer survivors without BCRL had at-risk to contralateral side ratios for forearm, upper arm and middle lateral thorax of 1.00 ± 0.09, 1.01 ± 0.15, and 1.06 ± 0.10, respectively (90). These ratios differed from those similarly measured in 78 breast cancer survivors diagnosed with BCRL in whom corresponding inter-side ratios were 1.29 ± 0.36, 1.25 ± 0.41, and 1.07 ± 0.12, respectively (90). In this study, time since breast surgery was 8.4 ± 6.7 years with 12.8 ± 8.7 nodes removed. The non-BCRL control patients were 6.9 ± 6.7 years post-surgery and had 6.1 ± 7.3 nodes removed. Based on a 3SD threshold for control ratios, an inter-arm BCRL threshold may be calculated as 1.27, 1.46 and 1.36 for forearm, upper arm and thorax. A slightly lower thorax-to-thorax inter-side ratio of 1.38 has been reported from measurements on 120 women awaiting breast cancer surgery (10). A reference range for inter-hand TDC ratios has been determined via measurements in 70 healthy women to be 1.326 (116).

IMAGING-BASED MEASUREMENT METHODS

There have been several reports describing efforts to use 3-D photography and whole-body scanning systems to assess arm volumes (25–27, 117–120). Future progress in these areas is likely but currently are probably not suitable for routine clinical application. Ultrasound provides an additional potential diagnostic modality. It has been used to detect changes in cutaneous water (121, 122) and thickness changes (32, 123) and, when used in combination with shear wave elastography (124–126), shows promise to assess BCRL features based on cutaneous and subcutaneous dermal thickening and stiffness increases detectable by increased shear-wave velocity resulting from an increased shear modulus. Magnetic resonance imaging (MRI) is another imaging modality with potential efficacy in characterizing aspects of BCRL. A recent study used a multi-echo spin echo protocol to evaluate T2-relaxation times in upper arms of women with and without BCRL (127). On the basis that these T2 values reflect relative tissue fluid content, a 7–13% greater fluid amount in BCRL arms was reported. However, major limitations of MRI include its cost and accessibility and the absence of currently defined diagnostic threshold criteria. Another promising approach is that of non-contrast magnetic resonance lymphography (NMRL) that visualizes lymphatic vessels (128, 129) for which a partial scoring system has recently been suggested (130). However, as with any MRI-related approach, cost, required patient time for measurement, and availability are major limitations when compared with the portable hands-on methods of measurement previously discussed. However, MRI-related procedures can valuably add to the understanding of lymphatic physiology and pathophysiology as in BCRL.

CONCLUSION

It has been long recognized (48, 49) that in addition to changes in interstitial fluid content accompanying developing lymphedema, there are progressive changes in tissue content, structure, and physical properties. Such changes include increases in arm fat, muscle, and bone as has been demonstrated via dual energy x-ray absorptiometry (DXA) in a group of 18 women with BCRL (131). It is thus likely that such complex changes, that do contribute to arm volume increases, will not directly be reflected as decreases in measured arm impedance. These complexities have been more recently investigated using MRI (132) in which excess fat volume was observed in both intra- and inter muscular compartments of seven patients with BCRL. An increasing relative amount of fat accumulation would increase measured arm impedance even though arm volume was increasing further suggesting a limitation to BIS tracking in such cases. Other factors to be considered relevant to BCRL portable or semi-portable measurement techniques is their relative initial cost, continuing supply needs and operating costs, maintenance needs, ease of use, and difficulties with measurement. Based on such considerations, the relatively non-portable Perometer system cost (350NT) of at least $33,000 may be most useful for high volume screening facilities. Contrastingly, the hand-held TDC device, costing about $4000 with no subsequent operating costs, may be most useful for rapid routine physician or therapist initial detection and follow-up assessments of localized BCRL or for such measurements at any other anatomical site related to BCRL such as breast or thorax. Use of BIS may also be most useful for high volume screening and follow-up purposes in which sensitivity to small-to-moderate free and bound water increases are not important. Initial unit cost is about $8000 with a continuing electrode cost per patient. A comparison between BIS and TDC methods in 100 women with BCRL has reported TDC having a greater sensitivity at detecting early lymphedema (133). This is in part due to lymphedema that is more superficial. They also suggest complementary use of TDC and volume assessments and indicate a number of practical advantages of TDC. These are reported to include the contradictory use of BIS in patients who are pregnant, have pacemakers or metal implants and patients being in contact with a metal surface. However, a case has been put forward that BIS should be considered as a gold standard for assessing limb lymphedema (66) and a summary of historical estimates of its sensitivity and specificity have recently been reported (18). From the point of view of cost, tape measure procedures with volume conversion and limb volumes via water displacement require the least for equipment, but measurement time and patient acceptance need to be considered. Tape measurements are well accepted by patients but may require extended therapist measurement time. In the case of water-displacement measurements, patient positioning and discomfort as with all methods are to be considered. The shorter the required measurement time and the less intrusive to the patient, the better tolerated is the measurement process.

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