# PRE-SURGICAL BIOPHYSICAL LYMPHEDEMA ASSESSMENTS OF PATIENTS WITH BREAST CANCER: POTENTIAL UTILITY OF LOCAL TISSUE WATER MEASUREMENTS

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## INTRODUCTION AND BACKGROUND

Early detection of breast cancer treatment-related lymphedema (BCRL) may allow for early lymphedema treatment that potentially optimizes therapeutic outcomes. Pre-surgical evaluations of patients followed by periodic follow-ups measurements is the best approach, but pre-surgical assessments are often not done for a variety of reasons with patients being seen for lymphedema assessment for the first time sometime after surgery and/or radiotherapy. Because BCRL is most often unilateral, it would thus be useful to know if breast cancer presence in of itself alters side-to-side values of assessment parameters that will or might be subsequently used to detect post-surgical/radiation latent preclinical lymphedema. Currently there are several methods that may have the potential to unmask latent lymphedema based on comparisons of parameters measured in the at-risk arm compared to the 'normal' arm or to pre-surgical values. These include arm metrics or volumes[1] arm electrical impedance values (bioimpedance[2, 3]) and local tissue water based on tissue dielectric constant (TDC) values[4-8]. The use of arm volume or bioimpedance changes from a pre-surgical baseline requires specification of a suitable threshold that defines the lymphedematous condition and various criteria have been analyzed[1, 9-11]. Both methods however are restricted to limb measurements. Contrastingly, the TDC method permits assessment of local tissue water at any body site including the trunk and axillary region. Secondly, by using different sized probes, it permits measurement of tissue water included within different tissue depths and may thereby provide additional information not available with other methods. Thus the goals of this research were; 1) to use the TDC method to evaluate and document pre-surgical local tissue water (LTW) in newly diagnosed breast cancer patients at the forearm, biceps, axilla and lateral thoracic trunk that are sites that often subsequently show early lymphedematous changes, 2) to determine the variation in LTW with tissue depth in the forearm and 3) to determine if arm LTW values as determined by the TDC method correlate with arm bioimpedance and volume values.

## METHODS

***Subjects:*** A total of 50 women with ages (mean ± SD) of 60.7 ± 13.8 years (28 to 81 years), were evaluated after signing a University Institutional Review Board approved consent. All women had recently (within one month) been diagnosed with breast cancer and were awaiting breast cancer surgery. Height, weight and body mass index were respectively 1.61± 0.07 m (1.42 to 1.75 m), 74.5 ± 16.7 Kg (45.5 to 124.5 Kg) and 28.7 ± 6.8 Kg/m$^2$ (18.0 to 48.1 Kg/m$^2$).

***Arm Volume Measurements:*** Circumferences of at-risk arms (side with diagnosed breast cancer) and control arms were measured with a calibrated spring-loaded tape-measure starting at the wrist with measurements repeated at 4 cm intervals extending up the arm toward the axilla. Arm volumes were calculated using circumference values in a truncated-cone model with calculations done using an automated software algorithm (Limb Volumes Professional 5.0, www.limbvolumes.org). This method of estimating limb volume has been extensively tested and validated[12, 13]

***TDC Measurements:*** The device used to measure tissue dielectric constant was the MoistureMeter-D, (Delfin Technologies Ltd, Kuopio Finland). It consists of a cylindrical probe connected to a control unit that displays the tissue dielectric constant when the probe is placed in contact with the skin for about 10 seconds. The physics and principle of operation has been well described[14-16]. For reference, pure water has a value of about 78. Bilateral TDC measurements were made at four paired standardized sites to a measurement depth of 2.5 mm after subjects had lied supine for 15 minutes. Measurement sites were; volar forearms 6 cm distal to the olecranon, medial biceps 6 cm proximal to the olecranon, axilla and lateral thorax 10 cm below the axilla. At the forearm site additional TDC measurements were made using probes with effective measuring depths of 0.5, 1.5, 2.5 and 5.0 mm with a one minute wait between changing probes. Measurements with each probe and at each site were done in triplicate and averaged to characterize the site average TDC value.

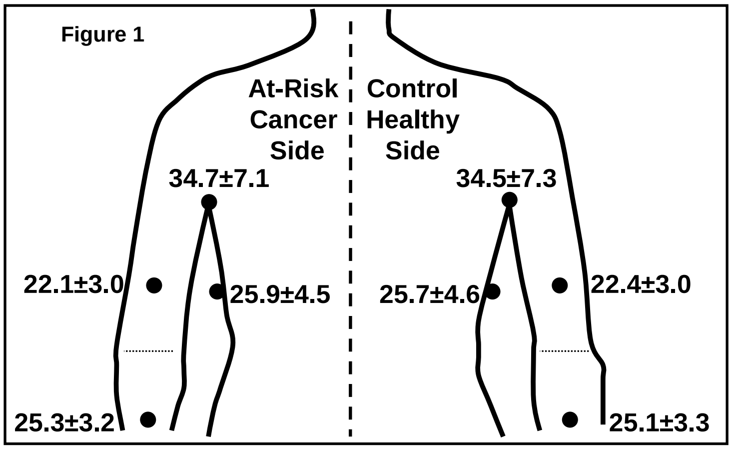
***Arm Bioimpedance Measurements:*** Arm bioimpedance values were then determined using the Imp-XCA device (ImpediMed Ltd, Australia). Measurements were done according to manufacturers instructions using five electrodes; two pairs on the dorsal surface of the hand separated by five cm and one on the foot dorsum. After cleaning sites with alcohol, measurement electrodes were placed on the wrist at the level of the process of the radial and ulnar bones and the driving electrodes were placed at least five cm distal on the dorsal surface of the third metacarpal bone of the hands. Impedance measurements were taken with the subject supine with the arms slightly abducted and palms down. Smaller impedance values reflect greater amounts of total arm extracellular water.

***Data Reduction and Analysis:*** Arm volumes and impedances and TDC values at all sites (mean values ± SD) and their ratios between sides (at-risk/control) were determined. Tests for differences between paired arm volumes and impedances were based on paired t-tests with a p-value $<0.05$ taken as significant. Tests for differences among TDC values at the four measured arm depths was based on a general linear model (GLM) for repeated measures with depth as the within factor. Tests for differences among the four anatomical sites at which TDC was measured was done using analysis of variance (ANOVA) with site as a factor. Testing for correlations among the parameters was done using Pearson coefficients. All statistical analyses were done using SPSS version 12.0.

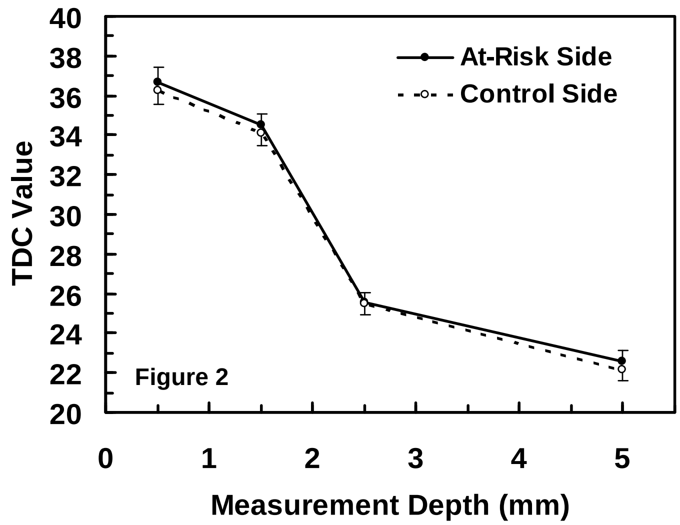
## RESULTS

***Body Side Comparisons:*** Comparisons of at-risk cancer sides vs. control healthy sides values (mean ± SD) showed no significant difference in arm volumes (2297±706 vs. 2314±696 ml) or arm impedance values (293.6±43.2 vs.293.8±42.1). Comparisons of TDC values between paired at-risk vs. control sides for each of the four measured anatomical sites to a 2.5 mm depth also showed no significant difference for any paired site as summarized in Figure 1. However an overall significant difference in TDC values among anatomical sites was found ($p<0.001$) with the largest TDC value at the axilla (34.6±7.4), which was significantly greater than at all other sites ($p<0.001$). The lowest TDC value (22.3±3.0) was found at the biceps which was significantly less than at all other sites ($p<0.001$). There was no significant difference in TDC values between forearm (25.2±3.3) and thorax (25.8±4.5). TDC ratios (at-risk/control) for forearm, biceps, axilla and thorax (mean ± SD) were respectively 1.015±0.101, 0.989±0.080, 1.030±0.187 and 1.020±0.147 with no significant difference among these ratios ($p=0.46$). The corresponding arm volume ratio was 0.991±0.52.

Figure 1



***Forearm TDC Depth Measurements:*** TDC values obtained at each depth were significantly different from all others ($p<0.001$). The pattern of differences, shown in figure 2 with corresponding sem bars, was nearly identical for both arms. There was a monotonic decrease in TDC values with increasing TDC effective measurement depth with a sharp decrease between 1.5 and 2.5 mm depths. TDC values (mean ± SD) for 0.5, 1.5, 2.5 and 5.0 mm depths for both arms combined (100 arms) were respectively 36.5±5.0, 34.3±4.2, 25.5±3.7 and 22.4±3.9. TDC values at a 5 mm depth showed a significant ($p<0.01$) but weak positive correlation with arm volumes ($r=0.280$) but TDC values at all other depths showed no significant correlation with arm volumes. There was no significant correlation between TDC at any depth and arm impedance values.




## DISCUSSION

The main goal of this study was to define pre-surgical values of local tissue water using the tissue dielectric constant (TDC) method in women diagnosed with unilateral breast cancer. Although use of this method has been able to separate lymphedematous from non-lymphedematous tissue[4] and quantify changes in local tissue water of lymphedematous limbs[6], its possible use as a predictive measure of pre-clinical or latent lymphedema has been suggested[17] but not established. Though it is likely that early detection of latent lymphedema using any quantitative measure would be facilitated by pre-surgical measurements the fact is that often such measurements are not made. Thus the question arises whether measurements made after treatment could be sufficient. Central to this query is the extent of pre-surgical differentials between at-risk and control sides at anatomical sites that often demonstrate lymphedematous changes. Thus the impetuous for the present study was to ascertain reference, pre-surgical TDC baseline values and their side-to-side differentials as an initial step toward the potential use of this method for early detection of subsequent changes.

The importance of TDC measures of local tissue water as opposed to whole arm assessments derives in part from the fact that standard bioimpedance and volume assessments can be usefully applied only to limbs whereas the TDC method can in principle be used on any body site. Since BCRL may occur at a variety of at-risk sites including the thorax and axilla areas, and it is unknown at which site or at which tissue depth the earliest pre-clinical changes are most likely to occur, the TDC approach offers a potentially valuable addition to the clinical and research armamentarium.

The TDC findings with respect to present group of newly diagnosed breast cancer patients indicate no significant difference in local tissue water between paired body sides measured at corresponding anatomical sites. This suggests that the cancer presence did not detectibly modify the tissue water status and moreover the closeness of side-to-side values suggests that when it is not possible to obtain pre-surgery measurements, subsequent differentials between sides that exceed defined thresholds may still be useful for diagnostic purposes.  Based on the standard deviations obtained at each of the sites such a threshold differential may be developed and used to help determine the presence of sub-clinical lymphedema when patients are measured at later times. This possibility needs to be investigated and validated with further clinical research.

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