

# Patterns of Temporal Changes in Tissue Dielectric Constant as Indices of Localized Skin Water Changes in Women Treated for Breast Cancer: A Pilot Study

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## Abstract

**Background:** Our goal was to characterize temporal patterns of skin Tissue Dielectric Constant (TDC) as a foundation for possible TDC use to detect and quantify lymphedema. Although limb volumes and bioimpedance analysis (BIA) are used for this purpose, potential TDC-method advantages are that it can be done in about 10 seconds at any body site to depths from 0.5 to 5.0 mm below the epidermis.

**Methods and Results:** TDC at forearm, biceps, axilla, and lateral thorax, and BIA values and arm volumes were measured in 80 women with breast cancer prior to surgery and in decreasing numbers at 3, 6, 12, 18, and 24 months post-surgery. Results show that TDC values, reflecting water content in the measurement volume, vary by site and depth but that at-risk/contralateral side ratio (A/C) is relatively independent of site and depth and is the preferred TDC parameter to detect tissue water changes over time in unilateral conditions. Among sites measured, lateral thorax, followed by forearm, appears most useful for TDC measurements with axilla least useful. Pre-surgery TDC inter-side values and A/C ratios showed no significant inter-side differences, suggesting that breast cancer presence per se did not alter tissue water status in this patient population. Sequential changes in TDC A/C ratios detected a greater number of patients who had inter-arm ratio increases exceeding 10% than were detected using BIA ratios. This may indicate a greater sensitivity to localized tissue water changes with the TDC-method.

**Conclusions:** TDC is a technically viable and potentially useful method to track skin water changes in persons treated for breast cancer.

## Introduction

REPORTS SUGGEST THAT THERE is at least a 1 in 5 chance of a woman developing breast cancer treatment-related lymphedema (BCRL)<sup>1</sup> with a greater chance depending on risk factors<sup>2-5</sup> such as surgery extent,<sup>6</sup> radiation use and type, chemotherapy, and being greatly overweight. The fact that lymphedema progresses in severity if treatment is not started<sup>7</sup> emphasizes the need for the earliest possible diagnosis. Recognizing this need, investigators have estimated BCRL prevalence and tried to predict its occurrence in its earliest stages using methods suitable for routine use such as metric arm measurements<sup>8</sup> (including girth at various arm locations and arm volumes) and biophysical measurements such as arm electrical impedance.<sup>9</sup> Different metric-based criteria have

been tested to define and detect BCRL presence. These include inter-arm girth differences or changes greater than 2 cm at any measured arm site,<sup>10,11</sup> inter-arm volume differences greater than 200 mL,<sup>10</sup> and volumes greater than 10% between at-risk and contralateral arms or changes in these amounts as measured on at-risk arms compared with at-risk arm pre-surgery values.<sup>10,12,13</sup>

Application of these and related criteria and patient follow-ups for 12 months<sup>10</sup> and 30 months<sup>12</sup> showed the prediction of lymphedema presence was dependent on which parameter and threshold criteria were used. Whole arm bioimpedance measurements and analysis (BIA) using single<sup>14</sup> or multiple frequencies<sup>15-17</sup> have also been used to assess BCRL.<sup>18,19</sup> An approach to judge lymphedema presence with BIA was to determine if a pre-surgical inter-arm impedance ratio

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(contralateral arm/at-risk arm) subsequently increased by an amount greater than three standard deviations (3SD) of inter-arm impedance ratios previously determined in 60 healthy subjects.<sup>18</sup> The approach was subsequently updated using 172 healthy women.<sup>19</sup>

These prior efforts have led to a better understanding of the lymphedema condition and have in some cases led to proposed threshold values potentially characteristic of early lymphedema.<sup>18–23</sup> An additional biophysical parameter that has been suggested as useful to help characterize the lymphedematous state is the tissue dielectric constant (TDC) measured at a frequency of 300 MHz that serves as an index of localized tissue water to depths ranging from 0.5 to 5.0 mm below the epidermis. There are at least two features associated with this technology that render it different from and possibly complementary to whole limb volume and BIA; 1) It can rapidly and noninvasively measure any body surface area, thereby yielding local tissue water indices in any body region and is not restricted to just measurements of arms or legs, and 2) it is capable of easily interrogating tissue volumes to different depths, thereby potentially revealing progressive changes in the relative depth distribution of water from epidermis to hypodermis. Although the physics of this method is well described<sup>24–28</sup> and some information regarding TDC values in various conditions is available,<sup>29–37</sup> there has been little if any characterization of the pattern of sequential changes in TDC subsequent to breast cancer treatment. These patterns may be revealing as to the natural temporal history of the post-surgical sequence and thereby have potential utility as a subsequent basis for early detection. Thus the main purpose of the present pilot research study was to investigate and characterize TDC sequential patterns in women treated for breast cancer with an ultimate goal of potentially using such measures in future for lymphedema

detection or assessment. A secondary goal was to compare the TDC sequential patterns with those determined by arm volume and BIA.

## Methods

### Subjects

Women who were newly diagnosed with breast cancer and referred for surgery were asked to participate in this study upon their initial visit to the surgeon. The Institutional Review Board (IRB) approved study design called for including the first 80 patients who consented to participate. Once that number was achieved, no further patients were entered. Patients who agreed to participate signed an IRB approved consent and were evaluated within 2 weeks of their impending surgery. Patient selection was based on their agreement to participate and their stated commitment to continue with follow-up assessments. Thus the patient population evaluated would be those who had access to transportation either by self or by someone else.

The initial pre-surgery evaluation is referred to as month 0. According to study design, follow-up evaluations were planned for 3, 6, 12, 18, and 24 months after the patient's surgery. Of the 80 women evaluated pre-surgery, decreasing numbers chose to return for subsequent evaluations, resulting in evaluated subsets with diminishing numbers of patients seen at planned evaluation months. This resulted in subsets in which 60 patients were evaluated at months 0–3; 53 patients evaluated at months 0–3–6; 47 patients evaluated at months 0–3–6–12; 41 patients evaluated at months 0–3–6–12–18; and 35 patients evaluated at all months, 0–3–6–12–18–24. Table 1 summarizes characteristic features of the initial 80 subjects and the subsets. The initial group ( $N=80$ ) had an average age (mean  $\pm$  SD) of 59.5  $\pm$  12.9 years (range 28 to 82

TABLE 1. SUBJECT SUBSET COMPARISONS

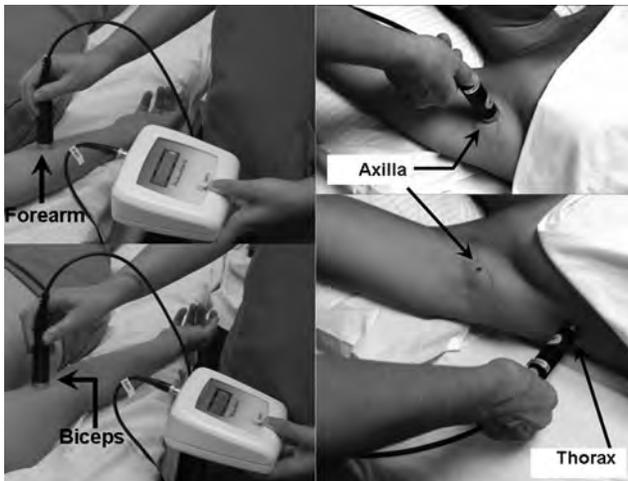
	Pre-Surgery = 0	Months at which same patients were evaluated				
		0–3	0–3–6	0–3–6–12	0–3–6–12–18	0–3–6–12–18–24
Number of subjects evaluated	80	60	53	47	41	35
Age	59.9 $\pm$ 12.9	58.2 $\pm$ 12.8	57.4 $\pm$ 12.4	57.5 $\pm$ 12.3	58.1 $\pm$ 12.5	58.1 $\pm$ 11.6
BMI	28.3 $\pm$ 7.0	28.3 $\pm$ 6.7	28.3 $\pm$ 6.5	28.4 $\pm$ 6.8	28.1 $\pm$ 7.0	28.0 $\pm$ 7.0
Number of nodes removed	9.8 $\pm$ 9.9	9.9 $\pm$ 9.7	9.7 $\pm$ 9.4	10.0 $\pm$ 9.4	9.4 $\pm$ 9.4	9.0 $\pm$ 9.3
Right arm is the dominant arm	73 (92.5%)	59 (98.3%)	52 (98.1%)	46 (97.9%)	40 (97.6%)	34 (97.1%)
At-risk arm is the dominant arm	40 (50.0%)	31 (51.7%)	25 (47.2%)	20 (42.6%)	18 (43.9%)	16 (45.7%)
Surgery Type						
Lumpectomy + SLNB	47 (58.6%)	32 (53.3%)	30 (56.6%)	27 (57.4%)	24 (58.5%)	22 (62.9%)
Lumpectomy + ALND	11 (13.8%)	11 (18.3%)	9 (17.0%)	9 (19.1%)	7 (17.1%)	3 (17.1%)
Mastectomy + SLNB	9 (11.3%)	6 (10.0)	5 (9.4%)	4 (8.6%)	4 (9.8%)	4 (11.4%)
Mastectomy + ALND	13 (16.3%)	11 (18.4%)	9 (17.0%)	7 (14.9%)	6 (14.6%)	6 (17.1%)
Radiation type						
None	26 (32.4%)	18 (30.0%)	18 (34.0%)	15 (31.9%)	14 (34.1%)	11 (31.4%)
Brachytherapy	30 (37.5%)	23 (38.3%)	20 (37.7%)	19 (40.4%)	18 (43.9%)	15 (42.9%)
External beam	21 (26.3%)	16 (26.7%)	12 (22.6%)	10 (21.3%)	7 (17.1%)	7 (20.0%)
Brachytherapy + External beam	3 (3.8%)	3 (5.0%)	3 (5.7%)	3 (6.4%)	2 (4.9%)	2 (5.7%)

ALND, Axillary lymph node dissection; SLNB, Sentinel lymph node biopsy.

years) with a body mass index (BMI) of  $28.3 \pm 7.0 \text{ Kg/m}^2$  (range 17.8 to  $48.1 \text{ Kg/m}^2$ ). This group average BMI indicates a group classified as overweight. A further breakdown of the distribution of the BMI values showed that with respect to BMI classification, the percentage of patients considered to be; obese (BMI  $\geq 30 \text{ Kg/m}^2$ ) was 31%, overweight (BMI  $\geq 25 \text{ Kg/m}^2$  and  $< 30 \text{ Kg/m}^2$ ) was 32.5%, normal weight (BMI  $\geq 18.5 \text{ Kg/m}^2$  and  $< 25 \text{ Kg/m}^2$ ) was 35.1% and underweight (BMI  $< 18.5 \text{ Kg/m}^2$ ) was 1.4%. The surgical procedure experienced by more than half the group was a lumpectomy + SLND (sentinel lymph node dissection), which represented 58.6% of cases, whereas mastectomies either with SLNB or ALND (axillary lymph node dissection) combined represented 27.6% of cases with the remainder being lumpectomy + ALND (13.8% of cases). For the total group the average number of lymph nodes removed was  $9.8 \pm 9.9$  with a range of 1 to 30. About two-thirds (67.6%) of patients received radiotherapy that included brachytherapy, external beam, or both. Although there was continuous loss to follow-up from the pre-surgery evaluation through the 24-month evaluation, the characteristics of the subsets evaluated at each of the planned evaluation months did not significantly differ from the initial group with respect to age, BMI, hand dominance, type of surgery, number of nodes removed, and radiation type.

#### Measurements

**Tissue Dielectric Constant (TDC).** Bilateral TDC values were measured at four sites using the MoistureMeter-D (Delfin Ltd. Kupio, Finland). Measurements (Fig. 1) were done in the following order: 1) anterior forearm (6 cm distal to the antecubital fossa); 2) anterior biceps (8 cm proximal to the antecubital fossa); 3) within the axilla center; and 4) at the lateral thorax (10 cm inferior to the axilla). After completing the TDC measurements to a depth of 2.5 mm, additional TDC measurements were made bilaterally at the forearm site to

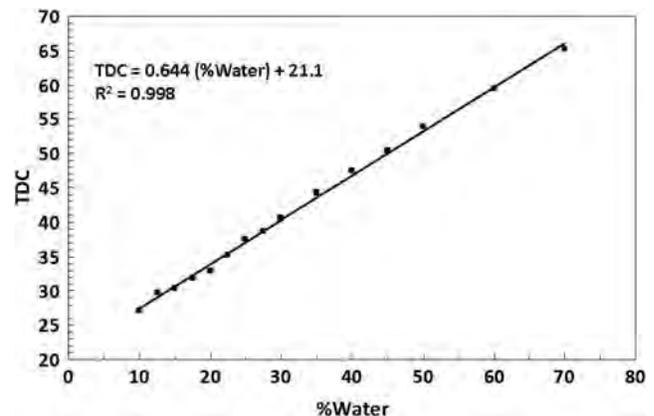


**FIG. 1.** Tissue Dielectric Constant (TDC) measurements and sites. Measurements were to an effective depth of 2.5 mm at anterior forearm (6 cm distal to the antecubital fossa), anterior biceps (8 cm proximal to the antecubital fossa), within the axilla, and also at the lateral thorax (10 cm inferior to the axilla). Each measurement takes about 10 seconds and starts when the probe is placed on the skin.

depths of 0.5, 1.5, 2.5, and 5.0 mm. Measurements were made with four different probes whose diameter and design determined measurement depth with the smallest probe measuring to 0.5 mm and the largest probe measuring to 5.0 mm.

All TDC measurements were done with subjects in a supine position with measurements started after they had been resting in this position on a padded examination table for about 10 minutes. For each measurement set, TDC measurements were done in triplicate and then averaged. Each TDC measurement takes about 10 seconds and is triggered when the probe makes contact with the skin. The measuring device has a display that reads the dielectric constant value, also called the relative permittivity, from 1 to 80. For reference, the dielectric constant of distilled water is about 76 at  $32^\circ\text{C}$ . Calibrations are achieved by measuring the dielectric constant of varying concentrations of ethanol–water solutions and comparing against known dielectric values for given concentrations. An example calibration curve showing the linear TDC vs. %Water relationship is shown in Figure 2.

The physics underlying this method is well described in the literature.<sup>24–27,38</sup> Briefly, a probe in contact with skin acts as a coaxial transmission line through which a 300 MHz signal is transmitted to tissue. Part of the signal is absorbed by the tissue and part is reflected back to be processed by the control unit. Reflections from the end of this coaxial transmission line depend on the complex permittivity of the tissue which depends on the signal frequency and on the dielectric constant (the real part of the complex permittivity) and the conductivity of the tissue with which the probe is in contact. At 300 MHz the contribution of the conductivity to the overall value of the permittivity is small and the dielectric constant is mainly determined by water molecules (free and bound). Consequently, the device includes and analyzes only the dielectric constant (TDC) that is directly proportional to tissue water content. An approximate relationship between local tissue water percentage (LTW%) and TDC value, potentially useful for tracking tissue water changes but not necessary for comparing tissue water values between subjects,<sup>39</sup> has been previously reported<sup>27</sup> as  $\text{LTW}\% = [100(\text{TDC} -$



**FIG. 2.** Sample TDC probe calibration curve using various alcohol–water concentrations. Each probe is calibrated by exposing the probe measuring head to varying ethanol–water concentrations. This figure is for a 2.5 mm effective measurement depth probe and illustrates the essentially linear dependence of the TDC value with water concentration (%Water).

1)]77.5. However, in the present report all values are presented in the directly measured TDC values. For reference, approximate dielectric constant values at 300 MHz for dry skin and fat are 60 and 6, respectively.<sup>40</sup> Short- and long-term coefficients of variation of TDC values as measured on human skin have been reported<sup>27</sup> as 2% and 5%, respectively, and intraclass coefficients (ICC) have been reported<sup>29</sup> as 0.94 on leg skin with 95% confidence intervals of 0.89–0.96.

**Arm girths and volumes.** Arm volumes were calculated by measuring arm girths (circumferences) at 4 cm intervals with a spring tension tape measure and calculating volume from the sum of segmental volumes<sup>7,41</sup> using a validated frustum model.<sup>42–46</sup> Girths were measured starting at the wrist and continuing up the arm until reaching a pre-marked level close to the level of the axilla. Thus, the length of the last segment for the calculation of limb volume could be 4 cm or less depending on the length of the arm. All other segment lengths used in the arm volume calculation were 4 cm.

**Arm bioimpedance (BIA) measurements.** Arm BIA values were determined with the Imp-XCA device (ImpediMed Ltd, Australia). Measurements were done according to manufacturers instructions using five electrodes; two pairs on the dorsal hand surface separated by 5 cm, and one on foot dorsum. After cleaning sites with alcohol, measuring electrodes were put on the wrist at the level of the process of radial and ulnar bones and driving electrodes were put at least 5 cm distal on the hand dorsum near the third metacarpal bone. Measurements were done with the subject supine with arms slightly abducted and palms down. Smaller BIA values reflect greater amounts of total arm extracellular water. The Imp-XCA device measures impedance at a single frequency stated by the manufacturer as being less than 30 KHz but not further specified. It has been reported that optimum bioimpedance frequencies for detection of lymphedema should be less than 30 KHz<sup>47</sup> placing this device's operating frequency in this range. Also, it has been reported that this single frequency impedance device produces similar results as compared with multi-frequency bioimpedance spectroscopy devices.<sup>14</sup>

#### Procedure sequence and order

All measurements were done at the same clinic with more than 90% of all patient evaluations done by one experienced therapist. For the 35 patients seen at each of the planned

evaluations (months 0, 3, 6, 12, 18, and 24) one therapist completed all measurements on 33 (94%) of the patients in this subgroup. At each visit the patient was helped to a supine position on a padded examining table in a private room. Using a surgical pen the sites for subsequent girth measurements were measured and marked at 4 cm intervals starting at the wrist. In addition, marks were made for subsequent TDC measurements bilaterally 6 cm distal to the antecubital crease, 8 cm proximal to the antecubital crease, 10 cm inferior to the axilla on the lateral thorax and centered in the axilla. Girth measurements were then made and recorded. TDC measurements were then begun starting with the 2.5 mm effective depth probe at the at-risk forearm and progressing to the biceps, axilla, and thorax measurements, all in triplicate. Immediately thereafter the same TDC measurement sequence was done on the other body side. TDC measurements were then made to effective depths 0.5, 1.5, 2.5, and 5.0 mm at the forearm site. For each depth measurement the first measurement was on the at-risk forearm and a paired-measurement on the other forearm. Three pairs of these alternately arm-to-arm measured values constituted the measurement set for each depth. At the end of the TDC measurements the bioimpedance electrodes were fitted as previously described and bioimpedance measurements made. Prior to the start of any measurements the patient completed a questionnaire aimed at soliciting her perceived symptoms. The questionnaire asked if any of 12 sensations were presently being experienced or had been experienced since her last visit in her arm, hand, fingers, axilla, or chest. The queried sensations were; fullness, heaviness, tightness, numbness, tingling, tenderness, aching, pain, warmth, cold, swelling, and stiffness.

#### Analysis

Characteristics of the initially seen patients ( $N=80$ ) prior to their surgery were assessed by determining absolute TDC values, arm volumes, and BIA values, as well as inter-side differences and inter-side ratios for both at-risk side and dominant-arm side when forming these ratios. Normality of absolute values was tested using the Shapiro-Wilk test that indicated normality could not be rejected ( $p>0.05$ ) except for arm volumes (both at-risk and control) that showed a significantly non-Normal distribution ( $p<0.01$ ). Thus, significance of differences between sides (at-risk vs. control and dominant vs. non-dominant) was evaluated using paired  $t$ -tests except for arm volumes for which the nonparametric

TABLE 2. PRE-SURGERY TDC AND ARM BIOIMPEDANCE AND VOLUMES

TDC	At-Risk	Control	$p$ -value	Ratio (A/C) <sup>§</sup>	Ratio (D/ND) <sup>†</sup>	P value
Forearm	27.4 ± 3.6	27.7 ± 4.2	0.270	0.995 ± 0.085	0.994 ± 0.087	0.937
Biceps	24.4 ± 4.0	24.4 ± 4.6	0.917	1.014 ± 0.157	1.015 ± 0.150	0.924
Axilla	38.5 ± 7.8	38.4 ± 9.0	0.883	1.029 ± 0.196	1.050 ± 0.213	0.438
Lateral thorax	29.7 ± 5.3	30.1 ± 6.0	0.396	0.999 ± 0.119	1.002 ± 0.119	0.874
Bioimpedance (Ohms)	288 ± 54	287 ± 55	0.616	1.005 ± 0.053	0.998 ± 0.053	0.938
Arm volume (mL)	2287 ± 739	2301 ± 738	0.306	0.993 ± 0.051	1.000 ± 0.052	0.408

Table entries are mean ± SD tissue dielectric constant (TDC), arm bioimpedance and volume for at-risk and control (contralateral) sides determined for 80 patients prior to surgery. Side-to-side values did not significantly differ for any measured parameter but TDC values significantly differed among sites ( $p<0.001$ ) with each site significantly different from each other site ( $p<0.001$ ). <sup>§</sup>Ratios are at-risk to contralateral (A/C) sides. <sup>†</sup>Ratios are dominant to nondominant sides (D/ND). The ratios A/C and D/ND did not significantly differ from each other for any parameter. TDC values are dimensionless being the ratio of the tissue dielectric constant of the tissue to that of vacuum.

Mann-Whitney test was used. Comparisons of TDC values among sites was done using the side averages in an analysis of variance analysis (ANOVA) with site as the between variable.

The primary sequential analysis group included patients seen and evaluated at each planned visit (pre-surgery and months 3, 6, 12, 18, and 24 post-surgery). Sequential patterns in TDC and arm volumes and BIA values found for this group were subsequently compared to those of subset groups comprised of patients who had been seen consecutively for up to 18, 12, 6, or 3 months post-surgery. Since by 24 months post-surgery the number of the same patients seen at each planned visit was reduced by attrition to 35 from the initial 80 patients evaluated pre-surgery, the additional subset analyses were done to determine if the significance of any observed pattern for the 0–24 month data set would be consistent with or better clarified when greater numbers of patients were included at specific follow-up months. Tests for statistical significance of pattern changes over time were based on a general linear model (GLM) analysis with repeated measures (month) as the repeated (within) measure and the significance of changes at any given month as compared to pre-surgery assessed via within-contrasts analysis. Tests for significance of overall arm volume pattern changes were done using the nonparametric Friedman test. All statistical tests were done using SPSS version 13. An estimate of the long-term intrarater reliability for sequential TDC measurements was done by determining the intraclass correlation coefficient (ICC) for continuous data using the sequential data sets obtained on the control arm for months 0, 3, 6, 12, 18, and 24 as repeated measures for the 33 patients evaluated by the same therapist. Done in this way the ICC represents the amount of variance attributable to variations among patients not due to therapist measurements. A high ICC value implies good repeatability of the measurement.

**Results**

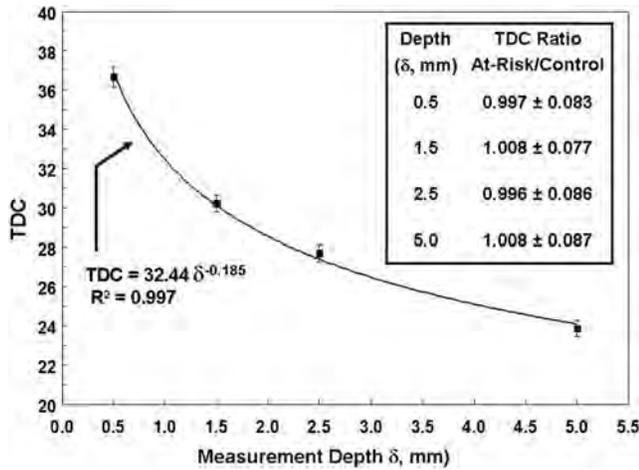
*Pre-surgery parameter values*

Pre-surgery (month 0) TDC measurement values, arm volume and BIA values obtained for 80 patients are summarized in Table 2. Comparisons between at-risk side (side of breast cancer diagnosis) and contralateral (control) side (referred to as the A/C ratio below), showed inter-side differences to be small with no statistically significant inter-side differences with respect to absolute arm volume, arm BIA, or TDC values. However, absolute TDC values differed significantly among the four TDC-measured sites. When TDC values obtained for the two sides were averaged to obtain site average values (mean ± SD) results for forearm, biceps, axilla, and thorax were 27.5 ± 3.8, 24.4 ± 3.8, 38.5 ± 7.9, and 29.9 ± 5.3, respectively. ANOVA indicates an overall highly significant difference among sites ( $p < 0.0001$ ) with each site TDC value significantly different from each other site ( $p < 0.001$ ). Contrastingly, TDC ratios, determined as at-risk to contralateral side (A/C) that ranged from 0.995 ± 0.085 for forearm to 1.029 ± 0.196 for axial, and dominant to non-dominant side (D/ND) that ranged from 0.994 ± 0.087 for forearm to 1.015 ± 0.150 for biceps, were not significantly different among sites nor were these ratios different from similarly determined arm volume and BIA ratios as summarized in Table 2. Further, comparison of the A/C ratios for

TABLE 3. COMPARISON OF (AT-RISK/CONTROL SIDE) RATIOS: DEPENDENCE ON DOMINANCE OF AT-RISK ARM

	Pre-surgery ratios: (At-Risk side/Control side)											
	TDC ratios						Whole arm					
	Forearm		Biceps		Axilla		Thorax		Volume		Bioimpedance	
RSK = D	RSK = ND	RSK = D	RSK = ND	RSK = D	RSK = ND	RSK = D	RSK = ND	RSK = D	RSK = ND	RSK = D	RSK = ND	
mean	0.985	1.005	1.020	1.007	1.064	0.994	0.995	1.003	0.994	0.992	1.002	1.007
SD	0.083	0.087	0.166	0.150	0.172	0.214	0.122	0.117	0.043	0.060	0.060	0.045
P value	0.316		0.722		0.107		0.736		0.793		0.624	

Table entries are pre-surgery ratios of at-risk (RSK) to control sides when the at-risk arm (RSK) is the patient's dominant (D) arm ( $N = 40$ ) compared to the at-risk to control sides when the at-risk arm is the patient's nondominant (ND) arm ( $N = 40$ ) for TDC values of forearm, biceps, axilla, and thorax. Whole arm ratios are for arm volumes and bioimpedance values.



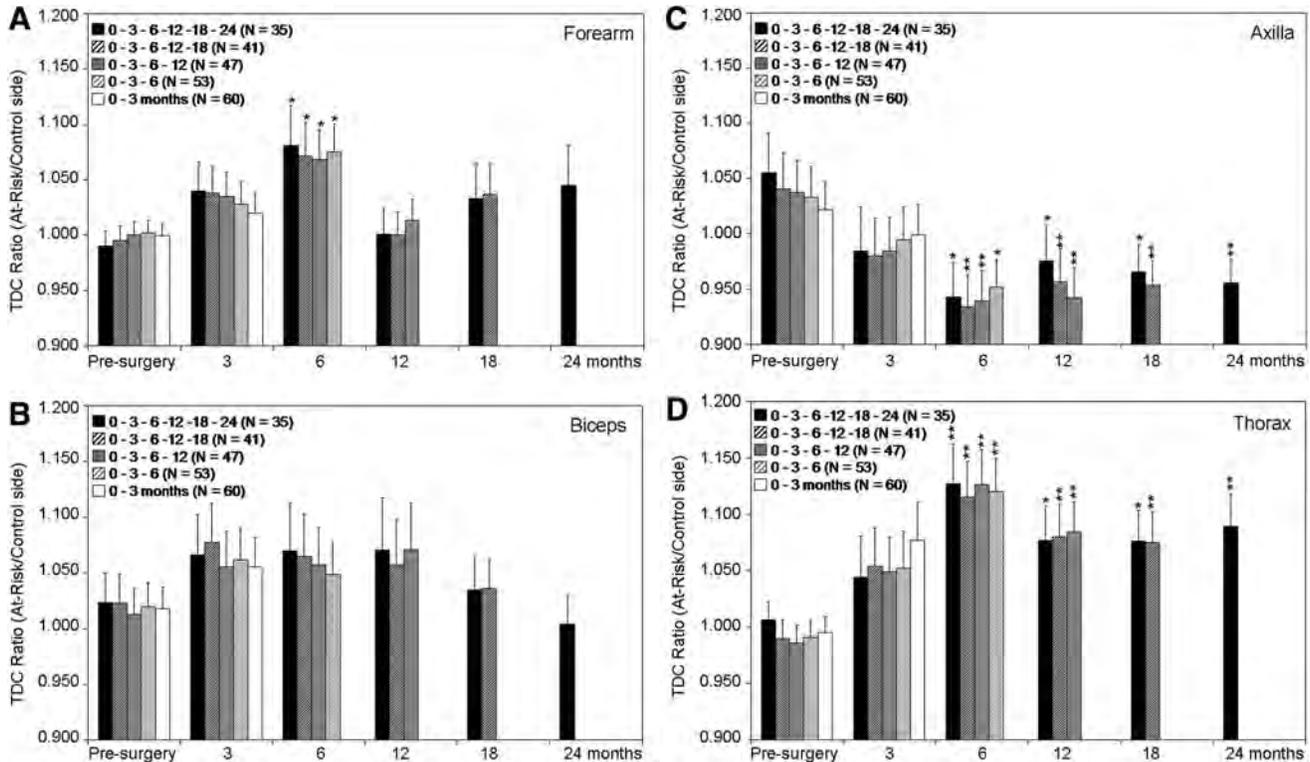
**FIG. 3.** Forearm TDC measurement depth-dependence: Presurgery Data points are pre-surgery mean TDC values for 80 patients with individual patient TDC values calculated as the average of both forearms. Error bars are  $\pm 1$  sem. Solid line is non-linear (power-law) regression with the equation  $TDC = 32.44 \delta^{-0.185}$  determined based on 80 TDC measurements at each depth. *Inset* shows at-risk/control arm ratio with associated SD.

the group of patients in whom the at-risk arm was their dominant arm ( $N=40$ ) vs. the group of patients in whom the at-risk arm was their nondominant arm ( $N=40$ ) showed no significant difference in the A/C ratio between these groups at any site as summarized in Table 3.

The pattern of forearm TDC values determined for different measurement depths is shown in Figure 3. A progressive increase in measurement depth from 0.5 mm to 5.0 mm was associated with a nonlinear decrease in TDC values that was closely fitted ( $R^2=0.997, p<0.001$ ) with a power regression with the equation  $TDC = 32.44 \delta^{-0.185}$  in which  $\delta$  is measurement depth. Considering at-risk and contralateral (control) arm values individually resulted in very similar relationships (not shown). A similar pattern of depth-dependence, in which TDC values decreased with increasing depth has previously been observed and was attributed to the inclusion of increasing amounts of low water content fat in the measurement volume with increasing depth.<sup>48</sup> Although absolute TDC values decreased with increasing depth the inter-arm TDC ratio (at-risk/control) did not differ among depths. Ratios ranged from  $0.997 \pm 0.083$  at the most shallow depth (0.5 mm) to  $1.008 \pm 0.087$  at the deepest depth (5.0 mm).

*Patterns of sequential changes in at-risk/control side ratios*

TDC ratios. The pattern of sequential changes in TDC ratios (at-risk/control) for each site is shown in Figure 4 for patients followed for the full 24 months and also for each of the other subsets. Considering first the 35 patients evaluated at each planned visit (solid black bars in Fig. 4) reveals a site-dependent sequential pattern in which forearm and thorax TDC ratios show an apparent peaking at 6 months post-surgery, whereas axilla TDC ratios show an apparent near



**FIG. 4.** Sequential patterns of TDC ratios. TDC ratios (at-risk/control) are shown for patients followed for the full 24 months and for each of the other subsets. Error bars are the standard error of the mean and the *single* and *double asterisk* signify mean ratios different than pre-surgery at  $<0.05$  or  $<0.01$  levels, respectively. Basic pattern over time indicates an apparent peak in the ratio at 6 months post-surgery at least at forearm (A) and lateral thorax (D) with a corresponding decrease at the axilla (C). The increase is sustained at thorax and the decrease is sustained at the axilla.

minimum occurring at 6 months. The increased thorax TDC ratio and decreased axilla TDC ratio starting at 6 months was sustained throughout 24 months, with 24 month values being significantly different than pre-surgery ratios ( $p < 0.01$ ). Contrastingly the increased forearm TDC ratio at 6 months was not significantly greater than pre-surgery beyond 6 months. Biceps TDC values were not significantly greater than pre-surgery values at any month. The sequential pattern of the 24 month patient subset was mimicked by the pattern of each subset. For example, in patient subsets evaluated up to and including post-surgery month 18 ( $N=41$ ) and month 12 ( $N=47$ ) the 6 month peaking and subsequent decline in forearm TDC ratios was as was the 6 month peaking and subsequent maintenance of the thorax TDC ratio. Further, the reduced axilla TDC ratio, first evident at 6 months was observed to be sustained.

**Arm volume and BIA ratios.** The sequential arm volume pattern (Fig. 5A) shows a peaking in at-risk to control arm ratios at 3 and 6 months post-surgery ( $p < 0.05$ ) but this increase was not sustained beyond 6 months. In contrast to patterns of change in TDC and arm volume ratios, no sig-

nificant change over time in arm bioimpedance ratios was observed (Fig. 5B).

*Patterns of absolute values*

Additional insight into post-surgery patterns is gained using absolute values of at-risk and control sides as shown in Table 4 for patients seen for all visits up to 24 months post-surgery. Results indicate no significant differences between sides for volume or bioimpedance at any month. Contrastingly, thorax at-risk TDC values become significantly greater than control sides at 6 months with increases sustained through 24 months. Also, at-risk side axilla TDC values showed a significant reduction at 6 months, with the decrease also noted at 24 months post-surgery. The intraclass correlation coefficient (ICC) for sequential measurements of the control side ranged from a maximum of 0.989 for arm volume measurements to a minimum of 0.814 for axilla TDC measurements.

*Changes in TDC with measurement depth*

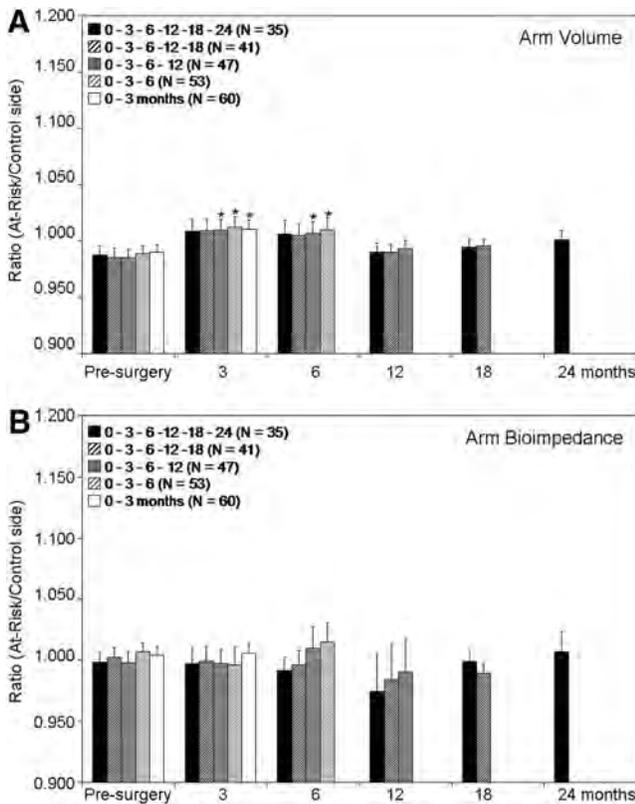
At all months, and for all patient subsets, forearm TDC values monotonically decreased with increasing measurement depth in a manner similar to that shown in Figure 3. An example of the smallness of the pattern change is illustrated in Figure 6 that shows the at-risk forearm TDC depth dependence pre-surgery and then again 24 months post-surgery. The nonlinear (power-law) regression for month 0 had the equation  $TDC = 32.4 \delta^{-0.177}$  and the regression for month 24 had the equation  $TDC = 32.7 \delta^{-0.175}$ . TDC values at each depth ( $\delta$ ) differed significantly ( $p < 0.001$ ) from each other but the relationship between TDC value and depth remained unchanged from pre-surgery through 24 months.

*Patients experiencing changes in side-to-side ratios*

The percentage of patients who experienced increases in at-risk to control side (A/C) ratios that were equal to or greater than 10%, 15%, and 20% of the pre-surgery ratio was determined and expressed as threshold ratios of 1.10, 1.15, and 1.20 in Figure 7 for patients seen through 24 months post-surgery. The general pattern of these changes shows that for any given threshold ratio the percentage of patients experiencing increases above that threshold was greater for TDC measurements than for whole arm BIA or arm volumes. This may suggest that the TDC measurement is more sensitive to tissue water changes. Further, among the TDC sites measured, the greatest percentage of patients exceeding 10, 15, and 20% of pre-surgery ratios occurred for TDC measurements made on the thorax. For the thorax the greatest percentage of patients exceeding the threshold occurred at 12 months post-surgery where 42.9% exceeded pre-surgery by at least 10%, 40.0% by at least 15% and 25.7% by at least 20%. At 24 months these percentages were slightly reduced to 31.4%, 28.6%, and 22.9%, respectively, but were greater than all other TDC sites. By comparison, 24 month percentages for forearm were 20%, 14.3%, and 8.5% for ratios of 1.1, 1.5, and 1.20, respectively.

*Patients experienced symptoms at 24 months post-surgery*

Six of the 35 patients (17%) evaluated at 24 months reported one or more symptoms at 24 months not previously



**FIG. 5.** Arm volume and bioimpedance sequential patterns. Arm volume and arm bioimpedance ratios (at-risk/control) are shown for patients followed for the full 24 months and for each of the other subsets. Error bars are the standard error of the mean and the asterisks signifies mean ratios different than pre-surgery at  $< 0.05$  significance levels. Basic pattern over time indicates an apparent peak in the at-risk arm volume at 3 and 6 months post-surgery that is not sustained beyond 6 months. Arm bioimpedance demonstrates no apparent change from pre-surgery.

TABLE 4. AT-RISK VS. CONTROL SIDE SEQUENTIAL VALUES THROUGH 24 MONTHS

TDC Values	Pre-surgery						Months post-surgery												Control side measurements		
	0		3		6		12		18		24		24		ICC	ICC 95% CI					
	RSK	CON	RSK	CON	RSK	CON	RSK	CON	RSK	CON	RSK	CON	RSK	CON	ICC	ICC 95% CI					
Forearm	27.6	28.1	28.6	27.6	29.8	27.9	29.2	29.2	28.5	27.8	27.8	26.8	27.8	26.8	0.900	0.835-0.946					
SD	4.1	4.7	5.4	4.1	5.6	4.9	5.9	4.7	5.7	4.3	4.3	4.7	6.4	4.7							
Biceps	23.8	23.6	24.9	23.7	26.3	24.8	25.9	24.7	23.6	23.2	23.2	23.4	23.3	23.4	0.855	0.760-0.921					
SD	3.8	4.4	4.9	4.4	6.8	4.9	6.2	5.2	5.0	4.9	4.9	4.4	4.8	4.4							
Axilla	38.3	37.6	35.4	37.0	35.4*	37.9	36.6	38.4	36.9	38.4	38.4	37.0	35.2*	37.0	0.814	0.692-0.898					
SD	8.5	10.3	10.0	9.4	8.7	7.8	7.7	8.1	7.8	7.0	7.0	7.6	8.0	7.6							
Thorax	29.3	29.3	33.3	32.2	33.9**	30.5	32.9*	30.9	34.3*	32.2	32.2	31.0	33.9**	31.0	0.824	0.710-0.904					
SD	5.5	5.5	7.7	5.1	6.4	4.7	7.1	5.8	6.2	5.7	6.8	6.8	7.2	6.8							
Arm BIOZ (Ohms)	300	299	300	299	281	278	281	274	298	297	297	298	295	298	0.865	0.773-0.928					
SD	41	45	47	49	66	67	64	78	47	46	55	55	60	55							
Arm Volume (ml)	2193	2212	2225	2199	2248	2222	2207	2232	2199	2214	2214	2184	2198	2184	0.989	0.981-0.994					
SD	637	584	742	678	741	631	658	661	586	593	593	588	676	588							

Table entries are mean and SD for at-risk (RSK) and control (CON) sides for 35 patients prior to surgery (0) and 3, 6, 12, 18, and 24 months post-surgery. BIOZ is the impedance value determined by BIA. Symbols \* and \*\* indicate RSK and CON sides significantly different at  $p < 0.05$  and  $p < 0.01$  levels, respectively. No significant differences between sides were found for volume or bioimpedance at any month. At 6 months thorax at-risk TDC values become significantly greater than CON sides with the increase sustained through 24 months. TDC values obtained from the axilla of the at-risk side showed a reduction as compared to control sides at 6 and 24 months post-surgery. ICC is the intraclass correlation coefficient for measurements on the control side for each variable and ICC 95% CI is the 95% confidence interval on CI.

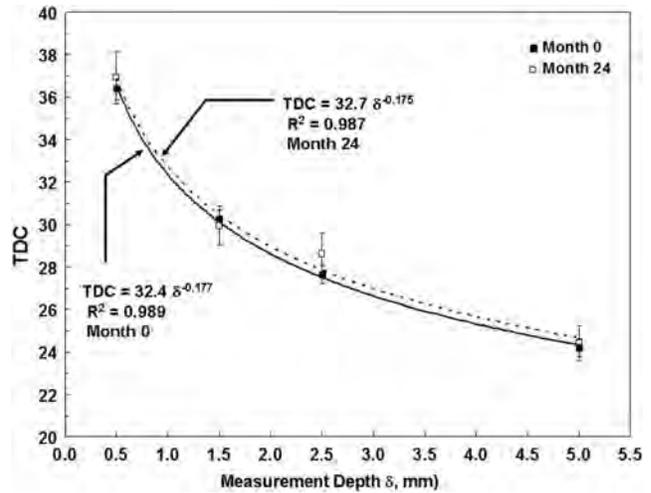


FIG. 6. Depth dependence of forearm TDC values: Pre-surgery through 24 months. Data points are mean TDC values of the at-risk forearm for 35 patients evaluated at pre-surgery (month 0) and also evaluated at 24 months post-surgery. Error bars are  $\pm 1$  sem. Solid line is the nonlinear (power-law) regression for month 0 with the equation  $TDC = 32.4 \delta^{-0.177}$  and dotted line is the regression for month 24 with the equation  $TDC = 32.7 \delta^{-0.175}$ . TDC values at each depth ( $\delta$ ) differed significantly ( $p < 0.001$ ) from each other but the relationship between TDC value and depth remained unchanged from pre-surgery through 24 months.

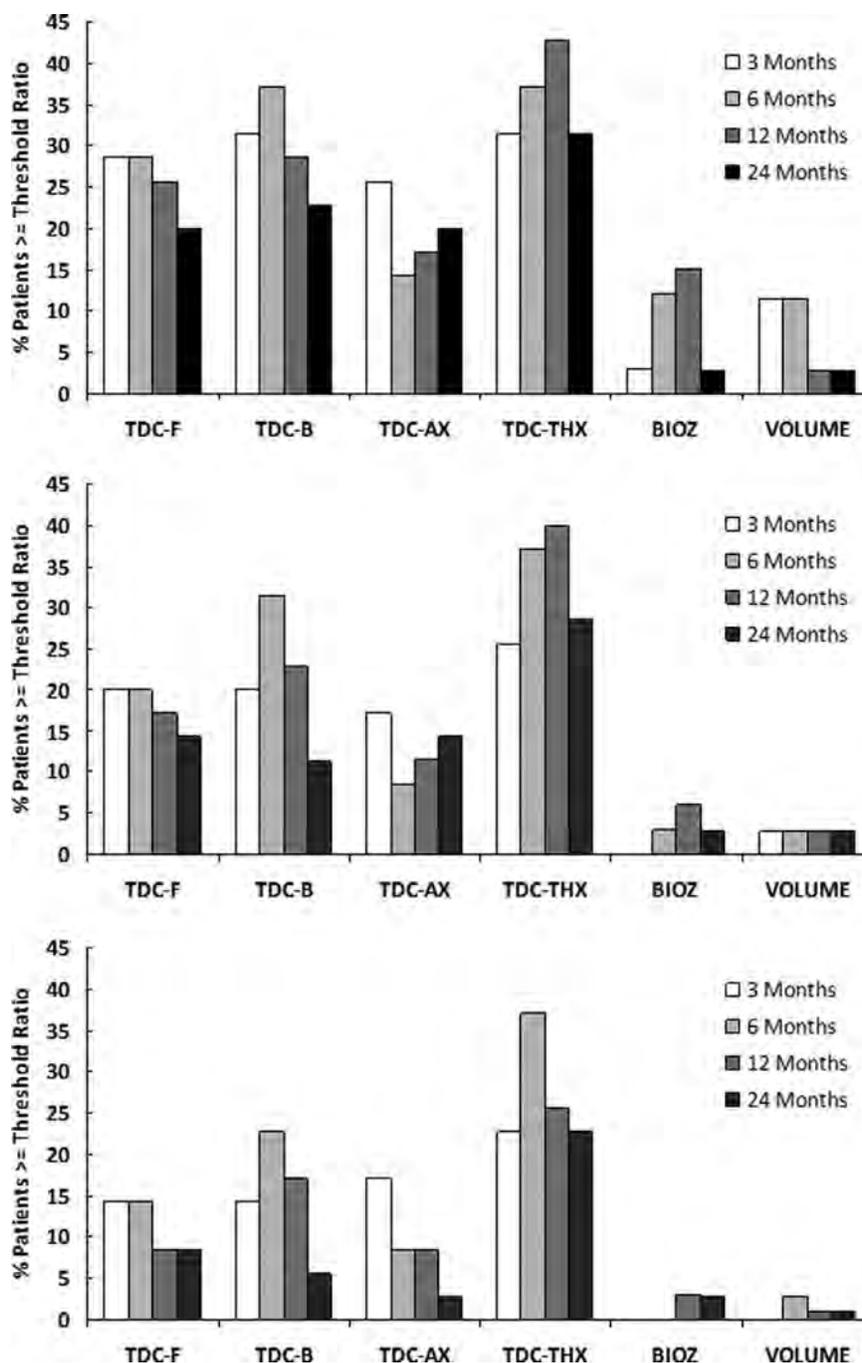
experienced that they described as follows: (1) tightness and fullness of the upper arm and lateral chest wall; (2) tightness and fullness of the hand; (3) fullness of the lateral chest wall and arm pain after mild exercise; (4) stiffness of the axilla and fullness of the lateral chest wall; (5) numbness of the axilla and lateral chest wall and (6) axilla stiffness. An examination of the measurement data of these six patients did not reveal a significant pattern of differences between them and the patients not reporting symptoms.

**Discussion**

The main aim of the present research was to characterize the pattern of TDC values and their changes to provide a foundation for the possible informed use of this measurement method to detect and quantify lymphedema that may develop in persons treated for breast cancer and in other conditions associated with progressive edema. Although several methods may be useful for this purpose, a seemingly major advantage of the TDC method is that it can be rapidly done, taking less than 10 seconds per measurement, and the method can be used on any body site of clinical interest with the possibility of measurements taken to varying depths from 0.5 mm to 5.0 mm below the epidermis.

*Pre-surgery*

Analysis of the pre-surgery data has shown that absolute TDC values vary among anatomical sites and TDC values decrease with increasing depth at all sites. The depth decrease is likely in part attributable to the greater percentage of low water content fat at deeper layers, whereas site variability is likely due to normal anatomical variations in skin structural,



**FIG. 7.** Percentage of patients experiencing increases in at-risk to control side ratios. *Bar heights* show percentage of patients evaluated through 24 months who, at the evaluation month indicated, had at-risk to control side ratios greater than their pre-surgery ratios by at least the threshold amounts of 10%, (1.10), 15% (1.15), and 20% (1.20). F, B, AX, THX denote forearm, biceps, axilla, and thorax, and BIOZ refers to BIA determined values.

physical, and water binding properties. However, when inter-arm TDC ratios were calculated, it was found that these ratios did not differ with respect to the measured sites or between depths at a given site. This was true when ratios were expressed as (at-risk side/contralateral side) or (dominant side/nondominant side). From the point of view of possible clinical assessment, this suggests a rather robust index provided that one is dealing with potential unilateral edema or lymphedema. A further finding suggesting the robustness of such

TDC ratios is the fact that the TDC ratio (at-risk/contralateral) was insignificantly different whether the patient’s dominant side was the at-risk side or if it were the patient’s nondominant side. This would suggest that there would be little need for adjustment factors that were dependent on hand dominance. Based on standard deviations (SD) of pre-surgery TDC measurements, one can put forward theoretical estimates of thresholds that might be useful in detecting the early occurrence of lymphedema in a manner similar to that done

with whole arm bioimpedance. However, in the case of forearm TDC ratios, it is necessary to specify a measurement depth since SD vary somewhat among measurement depths. For any measurement depth the theoretical threshold would be determined as the mean pre-surgery value + 3 SD. In the present case for the 2.5 mm depth the forearm, biceps, and thorax thresholds would be approximately 1.25, 1.50, and 1.35. Other thresholds for different depths or sites could similarly be determined but any theoretical TDC threshold ratio needs to be prospectively tested in future.

#### *Temporal changes*

The temporal pattern of absolute TDC values from pre-surgery through 24 months showed that average inter-side values were not significantly different from each other at any measured depth or at any month except for the observed increase in the at-risk side lateral thorax and the decrease in the at-risk side axilla. The decrease in axilla TDC, initially observed 6 months after surgery, was sustained through 24 months. This reduction might be due to fibrosis that developed in association with the original surgery. Based on the observed decrease in TDC and its likely cause, it is concluded that this site is not optimal from the point of view of detecting developing lymphedema. Contrastingly, at-risk side thorax TDC values increased at 6 months post-surgery and on average were significantly greater than the contralateral side at all subsequent months. This finding suggests that from the point of view of early detection of tissue water changes, the lateral thorax may be a useful site. A similar but somewhat different temporal sequential pattern was seen when the TDC ratio of (at-risk/contralateral side) was used as the assessment parameter. Except for the axilla, the other TDC measured sites (forearm, biceps, and thorax) each tended to increase above pre-surgery values at 3 months but only became statistically significant at 6 months for thorax and forearm. For all subgroups, this overall significance was sustained only for the thorax ratio through 24 months. The at-risk to contralateral side arm volume ratio was also observed to increase at 3 and 6 months but no increase in BIA ratios was observed for any subset.

It is not clear if the absence of a sustained increase in volume ratios and forearm TDC ratios beyond 6 months is in part attributable to the declining numbers included in the other patient subsets. Thus among evaluated measures (TDC, BIA, and volume) in patients seen at 24 months there was a significant difference in inter-arm ratios as compared to pre-surgery only in TDC values at axilla and thorax.

#### *Previous findings comparisons*

Prior work has importantly addressed the question of how to best quantify lymphedema as a way to increase our ability to detect, track, and characterize its incidence. It is thus of relevance to compare some of these prior findings in relationship to the current results. Of specific interest is what might be termed the quest for the parameter value best characterizing a lymphedema threshold. In the present study we attempted to characterize the natural progression of changes over time by comparing the percentage of patients who showed an increase to and above a threshold level in comparison to their pre-surgery parameter values. TDC, BIA, and arm volumes were included in the analysis and thresholds

of 10%, 15%, and 20% were examined as these represented clinically relevant changes. These analyses revealed that at least 20% of patients exceeded the 10% increase threshold for TDC ratios at forearm, biceps and thorax for all post-surgery months. The overall change pattern showed that at 24 months post-surgery, at least 20% of patients demonstrated an inter-arm TDC ratio at forearm and biceps that exceeded the 10% threshold whereas less than 5% of patients demonstrated BIA and volume ratios that exceeded this threshold. Corresponding thorax TDC ratios at 24 months were exceeded by greater than 30% of patients. Thus, despite the fact that the overall group difference in inter-side ratios was statistically significant only for TDC measurements at axilla and thorax, there is a larger fraction of patients that demonstrate increases in inter-arm TDC ratios than with either arm volumes or BIA values and even a greater percentage that exceed the TDC inter-side thorax ratio.

Prior work using arm measurements showed that 10% differences in inter-arm volume led to the lowest estimate of the lymphedema incidence rate and 2 cm girth differences led to the highest estimated 24 month incidence rate (85%).<sup>12</sup> For the 10% volume change criteria estimates of lymphedema occurrence rates were reported as 7% at 6 months,<sup>49</sup> 22% at 12 months,<sup>12</sup> 18.8% at 18 months,<sup>50</sup> 34% at 24 months,<sup>12</sup> and 13% at 60 months.<sup>49</sup> Data from the present study indicate that at 6 months ( $N=53$ ) the percentage of patients with arm volume ratio increases at or above 10% was 15.1% and 8.5% at 12 months ( $N=47$ ). Differences in surgical procedure likely impact the various predicted BCRL rates as suggested by the 12 month incidence rates reported as 13%<sup>51</sup> or 19%<sup>13</sup> for patients experiencing axillary lymph node dissection (ALND) as compared to 5%<sup>51</sup> and 3%<sup>13</sup> for patients experiencing sentinel lymph node biopsy (SLNB).<sup>13</sup> Other metric difference criteria have also been used to distinguish mild, moderate, and severe lymphedema.<sup>52</sup> Some workers have even used a 3% volume change to define subclinical lymphedema.<sup>53</sup> This criterion led to a predicted 21.9% lymphedema incidence with an average onset 6.9 months after a pre-surgery assessment.<sup>53</sup> If this criterion were applied to the present data for patients seen through 24 months, then 37.1% of patients would have exceeded that low threshold at 6 months. Others have used criterion based on volume increases greater than or equal to 5%<sup>54, 55</sup> which if applied to other literature data<sup>54</sup> would lead to a 36-month lymphedema incidence prediction of 11.2%. If applied to the present data set, this criterion would result in a 24-month incidence of 24.5%

Using the BIA method it was reported that of 102 patients tracked for up to 24 months post surgery, 22 exceeded the BIA threshold and of these, 20 of these were subsequently clinically confirmed to have lymphedema at times ranging from immediately to 10 months after the elevated impedance measurement. In that study the lymphedema clinical assessment criteria were not stated. The original 3SD criteria value of 0.102<sup>18</sup> was subsequently reported as 0.120 in a group of 172 healthy women.<sup>19</sup> Based on the original 3SD threshold criterion, point prevalence of BCRL at 12, 18, and 72 months was reported as 8%<sup>21</sup>, 14.9%<sup>21</sup> and 6.5%<sup>20</sup>. Pre-surgical BIA assessments, using an inter-arm ratio of 1.134 as a threshold when the at-risk arm was the dominant arm and 1.106 when it was the nondominant arm indicated that pre-surgical threshold ratios were exceeded in less than 1% of cases.<sup>23</sup>

In the present study, half of the patients evaluated pre-surgery had their at-risk arm the dominant arm ( $N=40$ ) and half had their at-risk arm the nondominant arm. Applying the above dominant arm dependent criterion to the present patients indicates that 2/80 (2.5%) of them exceed the threshold, both being patients in whom their at-risk arm was their dominant arm. Other BIA ratios of 1.139 and 1.066 have been used as dominant and nondominant arm thresholds to study patients from 3 to 15 month post-surgery with the suggestion that swelling was often transient during the first year.<sup>22</sup> In the present study, for patients seen through 12 months ( $N=47$ ) there were 20 patients in whom their at-risk arm was their dominant arm and 27 in whom their at-risk arm was their nondominant arm. The percentage of these patients exceeding the BIA thresholds did slightly vary ranging from 12.8% at 3 months to 17.0% at 6 months and 14.9% at 12 months.

#### Study limitations

Perhaps the main study limitation was the loss of patients to follow-up that resulted in only 35 of the same patients being evaluated at each planned post-surgery visit through 24 months. However, this limitation was partially off-set by examining details and temporal patterns of larger subsets who made it through to 6, 12, and 18 months with the observation that most parameter value patterns were similar. None-the-less judgments as to the 2-year post surgical findings herein reported should be judged in context.

#### Conclusions

(1) Absolute TDC values can be rapidly and reliably measured at most anatomical sites; values reflect water content in the measurement volume. Since TDC values vary by site and depth, the use of absolute values as threshold parameters should take both of these aspects into account.

(2) Side-to-side TDC ratios are relatively independent of site and depth and are the preferred TDC parameter if used to try to detect tissue water changes over time in unilateral conditions. Pre-surgery TDC values herein provided may be useful to establish theoretical thresholds for prospective evaluation.

(3) Among anatomical sites evaluated, the lateral thorax, followed by anterior forearm, appears to be useful for TDC measurements but measurements at the axilla appear to be least useful.

(4) Measured pre-surgery TDC inter-side values and at-risk/contralateral side ratios show no significant inter-side differences, thereby suggesting that the presence of the breast cancer itself did not alter the tissue water status in the present population.

(5) Sequential changes in TDC ratios show a greater number of patients being detected with inter-arm ratio increases exceeding 10% than detected using BIA ratios. This may indicate a greater sensitivity to localized tissue water changes with the TDC method.

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#### Author Disclosure Statement

All authors declare that no competing financial interests exist.

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