Assessing Tissue Dielectric Constant Values in Tumor Bearing and Healthy Breasts

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ABSTRACT

Background: This study's aims were to investigate, characterize, and provide quantitative reference data on tissue dielectric constant (TDC) values of female breasts when measurements were made to 5 mm depths and determine the utility of these measurements to differentiate between benign and malignant breast tumors.

Methods and Results: Breast TDC was measured bilaterally in 82 women just prior to an ultrasound-guided diagnostic biopsy of one tumor in one breast. TDC was measured in triplicate over the tumor and the contralateral healthy breast. Considering all paired breasts, the average TDC (mean ± SD) for healthy breasts was less than for tumor-bearing breasts (26.7 ± 4.5 vs. 29.9 ± 8.5, p = 0.0003).

Conclusions: Breast TDC values measured to 5 mm in 82 healthy non-edematous breasts provide a two-SD threshold reference value of 35.7. This represents a TDC value above which the presence of breast edema/lymphedema may be indicated based on the two-SD threshold criterion. For unilateral cases, an inter-breast TDC ratio exceeding 1.275 may be considered a breast edema/lymphedema indicator also based on the two SD criterion used. These thresholds may have utility for early detection and to track breast edema/lymphedema changes. A comparison of these TDC values obtained from benign vs. malignant tumors indicates no statistically significant difference between them. However, inter-breast TDC ratios were statistically higher for breasts with malignant vs. benign tumors. However, the large overlap of the ratio values renders this method of discrimination between benign vs. malignant tumors inadequate based on the present findings.

CONDENSED ABSTRACT

We aimed to provide quantitative references of breast tissue dielectric constant (TDC) values to 5 mm depths and determine their utility to differentiate benign vs. malignant breast tumors. Breast TDC was measured bilaterally in 82 women just prior to their biopsy. A two-SD threshold reference of 35.7 was determined which represents a value above which breast edema/lymphedema may be indicated. For unilateral cases, inter-breast TDC ratios exceeding 1.275 may indicate breast edema/lymphedema. Inter-breast TDC ratios were statistically higher for breasts with malignant vs. benign tumors. However, the large overlap of ratio values renders this method of discrimination inadequate.

INTRODUCTION

Breast edema has been reported to be a useful marker of aggressive late-stage breast cancer[1], useful for the prognosis of patients with breast cancer after neoadjuvant chemotherapy[2], and useful for helping to guide breast cancer treatment in patients with aggressive forms[3]. The enigma and far-reaching aspects of breast edema have recently been reviewed[4] and cancer-related breast edema has been reported to occur with an incidence that ranges widely from about 10%[5] to 90%[6]. Furthermore, in patients who have had a lumpectomy and radiation, there may be mammographic evidence of breast edema and skin thickening following treatment which may take as long as three years to normalize [7]. Clinical assessments[8] or with Ultrasound[9] indicate that for patients treated for breast cancer, the occurrence of breast edema is impacted by the extent of axillary surgery and radiotherapy. This is highlighted by the findings on 836 women who were treated with breast-conserving surgery and subsequent radiotherapy[10]. In that study, 24.8% of the women reported breast edema at some time during a 28-month follow-up.

However, the methods used to assess breast edema and its extent are quite variable. They include evaluating patient perceptions using surveys[10], symptoms[11], clinical perceptions[12], ultrasound for breast skin thickness measurements[13], elastography to measure tissue property changes[14], use of various formulas to calculate breast volume changes[15-17], and MRI imaging approaches [1-3]. Other approaches used tissue dielectric constant (TDC) measurements the values of which are sensitive to local breast tissue water thereby useful to assess breast edema after breast-conserving surgery and radiotherapy[18-20]. More recently TDC measurements were made on the breasts of 61 women who were about to undergo diagnostic biopsies[21]. Measurements made to an effective depth of 2.5 mm on the non-affected breast yielded a reference TDC range of 29.5 ± 4.6 (mean ±SD). Such measurements can provide a useful quantitative index of tissue water locally for assessing breast

edema. However, since these prior breast measurements were made to a fixed, somewhat shallow depth of 2.5 mm it was unclear what effect the specific breast anatomy and content at deeper depths might have on TDC values. Thus, one aim of the present study was to investigate, characterize and provide quantitative reference data on TDC values of the female breast when measurements were made to an effective depth of 5 mm. A secondary aim was to determine the utility of these TDC measurements to differentiate between breast tumors that are benign from those that are malignant.

METHODS

Subjects

Participants were 82 women who had a mass (tumor) in one breast and who were scheduled to have a diagnostic biopsy. Overall ages and body mass index (BMI) expressed as mean ± SD and (ranges) were, 60.7 ± 12.1 (31–86 years) and 29.4 ± 7.1 (19.3 – 50.1 Kg/m^2). Participant entry requirements were: (1) being 18 years of age or older, (2) having a breast mass that had been identified as abnormal by mammographic, ultrasound, and/or MRI imaging modalities, and (3) were scheduled to undergo a diagnostic surgical biopsy. Exclusionary conditions were: (1) non-intact skin at the planned breast measurement sites, (2) a history of prior breast cancer or breast surgery or radiation therapy, (3) a history of breast implants or having undergone breast augmentation or reconstructive surgery, (4) having a pacemaker or any implantable devices or wires, (5) currently pregnant. This study was approved by the Nova Southeastern University Institutional Review Board (IRB-2021-307). Women were evaluated after they read and signed the IRB approved consent.

Measurement Sites

Measurements were made on the breast that had the tumor at the site of the tumor and also on the contralateral breast at a corresponding anatomical site. The breast to be biopsied is referred to as the tumor-breast and the non-affected

contralateral breast is referred to as the healthy-breast. During measurements, the patient was in a supine position with the head of the bed adjusted to a thirty-degree angle. For the measurement, the patient's arms were positioned at her side.

Measurements

TDC was measured in triplicate at each site using a hand-held 50 mm diameter cylindrical probe that was connected through a coaxial cable to a control box (MoistureMeterD, Delfin Kuopio, Finland). This probe is designated by the manufacturer as L50. Each TDC measurement took about seven seconds and was triggered when the probe contacted the skin. Measurements were started after the patient had been supine for at least 5-minutes. The TDC device displayed the measured TDC value obtained at a frequency of 300 MHz. For reference, water's dielectric constant is about 76 at 32^{o}C. Calibrations are done by measuring the dielectric constant of various concentrations of ethanol-water solutions and comparing against known dielectric values.

The physics of this method is well described in the literature [22-27]. Briefly, the TDC probe in contact with skin acts as a coaxial transmission line through which a signal is transmitted to the tissue. Some of the signal is absorbed and some is reflected back to be processed by the control unit. Reflected energy depends on the tissue's complex permittivity which depends on signal frequency and on the dielectric constant (real part of the complex permittivity) and tissue conductivity. At 300 MHz the contribution of the conductivity to permittivity is small and the dielectric constant is determined by water molecules (free and bound) and other aspects of the tissue. The 50-mm diameter probe has an effective penetration depth of 5 mm and has been used in multiple studies[28-31]. Skin temperature was measured at the sites of the TDC measurements after the TDC measurements were completed using a skin thermometer (Exergen precision IR thermometer, model DX501.Watertown MA, USA).

Analysis

Triplicate TDC measurements were averaged to get one TDC value for each breast's measured site. Values were tested for normality with the Shapiro-Wilke statistic. The coefficient of variation (CV) of the three measurements per site was determined for each patient and an overall measurement CV determined for all patients and separately for healthy-breasts and tumor-breasts. Comparisons of TDC values between breasts was based on the non-parametric Wilcoxon signed-rank test and comparisons between TDC value for benign vs. malignant tumors was based on the non-parametric Mann-Whitney test. In these tests a statistically significant difference was accepted at a p-value < 0.05. Comparisons between tumor site locations within the breast were done using chi square analyses. Results are presented as mean ± standard deviation (SD) unless otherwise noted.

RESULTS

Patient and Tumor Data

A total of 82 patients were evaluated. Benign tumors were present in 48 patients (58.5%) and malignant tumors in 34 (41.5%). Patients with malignant tumors were older (64.9 ± 9.0 years) than those with benign tumors (57.7 ± 13.2 years, $p < 0.01$ although benign and malignant tumor volumes were not significantly different from each other (4.62 ± 21.0 mm^3 vs. 4.41 ± 10.7 mm^3). For benign tumors 47.9% were located in the left breast whereas for malignant tumors 64.7% were located so. However, this difference was not statistically significant based on a chi square analysis ($p = 0.132$). Tumor locations within breast quadrants are shown in **figure 1**. Differences in locations of benign and malignant tumors between upper and lower breast quadrants were not significant ($p = 0.427$). Overall, for combined benign and malignant tumors, 53.7% were upper, 29.3% were lower, 11.0% were midline and 6.1% were centrally located. For the malignant tumors, 76.5% were invasive ductal carcinoma and 23.5% were ductal carcinoma in situ.

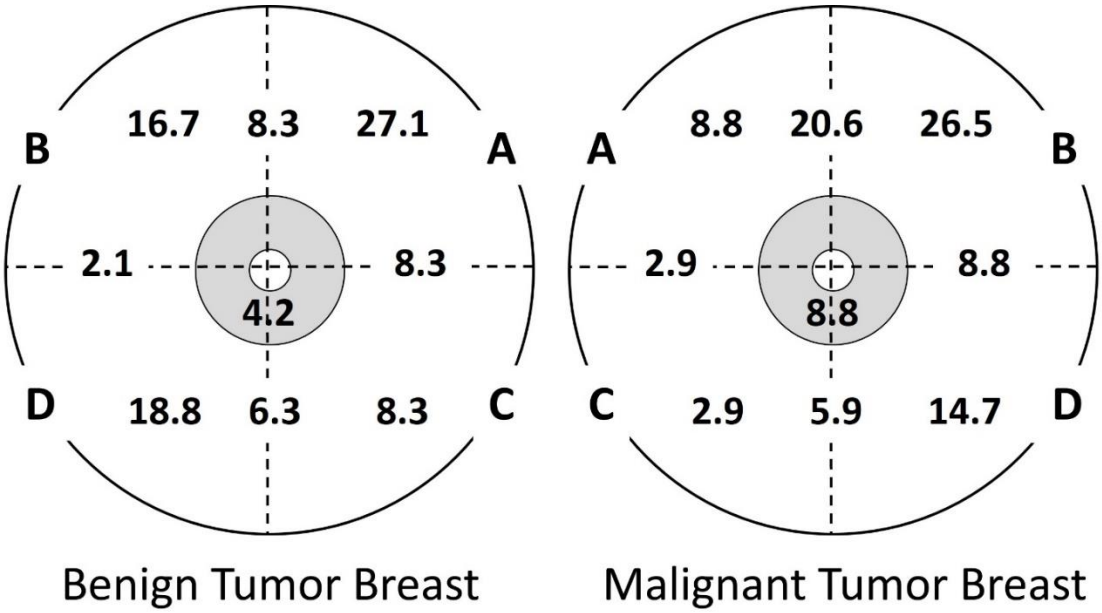

Figure 1. Tumor locations within breast quadrants.

Breasts are shown divided into four quadrants A, B, C, and D corresponding to upper-inner, upper-outer, lower-inner, and lower-outer respectively. Quadrants A and B represent upper and quadrants C and D represent lower regions of the breast. Numbers indicate the percentage of total tumors for each type that are located within each quadrant. Tumors close to or on the midlines (dashed line) are indicated as shown. Centrally located tumors are shown in the center grey area. The tumor locations and their mirror images on the healthy breast are the sites at which TDC measurements were made.

Breast Skin Temperatures

Skin temperatures of the tumor-breast did not differ from the healthy breast (34.2 ± 2.3 ºC vs. 34.2 ± 1.7 ºC, p = 0.979). However, comparing those breasts carrying malignant tumors vs. those carrying benign tumors shows a slight elevation of the cancer bearing breast temperature (35.1 ± 2.2 ºC vs. 34.3 ± 1.8 ºC, p = 0.049). Thus, there was a slightly higher skin temperature (0.8 ºC) of breasts that had malignant tumors compared to those that had benign tumors.

Breast TDC Values

The Shapiro-Wilk test showed significant departures from normality ($p<0.001$) for both healthy-breast and tumor-breast TDC values with distributions as shown in **figure 2**. Comparisons of TDC values between healthy-breasts and tumor bearing breasts (N =82), based on the non-parametric Wilcoxon signed ranks test (WSR), show that the tumor-breast values are significantly greater (29.9 ± 8.5 vs. 26.7 ± 4.5, $p = 0.0003$). Considering only patients whose tumors were diagnosed as malignant (N=34), the TDC values of the tumor-bearing breast were significantly greater than the contralateral healthy breast (31.9 ± 10.8 vs. 25.9 ± 4.9, $p = 0.00009$) via the WSR test. Contrastingly, for patients whose tumor was diagnosed as benign, TDC values of the tumor-bearing breast did not significantly differ from the healthy-breast (28.5 ± 6.2 vs. 27.3 ± 4.2, $p = 0.335$ via the WSR test.

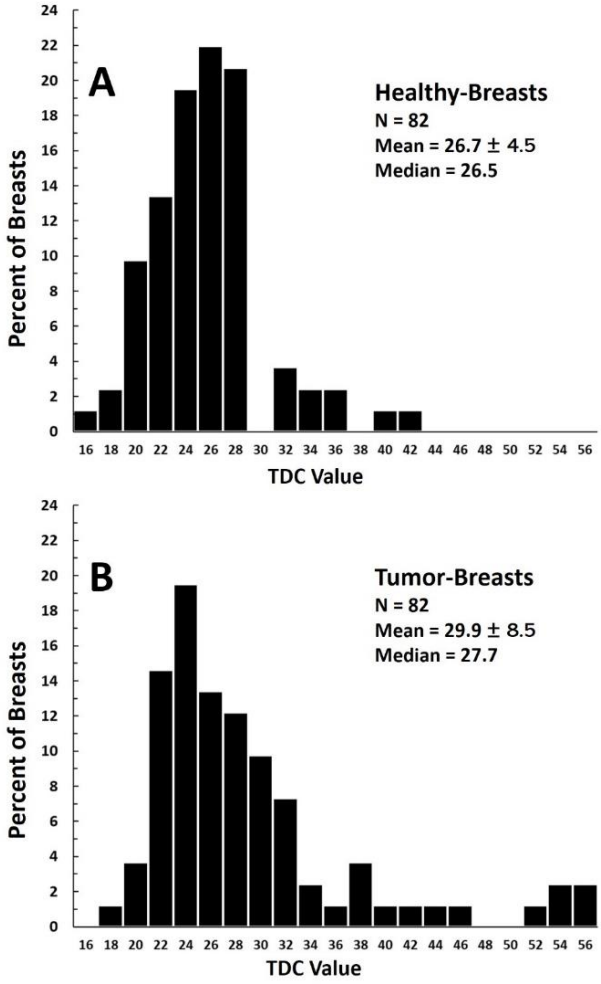

Figure 2. Distributions of TDC values for healthy and tumor-bearing breasts *Healthy-Breasts (A) are those without a tumor and Tumor-Breasts (B) are those that are tumor-bearing whether benign or malignant. Neither distribution is Gaussian based on the Shapiro-Wilks test ($p < 0.001$). The Bin width for the TDC value is 2 TDC units with the number indicating the start of the bin.*

However, comparisons between TDC values of tumors diagnosed as malignant (N = 34) vs. those diagnosed as benign (N=48), the distribution of which is shown in **figure 3**, were not statistically different (p = 0.296 via Mann-Whitney test). Although absolute TDC values were not significantly different, calculations of the inter-breast TDC ratio (tumor-bearing/healthy) for patients with malignant tumors was significantly greater than for those with benign tumors (1.234 ± 0.348 vs. 1.052 ± 0.223, p = 0.002) via Mann-Whitney test and the corresponding inverse ratio (healthy/tumor-bearing) was significantly less for breasts with malignant tumors (0.859 ± 0.184 vs. 0.977 ± 0.136, p = 0.002).

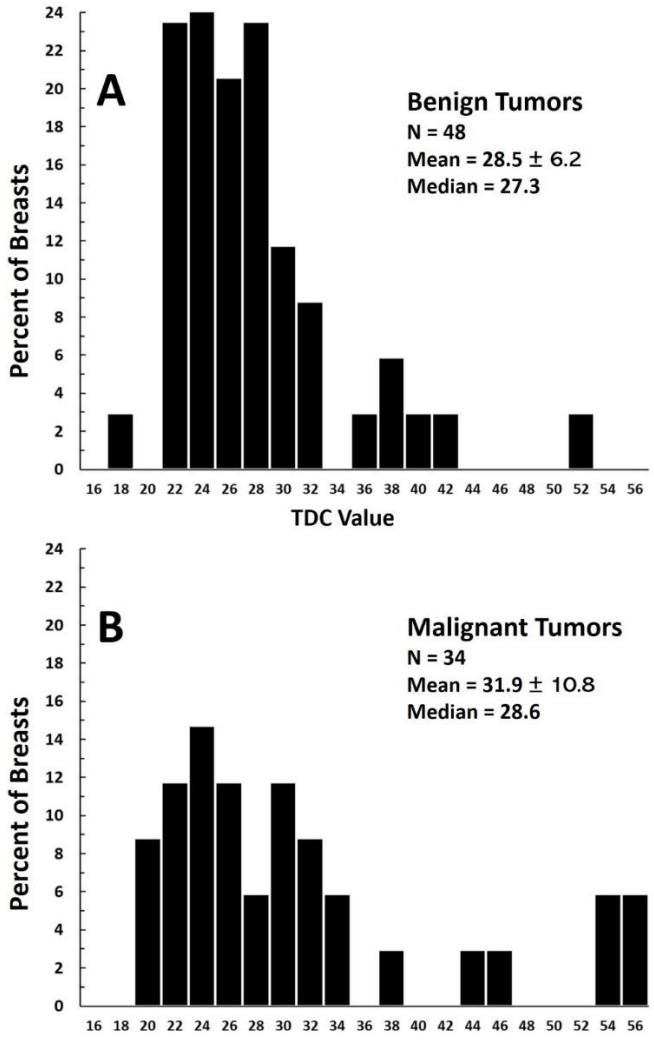

Figure 3. Distributions of TDC values for Benign vs. Malignant tumors

Benign tumors in (A) and malignant tumors in (B). Neither distribution is Gaussian based on the Shapiro-Wilks test (p <0.001). The Bin width for the TDC value is 2 TDC units with the number indicating the start of the bin.

TDC Coefficients of Variation

The average coefficient of variation (CV) of triplicate TDC measurements on healthy-breasts was 2.2 ± 1.5% and on tumor-carrying breasts was 2.8 ± 1.8%. For patients who had benign tumors (N = 48) the CV on healthy breasts was 2.2 ± 1.5% and 2.5 ± 1.5% on tumor carrying breasts. For patients who had malignant tumors (N =34), the CV was 2.2 ± 1.9% on healthy breasts and 3.0 ± 2.1% on tumor carrying breasts. The overall CV considering all breast TDC measurements (N = 164) was 2.5 ± 1.7%. These values were similar to but less than those previously reported for breast measurements using a probe with an effective measurement depth of 2.5 mm[21].

DISCUSSION

One aim of the present study was to provide reference data on TDC values of the female breast when measurements were made to an effective depth of five mm. This task was undertaken to compare prior TDC values obtained when breasts were measured to half that depth[21]. Herein it was hypothesized that because the deeper measurement uses a larger surface area probe it might have a more representative sample of the breast's TDC value while providing a greater short-term repeatability. The overriding purpose of such TDC measurements is to provide a method for a rapid and easily applied method to quantitatively assess breast edema and its change. A secondary aim was to determine the utility of TDC measurements to differentiate between breast tumors that are benign from those that are malignant.

TDC as an indicator in healthy breasts

The findings indicate that the present deeper measurements on 82 healthy non-tumor bearing breasts using a 5 mm measurement depth compared to a 2.5 mm depth yields a lower TDC value (26.7 ± 4.5 vs. 29.5 ± 4.6, p = 0.0003, and a lower coefficient of variation (2.2 ± 1.5 % vs. 3.0 ± 2.2%, p = 0.016). The lower TDC value obtained for deeper measurements is likely due to the inclusion of a greater percentage of fat within the measurement volume and the fat's lower dielectric

constant compared to skin[22, 24]. Based on the 82 TDC values of healthy breasts, a two SD increase from the mean is calculated to be 35.7. This value represents a TDC value above which the presence of breast edema is indicated if the two SD threshold criterion is used. Such absolute values may also be of use when it is unknown if there were changes in both breasts. The corresponding TDC threshold if measured to a depth of 2.5 mm would be calculated to be 38.7.

In cases of possible unilateral breast edema, then inter-breast TDC ratios may be considered. For the 48 benign tumors herein measured, an inter-breast TDC ratio (benign tumor breast/healthy breast) of 1.052 ± 0.223 is calculated. This then leads to a two SD threshold ratio of 1.275. This threshold ratio is similar to that previously reported (1.28) when standard sites on both tumor-bearing and healthy breasts were measured to a depth of 2.5 mm[21]. An alternative TDC ratio to consider is the inverse ratio (healthy breast/benign tumor breast) that is calculated to be 0.977 ± 0.136 and leads to a two SD threshold of 1.25.

Location and Tumor Property Considerations

Breast skin thickening and edema as a consequence of cancer cell blockage of breast lymphatic vessels was described as early as 1909 in which skin thickening was used as an indication of edema[32]. Following along those lines, skin thickness was measured in a mammographic study of 205 women with breast cancer[33]. In this study, differences in breast skin thickness greater than 0.25 mm between the tumor-carrying breast and the healthy contralateral breast was taken as a measure of breast skin edema. Breast edema was reported present in 70% of cases with its presence in inner (78%) and lower (86%) quadrants independent of the tumor location[33]. The composite data suggested that the skin thickening was directly related to the diameter of the tumor and overall, the lower-inner quadrant was the most frequent location for observing the skin thickening.

Considering the current data as to tumor location, 23 (28%) were located in the bottom half of the breast, 46 (56%) in the upper half and 13 (16%) in the middle. For tumor bearing breasts, the TDC values for lower and upper parts were not significantly different from each other (31.6 ± 9.3 vs. 28.9 ± 8.8, p=0.262). Absence of a significant difference was also true of prior measurements in lower vs. upper parts of tumor bearing breasts to a depth of 2.5 mm calculated from the prior study data[21], as (34.1 ± 7.2 vs. 30.8 ± 6.8, p = 0.139). However, for healthy breasts measured in the present study the lower part of the breast had slightly greater TDC value than the upper (28.4 ± 5.7 vs. 25.7 ± 3.3, p = 0.045). This was also true for prior measurements made to a depth of 2.5 mm (32.4 ± 6.2 vs. 27.9 ± 6.0, p = 0.018). Thus, for both measurement depths the lower part of healthy breasts had a statistically greater TDC value. Further, TDC values measured at the 5 mm depth were greater at both upper and lower parts compared to values measured to a 2.5 mm depth (p = 0.046).

This variation in TDC values between upper and lower breast regions may be considered when assessing appropriate edematous threshold values. Using the two SD approach, TDC thresholds for measurements to a 5 mm depth in lower (quadrants C and D) and upper parts (quadrants A and B) would be 39.8 and 32.3 respectively.

The corresponding inter-breast TDC ratios (benign tumor breast / healthy breast) for TDC 5 mm depth measurements in upper and lower breast regions are 1.003 ± 0.105 vs. 1.107 ± 0.364, p = 0.754). These ratios lead to thresholds of 1.213 and 1.835 for the upper and lower breast regions respectively. Similar calculations based on the prior 2.5 mm study data show inter-breast ratios of 1.016 ± 0.077 vs. 1.052 ± 0.061, p = 0.379.

TDC as a differentiator of benign vs. malignant breast tumors

The present findings indicate that although there is a significant difference between TDC values obtained on breasts that have vs. don't have a tumor (29.9 ± 8.5 vs. 26.7 ± 4.5, p = 0.0002), there was no significant difference between TDC values measured on breasts with a malignant (N = 34) vs. a benign (48) tumors (31.9 ± 10.8

vs. 28.5 ± 6.2, p = 0.296 by M-W test. Considering inter-breast ratios instead of absolute TDC values as potential discriminators indicates the inter-breast TDC ratio (tumor breast/healthy breast) for malignant tumors is greater than for benign tumors (1.233 ± 0.348 vs. 1.052 ± 0.233, p = 0.002). However, the practical discriminatory power is quite limited due to the substantial overlap as shown in **figure 4**. It may be seen that only six patients (17.6%) who had malignant tumors would have inter-breast TDC ratios that would permit potential discrimination from benign tumors.

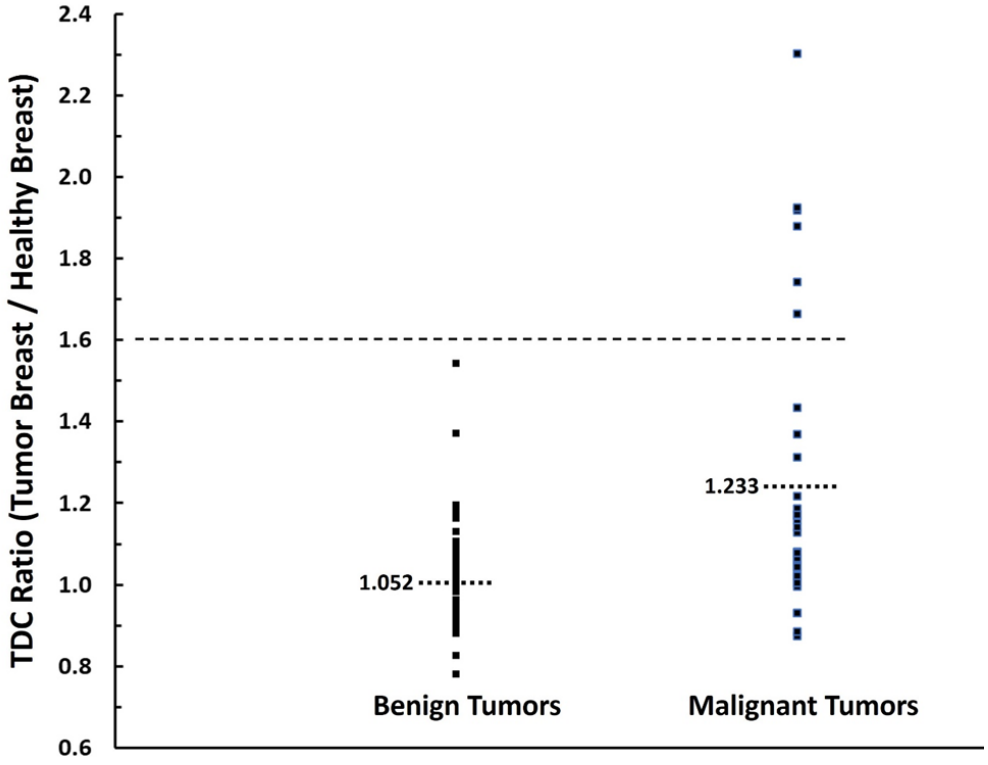

Figure 4. Inter-Breast TDC ratios

TDC values were measured at the tumor site on tumor-bearing breasts and on the contralateral healthy breast at the corresponding anatomical location and the inter-breast ratio (tumor breast/healthy breast) was calculated. The mean values of the ratio are indicated by the horizontal dotted line. The dashed horizontal line at a ratio of 1.6 indicates the approximate ratio for which all benign tumors were below. There were six patients who had malignant tumors who had a ratio greater than 1.6.

Breast TDC Value Comparisons

To the author's knowledge there have been no prior breast measurements made to the 5 mm depth herein reported. However, pioneering approaches to characterize breast TDC values under certain conditions have been implemented by Johansson and colleagues [18-20]. One approach investigated 118 patients treated for breast cancer but prior to radiotherapy treatment (RT) and following RT[18]. In that study TDC was measured to a depth of 2.5 mm and the averaged values from the four breast quadrants used to characterize the breasts TDC value. An important finding was that the surgically treated cancerous breast, even prior to RT, had an elevated TDC value compared to the non-affected breast (36.0 ± 9.5 vs. 27.8 ± 4.8, $p < 0.001$). The healthy breast mean TDC value and SD is slightly greater than determined in the present study at a measurement depth of 5 mm (26.7 ± 4.5).

The potential presence of breast edema in the prior study was based on an inter-breast threshold ratio of 1.4, a value that was derived from bilateral breast TDC measurements in 15 healthy women[18]. In the present study the threshold inter-breast ratio was 1.275 which may indicate a slightly better sensitivity using a 5 mm depth measurement. Follow-up TDC measurements on 65 patients indicated that the elevated TDC value was maintained at least for two years with 28% of **patients** exceeding the 1.4 threshold at a two-year endpoint[20]. Comparative data to a measurement depth of 5 mm not yet available.

CONCLUSION

Breast TDC values obtained to a depth of 5 mm from 82 healthy non-edematous breasts provides a two SD threshold reference value of 35.7. This value represents a TDC value above which the presence of breast edema is indicated if the two SD threshold criterion is used. For unilateral cases, an inter-breast TDC ratio that exceeds 1.275 may be considered as a breast edema/lymphedema indicator. These thresholds may have utility for early detection in at-risk patients and those having or suspected of having unilateral breast edema or lymphedema.

Comparison of TDC values measured to a depth of 5 mm on benign vs. malignant tumors indicates no statistically significant difference between them, whereas inter-breast TDC ratios are higher for breasts with malignant tumors vs. benign tumors. However, overlap of values renders this method of discrimination between benign vs. malignant tumors inadequate based on the present findings.

The potential advantages of measuring breast TDC values using a larger probe surface with greater penetration depth is its larger tissue sampling volume and lower coefficient of variation. Its disadvantage is that smaller areas of interest are more difficult to evaluate.

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AUTHOR CONTRIBUTIONS

All authors contributed to and reviewed this manuscript and approved the final article.

AUTHOR DISCLOSURE STATEMENTS

Each author declares to have no conflict of interest and no competing financial interests.

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