Original Studies

Tissue Dielectric Constant Differentials between Malignant and Benign Breast Tumors

Harvey N. Mayrovitz,[1] Daniel N. Weingrad[2]

Abstract

Tissue dielectric constant (TDC) values of malignant and benign breast tumors were evaluated in 59 women (29 malignant) to assess TDC use in discriminating between these tumor types. Inter-breast TDC ratios (tumor breast/contralateral breast) showed promise for such discrimination with none of 30 benign tumor ratios exceeding an inter-breast ratio of 1.15. Findings open the possibility for potential clinical use.

Introduction: This study's purpose was to characterize tissue dielectric constant (TDC) values of malignant and benign breast tumors and assess the potential utility of TDC differentials to help distinguish between malignant and benign tumors. **Methods:** Prior to their diagnostic biopsy, TDC was measured at 300 MHz in 59 women with previously detected breast tumors. TDC measurements were made by touching skin directly over the tumor and on the non-affected breast with a hand-held 22 mm diameter probe. Each measurement took less than 10 seconds. An inter-breast TDC ratio (RATIO) was calculated as the ratio of the tumor breast TDC value divided by the non-affected breast TDC value measured on the contralateral breast at a corresponding anatomical site. Absolute TDC values and RATIOS were compared for malignant and benign tumors based on post-measurement biopsy determinations. **Results:** Biopsy findings indicated tumors were malignant in 29 patients and benign in 30. Compared to the non-affected breast, malignant tumor TDC values were greater ($P = .0002$) whereas for benign tumors, there was no inter-breast difference ($P = .256$). No patient with a benign tumor exceeded a RATIO of 1.15 whereas 12 of the 29 patients with malignant tumors exceeded this threshold and tended to have larger volume tumors. **Conclusion:** A tentative threshold RATIO of 1.15 may be discriminatory between malignant and benign tumors if the tumor is sufficiently large. Further research using a probe with a greater penetration depth is warranted to potentially increase discrimination.

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Introduction

Distinguishing between malignant or benign tumors ultimately depends on a pathologist's careful examination of biopsied or otherwise excised tissue samples. Despite the recognition of this gold standard, there is potential utility in searching for non-invasive methods to help aid in the initial diagnostic process. With respect to breast cancer, which is the focus of this investigation, there are broadly 2 main goals; (1) to provide the earliest possible detection of the presence of a tumor and (2) to distinguish between malignant and benign tumors. With regard to detection, self-examination,[1-3] mammography (2-dimensional[4] or 3-dimensional[5-7]) and ultrasonography,[8,9] are current and historical mainstays. Refinements and newer and advanced approaches in various stages of development and evaluation include; improved imaging algorithms,[10] the use of neural network detection schemes,[11,12] microwave imaging,[13,14] possible reemergence of thermography as an adjunctive method[15,16] and the potential utility of various biomarkers.[17-21] Once a breast tumor is detected, the malignant-vs.-benign decision may be aided by pre-biopsy assessments that have varying degrees of complexity and cost and are in various stages of development and evaluation. These include; dual-energy computed tomography,[22] blood oxygenation level dependent magnetic resonance imaging (Bold-MRI),[23] digital breast tomosynthesis,[24] ultrasound advanced image processing[25,26] and combined image biomarkers and clinical information.[27] Indeed, nearly 25 years ago Park and co-workers evaluated the use of proton magnetic resonance to differentiate between malignant and benign breast tumors using differences in choline compound detection.[28] However, it would be useful to have a way in which malignant-benign discrimination probabilities could be enhanced by an examining physician to help aid in the initial decision-making process. Such could be based on some global easily measured parameter difference between in vivo properties of malig-

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nant vs. benign breast tumors, perhaps with an approach similar to that for skin cancer.[29] One such reported differential property is the dielectric constant, also known as relative permittivity.[30-32] Differences in electrical properties, including dielectric constant, of benign vs. malignant tumors have been reported based on in vitro measurements of biopsied or excised tissue[30,32-36] but corresponding information is not available for in vivo measurements made directly on breasts. It was thus the purpose of the present investigation to (1) characterize malignant-benign differential relative permittivity of breast tumors evaluated in vivo and (2) assess the potential utility of such dielectric constant measurements to adequately distinguish between malignant and benign tumors.

Methods

Subjects

Participants were 59 women who had a mass (tumor) in one of their breasts and were scheduled to have a diagnostic biopsy. Study entry requirements were that patients have a breast mass that had been identified as abnormal by mammographic, ultrasound, and/or MRI imaging modalities and were planning to undergo a diagnostic surgical biopsy. Exclusionary conditions were (1) the presence of nonintact skin at the planned breast measurement site, (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, and (5) currently pregnant. The study was approved by the Nova Southeastern University Institutional Review Board (IRB, 2019-7-Non-NSU-Health) and registered with Clinical Trials .org (NCT04561297). Women were evaluated after reading and signing an IRB approved consent.

Tissue Dielectric Constant (TDC) Measurement Device

TDC was measured using an open-ended coaxial probe operating at a frequency of 300 MHz (MoistureMeterD, Delfin Technologies, Kuopio, FL). This handheld probe has a manufacture's designation of M25, a diameter of 22 mm and a specified effective penetration depth of 2.5 mm but with signal energy received from deeper. The principle of operation and validation has been previously described.[37,38] In brief, the probe acts as an open-ended coaxial transmission line through the 300-MHz signal is transmitted.[39,40] Reflected energy depends on the tissue's complex permittivity, which in-turn depends on signal frequency and the tissue dielectric constant (the real part of the complex permittivity). At 300 MHz, the contribution of conductivity to permittivity is small, so TDC is determined mainly by water molecules (free and bound) and the other tissue constituents. TDC measurements have been used to measure TDC in conjunction with breast cancer related lymphedema,[41-43] lower extremity lymphedema,[44,45] breast edema,[46,47] truncal lymphedema[48,49] and skin cancer.[29]

Procedure and Measurements

Tumors were targeted in patients with Breast Imaging Reporting and Data System (BI-RADS) 4 or 5 lesions for biopsy under ultrasound. Just prior to the biopsy TDC of the tumor was measured in triplicate by placing the measurement probe in contact with the breast skin directly over the tumor as localized by ultrasound. When the probe is properly in contact with the skin the measurement starts automatically and takes less than 10 seconds to complete each TDC measurement. The measurement sequence was then repeated on the contralateral breast at a corresponding mirror image anatomical site. Tumor dimensions were determined via standard ultrasound measurements using the GE LOGIQE9 ultrasound machine operating at 10 MHz from which tumor volume was estimated based on an ellipsoid model calculation ($V = \frac{4}{3}\pi xyz$). Thereafter the scheduled biopsy was performed. Measurements and biopsies were done in the clinical offices of Surgical Specialists of Miami, Aventura Florida.

Table 1 Patient and Tumor Features

	Benign Tumors	Malignant Tumors
Number of Patients	30 (50.8%)	29 (49.2%)
Age (years)	62.6 ± 10.6	69.9 ± 10.0*
BMI (Kg/m^2)	29.9 ± 4.7	28.0 ± 5.4
Tumor Breast		
Right	12 (40.0%)	14 (48.2%)
Left	18 (60.0%)	15 (51.8%)
Tumor Quadrant		
Upper-Inner	4 (13.3%)	8 (27.6%)
Upper-Outer	18 (60.0%)	15 (51.7%)
Lower-Inner	4 (13.3%)	3 (10.3%)
Lower-Outer	4 (13.3%)	3 (10.3%)
Tumor Volume (mL)	0.38 ± 0.71	1.38 ± 3.3*
Cancer Type		
Infiltrating ductal		19
Invasive lobular		6
Invasive ductal		3
Ductal in situ		1

Patients with malignant tumors were older and tended to have larger tumors (* $P < .05$).

Analysis

Tests for differences between paired-breasts was done using paired t-tests and tests for differences between breasts with malignant tumors vs. benign tumors (inter-breast differences) was done using independent t-tests. In both types of analyses a difference was considered statistically significant for *P*-values less than .05.

Results

Patient demographics, tumor features and biopsy results are shown in Table 1. Overall group age (mean ± SD) was 66.2 ± 10.9 years with body mass index (BMI) of 29.0 ± 5.1 Kg/m^2. Benign tumors were present in 30 patients (50.8%) and malignant tumors in 29 (49.2%). Patients with malignant tumors tended to be older (69.9 ± 10.0 years) than patients with benign tumors (62.6 ± 10.6 years, $P < .05$ via Mann–Whitney test). The malignant tumor volume was also greater than benign tumors (1.38 ± 3.3 cm^3 vs. 0.38 ± 0.71 cm^3, $P < .05$) with tumor volume ranges of 0.02 to 17.4 cm^3 for malignant tumors and 0.004 to 3.39 cm^3 for benign tumors. Upper breast quadrants (inner plus outer) accounted for 77.3% of benign tumors and 78.6% of malignant tumors.

The main results with respect to absolute TDC values are shown in Table 2. For patients with malignant tumors, the tumor TDC

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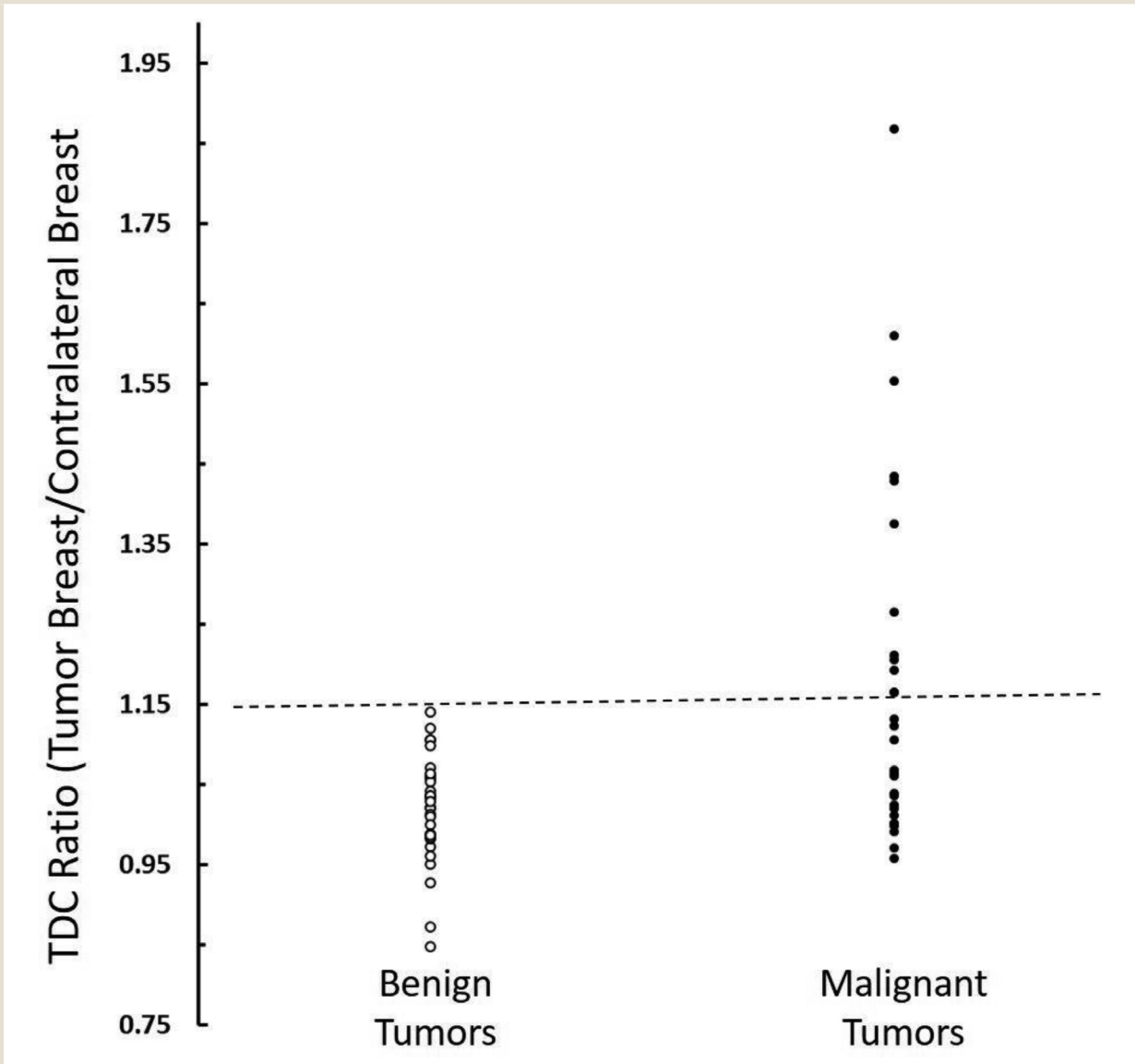
Table 2 TDC Values for Patients with Malignant and Benign Breast Tumors

Malignant Tumors (N =30)			Benign Tumors (N = 29)		
HealthyBreast	TumorBreast	*P*-value	HealthyBreast	TumorBreast	*P*-value
28.2 ± 6.3	32.7 ± 7.2*	.0002	28.8 ± 5.8	29.3 ± 5.4	.256

Data entries are TDC values ± SD. The p-values are based on paired t-tests for inter-breast comparisons (healthy vs. tumor breasts).
* $P < .05$ between malignant and benign tumor breasts based on independent t-tests.

Figure 1 Inter-breast TDC ratios. Open circles are for benign tumors and filled-in circles are for malignant tumors. The maximum inter-breast TDC ratio for patients with benign tumors was 1.14. This value was exceeded by 41.4 % of patients that had malignant tumors.



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value was greater than on the non-affected contralateral breast (32.7 ± 7.2 vs. 28.2 ± 6.3, $P = .0002$). Contrastingly, for patients who had benign tumors there was no difference in TDC values between tumor site and contralateral breast site (29.3 ± 5.4 vs. 28.8 ± 5.8, $P = .256$). Comparisons of patients who had malignant vs. benign tumors indicated no significant difference in TDC values for healthy breasts (28.2 ± 6.3 vs. 28.8 ± 5.8, $P = 0.686$). Contrastingly, malignant tumor sites had greater TDC values than benign tumor sites (32.7 ± 7.2 vs. 29.3 ± 5.4, $P = .048$). The ratio of TDC values measured on breasts with tumors to their paired healthy contralateral breast, are shown in Figure 1. Inter-breast TDC ratios were greater when the tumor breast was malignant vs. if it were benign. (1.175 ± 0.221 vs. 1.019 ± 0.067, $P < .001$). For patients who had benign tumors, the maximum inter-breast ratio was 1.14. This maximum inter-breast ratio was exceeded by 12 (41.4%) patients who had malignant tumors. Based on the present data set and using a threshold ratio of 1.15, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) are calculated to be 0.414, 1.0, 1.0 and 0.638 respectively. Thus, if considered as a diagnostic test it has low sensitivity but high PPV and high specificity but moderated NPV.

Discussion

There were 2 main aims of the present investigation. One was to characterize TDC differentials between malignant and benign breast tumors and the other was to assess the possible use of such TDC measurements to help distinguish malignant from benign tumors. With respect to the first aim, the study findings indicate a small but statistically significant greater TDC value for malignant tumor sites compare to the contralateral healthy breast. The tumor bearing breast TDC average was 16% greater than the contralateral healthy breast with an inter-breast TDC ratio (tumor breast / healthy breast) of 1.175 ± 0.221. Contrastingly, there was no inter-breast TDC difference for patients who had benign tumors.

Despite the statistical difference in TDC values between malignant and benign tumors, there was considerable overlap in TDC values, with less than half of patients with malignant tumors exceeding the maximum inter-breast TDC ratio of patients with benign tumors. It is likely that tumor size (volume) is at least partly responsible for this overlap in TDC values. This follows because the malignant tumor water content is far greater than the breast tissue in which it is imbedded.[50-52] Consequently, a larger tumor volume would be associated with a greater TDC value. This possibility is supported by the present measurements in which the correlation between measured TDC values and tumor volumes was evaluated for malignant and benign tumors independently. For malignant tumors, the Pearson correlation coefficient (r) was significant ($r = 0.546$, $P = .002$). Contrastingly for the smaller average volume of benign tumors, there was no correlation between tumor volume and TDC value. Thus, it appears that sufficiently large malignant tumors may be detectible via their inter-breast TDC ratios. Based on the current evaluated group the present threshold would require and inter-breast ratio greater than 1.15.

However, with the present group of patients who had malignant tumors, only 12 (41.4%) of them had inter-breast ratios that exceeded this value. The possible role of tumor volume in this process was investigated by evaluating tumor volumes of those 12 patients revealing that their average tumor volume was 2.8 ± 4.8 cm^3. The remaining 17 patients who had inter-breast ratios less than 1.15 had a malignant tumor volume of 0.48 ± 0.55 cm^3. The difference between these tumor volumes was not quite statistically significant ($P = 0.059$). However, the data suggests there is likely a tumor volume dependence. This is not unexpected since tumor size impacts the TDC value in 2 ways. The larger the volume the greater is the separation between the tumor's substantial water content and the low water content of fat within breast tissue. Secondly, the larger the tumor the more likely it is for one of its surfaces to be closer to the skin and be detectible by the measurement probe in contact with breast skin. For these reasons we believe that detection might be improved by sampling a greater breast tissue volume and to a greater depth than was achievable using the current probe. Future studies would benefit from the inclusion of tumor depth measurements with ultrasound and the use of a probe that has a greater depth of penetration.

Despite these possible limitations, the present data suggest a potential utility for the TDC inter-breast measurement to help discriminate between malignant vs. benign tumors for sufficiently large tumors. Based on the current findings it appears that an inter-breast TDC ratio measured at the tumor site that exceeds 1.15 should be viewed as a potentially malignant tumor. Contrastingly, inter-breast ratios less than 1.15 offer little discrimination value. Further prospective research using a probe with greater depth and volume measurement along with ultrasound tumor depth measurements will help clarify the role of volume and tumor depth and may add to malignancy discrimination of this method.

Conclusion

Comparison of TDC values of malignant and benign breast tumors indicate the presence of inter-breast differences in TDC values for malignant tumors but not for benign tumors. A tentative threshold ratio (tumor breast/contralateral breast) of 1.15 may be discriminatory between malignant and benign tumors if the tumor is sufficiently large. Further research using a probe with a greater penetration depth is warranted to potentially increase discrimination.

Clinical practice points

Prior work has reported on in vitro measurements of electrical properties of malignant and benign tumors of various types including those of the breast. Some of these reports have indicated a measurable difference in the tissue dielectric constant (TDC) value obtained from malignant vs. benign tumors. However, data regarding the detectability of such differences when measured simply and non-invasively on breasts in vivo is absent. The present findings provide this new information in which absolute TDC values and inter-breast TDC ratios for breasts with malignant vs. benign tumors are compared. A main new finding is the fact that inter-breast TDC ratios statistically differ between tumor types and that there is an initial inter-breast threshold ratio that no patient with a benign tumor exceeded. This opens the door for the further study and possible use of this method as an aid to early initial differential diagnosis.

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Clinical practice points

The present findings provide an initial framework for the potential use of breast TDC measurements to aid in the process of differentiating between malignant and benign breast tumors.

Disclosure

The authors have stated that they have no conflicts of interest.

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