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Differentiation Among Basal Cell Carcinoma, Benign Lesions, and Normal Skin Using Electric Impedance

Daryl G. Beetner*, *Senior Member, IEEE*, Sanat Kapoor, *Member, IEEE*, Shivappa Manjunath, Xiangyang Zhou, and William V. Stoecker

***Abstract*—This paper presents a preliminary study showing the diagnostic potential of electrical impedance to detect basal cell carcinoma (BCC). Electrical impedance was measured *in vivo* from 1 kHz to 1 MHz on 24 human subjects over BCC (19 lesions), over benign tumors (11 lesions), and over normal skin (all 24 patients). Lesions ranged from 2–15 mm in diameter. Indexes based on the magnitude (MIX), phase (PIX), real-part (RIX) and imaginary-part (IMIX) of impedance were calculated for each measurement. Significant differences were found between measurements over BCC, benign lesions and normal skin for indexes MIX, PIX, and IMIX ($P = 0.04$ to $P = 7 \times 10^{-7}$). Indexes were generally smaller for measurements of BCC than for benign lesions or normal skin. Differences were not a result of differences in the patient's age or the measurement location. The large size of our measurement electrode (10 mm) probably limited our ability to differentiate lesions because significant amounts of normal skin were included in each lesion measurement. A linear regression fit of data with tumor size suggests that a smaller probe or more sophisticated analysis techniques may improve differentiation. Results suggest that electrical impedance could be used to provide rapid and noninvasive differentiation of BCC from similar looking benign lesions.**

***Index Terms*—Basal cell carcinoma, bioelectrical impedance, electric conductivity, spectrum analysis, tissue characterization.**

I. Introduction

BASAL CELL carcinoma (BCC) is the most common malignancy. Left untreated, it can cause significant morbidity and disfigurement and, rarely, death. Fortunately, BCC has a better than 95% cure rate if detected and treated early. The primary means of detecting BCC is through visual inspection followed by biopsy and pathological examination if the physician finds the lesion suspicious. Unfortunately, not all malignant lesions are identified through visual inspection. Presently, there are no generally accepted tools the physician can use to immediately validate their visual diagnosis in the clinic. An inexpensive, noninvasive technique that complements information from visual inspection could help prevent misdiagnosis of BCC and other types of skin cancer and would aid early detection and treatment.

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Previous work suggests that electrical impedance may distinguish skin cancer from other tissue. The electrical impedance of a tissue depends on its macro- and micro-structural characteristics as well as its chemical composition. Studies have shown a wide degree of variation in the bio-electric properties between tissue types and between tissue states [1]. The changes that occur with cancer or other diseases manifest themselves as changes in impedance. *Ex vivo* studies have shown significant differences between the bioimpedance of normal and cancerous breast tissue [2]–[4] and between skin cancer and normal skin [2]. *In vivo* studies have shown differences in the electrical impedance of the skin as a result of irritation, allergic reaction (wheals), age, sex, location, and hydration [5]–[9]. A small clinical study has also shown significant differences between nodular BCC and normal skin [10].

Most of the *in vivo* studies of the skin mentioned above used measurements from an instrument called the impedance spectrometer and were based on a comparison of four indexes: magnitude index (MIX), phase index (PIX), real-part index (RIX), and imaginary-part index (IMIX), defined as [11]

$$\begin{aligned}
\text{MIX} &= \frac{abs\,(Z_{20\text{ kHz}})}{abs\,(Z_{500\text{ kHz}})} \\
\text{PIX} &= \arg\,(Z_{20\text{ kHz}}) - \arg\,(Z_{500\text{ kHz}}) \\
\text{RIX} &= \frac{\text{Re}\,(Z_{20\text{ kHz}})}{(Z_{500\text{ kHz}})} \\
\text{IMIX} &= \frac{\text{Im}\,(Z_{20\text{ kHz}})}{abs\,(Z_{500\text{ kHz}})}
\end{aligned}$$

where $Z_{20\text{ kHz}}$ is the measured impedance at 20 kHz, $Z_{500\text{ kHz}}$ is the impedance at 500 kHz.

Emtestam *et al.* compared measurements of MIX, PIX, RIX, and IMIX over normal skin and over lesions of nodular BCC [10]. A total of 12 tumors were studied. Tumors were 10 mm or more in diameter—the size of the probe electrode used to measure impedance. Significant differences were found between values of MIX, and IMIX measured over the tumor and over normal skin ($P < 0.001$), suggesting that electrical impedance might be used as a diagnostic tool for BCC.

Our study builds on the study of Emtestam *et al.* and compares electrical impedance among normal skin and benign and malignant lesions of relatively small size. The purpose of our study is twofold: to show that the results of Emtestam *et al.* can be applied clinically to relatively small tumors (less than 10 mm); and to show the potential of electrical impedance to differentiate between BCC and benign lesions. Such a study is useful for future clinical application of electrical impedance, because the physician would apply techniques to

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TABLE I
LOCATION OF LESIONS

Location	BCC	Benign
Head	16	7
Neck	1	
Chest		1
Back	2	1
Arm		2

lesions of small size and would be interested in distinguishing malignancies from benign tumors.

II. METHODS

Impedance of malignant and benign lesions was measured prospectively on human patients during a dermatological exam, following procedures approved by the University of Missouri Institutional Review Board. Lesions were studied only if they were marked for removal and biopsy by a dermatologist as part of the normal course of treatment. A total of 24 patients were studied, some of whom had multiple lesions. Patients were recruited consecutively and were rejected only for technical reasons, i.e., equipment failure or location of the lesion on a highly contoured area unsuitable for a 10-mm probe (e.g., the ears and perinasal areas).

Measurements were made on 19 BCC and 11 benign lesions. The group with BCC ranged in age from 28 to 85 years with an average age of 71 years. The group with benign lesions ranged in age from 39 to 80 years with an average age of 61 years. The location of lesions is summarized in Table I. Patients were generally fair-skinned, over 80% Fitzpatrick types I and II. Fitzpatrick type I skin always burns with sun exposure and Fitzpatrick type II usually burns with sun exposure. Lesions ranged in size from 2 mm to 15 mm for BCC and from 2 mm to 10 mm for benign lesions. The group of benign lesions included two actinic keratoses, one compound nevus, three intradermal nevi, one chromoblastomycosis, one cutaneous polyp, one nevus lipomatosus, and two seborrheic keratoses. These lesions appeared consecutively in those who were undergoing biopsy or when the equipment was available. None of the lesions encountered were ulcerative or highly keratotic. After impedance measurements were made, the lesion was shave biopsied and lesion type was confirmed histologically.

Impedance was measured using the impedance spectrometer (SciBase AB, Huddinge, Sweden) as in the study by Emtestam *et al.* [10]. The spectrometer measures impedance at 31 logarithmically separated frequencies from 1 kHz to 1 MHz. Measurements were made with the hand-held probe shown in Fig. 1. The probe has four electrodes shaped in a bullseye pattern. The middle electrode is a sink electrode, the next electrode is a guard electrode that reduces effects of surface currents and the outer two electrodes are source electrodes. The outermost electrode isapproximately 10 mm in diameter. By changing the distribution of current between the two source electrodes, the position of a "virtual" electrode between them can be changed. By varying this position, the spectrometer can measure impedance at five "depths" ranging from very shallow measurements including only a superficial portion of the dermis to measurements up to a few millimeters deep.

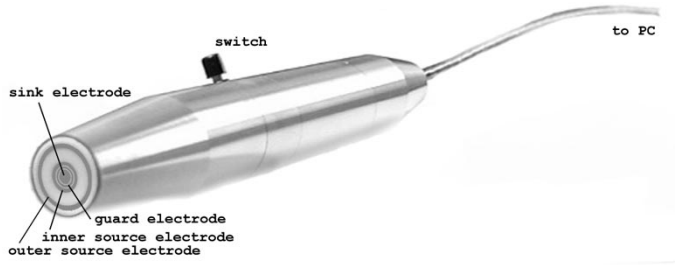

Fig. 1. Hand-held probe used to measure impedance.

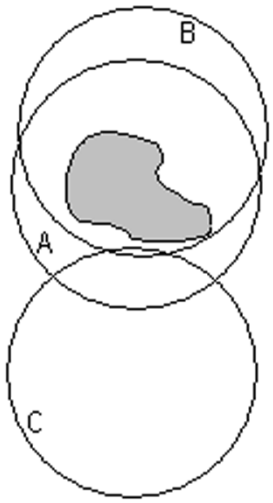

Fig. 2. (A) Measurements were made with the probe centered on the lesion (B) with the probe just on the periphery of the lesion and (C) with the probe placed on normal skin immediately adjacent to the lesion.

Before measuring impedance, the skin was soaked with a 0.9% saline solution for two minutes to increase the conductivity of the stratum corneum and for 1 min between subsequent measurements of the same site. Impedance was measured both on the lesion and on normal skin adjacent to the lesion. The basic measurement positions are shown in Fig. 2, except that each off-center measurement was made twice, once on each side of the lesion. The probe was positioned both over the center of the lesion and over its periphery in an attempt to obtain at least one measurement that included the maximum amount of tissue of interest. When the lesion is small, a good deal of the lesion could be "hidden" beneath the center electrode, preventing the best possible measurement. In that case, an off-center measurement may return better results. Multiple measurements were made to ensure accuracy. Measurements of adjacent normal skin were made for comparison. Unrealistic measurements (measurements containing impedance with zero magnitude, change in sign of phase, sudden and uncharacteristic changes in magnitude, etc) were repeated when possible or were discarded [12].

III. RESULTS

Measured values of MIX, PIX, RIX, and IMIX are shown in Fig. 3. Values are shown over BCC, benign lesions and normal skin as a function of depth measured by the virtual electrode. Depth is shown along the X axis from the most shallow depth

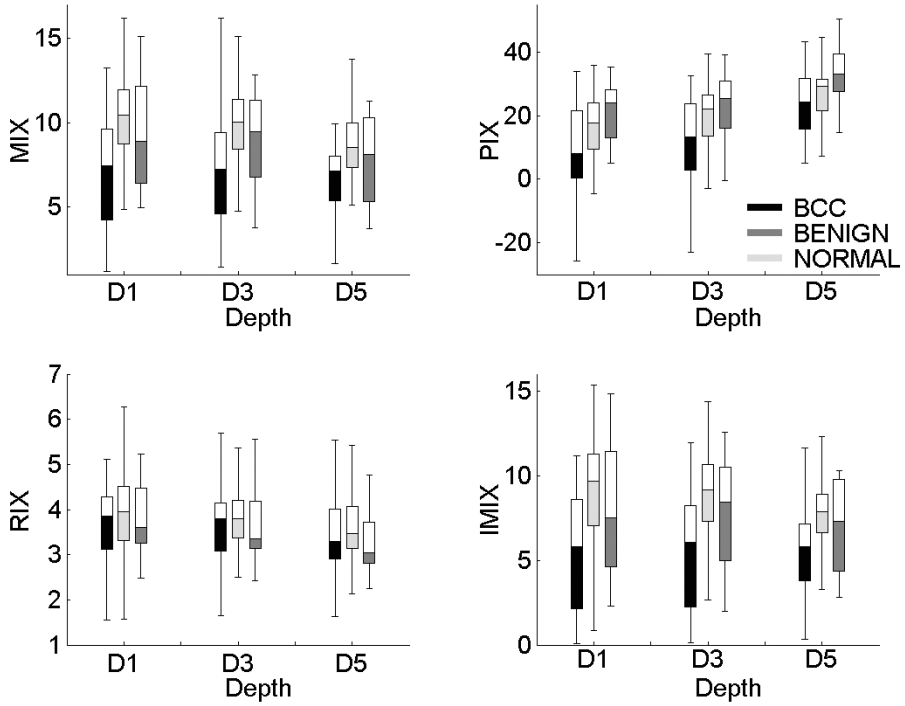

Fig. 3. Box and whisker plots for the four indexes at depths 1, 3, and 5. Boxes are partially shaded from dark to light to represent measurements over BCC, benign lesions, and normal skin, respectively. The line in the middle of each box represents the median value of the data. Boxes extend above and below the median to include 25% of the measured data points in each direction. Whiskers extend to the minimum and maximum measured value.

TABLE II
MEAN AND STANDARD DEVIATION OF INDEXES AT DEPTHS 1, 3, AND 5 [a]

		Depth 1	Depth 3	Depth 5
MIX	BCC	6.9±3.2	7.1±3.5	6.6±2.4
	NOR	10.2±3.2	9.9±2.8	8.8±2.2
	BEN	9.4±3.1	8.9±2.7	7.8±2.5
PIX	BCC	8.1±15.8	11.9±14.2	23.8±10.9
	NOR	12.8±16.8	18.0±14.4	27.7±10.4
	BEN	18.7±15.5	23.1±11.4	32.4±9.7
IMIX	BCC	5.4±3.6	5.5±3.4	5.5±2.6
	NOR	8.9±3.9	8.8±3.4	7.9±2.4
	BEN	8.0±3.7	7.9±3.0	6.9±2.6
RIX	BCC	3.9±1.5	4.0±2.2	3.4±0.9
	NOR	4.2±1.6	4.0±1.2	3.7±0.8
	BEN	4.1±1.4	3.8±1.2	3.3±0.8

[a] BCC stands for BCC, NOR for normal and BEN for benign.

TABLE III
PROBABILITY OF SIMILARITY BETWEEN IMPEDANCE MEASURES [a,b]

		Depth 1	Depth 3	Depth 5
MIX	BCC & NOR	**0.0000007**	**0.0000018**	**0.000012**
	BCC & BEN	**0.0027**	**0.0032**	**0.037**
	NOR& BEN	NS	NS	**0.041**
PIX	BCC& NOR	**0.042**	**0.008**	NS
	BCC & BEN	**0.0001**	**0.0001**	**0.0003**
	NOR & BEN	**0.014**	**0.034**	**0.028**
IMIX	BCC & NOR	**0.0000037**	**0.0000017**	**0.000006**
	BCC & BEN	**0.0012**	**0.0018**	**0.026**
	NOR & BEN	NS	NS	NS
RIX	BCC & NOR	NS	NS	NS
	BCC & BEN	NS	NS	NS
	NOR & BEN	NS	NS	**0.015**

[a] Statistical similarity calculated using the Wilcoxon signed rank test. Probability of similarity less than 0.05 indicates a significant difference.

[b] BCC stands for BCC, NOR for normal and BEN for benign. NS stands for "Not Significant".

(D1) of tissue that can be measured by the probe to the deepest (D5). Measurements at each position are included. Mean and standard deviation values are summarized in Table II. Statistically significant differences were estimated using the Wilcoxon signed rank test. Distributions are significantly different when the probability of similarity is less than 0.05. Probability of similarity between distributions at depths 1, 3, and 5 is shown in Table III. Similar results were found for depths 2 and 4, which are not shown. Values of MIX, IMIX, and PIX were significantly lower over BCC than over benign lesions or normal skin for almost all measured depths. The exception was depth 5, where there was no significant difference between BCC and normal skin. Significant differences generally were not found for RIX.

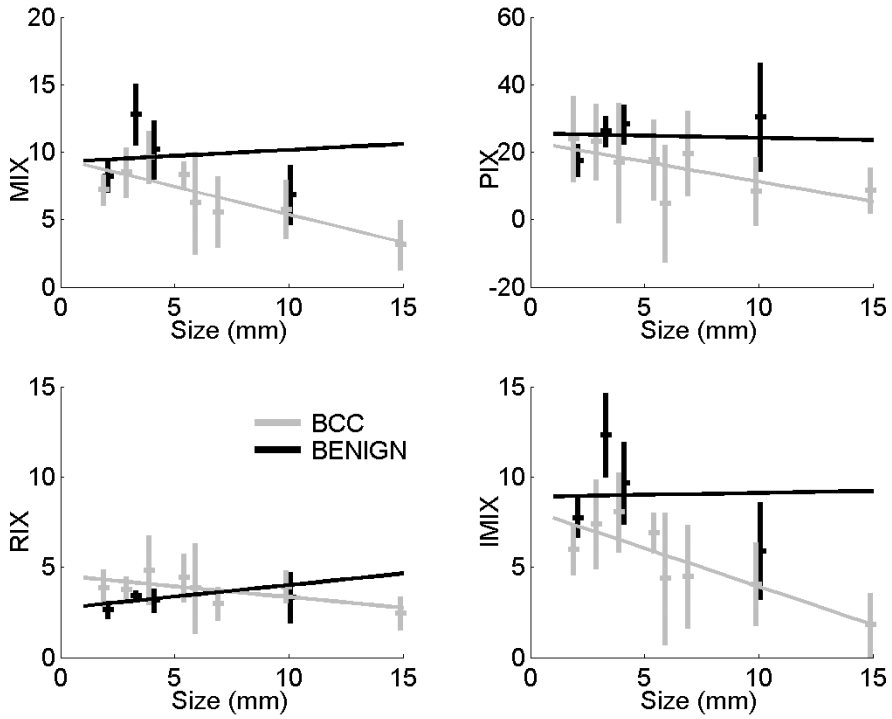

Fig. 4. Change of indexes with lesion size. Values of indexes over BCC and benign lesions are marked with light and dark lines, respectively. Index values are shown on the Y axis. Lesion size is shown on the X axis. Each vertical bar represents the mean value of the index plus or minus one standard-deviation for each lesion size. The best straight-line approximation of measured values over size was calculated as shown in this graph.

While normal skin generally had a higher index value than benign tissue for MIX, and IMIX, these differences were rarely significant. Normal skin had significantly lower values of PIX than benign lesions. The greatest differences were observed between BCC and the other two tissue types (normal and benign lesions).

Depth of measurement did not appear to have a large effect on results. Values of indexes on individual lesions would change from one depth to another, but the relative relationships between tissue types tend to remain the same. Little change in the average value of the index was observed with increasing depth for MIX or IMIX. The average index value rose slightly with increasing depth for PIX, but generally rose uniformly for each group of measurements.

While these results are encouraging, there is a greater overlap between measured values than one would like for differentiation of tissue type using electrical impedance. It is possible to discriminate malignant tumors from benign lesions in the dataset with a sensitivity around 90% using MIX, PIX, or IMIX, but specificity must fall to around 50% to achieve this result. One must consider, however, that every lesion measurement also includes normal skin. A lesion 2 mm in diameter constitutes only about 4% of the total area beneath the probe when using the outer source electrode. The rest of the tissue is normal skin. Even when measurements are made with only the inner source electrode, a great deal of normal tissue is likely to be included in the measurement. Differences in electrical impedance between BCC and benign lesions might be obscured by this normal tissue. If our hypothesis that normal skin is interfering with the measurement of small lesions is true, one would expect differences in measurements to increase with increasing lesion size. To test this hypothesis, measured index values at all five depths were plotted as a function of lesion size as shown in Fig. 4. The straight lines in each plot show the best straight-line approximation of index values as a function of size. While index values for BCC show a clear decrease with size, values for benign lesions change only slightly. Values for benign lesions may have only changed slightly because normal skin and benign lesions have similar index values.

IV. Discussion

Results comparing BCC and normal skin were similar to results reported by Emtestam *et al.* for lesions 10 mm or greater in size. Emtestam *et al.* also found a significant decrease in the value of MIX or IMIX over BCC compared with normal skin. Both studies showed few significant differences in the value of RIX. A small discrepancy between the studies occurs with PIX, where Emtestam *et al.* found no significant differences and our study found significant differences at some depths. The similarity in the outcomes of the two studies confirms our results and shows that the conclusions of Emtestam *et al.* may also apply to much smaller lesions.

In addition to confirmation of results of Emtestam *et al.* for smaller lesions, our study also found significant differences between BCC and benign lesions for the indexes MIX, IMIX, and PIX. Some statistically significant differences were found between normal skin and benign lesions for PIX. Values of MIX, IMIX, and PIX were generally statistically smaller over BCC than over normal skin or benign lesions. No significant differences were found for RIX.

TABLE IV
MEAN AND STANDARD DEVIATION OF IMPEDANCE MEASURES OVER NORMAL SKIN [a,b]

	MIX	PIX	IMIX	RIX
Average values, patients with BCC	10.2±3.0	11.8±15.9	8.7±3.8	4.4±1.6
Average values, patients with benign	10.5±3.6	12.6±17.9	9.2±4.1	4.4±1.8
Probability of similarity	0.74	0.87	0.68	0.95

[a] Measurements were made on normal skin adjacent to BCC and benign lesions. Probability of similarity was calculated between these two groups.
[b] Results are for depth 1. Similar results were found at other depths.

Explanation of the pathophysiological basis for these differences requires further study. Differences may result because BCC tumors may be better irrigated by the local blood supply than normal skin or benign lesions or because the stratum corneum is thinner or better hydrated over BCC. The nuclei of BCC cells also tend to be larger and the intercellular spaces smaller than for cells from normal skin. These structural differences appear to cause measurable differences in the impedance of the tissue as a function of frequency [13]. Malignant cell membranes also tend to have different electrochemical properties than normal cells, which may also contribute to the observed differences.

Previous studies have shown that the electrical impedance of the skin is affected by age and measurement site [7]. Because the average age of the group with BCC and the group with benign lesions differed and because more BCC occurred on the head and neck than benign lesions, we investigated the possibility that differences in electrical impedance were caused by these differences rather than differences in the lesions themselves. General changes in impedance with age or site should be reflected in the measures of normal skin adjacent to the lesion. Table IV shows the average value of the indexes on the normal skin adjacent to the lesion for the group of patients with BCC and for the group with benign lesions. The table also shows the statistical probability of similarity between these measures. The average value of the indexes were similar for both groups, indicating that differences found earlier between BCC and benign lesions were caused by the lesions and not by more general differences between the groups.

While results are encouraging, further studies are needed to confirm the potential diagnostic value of electrical impedance for BCC. Significant differences were found between the impedance of BCC and normal skin or benign lesions, but the separation was not large enough to facilitate clear identification of the lesion based only on impedance. However, the probe size was quite large compared with the size of most lesions and the normal skin included in each measurement probably obscured clear differentiation of results. Poor contact between the electrode and the skin and differences between individuals and measurement sites may have also obscured results. The fact that separation of the measures increases with lesion size indicates that better results might be obtained using a smaller or more sophisticated probe or using more sophisticated analysis techniques that take into account the combined measurement of normal skin and the suspect lesion.

From a clinical point of view, the usefulness of this technology would come primarily from a separation of benign and malignant lesions. It is a weakness of this study that different types of benign lesions are considered as a group, resulting in an inhomogeneous group of benign lesions. The small number for each benign diagnosis does not allow exploration of the feasibility of separation of different benign diagnoses. This is an important topic for future work.

It should be mentioned that diagnosis of malignancies using electrical impedance has some potential limitations, as presented in this paper. First, it is not clear that the results obtained for BCC can be generalized to other types of malignancy. For BCC, the tissue has a consistency that is considerably different from normal skin and this difference is not as great for other types of malignancies or even some variants of BCC not investigated here. Application to other malignancies needs to be studied. Second, because the probe must be placed on a suspected area, this technique does not resolve the problem of lesions that are completely overlooked at a screening session. On the other hand, it does appear that electrical impedance may provide additional diagnostic information to the physician that is not available from visual images, allowing them to verify or improve their diagnosis of suspect lesions. Improvements to the probe and to analysis techniques should substantially improve the diagnostic potential of electrical impedance, making it a useful companion to visual diagnosis of malignant lesions and possibly assisting in differentiation of uncommon variants of BCC or improvements in detecting BCC recurrence.

Visual diagnosis of the skin, by itself, is an imperfect means of detecting skin cancer. An inexpensive, rapid, and noninvasive diagnostic tool that could help the clinician identify cancer has obvious benefits. Results from this study show that electrical impedance may provide the basis for such a tool. The study suggests impedance may be used to separate BCC from benign lesions that have a similar appearance to BCC, even when tumor size is relatively small. Accurate methods of performing this differentiation may require a smaller or more sophisticated probe or a more sophisticated analysis technique than was used in this paper. Additional studies are needed to demonstrate the diagnostic potential of electrical impedance for BCC and other types of skin cancer.

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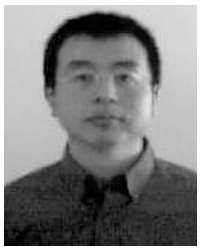

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