Skin Cancer Identification Using Multifrequency Electrical Impedance—A Potential Screening Tool

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Abstract—Electrical bio-impedance can be used to assess skin cancers and other cutaneous lesions. The aim of this study was to distinguish skin cancer from benign nevi using multifrequency impedance spectra. Electrical impedance spectra of about 100 skin cancers and 511 benign nevi were measured. Impedance of reference skin was measured ipsi-laterally to the lesions. The impedance relation between lesion and reference skin was used to distinguish the cancers from the nevi. It was found that it is possible to separate malignant melanoma from benign nevi with 75% specificity at 100% sensitivity, and to distinguish nonmelanoma skin cancer from benign nevi with 87% specificity at 100% sensitivity. The power of skin cancer detection using electrical impedance is as good as, or better than, conventional visual screening made by general practitioners.

Index Terms—Actinic keratosis, basal cell carcinoma, electrical impedance, malignant melanoma, pigmented nevus, squamous cell carcinoma.

I. BACKGROUND

IMPROVEMENTS of measurement technology and data processing facilitate clinically interesting discrimination power between malignant and harmless skin lesions. There are different kinds of skin cancer types, where malignant melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC) are the most significant. Actinic keratosis can degenerate to SCC and, hence, is considered as a potentially harmful lesion. BCC and SCC are called nonmelanoma skin cancers. Benign nevus, on the other hand, is a harmless and very common lesion type that can be mistaken for melanoma and, therefore, often excised for diagnostic purposes. A reduction of the excised nevi is economically motivated and would reduce discomfort and the risk of infections for the patients. Detailed information on these lesions can be found in [1]–[4].

Screening for skin cancer is usually made by visual inspection of the patients’ lesions using, e.g., the ABCD rule [5], and if the observer finds the appearance of the lesion under study is atypical, it is excised and the biopsy is examined histopathologically. The diagnostic accuracy of screening is dependent upon the skill of the observer [6]. It is desirable to replace this subjective procedure with a reliable, simple, and objective technique with high accuracy, but at the time of writing there are no practical alternatives. Dermoscopy has been proposed as an alternative to visual screening [7], but the technique is subjective and does not fulfil the clinical demands required for a straightforward screening tool.

The electrical impedance of a biological material reflects momentary physical properties of the tissue. Schwab identified specific frequency regions, dispersions, in electrical bio-impedance spectra describing special physical properties [8], [9]. One of the clinically most important, the β-dispersion, ranging between kilohertz to hundreds of megahertz depending on the tissue, is mainly affected by the shape of the cells, structure of the cell membranes, and the amount of intra and extracellular water. The fundamentals of electrical bio-impedance are described in [10]. Electrical bio-impedance can be used to assess properties of biologic materials, such as cancer [11]–[14]. Electrical impedance within the β-dispersion range of cancer differs from healthy tissues because the cancer cells are different in shape, size and orientation, criteria that is used in histopathological evaluation, the gold standard in cancer diagnosis.

Nicander et al. [15] showed that some histologically differentiable skin conditions give rise to specific skin impedance patterns. After this study, many technical problems have been solved and the technique is improved to a degree where it is applicable to implement the skin impedance methods in clinical applications, such as skin cancer assessments. The electric bio-impedance technique of skin is reviewed in [16]. It has been shown that there are statistically significant electrical impedance differences between reference skin and several lesion types (BCC, benign nevi, dysplastic nevi, and seborrheic keratosis) [17]–[19], as well as significant differences between BCC and benign nevi [18], [19]. In preliminary studies [20], [21], it was shown that it is possible to use the differences between BCC and benign nevi to identify the lesions with significant diagnostic power. Moreover, in another preliminary study [22] electrical impedance was used to detect 12 human melanoma lesions with 92% sensitivity and 67% specificity. There are no reports in the literature on electrical impedance assessments on actinic keratosis or SCC.

The aim of this study is to separate malignant melanoma, nonmelanoma cancers, and actinic keratosis from common benign nevi using multifrequency noninvasive impedance technique.
TABLE I
NUMBER OF UNIQUE IMPEDANCE READINGS OF THE LESION TYPES, NUMBER AND AGE OF PATIENTS, AND SIZE OF THE LESIONS INCLUDED IN THE STUDY

<table>
<thead>
<tr>
<th>Lesion type</th>
<th>Number of lesions</th>
<th>Number of patients</th>
<th>Age of patients</th>
<th>Lesion diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Benign nevi</td>
<td>511</td>
<td>289</td>
<td>111</td>
<td>178</td>
</tr>
<tr>
<td>Basal cell carcinoma (BCC)</td>
<td>79</td>
<td>54</td>
<td>33</td>
<td>21</td>
</tr>
<tr>
<td>Malignant melanoma (MM)</td>
<td>16</td>
<td>16</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Actinic keratosis (AK)</td>
<td>9</td>
<td>9</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Squamous cell carcinoma (SCC)</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

II. MATERIALS AND METHODS

This study, which was approved by the Huddinge University Hospital Ethical Committee for Human Research, was performed on patients as listed in Table I at the department of Surgery, Läkarutbildningen Hötorgst, Stockholm, Sweden. The patients included in the study came to the clinic after self-examination or as referral from other medical agencies. At the clinic, an experienced surgeon screened the patients for skin cancer. Measurements of suspicious lesions were made with an electrical impedance spectrometer both over the center of the lesion as well as from an ipsilateral reference skin site. The suspect lesions are located all over the body, with some lesion types preferentially in the head and shoulder region, which is more exposed to sun radiation. Before the measurements, the reference skin and lesions were soaked with 0.9% physiological saline solution (pH 6) for approximately 1 min to reduce the naturally high impedance of stratum corneum and to increase the contact between the probe and tissue. The lesions were then excised and diagnosed by histology. Subclassifications of the lesion types have not been considered in this study. The same operator was used throughout the study.

Electrical impedance was measured with the SciBase II depth selective impedance spectrometer (SciBase AB, Huddinge, Sweden), at 31 logarithmically distributed frequencies between 1 and 1000 kHz using a two-point noninvasive probe. The electrode system at the tip of the hand-held probe consists of four concentric circular gold electrodes on a ceramic plate, shown in Fig. 1. Voltage is applied at the two outermost electrodes and the current is sensed with the center electrode. A guard electrode in between the sense and drive electrodes eliminates unwanted leakage currents at the surface of the skin. A “virtual” electrode is created in between the two voltage electrodes. Varying the proportion of voltages applied at the two electrodes will enable the “virtual” electrode to move between the two. One factor determining depth penetration of currents is the distance between electrodes (a rule of thumb is that the depth penetration is approximately half the distance between electrodes) and, thus, it is possible to measure electrical impedance at different volumes, or depths, in the skin. Impedance spectra of the lesions and reference skin was measured at five depth steps, approximately 0.1–2 mm into the tissue [16]. Depth penetration of currents is also dependent upon frequency and layered structure of the skin. Depth selective impedance spectra of two lesions and reference skin are exemplified in Fig. 2.

It is known that the electrical impedance properties of human skin vary significantly with, e.g., location on the body, age, gender, and season [23]–[26]. These variations are considered to be biological noise that impairs the accuracy of skin cancer detection. Baseline skin impedance, i.e., impedance of skin ipsilateral to the lesions, was used to balance out some of the impedance variations not related to the lesions, and the relation between baseline and lesion impedance was used to identify skin cancer. The relation between electrical impedance of baseline skin and lesion was approximated using squared correlation coefficients of the linear dependency between reference and lesion phase, \( r^2_{\theta_{ref},\theta_{les}} \) and logarithmic magnitude, \( r^2_{\log[Z_{ref}],\log[Z_{les}]} \), given by (1) and (2), where \( \theta_{ref} \) is the phase, \( \overline{\theta} \) is the average phase, \( |Z_{ref}| \) is the magnitude, \( \log(Z) \) is the average logarithmic magnitude, \( f \) is a frequency within the range given by \( f_1 \) and \( f_2 \), and \( d \) is depth setting. In terms of electrical impedance of skin and lesions, \( r^2 \) is a value of the linear dependency between reference skin and lesion, a rough measure of how much the lesion resembles the surrounding reference skin. This is exemplified in Fig. 2, where \( r^2 \) of skin and two lesion types is shown. [See equations (1)–(2) at the bottom of the next page.] In order to sort out the cancers from the nevi, the frequency range, \( f_1 \) and \( f_2 \), was chosen based on visual inspection of the impedance spectra, \textit{a priori} knowledge, and receiver operating characteristic (ROC) methodology [27]. Frequencies between 1 and 1000 kHz was used to separate the nonmelanoma and actinic keratoses from the benign lesions, and magnitude between 1 and 10 kHz and phase between 0.1

Fig. 1. Noninvasive probe used throughout the study. The electrode system consists of four concentric electrodes attached to a ceramic plate. The two outermost electrodes drive the voltage, the second electrode from the center is guard, and the center is sink electrode. Diameter of the outermost electrode is approximately 10 mm.
and 1 MHz was used to sort out the melanoma from the benign nevi.

It was considered important to keep the identification of the lesions simple, and linear cutoffs, rather than more complex curves or artificial neural networks, were used to reduce the possibility of over-fitting, which is an obvious risk when there are few observations (e.g., 16 melanoma lesions). Moreover, it is crucial to identify as many malignant lesions as possible with the price of misjudging some benign nevi (it is worse to miss a cancer than to misjudge a benign nevus as malignant). For the very dangerous melanoma it is of vital importance not to miss any lesions at an early stage since this could be equivalent to a death sentence, i.e., sensitivity should be 100%. Hence, according to these clinical requirements, the cutoff limits were chosen to maximize the sensitivity rather than the specificity. In practice, this means that the linear cutoff limits were set at maximal specificity where the sensitivity was 100%. Sensitivity was defined as the percentage of the histologically diagnosed cancer lesions recognized by the impedance technique, and specificity as the percentage of the histologically diagnosed nevi recognized by the impedance technique. ROC methodology was used in the data analysis. If the cutoff is shifted iteratively, sensitivity and specificity can be calculated for each iteration. A plot of specificity versus sensitivity forms a ROC curve. The area under the curve is a measure of the accuracy of the classification. If the area is equal to one, there is ideal separation between the lesion
types and the technique will classify all lesions correctly, and if the area is 0.5, the lesion groups are overlapping and the accuracy is as bad as random classification [27].

For pedagogic purposes, the logarithmic of one minus squared correlation coefficient, log(1 − r²) rather than r², is used to visualise the relation between the lesions because the distribution of r² of our data was close to exponential, whereas the log(1 − r²) was closer to Gaussian, which is obviously easier to interpret.

III. RESULTS

The area under ROC curve of the identification of actinic keratoses and nonmelanoma cancers from benign nevi was 98.3%, and 89.0% for the malignant melanoma versus benign nevi separation, shown in Fig. 3. Using the clinical requirements of the cutoff levels mentioned in Section II, it was possible to separate the nonmelanoma skin cancers and actinic keratoses from the benign nevi with 86.9% specificity (444/511) at 100% sensitivity (94/94), shown in Fig. 4, and to identify the melanoma lesions from the nevi with 75.3% specificity (385/511) at 100% sensitivity (16/16), shown in Fig. 5.

IV. DISCUSSION

Our results indicate that the noninvasive multifrequency bio-electrical impedance technique is a powerful tool in identifying skin cancer, in particular nonmelanoma skin cancers and actinic keratosis. Although we did not use conventional visual screening and dermoscopy in this study, the sensitivity and specificity of the impedance technique seem to be as good as, or better than, visual screening made by general practitioners [6], [28], and in the same order as dermoscopy [7].

The results of the BCC identification from benign nevi are in line with [20], however, a much higher accuracy was attained although the same frequency interval and depth settings were used. We believe that the accuracy difference is due to the fact that a different impedance spectrometer, virtually immune to external electromagnetic noise, was used in this study. Moreover, we used a much larger population (e.g., 16 versus 511 benign lesions) and more robust numerical methods than [21] and achieved similar accuracy, which confirms their results. In [22], only one frequency (2 kHz) at a fixed depth setting was used to separate melanoma and benign lesions, and this might explain their somewhat lower accuracy.

In parts of this study, we separated nonmelanoma skin cancers and actinic keratoses from benign pigmented nevi. Trained general practitioners can separate them by visual screening, and
the clinical relevance of this comparison may, thus, be limited. However, technically, our results demonstrate a significant potential of the method, despite the fact that the choice of lesions was motivated by experimental availability rather than clinical urgency.

It should be noted that the cutoffs presented in this manuscript represent the maximal accuracy found for the lesions in this study. In a future practical situation at the clinic, where the instrument is used in screening, the cutoffs should be adjusted to get a satisfactory safety margin in order to identify all possible cancer variations, and the specificity would, thus, decrease somewhat.

The diameter of the outer electrode of the probe is larger than most of the lesions in the study, and measurements of small lesions will include impedance of both lesion and nearby skin and, thus, dilute the lesion impedance. However, in [21] it was found that simple normalization using reference skin close to the lesion was better for skin cancer detection than adjusting the measured impedance with lesion size. The lesions included in our study are obviously big enough to influence the pattern of the impedance spectra in a characteristic way. Of course, there will be a lower limit that can be allowed in order to get data above the noise level, but this is not sufficiently investigated at this point. It is possible to reduce the size of the electrode system somewhat to accommodate smaller lesions but it must be kept in mind that the skin surface structure sets a limit for meaningful reduction of the electrodes.

From Figs. 2, 4, and 5 it can be concluded that electrical impedance of nevi is more related to reference skin than the cancers. The impedance difference between nevi and nonmelanoma skin cancer is most likely due to the status of the stratum corneum. The stratum corneum of benign nevi is intact, whereas the nonmelanomas are often scaly and occasionally ulcerated, and the barrier function of stratum corneum of nonmelanoma skin cancers is, thus, degenerated, which easily can be detected with the electrical impedance technique [16]. Melanoma often manifest in the region between the epidermal and dermal layers, and do not affect the stratum corneum until the cancer has grown out to the surface of the skin, and the impedance difference between nevi and melanoma is more sublime because the features of the stratum corneum are similar. It is not fully investigated why the impedance of melanoma differed from nevi, but it is most likely correlated to the cellular differences that can be seen histopathologically, e.g., shape, size, and orientation differences. Hence, impedance of nevi versus melanoma is more overlapping than impedance of nonmelanoma versus nevi, and the accuracy is, thus, higher for the nonmelanoma than the melanoma lesions.

In [18] and [20] it was suggested that using a new prototype probe with a dedicated surface with extremely small spikes that penetrate through the stratum corneum, but not through dermis, demonstrated by Griss et al. [29], will reduce the biological impedance variations not related to skin lesions and, hence, improve skin cancer detection [30]. Measurements with spike probes are in progress and preliminary results are promising. We believe that this technical addition will facilitate identification of other harmful cutaneous lesions, such as dysplastic nevi, and enhance the accuracy of melanoma detection in the future.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the staff at Department of Surgery, Läkartidningen Hötorget, Stockholm, Sweden.

REFERENCES


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