Electrical impedance spectroscopy as a potential adjunct diagnostic tool for cutaneous melanoma

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Background: Previous studies have shown statistically significant differences in electrical impedance between various cutaneous lesions. Electrical impedance spectroscopy (EIS) may therefore be able to aid clinicians in differentiating between benign and malignant skin lesions.

Objectives: The aim of the study was to develop a classification algorithm to distinguish between melanoma and benign lesions of the skin with a sensitivity of at least 98% and a specificity approximately 20% higher than the diagnostic accuracy of dermatologists.

Patients/Methods: A total of 1300 lesions were collected in a multicentre, prospective, non-randomized clinical trial from 19 centres around Europe. All lesions were excised and subsequently evaluated independently by a panel of three expert dermatopathologists. From the data two classification algorithms were developed and verified.

Results: For the first classification algorithm, approximately 40% of the data were used for calibration and 60% for testing. The observed sensitivity for melanoma was 98.1% (101/103), non-melanoma skin cancer 100% (25/25) and dysplastic nevus with severe atypia 84.2% (32/38). The overall observed specificity was 23.6% (66/280). For the second classification algorithm, approximately 55% of the data were used for calibration. The observed sensitivity for melanoma was 99.4% (161/162), for non-melanoma skin cancer was 98.0% (49/50) and dysplastic nevus with severe atypia was 93.8% (60/64). The overall observed specificity was 24.5% (116/474).

Conclusion: EIS has the potential to be an adjunct diagnostic tool to help clinicians differentiate between benign and malignant (melanocytic and non-melanocytic) skin lesions. Further studies are needed to confirm the validity of the automatic assessment algorithm.

Key words: diagnostics – electric impedance – melanoma – sensitivity and specificity – skin cancer

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THE WESTERN lifestyle over recent decades has been associated with substantial levels of ultraviolet radiation from the sun, the main cause of skin cancer (1–4). Despite good evidence for the risks of skin cancer from excessive sun exposure, the habits remain. Melanoma is the leading cause of death from skin cancer. Early detection is vital, as an in situ melanoma, once removed, has a survival rate close to 100%, whereas a Stage IV melanoma has a...
5-year survival rate of less than 15% with a median survival of 6–10 months (5). In the last decade early detection has improved through public awareness campaigns (6) and, not the least, by the introduction of dermoscopy into general practice (7–11). Although advances have been made in the detection of melanoma, visual recognition especially of early melanoma remains challenging. Numerous techniques are therefore evolving to further assist the physician (12). Among these, only a few incorporate an automated assessment algorithm, one of them being electrical impedance spectroscopy (EIS). Previous studies with EIS, conducted with a prototype device, obtained good accuracy for the detection of melanoma. As it was, however, found to be insufficient for the usage as an adjunct diagnostic tool (13), the device has been upgraded with revisions to electrode and probe designs plus the measurement procedure. This second international study, using the refined techniques and equipment has been set up to develop an automatic classification algorithm for melanoma.

The aim of this study was to calibrate and verify a classification algorithm designed to assist the dermatologist in the detection of primary cutaneous melanoma. In this study, the results of the clinical trial are presented, and discussed in the context of the regulatory definitions of an adjunct device.

**Material and Methods**

**Data collection**

An international, multicenter, prospective, non-controlled, non-randomized, clinical trial was conducted at 19 private and/or academic dermatological centres in Germany, Hungary, Sweden, Switzerland and the United Kingdom. Prior to initiation, the study was approved by national and local ethics committees and carried out in accordance with international conference of harmonization of good clinical practice (ICH-GCP).

After obtaining informed consent from each patient, eligible lesions destined for excision were measured with the SciBase III electrical impedance spectrometer (SciBase AB, Stockholm, Sweden). After a maximum of 14 days the lesions were surgically excised and subjected to histopathological evaluation. The first pathological analysis was performed by the local pathologist and a second analysis, the gold standard, was performed independently by a panel of three expert histopathologists. All patients who fulfilled the following inclusion criteria were enrolled: men or women of any ethnic group, aged at least 18, with one or more primary skin lesion(s) (not metastatic or recurrent), at least 2 mm in diameter, located on normal uninfamed skin and requiring full excision for histopathological analysis. A maximum number of eight lesions per patient could be included into the study. Exclusion criteria included patients with lesions under finger and toe nails, in sites where the electrode could not reach, e.g. between toes, those lesions with abnormal reference areas (usually inflammatory skin disease like eczema and psoriasis), those with lesion in scars or striae, crusted lesions and those previously subjected to any surgical procedure. The period of inclusion spanned between January 2009 and November 2010, during which a total of 1300 lesions from 1134 patients were enrolled into the study.

The exclusion criteria during the training study were purposefully kept wide to enable the evaluation of a large cohort of different types of lesions. The exclusion criteria were reviewed and expanded during the classification algorithm development, and additional inclusion and exclusion criteria were introduced, as depicted in Table 1.

Out of these, 751 lesions from 681 patients were considered eligible for analysis. A summary of reason for exclusion can be found in Table 1.

**Electrical impedance spectrometer measurements**

Electrical impedance was measured with the SciBase III electrical impedance spectrometer, equipped with a spring-loaded probe and a disposable five-bar electrode. The system measures bio-impedance of the skin at 35 different frequencies, logarithmically distributed from 1.0 kHz to 2.5 MHz, at four different depths utilizing 10 permutations. The depth selectivity is facilitated by the use of one sense and one injection bar of the electrode. The spatial localization of the sense and injection bar of the electrode determines the depth penetration as illustrated in Figure 1a.

The surface of each electrode bar is furnished with small micro-invasive pins covered with
Measurements

Electrical impedance measurements were performed at least twice. The first reference measurement was taken on healthy skin located 2–3 cm away from the lesion or on the contralateral side. By measuring the healthy adjacent or similar contralateral skin, each lesion had an intraindividual reference measurement, taking into account the variability of the skin due to both intrinsic and extrinsic factors.

Prior to all the measurements the skin site was soaked with 0.9% saline solution for at least 30 seconds. One or more measurements were conducted on the lesion itself depending on the size of the lesion. The electrode is approximately 5 × 5 mm², so with lesions greater than 5 mm diameter, multiple measurements were taken for a full evaluation.

Classification algorithm training and testing

Pre-processing: All forms of electrical equipment can be subject to electromagnetic interference and even though steps are taken to reduce electromagnetic interference (for example by adhering to the electromagnetic compatibility standard IEC-60601-1), some electric spike and noise interference from surrounding equipment or electrical mains can occasionally be identified in the electrical impedance measurements. To ensure that the electromagnetic noise did not impact the outcome of the classification algorithm, a pre-processing algorithm was implemented to filter out noise and remove unwanted spikes from the measurements.

Calibration and test cohorts: Classification algorithm calibration and testing was conducted in two stages. In the first stage of development, the data were randomized into two cohorts for

Table 1. Reasons for exclusion of lesions from the analysis

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Number of lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled lesions</td>
<td>1300</td>
</tr>
<tr>
<td>Exclusions</td>
<td></td>
</tr>
<tr>
<td>Screening failure</td>
<td>2</td>
</tr>
<tr>
<td>Protocol violations</td>
<td>72</td>
</tr>
<tr>
<td>No measurements performed</td>
<td>35</td>
</tr>
<tr>
<td>Unable to map lesions with measurements</td>
<td>9</td>
</tr>
<tr>
<td>Lesion not excised</td>
<td>18</td>
</tr>
<tr>
<td>Poor histopathology</td>
<td>11</td>
</tr>
<tr>
<td>No consensus diagnosis reached by pathologists</td>
<td>20</td>
</tr>
<tr>
<td>Expanded Exclusions</td>
<td></td>
</tr>
<tr>
<td>Bleeding, traumatized or ulcerated lesion*</td>
<td>38</td>
</tr>
<tr>
<td>Lesion located on acral skin†</td>
<td>11</td>
</tr>
<tr>
<td>Surface area not measurable‡</td>
<td>34</td>
</tr>
<tr>
<td>Insufficiently covered with measurements§</td>
<td>2</td>
</tr>
<tr>
<td>No clinical suspicion of melanoma¶</td>
<td>5</td>
</tr>
<tr>
<td>Hair-bearing areas**</td>
<td>2</td>
</tr>
<tr>
<td>Reference Quality Algorithm</td>
<td></td>
</tr>
<tr>
<td>Poor reference measurement quality††</td>
<td>290</td>
</tr>
</tbody>
</table>

*The measured electrical impedance is governed by the bleeding, traumatization or ulceration part of the lesion independently of whether the lesion is benign or malignant, and the lesions were therefore excluded.
†The thick stratum corneum on acral skin makes it extremely difficult to detect changes that occur in the lower layers of the skin and the lesions were therefore excluded.
‡Lesions where the whole lesion surface is not possible to measure, e.g. lesion on a stalk, or where insufficiently covered were excluded. As the electrical impedance methodology can only detect changes that occur underneath the electrode, and not in its vicinity, the whole lesion needs to be measured to ensure that the malignancy is not missed.
§Lesions such as obvious neurolipomas or epidermoid (follicular) cysts were excluded.
**It is difficult to both gain access and moisten the lesion hair-bearing areas and the lesions were therefore excluded.
††The main purpose of the reference quality algorithm is to ensure that measurements are performed with sufficient quality. In future use of the device, the reference quality algorithm will be implemented, which enables the operator to redo the measurement with insufficient quality. The exclusions due to an inadequate reference measurement will then drop substantially.

Fig. 1. (a) Schematic overview of the five-bar electrode. (b) Scanning microscope image of micro-invasive pins.
calibration and verification, utilizing 40% and 60% of the available data respectively. In the second stage approximately 55% of the data were used for calibration and the whole data set was used for verification.

Previously five different algorithm candidates, based on partial least-square discriminant analysis, artificial neural networks, k-nearest neighbours and support vector machine, were evaluated for the electrical impedance data gathered during the first part of the international melanoma algorithm training study (13). The best performance was established with a support vector machine, which is in line with general consensus in the field of machine learning of dichotomous classification tasks (14). Therefore two support vector machine classifiers were trained using EIS data for the two cohorts.

**Feature selection:** The electrical impedance data obtained from each measurement represented a very large data set consisting of the complex ratio of voltage to current, composed of the magnitude and phase shift at 35 frequencies for 10 permutations yielding a data set of 700 variables for each measurement. By combining permutations and frequencies, a large EIS feature space could be constructed. The features’ ability to differentiate between melanoma and benign cutaneous lesions was then ranked and, by means of cross-validation, the optimum number of features was extracted.

**Histopathology reference standard**
Out of all eligible lesions included in the study 99% were excised and subjected to histopathological evaluation. Approximately 1% of the eligible lesions included in the study did not undergo excision or could not be evaluated histopathologically. The first analysis was performed by a local pathologist and a second analysis, the study gold standard, was performed independently by a panel of three pathologists.

The clinical sensitivity and specificity was evaluated by reviewing the clinical diagnosis as well as the histopathology referral reason. Lesions having a benign histopathology referral were considered negative, whereas all other lesions were considered to be positive. The clinical diagnoses were then evaluated against the study gold standard (reference).

Furthermore, the sensitivity and specificity of the local pathologist, the gold standard used for clinical treatment, was evaluated by comparison with the study gold standard.

A total of 1116 lesions from 979 patients were available for histopathological evaluation. It is important to note that the local histopathological diagnosis stems not from one individual, but from a large cohort of pathologists from five different countries. The observed sensitivity and specificity values for the local histopathologist are therefore to be viewed as a measure of an average performance.

**Statistics**
The accuracy of the classification algorithm was described in terms of sensitivity and specificity at a set cut-off, defined as

\[
\text{Sensitivity} = \frac{\text{Number of true positives}}{\text{Number of true positives} + \text{Number of false negatives}}
\]

\[
\text{Specificity} = \frac{\text{Number of true negatives}}{\text{Number of true negatives} + \text{Number of false positives}}
\]

where patients with malignant tumours or dysplastic nevi with severe atypia were considered positive, and patients without such lesions were considered negative. Lesions with either a severe cytologic atypia or architectural disorder were diagnosed as dysplastic nevi with severe atypia. Note that the sensitivity was evaluated for each positive group separately. The observed sensitivity and specificity values of the device and of the pathologists are presented with two-sided 95% confidence limits.

**Results**

**Classification algorithm outcome**
From the data a total of two classification algorithms were trained and verified. For the first classification algorithm approximately 40% of the data were used for training and 60% for testing. The observed sensitivity for melanoma was 98.1% (101/103) (93.2, 99.8) (observed sensitivity between 93.2 and 99.8 within a two-sided 95% confidence interval), non-melanoma skin cancer 100% (25/25) (86.3, 100) and dysplastic nevi with severe atypia 86.2% (32/38)
The observed specificity for dysplastic nevi with mild to moderate atypia was 20.5% (38/185) (15.0, 27.1), benign melanocytic nevi and variants 42.2% (27/64) (29.9, 55.2), seborrhoeic keratoses 0% (0/22) (0, 15.4) and other lesions 11.1% (1/9) (0.28, 48.2). The overall specificity was 23.6% (66/280) (18.7, 29.0). The results are summarized in Table 2.

For the second classification algorithm the whole data set was made available for training. In this case approximately 55% of the data were used for training and then evaluated on the whole data set, i.e. 45% of the data were not utilized for training. The observed sensitivity for melanoma was 99.4% (161/162) (96.9, 99.98), non-melanoma skin cancer 98.0% (49/50) (89.4, 99.95) and dysplastic nevi with severe atypia 93.8% (60/64) (84.8, 98.3). One microcystic adnexal carcinoma was included in the study and was correctly classified as positive. The observed specificity for dysplastic nevi with mild to moderate atypia was 23.9% (77/322) (19.4, 29.0), benign melanocytic nevi and variants 35.5% (38/107) (26.5, 45.4), seborrhoeic keratoses 0% (0/28) (0, 12.3) and other lesions 5.9% (1/17) (0.2, 28.7). The overall specificity was 24.5% (116/474) (20.7, 28.6). The results are summarized in Table 3.

**Histology reference standard**

The observed sensitivity of the local pathologist for melanoma was 86.1% (192/223) (80.9, 90.4), non-melanoma skin cancer 96.9% (95/98) (91.3, 99.4) and the observed specificity 92.6% (736/795) (90.5, 94.3). The observed sensitivity of the dermatologist, for the eligible lesions, was 100% (162/162) (97.8, 100) and the specificity was 8.4% (40/474) (6.1, 11.3). However, it is important to note that majority of the lesions included in the study were pre-selected for excision with a suspicion for melanoma, i.e. per trial design a clinical sensitivity of 100% and specificity of 0%.

**Discussion**

**Requirements and considerations for an adjunct diagnostic method**

When developing an adjunct diagnostic method aimed to be used in clinical practice several considerations need to be taken into account. Foremost is the requirement on sensitivity and specificity with the objective to increase the diagnostic accuracy in clinical decision making. Particularly in the field of cancer detection, the sensitivity is of utmost importance, as a missed diagnosis can have a great impact on survival (5).

Diagnostic accuracy of melanoma depends on clinical expertise, dermoscope use and the tumour cohort studied. Both sensitivity and specificity are relative values and depend on the type of lesions studied (15–42). In view of the absence of a recognized standard for sensitivity and specificity in melanoma recognition, whether by dermatological experts or by others using a dermoscope, it was felt beneficial to

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>TP</th>
<th>FN</th>
<th>TN</th>
<th>FP</th>
<th>EIS sensitivity</th>
<th>EIS specificity</th>
<th>Two-sided confidence bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma*</td>
<td>101</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>98.1</td>
<td>–</td>
<td>(93.2, 99.8)</td>
</tr>
<tr>
<td>Tis (N/A)</td>
<td>30</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>(88.4, 100)</td>
</tr>
<tr>
<td>T1 (&lt;1.0 mm)</td>
<td>46</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>95.8</td>
<td>–</td>
<td>(85.7, 99.5)</td>
</tr>
<tr>
<td>T2 (1.01–2.0 mm)</td>
<td>14</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>(76.8, 100)</td>
</tr>
<tr>
<td>T3 (2.01–4.0 mm)</td>
<td>5</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>(47.8, 100)</td>
</tr>
<tr>
<td>T4 (&gt;4.0 mm)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Undefined</td>
<td>6</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>(54.1, 100)</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>25</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>(86.3, 100)</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>21</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>(83.9, 100)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>4</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>(39.8, 100)</td>
</tr>
<tr>
<td>Dysplastic nevi with severe atypia†</td>
<td>32</td>
<td>6</td>
<td>–</td>
<td>–</td>
<td>84.2</td>
<td>–</td>
<td>(68.7, 94.0)</td>
</tr>
<tr>
<td>Dysplastic nevi with mild-to-moderate atypia</td>
<td>–</td>
<td>38</td>
<td>147</td>
<td>–</td>
<td>20.5</td>
<td>–</td>
<td>(15.0, 27.1)</td>
</tr>
<tr>
<td>Melanocytic nevi and variants</td>
<td>–</td>
<td>27</td>
<td>37</td>
<td>–</td>
<td>42.2</td>
<td>–</td>
<td>(30.0, 55.2)</td>
</tr>
<tr>
<td>Seborrhoeic keratoses</td>
<td>–</td>
<td>0</td>
<td>22</td>
<td>–</td>
<td>0</td>
<td>–</td>
<td>(0, 15.4)</td>
</tr>
<tr>
<td>Other lesions</td>
<td>–</td>
<td>1</td>
<td>8</td>
<td>–</td>
<td>11.1</td>
<td>–</td>
<td>(0.28, 48.2)</td>
</tr>
<tr>
<td>Total</td>
<td>158</td>
<td>8</td>
<td>66</td>
<td>214</td>
<td></td>
<td>23.6</td>
<td>(18.7, 29.0)</td>
</tr>
</tbody>
</table>

TP true positive, FN false negative, TN true negative, FP false positive

*Median Breslow thickness 0.43 mm.

†Lesions with either a severe cytologic atypia or architectural disorder.

EIS, a potential adjunct diagnostic tool for MM
investigate expectations of potential users of the device. However, full understanding of the concepts of sensitivity and specificity prior to the survey was not verified. The survey of 118 general practitioners and dermatologists investigated the minimum sensitivity and specificity required to enable confidence in skin cancer detection, revealed that a sensitivity of 97% was generally judged useful (range 65–100%). Specificity levels required were much wider, dropping as low as 5% for some respondents. Bearing in mind that any random diagnostic test will always yield a sensitivity plus specificity of 100%, an adjunct diagnostic method, with a distinct requirement on sensitivity, should be at least superior to a random technique.

Another consideration that must be taken into account is the evaluation of the performance of an adjunct diagnostic tool. The most common assessment is comparison with the histopathology gold standard, which has a hypothetical accuracy of 100%. However, in reality it is below 100% when regarding gaps in reproducibility and discordancess among different pathologists (43–45). This was reflected in the results of this study in which the local pathologists’ had an observed sensitivity of 86% with specificity of 93% compared with the reference standard. Using an imperfect gold standard without careful consideration might not only impair the classification algorithm training but also the validation, which could cause the diagnostic method to be perceived as having a lower accuracy than might be the actual case. Therefore, in concordance with the previous study (13), a reference panel of three pathologists was used to increase the accuracy of the gold standard in this study.

So far, all results in this study have been presented with a dichotomous outcome. An important consideration in this context is whether the method will be used as an adjunct diagnostic tool or as the diagnostic tool. The Food and Drug Administration (FDA – Regulatory authority in the United States) has defined that whenever a test result can overrule a pre-test clinical result, and the test outcome can function as a stand-alone test, i.e. it does not only provide additional information, it is to be considered as a diagnostic test (46). Is then a method with a dichotomous outcome by definition a diagnostic test?

Given that an adjunct diagnostic test is meant to provide additional information that in combination with the clinical judgment should generate a final clinical diagnosis, the question can clearly be answered with yes. Whenever a positive (1) or negative (0) test result overrules the pre-test clinical diagnosis, it is by this definition diagnostic, even though the information given just tends to tip the balance of the clinical diagnosis.

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>TP</th>
<th>FN</th>
<th>TN</th>
<th>FP</th>
<th>EIS sensitivity</th>
<th>EIS specificity</th>
<th>Two-sided confidence bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma*</td>
<td>161</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>99.4</td>
<td>–</td>
<td>(96.6, 99.98)</td>
</tr>
<tr>
<td>Tis (N/A)</td>
<td>45</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>97.8</td>
<td>–</td>
<td>(88.5, 99.9)</td>
</tr>
<tr>
<td>T1 (≤1.0 mm)</td>
<td>80</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>(95.5, 100)</td>
</tr>
<tr>
<td>T2 (1.01–2.0 mm)</td>
<td>21</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>(83.9, 100)</td>
</tr>
<tr>
<td>T3 (2.01–4.0 mm)</td>
<td>7</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>(59.0, 100)</td>
</tr>
<tr>
<td>T4 (&gt;4.0 mm)</td>
<td>–</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>(63.1, 100)</td>
</tr>
<tr>
<td>Undefined</td>
<td>–</td>
<td>45</td>
<td>–</td>
<td>–</td>
<td>98</td>
<td>–</td>
<td>(89.4, 99.95)</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>39</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>(91.0, 100)</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>10</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>90.9</td>
<td>–</td>
<td>(58.7, 99.8)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>1</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>(2.50, 100)</td>
</tr>
<tr>
<td>Dysplastic nevi with severe atypia1</td>
<td>60</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>93.8</td>
<td>–</td>
<td>(84.8, 98.3)</td>
</tr>
<tr>
<td>Dysplastic nevi with mild to moderate atypia</td>
<td>–</td>
<td>77</td>
<td>245</td>
<td>–</td>
<td>23.9</td>
<td>–</td>
<td>(19.4, 29.0)</td>
</tr>
<tr>
<td>Melanocytic nevi and variants</td>
<td>–</td>
<td>38</td>
<td>69</td>
<td>–</td>
<td>35.5</td>
<td>–</td>
<td>(26.5, 45.4)</td>
</tr>
<tr>
<td>Seborrhoeic keratoses</td>
<td>–</td>
<td>0</td>
<td>28</td>
<td>–</td>
<td>0</td>
<td>–</td>
<td>(0, 12.3)</td>
</tr>
<tr>
<td>Other lesions</td>
<td>–</td>
<td>1</td>
<td>16</td>
<td>–</td>
<td>5.9</td>
<td>–</td>
<td>(0.2, 28.7)</td>
</tr>
<tr>
<td>Total</td>
<td>271</td>
<td>6</td>
<td>116</td>
<td>358</td>
<td>24.5</td>
<td>–</td>
<td>(20.7, 28.6)</td>
</tr>
</tbody>
</table>

TP true positive, FN false negative, TN true negative, FP false positive

*Median Breslow thickness 0.45 mm

†Lesions with either a severe cytologic atypia or architectural disorder.

TABLE 3. Differentiated outcome and accuracy of all eligible lesions. The melanomas are differentiated according to Breslow thickness, the dysplastic nevi according to the degree of atypia.
One way to conform to the regulatory requirements for an adjunct diagnostic tool could be to incorporate a score output, e.g. 0–10, where 0 is considered as benign and 10 as malignant. This would provide additional information rather than a dichotomous outcome, which always can be viewed as a stand-alone test. An alternative approach to incorporate a score could be to give the clinician the possibility to adjust the cut-off for the dichotomous outcome, thus potentially making the method adjunctive rather than purely diagnostic, as it can no longer be considered as a truly stand-alone test.

Once all the above considerations have been taken into account, a final consideration still needs to be addressed is the intended use of the method, i.e. in what situations can clinical value be proven.

Classification algorithm findings
A classification algorithm was first developed using only 40% of the electrical impedance data, keeping the remaining 60% blinded to enable a validation of the developed classification algorithm. Once the first classification algorithm was finalized and the threshold set, the results showed a high accuracy for the detection of melanoma and non-melanoma skin cancer, though having a somewhat lower accuracy for dysplastic nevi with severe atypia. This result is to be expected to some degree, as the amount of tissue alteration in a dysplastic nevus with severe atypia is less than that of a melanoma. However, when reviewing the dysplastic nevi with severe atypia in the training set compared with the ones in the test set, more difficult cases were found in the test set rather than in the training set. Therefore, a consecutive training was undertaken where the whole data set was available for training, of which 55% was incorporated into the classification algorithm and 45% remained unseen.

As mentioned in the introduction, the previous study had been conducted with a prototype device and a number of improvements could be identified that might increase the accuracy of the device. After implementation of these improvements, the results of this study results showed that the device had a very high observed sensitivity for detecting melanoma, non-melanoma skin cancer and dysplastic nevi with severe atypia. Only four dysplastic nevi with severe atypia and one in situ melanoma were missed. These were all small lesions with a diameter of only 2–4 mm so that the volume of cellular atypia might have been too small to detect, as a certain degree of atypia needs to be present in a lesion for the method to distinguish the change from a benign lesion. However, as the remaining 7 melanomas of small size (2–4 mm) had been accurately classified as positive, the method in general seemed to have a good sensitivity for small lesions as well.

The observed sensitivity of the device clearly met the target of at least 98% sensitivity. However, it fell somewhat short on the 20 percentage points higher specificity than clinical diagnosis of dermatologists, i.e. given 8.4% clinical specificity should have resulted in device specificity of approximately 28.4%. The reason is primarily twofold: First, the participating dermatologists were highly experienced in diagnosing cutaneous tumours with the naked eye and by dermoscopy, and as such their diagnostic accuracy might have been higher than that of the average dermatologist (7–11). Secondly, the majority of the lesions included in this study had been suspicious for melanoma and were destined for excision, which is why the clinical sensitivity and specificity, by study design, was 100% and 0% respectively. However, the true clinical specificity in this trial could be considered to fall somewhere between 0% and 8.4% because a few lesions with a low probability for melanoma had been included.

Conclusion
EIS has the potential to be an adjunct diagnostic tool to help clinicians differentiate between benign and malignant cutaneous lesions. Further studies are needed to confirm the validity of the classification algorithm.

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Contributors
All authors were involved in the design of the research study. All authors together with all the principal investigators mentioned in the acknowledgement, except UB, collected the data. Data management was handled by UB and data monitoring was performed by Quintiles in conjunction with SciBase clinical research associates. UB analysed the data. UB wrote the first draft and all authors contributed in the manuscript finalization.

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