Analysis of an electrical impedance spectroscopy system in short-term digital dermoscopy imaging of melanocytic lesions

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Summary

Background Electrical impedance spectroscopy (EIS) is a noninvasive diagnostic technique that measures tissue impedance.

Objectives To evaluate the effect of adding an EIS measurement at baseline to suspicious melanocytic lesions undergoing routine short-term sequential digital dermoscopy imaging (SDDI).

Methods Patients presented with suspicious melanocytic lesions that were eligible for short-term SDDI (with no clear feature of melanoma on dermoscopy). EIS measurement was performed at the first visit following dermoscopic photography. Normally, an EIS score of ≥4 is considered positive; however, this protocol investigated a higher cut-off in combination with SDDI. When the EIS score was ≥7 the lesion was excised immediately owing to the high risk of melanoma. Lesions with a score <7 were monitored with standard SDDI over a 3-month period.

Results From a total of 160 lesions analysed, 128 of 154 benign lesions received an EIS score of 0–6, giving a specificity of the EIS method for the diagnosis of melanoma of 83.1% (95% confidence interval (CI) 76.3–88.7). Five of the six melanomas found in this study had an EIS score ≥7, with a sensitivity for melanoma diagnosis of 83.3% (95% CI 35.9–99.6). When EIS 0–6 lesions were subsequently followed up with SDDI, one additional melanoma was detected (EIS = 6) giving a sensitivity for the diagnosis of melanoma overall of 100% (95% CI 54.1–100; six of six malignant melanomas excised) and a specificity of 69.5% (95% CI 61.5–76.6; 107 of 154 benign lesions not excised).

Conclusions If utilizing a protocol where an EIS score ≤3 requires no SDDI and ≥7 requires immediate excision, it reduced the need for SDDI by 46.9% (n = 75/160; 95% CI 39.0–54.9).

What’s already known about this topic?
- Short-term sequential digital dermoscopy imaging (SDDI) allows the detection of dermoscopically featureless melanoma but requires a delay in diagnosis.
- Electrical impedance spectroscopy (EIS) has a high sensitivity for the diagnosis of melanoma but a suboptimal specificity.

What does this study add?
- By combining EIS at baseline with SDDI there was a reduced need to proceed to SDDI in just under half of cases.
Malignant melanoma (MM) may be clinically and dermoscopically indistinguishable from melanocytic naevi, making early recognition a diagnostic challenge. Confirming a diagnosis of MM requires obtaining a skin biopsy specimen. However, the impact of cost and morbidity of multiple biopsies have to be considered, especially in patients with high-risk melanoma.

New technologies for MM diagnosis have been developed to improve clinical accuracy. Electrical impedance spectroscopy (EIS) is a noninvasive diagnostic technique that evaluates tissue structures by applying alternating electric current and measuring tissue impedance. This method is based on inherent electrical differences between benign, well-organized tissues and malignant, chaotic tissues. Changes in cell shape, size and membrane composition can be detected by EIS.

Several studies have assessed performance of EIS in melanoma diagnosis. Glickman et al. and Har-shai et al. tested the first version of this device for melanoma diagnosis, known as TranScan. Further improvements were made in this technique. The last version of the SciBase EIS device, known as Nevisense (SciBase, Stockholm, Sweden), was first studied for MM diagnosis by Mohr et al. in a multicentre prospective study. They tested two classification algorithms, and the sensitivities for MM diagnosis for each of the algorithms were 98.1% and 99.4%, respectively; the overall specificities were 23.6% and 24.5%, respectively. Malvehy et al. assessed the effectiveness of the Nevisense in a total of 1946 lesions in a prospective multicentre study. All lesions were excised and subjected to histopathological evaluation. The authors reported a high sensitivity (96.6%) and a negative predictive value (NPV) of 98.2%. Out of 1457 benign lesions, 956 were classified as EIS false positive (score ≥ 4), showing low specificity (34.4%) and a positive predictive value (PPV) of 21.1%. They demonstrated that lesions with a score 0–3 have a NPV of 98% (low risk of malignant lesions) and lesions with a score of 7–10 are very suspicious (PPV 22–64%).

Short-term sequential digital dermoscopy imaging (SDDI) is an important adjunct for the management of melanocytic lesions that allows detection of dermoscopy-featureless MM and reduces the rate of excisions of benign lesions in both specialist and primary care. The predominant eligible lesions for short-term SDDI are moderately atypical, flat or only slightly raised melanocytic lesions, without a history of change or dermoscopy evidence of melanoma, or are mildly atypical lesions with a patient history of change. This imaging technique is performed during two different appointments separated by an interval of 3 months, and dermoscopic image comparison allows the detection of change in the monitored melanocytic lesion. Any morphological change after monitoring is considered an indication to excise. The sensitivity for the diagnosis of melanoma using short-term SDDI (excluding lentigo maligna, which requires longer interval monitoring) is 94% and the specificity is 84%.

This study aimed to evaluate the effect of adding an EIS measurement at baseline to suspicious melanocytic lesions undergoing routine short-term SDDI, with the primary aim of evaluating if featureless melanoma can be identified at baseline when scored ≥ 7 without requiring SDDI, and the secondary aim of evaluating if it is possible to discharge from monitoring lesions with an EIS score of 0–3.

### Materials and methods

#### Study design

An observational, prospective study was conducted at two melanoma centres in Australia (the Sydney Melanoma Diagnostic Centre at Royal Prince Alfred Hospital, and the Melanoma Institute Australia). The study was approved by national and local ethics committees and an informed consent form was obtained from each patient enrolled in this study (protocol reference: X14-0350 / HREC/14/RPAH/472).

The recruitment was conducted from January 2015 to January 2016 and the last patient follow-up was performed in April 2016 (3-month follow-up based on short-term SDDI).

All patients who presented with a suspicious melanocytic lesion in their regular clinical dermatological examination who were eligible for short-term SDDI were screened according to the exclusion criteria as defined in a previous study conducted with the Nevisense device (Table 1). All successive eligible patients were invited to enrol in the study.

At the first evaluation, eligible patients had their first dermoscopic image taken with a digital SDDI device [SolarScan (Polartechnics, Sydney, Australia) or Dermoscopix (Sydney, Australia)] for short-term SDDI according to standard clinical practice. However, 70% ethanol was placed on the lesion–camera interface to record digital surface microscopic images, avoiding oil interference in the EIS measurement.

The EIS measurement was performed with the Nevisense system (SciBase) at the first visit following the dermoscopic imaging.

| Exclusion criteria                                                                 | Men or women aged < 18 years | Lesion located on mucosal surface | Lesion with foreign matter, e.g. tattoo or splinter |
|-----------------------------------------------------------------------------------|-------------------------------|----------------------------------|-----------------------------------------------|
| Lesion metastases or recurrent lesions                                            |                               |                                  |                                               |
| Lesion < 2 mm or > 20 mm in diameter                                              |                               |                                  |                                               |
| Lesion located on acral skin, e.g. sole or palm                                   |                               |                                  |                                               |
| Lesion located on hair-covered areas, e.g. scalp, beard, moustaches or whiskers   |                               |                                  |                                               |
| Lesion located in genitalia                                                       |                               |                                  |                                               |
| Lesion located in an area that has been previously biopsied or subjected to any kind of surgical intervention or trauma |                               |                                  |                                               |
| Subject not willing or able to read, understand and sign the study-specific informed consent form |                               |                                  |                                               |
photography as previously described. The skin was moistened for 30 s with physiological saline and a reference measurement of healthy skin close to the lesion was taken before the lesion measurement. The measurement takes around 10 s and it is painless and noninvasive. The system computes both a score (0–10) and a dichotomous output (EIS negative/positive) at a fixed cut-off of < 4.

Based on the results published by Malvehy et al., the lesions were separated into three groups prior to the commencement of the study.

Lesion score < 4
Low-risk lesions with a NPV of 98% had the standard monitoring of short-term 3-monthly SDDI, and we evaluated retrospectively the possibility of discharging these lesions from SDDI in future protocols. Lesions with no dermoscopic change over 3 months were considered benign according to the standard of care, with any change leading to excision.

Lesions score 4–6
An intermediary score group with a PPV of 9–18% (from the SciBase Clinical Reference Guide) had the standard 3-month SDDI monitoring and follow-up as above.

Lesions score ≥ 7
High probability of melanoma lesions with a PPV of 22–64% (from the SciBase Clinical Reference Guide) underwent immediate excision (i.e. without SDDI).

A flowchart of recruited lesions is given in Figure 1. Of note, we excluded from analysis all nonmelanocytic lesions, lesions where no pathology consensus could be reached, lesions where the reading of EIS could not be obtained and lesions that could not be imaged at 3 months as the patient was lost to follow-up. Only melanocytic lesions and the ability to complete monitoring and EIS met the study criteria.

Statistical analysis
Patient characteristics are summarized by frequency for categorical variables and median (range) for continuous variables. The study was performed during a defined period of time. True-negative, true-positive, false-negative and false-positive results were determined using histopathological diagnosis, with unchanged SDDI lesions treated as benign. To validate the proposed change in the EIS score thresholds, sensitivity, specificity, PPV and NPV and their 95% confidence intervals (CIs) were computed for each diagnosis.

Fig 1. Study process. EIS, electrical impedance spectroscopy.
Results

Participants and lesions

From January 2015 to January 2016 a total of 118 patients (171 lesions) were enrolled. Nonmelanocytic lesions \( n = 3 \), equivocal melanocytic lesions \( n = 1 \), lesions where the EIS reading was technically impossible \( n = 4 \) and patients who could not attend follow-up \( n = 3 \) were excluded.

A total of 160 lesions were analysed in 112 patients (Table 2). The median age of the patients was 46 years (range 23–82 years) and 63/4% \( n = 71 \) of the patients were female. Most of the lesions were located on the trunk (51/2%), with 23 (14/4%) lesions located on abdomen, 51 (31/9%) on the back and shoulders, and eight (5/0%) on chest. In total, 26/9% \( n = 43 \) were located on the inferior extremities, 13/7% \( n = 22 \) on the superior extremities, 3/1% \( n = 5 \) on the buttocks and 5/0% \( n = 8 \) on the head and neck.

When it came to EIS measurement results, 31 lesions had a score \( \geq 7 \) and were excised. Five of these lesions were diagnosed as melanoma, 22 as dysplastic naevi and four as benign naevi. Eighty-five lesions had a score of 4–6 and 44 lesions had scores \( \leq 3 \) (Table 3).

At the end of recruitment, 128 of 154 benign lesions had an EIS score 0–6, giving a specificity of the EIS method for the diagnosis of melanoma at this higher cut-off of 83/1% (95% CI 76/3–88/7). Five of the six melanomas found in this study had an EIS score \( \geq 7 \). The negative melanoma lesion had an EIS score of 6 and was identified at the end of the SDDI following morphological change. Therefore, the observed sensitivity for the diagnosis of melanoma for the EIS device alone at this higher cut-off of \( \geq 7 \) (disregarding the association of subsequent SDDI) was 83/3% (95% CI 35/9–99/6). Of lesions with an intermediary EIS score (4–6), 61 lesions did not change on SDDI, and of the 24 changed and excised lesions,

Table 2

| Screened patients | 118 |
|-------------------|-----|
| Included patients \( n \) | 112 |
| Male/female (%) | 46/64 |
| Median (range) age (years) | 46 (23–82) |
| Screened lesions | 171 |
| Excluded lesions | 11 |
| Nonmelanocytic | 3 |
| Unclassifiable by pathology | 1 |
| EIS technical issue | 4 |
| Lost to follow-up for SDDI | 3 |
| Included lesions | 160 |
| Benign (total) | 154 |
| No change in SDDI | 101 |
| Histopathology | 53 |
| Melanoma (all histopathology confirmed) | 6 |

EIS, electrical impedance spectroscopy; SDDI, sequential digital dermoscopy imaging. *Equivocal/uncertain for malignancy.

Table 3

| SDDI | Group 1 (EIS score \( \leq 3 \)) | Group 2 (EIS score 4–6) | Group 3 (EIS score \( \geq 7 \)) |
|------|-------------------------------|-------------------------|-------------------------------|
| Unchanged | 40 | 61 | No monitoring (excised directly) |
| Changed | 3 | 22 | No monitoring (excised directly) |
| Lesions excised at first visit in groups 1 and 2 | 1 | 2 | – |
| Total lesions | 44 | 85 | 31 |
| Histopathological results | | | |
| Benign | 3 (1 excised before SDDI) | 6 (1 excised before SDDI) | 4 |
| Dysplastic | 1 | 17 (1 excised before SDDI) | 22 |
| Melanoma | 0 | 1 | 5 |

*The lesions were excised as requested by the patients at the first visit.

Fig 2. Overview. SDDI, sequential digital dermoscopy imaging; EIS, electrical impedance spectroscopy.
there was one melanoma, 17 dysplastic naevi and six benign naevi. Of the 44 lesions with an EIS negative score of 0–3, three lesions changed and were naevi on histology. Only three of 43 (7.0%) naevi monitored with a negative score of 0–3 changed following SDDI vs. 21 of 82 (25.6%) naevi monitored with an intermediate score of 4–6 ($P = 0.01$).

This study evaluated a predetermined protocol combining SDDI and EIS, where melanocytic lesions undergoing routine short-term SDDI have a baseline Nevisense measurement with a score of 0–3 indicating a benign lesion without requiring SDDI, a score of 4–6 indicating a benign lesion but requiring SDDI (and excised if change detected at 3 months) and a score 7–10 indicating possible melanoma and excised without SDDI. The sensitivity of this combined protocol for the diagnosis of melanoma was 100% (95% CI 54.1–100; six of six MM excised) and the specificity was 69.5% (95% CI 61.5–76.6; 107/154 benign lesions not excised). This protocol reduced the need for SDDI in routine practice by 46.9% ($n = 75/160$; 95% CI 39.0–54.9) (see the study overview in Fig. 2).

Analysis of the melanomas

A total of six MM were diagnosed in this study from the total 160 lesions analysed by the EIS/SDDI protocol. Five MM were identified by the EIS device at this higher cut-off of $\geq 7$ and were excised without the need for 3-monthly follow-up. Three lesions were scored as 7, one lesion as 8 and one lesion as 10. The in situ MM scored as 6 was identified by SDDI (the lesion had changed at 3-month monitoring; Fig. 3). All melanomas were in situ MM except for the lesion scored as 10 (Breslow thickness 0.8 mm).

Based on the dermoscopic criteria of Menzies et al., none of the MM lesions showed negative features. The MM lesion scored as 10 showed one positive feature (broadened network; Fig. 4).

Discussion

The main aim of this study was to examine the performance of an EIS device known as Nevisense (SciBase) at baseline in suspicious melanocytic lesions undergoing routine short-term digital dermoscopy imaging. It should be noted there is one prospective evaluation regarding EIS alone (lesions excised with a score of $\geq 7$), one prospective evaluation regarding the coupling of EIS and SDDI as was performed in the study (4–6 scored lesions undergoing SDDI) and one retrospective analysis of low EIS-scored ($\leq 3$) lesions as it could have been ideally performed (with no SDDI).

Previous studies have assessed the effectiveness of the Nevisense system in distinguishing between benign lesions of the skin from melanoma. The authors reported a high sensitivity (96.6%) and a NPV of 98.2% but a low specificity (34.4%) and PPV of 21.1%.

Short-term SDDI is a well-recognized method of evaluating suspicious melanocytic lesions with good diagnostic accuracy (94% sensitivity and 84% specificity), but the diagnosis is delayed by 3 months and requires the patient to return to the clinic. This study evaluated the role of performing a baseline EIS measurement in order to identify melanomas without the need for 3-month follow-up (score $\geq 7$) and potentially removing the need for follow-up of low-scored lesions (score 0–3).

The primary aim – of evaluating whether featureless melanoma can be identified at baseline (score $\geq 7$) without requiring SDDI, using the criteria of Menzies et al. – was achieved, as five of the six melanomas found in this study had
an EIS positive score $\geq 7$ and were excised immediately. A possible limitation of our study is that 3-month unchanged lesions were not followed up beyond that time period to confirm their benign nature. However, in our hands, when following up 3-month unchanged lesions beyond that time period, 99.2% were benign. Indeed, of the 0.8% that were subsequently found to be melanoma, it is impossible to know whether they had transformed from previously benign naevi or were melanoma at baseline.

A further limitation of our study is that we did not randomize lesions to the combined protocol (EIS and SDDI) with SDDI alone, which would have allowed a precise comparison of the number of lesions needed to be excised to find a melanoma between both of these groups. Furthermore, the clinician was not strictly blinded to the baseline EIS score when assessing SDDI change, which is a potential source of bias, and an independent panel of histopathologists did not review the cases. Finally, this study was not powered for sensitivity, indicated by the wide CIs in the sensitivity results. However, the sensitivity of both the EIS device and SDDI have been previously reported in studies with larger samples. 

The secondary aim was to evaluate if it is possible to discharge from monitoring lesions with an EIS score of 0–3. Of the 43 lesions with a score 0–3, three lesions changed and were benign on histology. Of note, we can expect that there was no melanoma in this group as the NPV of a score of 0–3 was 98% in a previously described large prospective trial, and 93% of the low-score lesions did not change with SDDI. In this sample, the EIS device showed a good performance in recognizing benign lesions scored as 0–3. Interestingly, the biological activity of these low-scoring naevi was significantly different than higher-scoring naevi, as only 7% of low scoring naevi changed morphologically over 3 months vs. 26% of those with an intermediate score.

We also studied the role of monitoring lesions with an EIS score of 4–6 rather than excising them according to the previous described protocol. From the 83 lesions scored 4–6, 22 lesions changed following monitoring (five were benign naevi, 16 were dysplastic naevi and one was an in situ melanoma). In our sample, the addition of SDDI to the EIS measurement was critical in identifying the melanoma scored 4–6 by EIS.

Our study demonstrated that adding the EIS technique at baseline to melanocytic lesions undergoing SDDI achieves good diagnostic accuracy while avoiding the need for follow-up in just under half of all cases. Furthermore, applying an EIS measurement at the first SDDI imaging can provide early excision of a malignant melanocytic lesion without the delay seen in 3-monthly monitoring, and also avoid potential problems of compliance (failure to return at 3 months).

Finally, we have to consider that the application of these diagnostic techniques depends on the clinician’s expertise to recognize correctly suspicious lesions suitable for SDDI. Further studies in other centres with larger samples are also needed to confirm the role of EIS in investigating suspicious melanocytic lesions using this protocol.

References
1. Puig S, Argenziano G, Zalaudek I et al. Melanomas that failed dermoscopic detection: a combined clinicodermoscopic approach for not missing melanoma. Dermatol Surg 2007; 33:1262–73.
2. Moloney FJ, Guitera P, Coates E et al. Detection of primary melanoma in individuals at extreme high risk: a prospective 5-year follow-up study. JAMA Dermatol 2014; 150:819–27.
3. March J, Hand M, Grossman D. Practical application of new technologies for melanoma diagnosis: Part I. Noninvasive approaches. J Am Acad Dermatol 2015; 72:929–41.
4. Morimoto T, Kimura S, Konishi Y et al. A study of the electrical bio-impedance of tumors. J Invest Surg 1993; 6:25–32.
5. Glickman YA, Filo O, David M et al. Electrical impedance scanning: a new approach to skin cancer diagnosis. Skin Res Technol 2003; 9:262–8.
6. Har-Shai Y, Glickman YA, Siller G et al. Electrical impedance scanning for melanoma diagnosis: a validation study. Plast Reconstr Surg 2005; 116:782–90.
7. Aberg P, Nicander I, Hansson J et al. Skin cancer identification using multifrequency electrical impedance – a potential screening tool. IEEE Trans Biomed Eng 2004; 51:2097–102.
8. Aberg P, Geladi P, Nicander I et al. Non-invasive and microinvasive electrical impedance spectra of skin cancer – a comparison between two techniques. Skin Res Technol 2005; 11:281–6.
9. Aberg P, Birgersson U, Eksner P et al. Electrical impedance spectroscopy and the diagnostic accuracy for malignant melanoma. Exp Dermatol 2011; 20:648–52.
Electrical impedance spectroscopy as a potential adjunct diagnostic tool for cutaneous melanoma. Skin Res Technol 2013; 19:75–83.

Clinical performance of the Nevisense system in cutaneous melanoma detection: an international, multi-centre, prospective and blinded clinical trial on efficacy and safety. Br J Dermatol 2014; 171:1099–107.

Short-term digital surface microscopic monitoring of atypical or changing melanocytic lesions. Arch Dermatol 2001; 137:1583–9.

Assessment of the optimal interval for and sensitivity of short-term sequential digital dermoscopy monitoring for the diagnosis of melanoma. Arch Dermatol 2008; 144:502–6.

The identification of clinically featureless incipient melanoma using sequential dermoscopy imaging. Arch Dermatol 2006; 142:1113–19.

Detection of primary melanoma in individuals at extreme high risk: a prospective five-year follow-up study. JAMA Dermatol 2014; 150:819–27.

Impact of dermoscopy and short-term sequential digital dermoscopy imaging for the management of pigmented lesions in primary care: a sequential intervention trial. Br J Dermatol 2009; 161:1270–7.

Availability of digital dermoscopy in daily practice dramatically reduces the number of excised melanocytic lesions: results from an observational study. Br J Dermatol 2012; 167:778–86.

Frequency and morphologic characteristics of invasive melanomas lacking specific surface microscopic features. Arch Dermatol 1996; 132:1178–82.