Evaluation of electrical impedance spectroscopy as an adjunct to dermoscopy in short-term monitoring of atypical melanocytic lesions

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ABSTRACT

Background: Early detection of melanoma is vital for treatment outcome and survival. Short-term sequential digital dermoscopic monitoring (ST-SDDM) involves the capture and assessment of dermoscopic images of one or more atypical melanocytic lesions (AMLs), at baseline and after four months, in order to detect early morphologic changes. Electrical impedance spectroscopy (EIS) is a diagnostic tool with high sensitivity for the detection of malignant melanocytic lesions.

Objectives: The aim of this study was to assess whether EIS, in addition to ST-SDDM, could improve the selection of AMLs requiring surgery.

Methods: In this retrospective descriptive study, 22 AMLs in 19 patients were monitored with both ST-SDDM and EIS. A modified EIS decision-making algorithm was established. AMLs were excised if any dermoscopic changes were seen and/or if the EIS score had increased significantly at follow-up. Statistical analyses were made including sensitivity, specificity, PPV and NPV.

Results: A total of seven lesions (32%) were excised. Four lesions (57%) were excised solely because of dermoscopic changes including a 0.4 mm-thick melanoma and three benign nevi. Three benign lesions (43%) were excised because of increased EIS scores without any dermoscopic changes. The EIS scores at follow-up showed high variability as compared to the initial scores.

Conclusion: The addition of EIS to ST-SDDM did not identify additional malignant lesions. There was no correlation between dermoscopic changes seen with ST-SDDM and increased EIS scores. Three histopathologically benign lesions were needlessly excised. Moreover, the low reproducibility and the possible interoperator variability of the method raised concerns.

Background

The concept of an atypical melanocytic lesion (AML) can be applied to any pigmented lesion in which the clinical and dermoscopic criteria are sufficient to classify it as melanocytic, but are insufficient to determine whether the lesion is a benign nevus or an early stage of melanoma. When patients present with one or more AMLs, excision for histopathological diagnosis may be necessary, but more advanced non-invasive diagnostic methods might be preferred.

Dermoscopy is a technique that uses a handheld magnifying device combined with either the application of immersion fluid between the transparent plate of the device and the skin or the use of cross-polarized light. This technique allows for visualization of diagnostic features of skin lesions not visible to the naked eye. It is a tool that helps the clinician to assess and differentiate between melanocytic and non-melanocytic lesions and determine whether they are benign or malignant. Several diagnostic algorithms can be used (e.g., pattern analysis, 7-point checklist, ABCD, Menzies' scoring method) [1,2]. Although dermoscopy is a very good complement to clinical evaluation, there will always be some lesions that lead to diagnostic uncertainty. To be able to identify and monitor these lesions without unnecessary excision, the use of short-term sequential digital dermoscopic monitoring (ST-SDDM) is valuable [3].

Sequential digital dermoscopic monitoring (SDDM) involves the capture and assessment of successive dermoscopic images of one or more AMLs separated by a specific time interval. SDDM is performed in two settings: long-term monitoring (LT-SDDM), where multiple AMLs are followed during regular surveillance periods (usually every 6-12 months) [4], and short-term monitoring (ST-SDDM), where one or a few AMLs are re-examined only once after a shorter surveillance period (3-4.5 months) [3]. Clinicians may choose to perform ST-SDDM of an AML based on slightly suspicious morphologic features observed during dermoscopy during a first visit or based on a worrisome patient history although the dermoscopic features of the AML appear to be benign.

Nevisense® (SciBase AB, Stockholm, Sweden) is a diagnostic tool based on electrical impedance spectroscopy (EIS) [5-7]. It measures tissue resistance by administering alternating electrical currents at various frequencies to the skin. Normal and abnormal tissue differ with regard to cell size, shape, density and structure of cell membranes. These different properties influence the ability of the tissue to conduct and store electricity and can influence the results of an EIS measurement [5]. Previous studies have resulted in an algorithm in which EIS scores in the range of 0-3 in the Nevisense® system represent a negative predictive value (NPV, i.e., the probability that the lesion is not a melanoma) of 98%, and scores of 4-10 represent steadily increasing positive predictive

TABLE 1. Negative and positive predictive values for EIS measurements according to previous study [14].

EIS	Predictive Value
0-3	98% (NPV*)
4	9% (PPV*)
5	13% (PPV*)
6	18% (PPV*)
7	22% (PPV*)
8	39% (PPV*)
9	51% (PPV*)
10	64% (PPV*)

* NPV, negative predictive value; PPV, positive predictive value.

values (PPVs) as shown in Table 1 [6,7]. EIS is approved for clinical use, but how the EIS score should be interpreted and used in clinical practice is still unclear.

At the Department of Dermatology, Sahlgrenska University Hospital, the combination of clinical examination and ST-SDDM after four months has been used in the assessment of AMLs requiring follow-up to determine whether they should be surgically removed or not.

Objectives

The objective of this study was to assess whether EIS in addition to conventional practice (ST-SDDM) could improve the selection of patients with AMLs needing surgery. The secondary objective was to determine the correlation between dermoscopic changes and EIS scores during short-term monitoring of AMLs.

Methods

In February 2015, EIS was introduced into clinical practice in combination with ST-SDDM at the Department of Dermatology, Sahlgrenska University Hospital. In this retrospective descriptive study, the clinical outcome of all patients with AMLs that were followed with ST-SDDM combined with EIS measurements during the period from February 1 to June 30, 2015, were analyzed. The Regional Ethical Review Board assessed the study as a retrospective appraisal of quality of care and therefore had no objections to the study.

All patients over the age of 18 years diagnosed with an AML and monitored with ST-SDDM and EIS during the study period were considered eligible. Patients lost to follow-up, not meeting EIS measurement criteria (see below), having insufficient patient notes or with dermoscopic images of poor quality were excluded. Certain criteria must be met for EIS measurements to be valid. The lesion must have a

Figure 1. Management algorithm. [Copyright: ©2016 Ceder et al.]

diameter of 2-20 mm, the skin must be intact (i.e., lesions are not ulcerated or bleeding), and the lesion should be free of scars or fibrosis and located in skin areas free from eczema, psoriasis, acute sunburn or terminal hair. Furthermore, the lesion should not be located in specific anatomical areas, such as acral skin, genitals, eyes or mucous membranes.

After a full-body skin examination, the physician decided which suspected AML(s) should be followed using ST-SDDM and EIS. First, a clinical and a dermoscopic image were taken with a Canon Digital Camera PowerShot G12, G15 or G16 (Canon, Tokyo, Japan) and the dermoscopy device Derm-Lite FOTO® (3Gen; Dermlite®, San Juan Capistrano, CA, USA) attached to the camera. A 70% solution of isopropyl alcohol in water was used as immersion fluid when acquiring the dermoscopic images. All images were stored in the patient's electronic journal. Subsequently, an EIS measurement was carried out by one of two certified users (HC and ASH) with the Nevisense® instrument, which is equipped with a probe and a disposable five-bar electrode with an area of 5 x 5 mm. 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. More exact details on
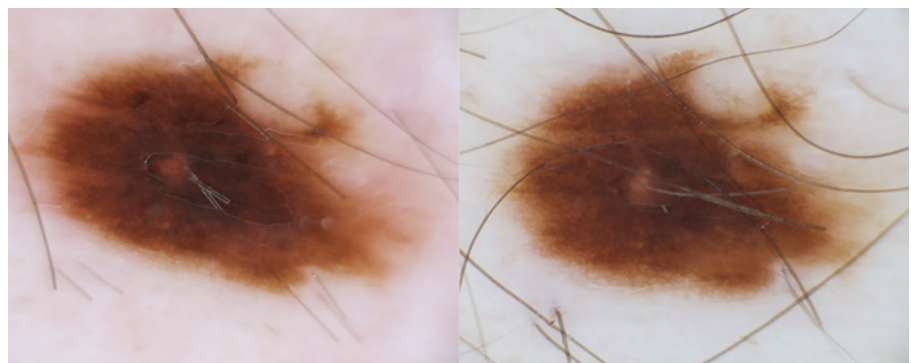
how EIS measurements are performed have been published earlier [6,7].

Since the specificity and the positive predictive value of EIS measurements from previous studies were considered too low to be clinically applicable, the authors suggested a novel algorithm for the clinical management based on the EIS score. A greater emphasis was placed on the clinical and dermoscopic evaluation of lesions than on the EIS scores. The patients returned after four months for a follow-up visit during which new clinical and dermoscopic images were taken and Nevisense® measurements were performed. The presence or absence of dermoscopic changes were visualized by comparing the two dermoscopic images on a digital monitor.

The management algorithm is presented in Figure 1. If the EIS score at visit 1 was 9 or 10, the lesion was excised regardless of the dermoscopic assessment. Otherwise, the AML(s) were followed up after four months. At follow-up, the dermoscopic images from both visits were compared. If dermoscopic changes were observed (e.g., growing or thickened network, new or bigger globules, new or growing negative network), the lesion was excised regardless of the EIS score at visit 2. Figures 2-3 show examples of AMLs with absence and presence of dermoscopic changes, respectively. If no dermoscopic changes were observed after four months, the EIS score determined the management decision. If the EIS score at visit 1 was 0-6 and had not increased by more than 1 point at follow-up or if the EIS score at visit 1 was 7-8 and had not increased at all after four months, the AML was determined to be a benign nevus. Larger increases in the EIS score were interpreted as a possible sign of evolving malignancy and prompted excision.

Statistical analyses were made to determine the sensitivity, specificity, PPV and NPV of the method.

Results

A total of 19 patients (12 women and 7 men) with 22 AMLs were examined with both ST-SDDM and EIS during the study period (Table 2). The short-term interval between visits ranged from 3.5-4 months. The median age of the patients was 53 years (range 23 to 69 years).
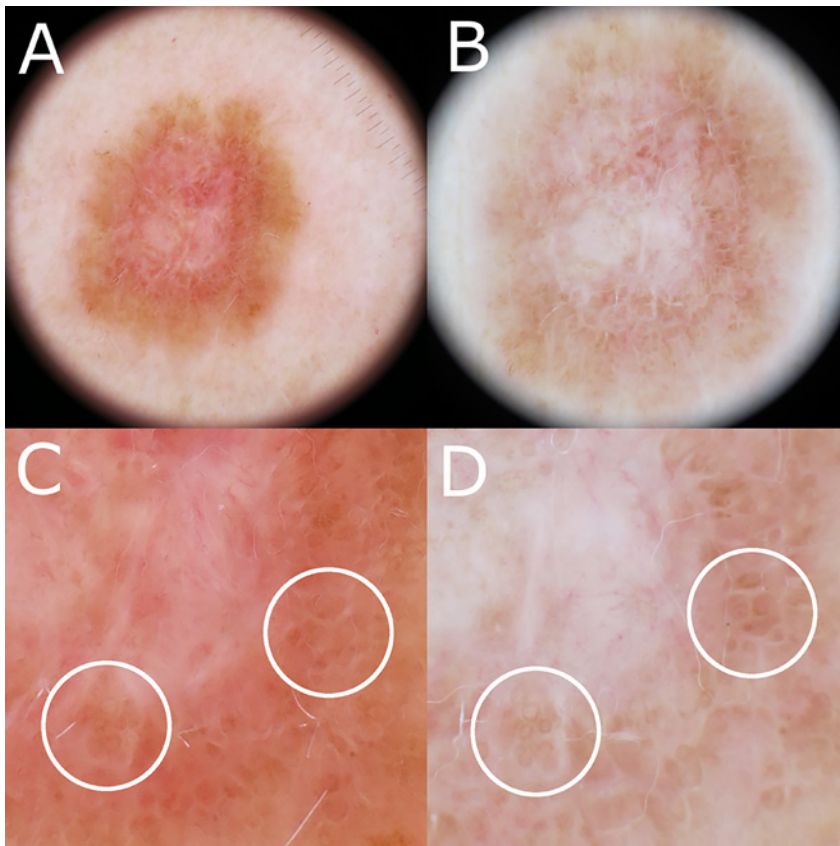

Figure 2. Atypical melanocytic lesion without dermoscopic changes after ST-SDDM. The EIS score was 8 at day 0 (left) and 6 at the follow-up visit (right). [Copyright: ©2016 Ceder et al.]

Figure 3. Atypical melanocytic lesion with dermoscopic changes between the baseline visit (A and C) and follow-up (B and D). The EIS score was 7 at baseline and 5 at follow-up four months later. The lesion diameter had increased (A→B) and several brown globules within a negative network had increased in size (circled areas in C and D). Histopathologically, this atypical melanocytic lesion was confirmed as a superficial spreading melanoma. [Copyright: ©2016 Ceder et al.]

A total of seven lesions (32%) were excised. Upon histopathological examination, four were dysplastic nevi, two were compound nevi and one was a thin superficial spreading melanoma with a Breslow thickness of 0.4 mm without ulceration (Figure 3). Four of the seven excised lesions (57%) were excised solely because of dermoscopic changes. In these cases, the EIS score was reduced by 2 points at follow-up in two lesions and unchanged in the other two. Three of the seven excised lesions (43%) were excised because of changes in the EIS score without any dermoscopic changes. These were all histopathologically benign. None of the seven excised lesions showed both dermoscopic changes and a significantly increased EIS score at follow-up.

The EIS scores at day 0 and at follow-up showed a rather high variability.

In 10 cases (45%), the difference in EIS scores was ≥2 points and differences up to ± 4 points were observed.

If the algorithm provided by the manufacturer had been followed, 19 AMLs would have been considered suspicious and excised. Of these, only one was malignant. Thus, in this very limited sample, and assuming that the non-excised lesions were correctly diagnosed using ST-SDDM, the positive predictive value (PPV) of EIS alone was 5.3% and the specificity was 14.3%. The sensitivity and negative predictive value (NPV) were both 100%.

Conclusions

Melanoma affects more than 3700 people in Sweden each year. After non-melanoma skin cancer, malignant melanoma is the cancer type whose incidence

is increasing most in Sweden [8]. Melanoma detection often poses a challenge in equivocal lesions or in patients with many AMLs. As early detection of melanoma is vital for treatment outcome and survival [9,10], additional objective information that could assist the clinician in obtaining a correct diagnosis and in deciding whether to excise the AML or not is desirable. The attempt in this study to use the EIS score algorithm to complement ST-SDDM did not seem to provide any additional help. Firstly, the evaluated algorithm did not identify additional malignant lesions. Furthermore, three histopathologically benign lesions were needlessly excised because of changes in the EIS score without any dermoscopic changes. These lesions would have been acquitted using only ST-SDDM. Moreover, the discrepancies between EIS scores over time were considerable in several cases, which raised concerns about the reproducibility and the possible interoperator variability of the method. Changes in EIS scores alone did not appear to correlate with malignancy. For example, a considerable increase of 2-4 EIS points between measurements did not correlate with histopathological malignancy, and it is difficult to interpret the meaning of a decrease of the EIS score by 4 points in a dermoscopically unchanged lesion. Lastly, none of the lesions showing dermoscopic change had an increased EIS score at follow-up, which further undermines the confidence in the measurement reliability.

According to the company that produces the Nevisense® instrument, the discrepancies between the EIS scores could depend on the use of different operators that may result in different reference measurement quality at the first visit and at follow-up. Another explanation may be the size of the lesion. The bigger the lesion is, the more measurements are required for each lesion, which may lead to errors.

There are several limitations to this study. The study was retrospectively

TABLE 2. Demographic data of all patients and clinical/histopathological characteristics of all atypical melanocytic lesions. [Copyright: ©2016 Ceder et al.]

Lesion	Sex*	Age	Location	Size** (mm)	EIS-score day 0	EIS-score follow-up	EIS score difference	Dermoscopic change	Treatment	Histopathology
1	M	64	Back	7×7	5	7	+2	No	Excision	Dysplastic nevus, moderate dysplasia
2	F	26	Abdomen	6×4	6	7	+1	No	None	-
3	M	37	Back	8×4	8	6	-2	No	None	-
4	M	41	Stomach	6×5	4	3	-1	No	None	-
5	F	24	Thorax	6×5	5	6	+1	No	None	-
6	F	60	Abdomen	14×12	7	5	-2	Yes	Excision	SSM, 0.4 mm
7	F	51	Gluteus	7×6	4	5	+1	No	None	-
8	F	66	Arm	2×3	5	3	-2	Yes	Excision	Compound nevus, inflamed
9	F	66	Back	7×5	8	5	-3	No	None	-
10	F	27	Back	10×11	3	7	+4	No	Excision	Dysplastic nevus, moderate dysplasia
11	M	66	Back	9×6	5	5	0	Yes	Excision	Dysplastic nevus, mild dysplasia
12	M	66	Abdomen	8×6	5	9	+4	No	Excision	Dysplastic nevus, mild dysplasia
13	F	69	Back	8×7	5	3	-2	No	None	-
14	F	28	Leg	6×7	7	7	0	No	None	-
15	F	56	Pubis	9×7	6	6	0	No	None	-
16	M	67	Leg	3×4	2	2	0	No	None	-
17	M	67	Leg	7×4	4	4	0	No	None	-
18	F	23	Head	3×3	4	1	-3	No	None	-
19	F	53	Leg	6×4	6	2	-4	No	None	-
20	F	36	Back	6×5	6	6	0	Yes	Excision	Compound nevus, strongly pigmented
21	M	24	Back	7×4	2	3	+1	No	None	-
22	M	53	Back	10×11	5	6	+1	No	None	-

*M, male; F, female; **Size, maximum × minimum diameter in mm.

designed and the sample size was small. The evaluation concerned EIS in conjunction with ST-SDDM, but ST-SDDM was at the same time used as the gold standard for diagnosis in non-excised lesions. A histopathological diagnosis of all the lesions would perhaps have allowed for a more certain evaluation, but was not considered ethical to carry out.

This is the first independent study, to our knowledge, in which EIS measurements have been carried out on the same melanocytic lesion at two different points in time to test reproducibility. Further studies on the reproducibility and interoperator reliability of EIS are needed before conclusions can be made.

EIS measurements on AMLs showed lower specificity compared with previous studies on EIS [5-7]. This may be due to the fact that the inclusion criteria in this study were different and that the sample size was smaller. Consequently, the studies cannot be directly compared. EIS combined with

additional techniques could perhaps increase the specificity when analyzing AMLs. For example, a study on the combination of EIS with near-infrared (NIR) spectroscopy for analyzing melanocytic lesions provided a specificity of 95%, albeit with a lower sensitivity of 83% [11].

Regarding the term AML that we use in this study, we propose that this term should replace the incorrectly used term of a clinically suspected "dysplastic nevus" which is unfortunately used by too many dermatologists today. A "dysplastic" nevus is a variant of a benign melanocytic nevus, which can only be diagnosed histopathologically with typical architectural disorder and varying degrees of nuclear atypia in intraepidermal melanocytes [12,13]. Between 2-18% of the population in Sweden have melanocytic lesions with a clinical suspicion of dysplastic nevus [14]. Nevertheless, the exact prevalence of dysplastic nevi is unknown since the clinicopathological correlation between clinical atypia and

histopathological dysplasia in melanocytic nevi is very poor [14-17]. Hence, the term "dysplastic nevus" is not a clinical diagnosis and should be abandoned [18]. If the clinical diagnosis of a melanocytic lesion is uncertain, the lesion should therefore be called an AML until the diagnosis is confirmed clinically with ST-SDDM or histopathologically after a complete excision of the lesion.

In this pilot study, the addition of EIS to ST-SDDM using a modified EIS algorithm did not identify additional pathological lesions. Instead, some histopathologically benign lesions were needlessly excised. In addition, there was no correlation between dermoscopic changes seen with ST-SDDM and significantly increased EIS scores. Also, the reproducibility of the EIS measurements was lower than expected, which is an issue that needs to be studied further before continuing to use this method in routine care. For now, we can therefore not recommend EIS in the standard management of monitoring AMLs.

Acknowledgements

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