# Dermatology Practical & Conceptual

# UV Irradiation of Nevi: Impact on Performance of Electrical Impedance Spectroscopy and a Convolution Neural Network

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**ABSTRACT**

**Introduction:** UV irradiation of nevi induces transient melanocytic activation with dermoscopic and histological changes.

**Objectives:** We investigated whether UV irradiation of nevi may influence electrical impedance spectroscopy (EIS) or convolution neural networks (CNN).

**Methods:** Prospective, controlled trial in 50 patients undergoing phototherapy (selective UV phototherapy (SUP), UVA1, SUP/UVA1, or PUVA). EIS (Nevisense, SciBase AB) and CNN scores (Moleanalyzer-Pro, FotoFinder Systems) of nevi were assessed before (V1) and after UV irradiation (V2). One nevus (nevus$_{irr}$) was exposed to UV light, another UV-shielded (nevus$_{non\text{-}irr}$).

**Results:** There were no significant differences in EIS scores of nevus$_{irr}$ before (2.99 [2.51-3.47]) and after irradiation (3.32 [2.86-3.78]; P = 0.163), which was on average 13.28 (range 4-47) days later. Similarly, UV-shielded nevus$_{non\text{-}irr}$ did not show significant changes of EIS scores (V1: 2.65 [2.19-3.11]), V2: 2.92 [2.50-3.34]; P = 0.094). Subgroup analysis by irradiation revealed a significant increase of EIS scores of nevus$_{irr}$ (V1: 2.69 [2.21-3.16], V2: 3.23 [2.72-3.73]; P = 0.044) and nevus$_{non\text{-}irr}$ (V1: 2.57 [2.07-3.07], V2: 3.03 [2.48-3.57]; P = 0.033) for patients receiving SUP. In contrast, CNN scores of nevus$_{irr}$ (P = 0.995) and nevus$_{non\text{-}irr}$ (P = 0.352) showed no significant differences before and after phototherapy.

**Conclusions:** For the tested EIS system increased EIS scores were found in nevi exposed to SUP. In contrast, CNN results were more robust against UV exposure.

## Introduction

Malignant melanoma accounts for the majority of skin cancer deaths and incidence remains at high levels in many countries of the world [1]. Thin melanomas are cured by surgical excision with a favorable prognosis. Hence, early diagnosis of melanoma is of utmost importance [1]. Although biopsy and histopathology remain the diagnostic standard, non-invasive diagnostic techniques are gaining importance [2]. Electrical impedance spectroscopy (EIS) has been evaluated as an adjunct tool for melanoma detection [3-6]. EIS applies alternating electric current and detects differences in the impedance between benign (well-organized) and malignant (more chaotic) tissues. Market approved EIS devices were shown to reach a sensitivity of more than 95% in melanocytic lesions [6]. Another promising non-invasive diagnostic technique is the assessment of dermoscopic images by artificial intelligence algorithms. To this end, deep learning convolutional neural networks (CNN) have been designed that work independently from predefined criteria and were shown to perform on, or even above, the level of trained dermatologists with regard to the classification of benign and malignant skin lesions [7-9].

Until today, skin cancer screenings that are assisted by the aforementioned diagnostic techniques have been offered throughout the entire year. However, even intermittent UV exposure was shown to induce transient melanocytic activation with morphological and histological changes [10, 11]. Dermoscopic features developing in UV exposed nevi include an increase in pigmentation and the appearance of black-brown globules [12, 13]. Histopathologic changes after UV exposition involve an increase in suprabasal melanocytes and an enhanced HMB45 expression [14]. In some cases UV-induced changes in benign nevi may be suggestive of malignant melanoma [15]. Thus, for clinicians it is an important question whether the diagnostic performance of EIS or CNN-based systems may be influenced by UV irradiation (eg during the summer months).

## Objectives

The primary objective of this study was to assess the influence of UV irradiation on the diagnostic scores of an EIS system (Nevisense, SciBase AB) and of a CNN (Moleanalyzer-Pro, FotoFinder Systems) when using these systems for examination of nevi. A secondary objective of this study was to address the reproducibility of EIS scores by performing 2 consecutive measurements for each lesion at each study visit.

## Methods

This clinical study was performed in a prospective controlled setting at the Department of Dermatology, University of Heidelberg in 50 patients with 100 common nevi and a medical indication for phototherapy. The study was conducted in accordance with the Declaration of Helsinki principles (2013) and applicable local government regulations and independent Ethics Committee policies and procedures (ethics approval number S-279/2017).

## Inclusion/Exclusion Criteria

Fifty patients scheduled for elective phototherapy with a minimum of 4 consecutive treatment sessions at our institution were included in this study. Participants had to be at least 18 years old and nevi needed to show the following characteristics: diameter between 2 mm and 20 mm; localized on intact skin without scarring, fibrosis, or other (inflammatory) skin conditions; not localized in hair-covered areas or special anatomic sites (i.e. acral skin, mucosa). We only included common nevi without any signs of malignancy.

## Study Procedure

A total of 100 nevi in 50 patients were assessed by EIS. Dermoscopic images were acquired at each study visit. For each participant, 1 nevus ($nevus_{irr}$) was exposed to UV irradiation, whereas a second nevus ($nevus_{non\text{-}irr}$) was covered with an UV-shielding sticker. EIS scores were evaluated at 3 study visits: before the start of phototherapy (V1), during phototherapy (V2), after termination of phototherapy not earlier than 4 weeks following the last irradiation (V3). $Nevus_{non\text{-}irr}$ was located in the same body area with similar size and shape as $nevus_{irr}$ and was used as an intraindividual control to account for changes not attributable to direct UV irradiation. Moreover, at each study visit EIS scores of nevi were measured twice to assess the reproducibility. Since all studied nevi were not intended for histological assessment by protocol, the diagnosis of a benign nevus (ground truth) was based on expert consent (JKW, HAH, CF). Only clearly benign looking nevi were included; hence follow-up of nevi included the study visits performed and a common skin cancer screening thereafter.

## UV Irradiation

Phototherapy was administered as part of clinical routine when indicated for treatment of diverse (inflammatory) skin diseases. Thus, the type of phototherapy was determined by the underlying skin condition and patient characteristics. Several treatments per week with increasing UV doses were administered. UVA1 phototherapy was performed with an UV-A1 lighting tube (Herbert Waldmann, spectral range 340–400 nm). SUP was administered with

a combination of UV-A and UV-B lighting tubes showing a spectral range of 280–400 nm (Herbert Waldmann). Psoralen-UV-A therapy (PUVA) was either performed as bath- or cream-PUVA-therapy (Herbert Waldmann, spectral range 315-400 nm).

## EIS Measurement

EIS scores were measured with the market approved Nevisense device (Scibase AB). According to the manufacturer instructions the skin was moistened with physiological saline for 30 seconds and a reference measurement of healthy skin close to the lesion was obtained. The system computed a score (0-10) reflecting the degree of atypia identified and the validated cut-off of < 4 versus ≥ 4 was used to differentiate EIS-negative (benign) from EIS-positive (malignant) lesions.

## CNN Assessment

Dermoscopic images were assessed by a marked approved deep learning CNN (Moleanalyzer-Pro®, FotoFinder Systems) based on a modified version of a pretrained GoogleNet Inception v4 architecture [8]. The CNN computed malignancy scores (0-1) with a predefined threshold for malignancy at more than 0.5.

## Statistical Analysis

Descriptive analyses were performed (frequency, mean, confidence intervals, range). For each nevus changes of EIS and CNN scores from visit 1 to 2 were assessed (intralesional differences). Additionally, for those nevi with measurements from all 3 visits changes of EIS and CNN scores from all timepoints were compared. Moreover, differences of scores between irradiated and non-irradiated lesions (nevus$_{irr}$ versus nevus$_{non-irr}$) were studied per visit (interlesional differences). Non-parametric tests were applied to assess for statistical significance (Wilcoxon signed rank, Friedmann and McNemar). According to the predefined cut-offs for malignancy, diagnostic specificities were calculated. A linear mixed effects model with a compound symmetry structure was applied to assess whether UV irradiation had an effect on the difference in EIS scores at V1 and V2. Baseline EIS scores, age, gender, and irradiation (yes/no) were used as fixed factors. The patient ID was included as a random factor. To evaluate reproducibility of EIS measurements an intra-class correlation coefficient was calculated. $P < 0.05$ was considered statistically significant. SPSS Version 25 (IBM, SPSS) and R (R Core Team, 2021) together with the package nlme (Pinheiro, 2021) were used [16,17].

# Results

## Patient Characteristics

Patients (N = 50) were recruited between June 2017 and August 2018 (Table 1). Mean age was 54.4 years (range 22-75), 24 male and 26 female patients were included. Most patients received UV therapy for eczema (42%) or nodular prurigo (26%), some for granuloma annulare (12%), morphea (8%), lichen planus (4%), mycosis fungoides (4%) or others (4%). Forty-one patients showed skin type II, 1 patient skin type II-III and 8 patients skin type III. Common nevi with a network pattern and located on trunk or extremities were included. A total of 35 patients received SUP, 11 patients UVA1, 3 patients PUVA and 1 patient SUP and UVA1 in a sequence (Table 2). Most patients (70%) received SUP and a median dosage of 0.26 J/cm² UVB and 13 J/cm² UVA was administered. Considering the skin types of patients, these doses corresponded to about 3-4 minimal erythema doses (MED) of UVB and less than 1 MED-UVA administered over 7.7 sessions. [18]. Figure 1 depicts representative images of a patient nevi 1 and 2 from all 3 study visits with accompanying EIS and CNN scores.

## Assessment of EIS Scores

Mean EIS score of the irradiated nevus$_{irr}$ slightly increased from 2.99 (2.51-3.47) at V1 to 3.32 (2.86-3.78) at V2 (Figure 2A). For patients attending V3 (N = 24) mean EIS score of nevus$_{irr}$ remained almost unchanged at

**Table 1.** Patient characteristics are depicted.

|  | Patients (N = 50) |
|---|---|
| Age in years (mean; range) | 54.4 (22-75) |
| Gender (male/female) | 24/ 26 |
| Skin condition, N (%) | |
| Eczema | 21 (42%) |
| Nodular prurigo | 13 (26%) |
| Granuloma annulare | 6 (12%) |
| Morphea | 4 (8%) |
| Lichen planus | 2 (4%) |
| Mycosis fungoides | 2 (4%) |
| Others | 2 (4%) |
| Skin type, N (%) | |
| II | 41 (82%) |
| II-III | 1 (2%) |
| III | 8 (16%) |
| Localization nevus1/nevus2, N/N | |
| Trunk | 36/36 |
| Upper extremities | 5/5 |
| Lower extremities | 9/9 |

3.25 (2.64-3.86) (Figure 2). The mean EIS score of nevus$_{non\text{-}irr}$ was 2.65 (2.19-3.11) at V1, 2.92 (2.50-3.34) at V2 and 2.94 (2.29-3.59) for patients attending V3 (Figure 2). First, we statistically compared EIS scores attained at V1 versus V2. There were no significant differences of EIS scores at V1 versus V2 neither for nevus$_{irr}$ (P = 0.163, intralesional difference) nor for nevus$_{non\text{-}irr}$ (P = 0.094, intralesional difference). Additionally, we neither found significant differences in EIS scores of nevus$_{irr}$ versus nevus$_{non\text{-}irr}$ at V1 (P = 0.393, interlesional difference)
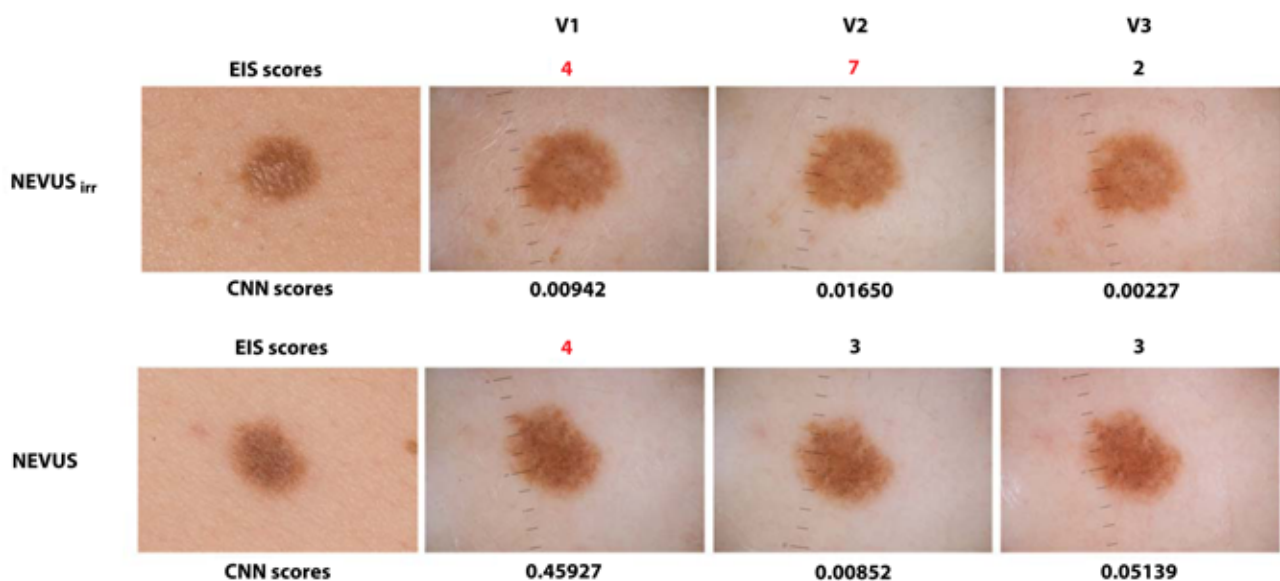
nor at V2 (P = 0.103, interlesional difference). Applying the predefined cut-off indicating malignancy (score ≥ 4), nevus$_{irr}$ was labeled "malignant" in 16 patients at V1 and in 20 patients at V2 (Figure 3). In contrast, nevus$_{non\text{-}irr}$ was labeled "malignant" in only 12 patients at V1 and in 13 patients at V2. Paired assessment revealed no significant difference in the number of nevi labeled "malignant" at V1 versus V2, neither for nevus$_{irr}$ (P = 0.424) nor for nevus$_{non\text{-}irr}$ (P = 1.0). For patients with measurements available from all 3 visits, EIS scores did not significantly vary between timepoints neither for nevus$_{irr}$ (P = 0.428) nor for nevus$_{non\text{-}irr}$ (P = 0.719). Finally, when including all EIS measurements performed, the device achieved an overall specificity (true-negative rate) of 49.3%.

## Regression Analysis Including EIS Scores

A linear mixed effects model was used to assess the impact of irradiation on the absolute and relative differences in EIS scores at V1 and V2 by comparing UV-irradiated versus shielded nevi. Here, irradiation was not a significant predictor (Table 3).

## Reproducibility of EIS Measurements

We performed 2 consecutive EIS measurements for each nevus and visit to investigate reproducibility. Overall, 232 pairs of scores were recorded and the mean difference between consecutive scores was 0.06 (-0.27-0.4). The intraclass correlation coefficient was 0.653 (0.551-0.732). According to the definition of Cicchetti this corresponds to a good reliability, according to Koo/Li to a moderate reliability [19,20]. For

**Table 2.** Details on UV irradiation administered.

| | Patients N = 50 |
|---|---|
| **UV irradiation, N** | |
| SUP | 35 |
| UVA1 | 11 |
| SUP/UVA1 | 1 |
| PUVA | 3 |
| **SUP** | |
| Treatments, N (mean; range) | 7.7 (3-16) |
| Dosage (J/cm$^2$) UVA (mean; SD) | 13.0; 7.8 |
| Dosage (J/cm$^2$) UVB (mean; SD) | 0.26; 0.16 |
| **UVA1** | |
| Treatments, N (mean; range) | 9.9 (3-15) |
| Dosage (J/cm$^2$) UVA1 (mean; SD) | 270; 140 |
| **PUVA** | |
| Bath/cream, N/N | 2/ 1 |
| Treatments, N (mean; range) | 12 (6-20) |
| Dosage (J/cm$^2$) UVA (mean; SD) | 6.6; 5.5 |



**Figure 1.** Nevus1 and nevus2 of a participating patient at all 3 study visits (V1-3) are depicted. From V1 to V2 nevus$_{irr}$ was irradiated with SUP during 10 appointments (cumulative dosage UVA 14.54 J/cm$^2$, UVB 0.29 J/cm$^2$), whereas nevus$_{non\text{-}irr}$ was UV-shielded. Corresponding electrical impedance spectroscopy (EIS) scores (0-10, top row) and convolution neural networks malignancy scores (0-1, bottom row) are depicted, scores marked in red illustrate a change in the diagnostic class, ie scores increased above the threshold for a malignant classification.
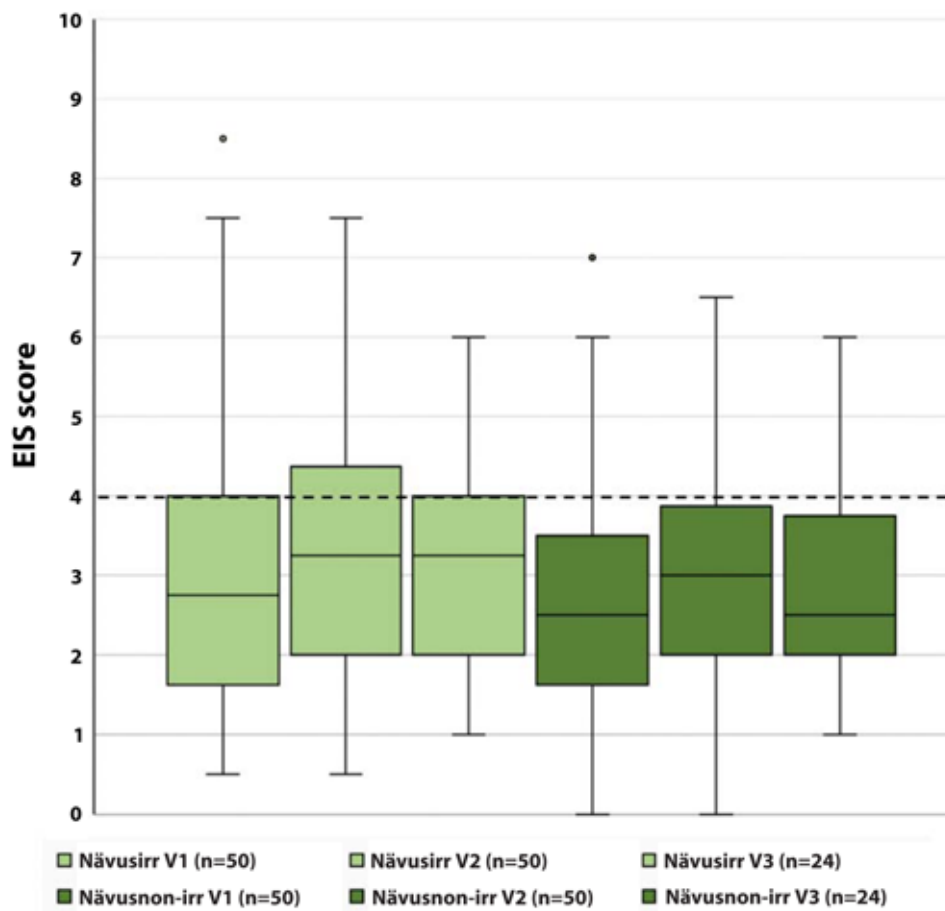
**Figure 2.** Boxplots show electrical impedance spectroscopy (EIS) scores of irradiated nevus$_{irr}$ and UV-shielded nevus$_{non-irr}$ at all 3 study visits (V1-before UV irradiation; V2-after UV irradiation; V3-not earlier than 4 weeks following the last irradiation). The upper and lower bounds of boxes represent the 25th and 75th percentiles while the median is given by the line intersecting both boxes. Whiskers present the full range of malignancy scores. The a priori cut-off for a malignant classification is indicated by dotted lines (EIS score ≥ 4).

70 of the 232 (30.2%) pairs of scores a class change from < 4 to ≥ 4 or vice versa was found.

### Assessment of CNN Scores

For 42 patients dermoscopic images were available from V1 and V2. Mean CNN scores of nevus$_{irr}$ were 0.06 (0.03-0.1) at V1, 0.06 (0.02-0.11) at V2, and 0.11 (-0.02-0.23) for the 15 patients with images available from V3 (Figure 4). Mean CNN scores of nevus$_{non-irr}$ were 0.05 (0.02-0.08) at V1, 0.04 (0.01-0.07) at V2, and 0.15 (0.05-0.25) at V3 (Figure 4). First, we statistically compared CNN scores before and after irradiation (V1 versus V2). There were no significant differences in CNN scores at V1 versus V2 neither for nevus$_{irr}$ (p = 0.995, intralesional difference) nor for nevus$_{non-irr}$ (P = 0.352, intralesional difference). Additionally, we found no significant differences in CNN scores of nevus$_{irr}$ versus nevus$_{non-irr}$ at V1 (P = 0.703, interlesional difference) and V2 (P = 0.675, interlesional difference). According to the predefined CNN threshold for malignancy, nevus$_{irr}$ was

classified "malignant" in none of the patients at V1, but in 2 patients at V2. Similarly, nevus$_{non-irr}$ was classified "malignant" in none of the patients at V1 but in 1 patient at V2. Paired assessments revealed no significant difference in the number of nevi classified "malignant" at V1 versus V2 neither for nevus$_{irr}$ (P = 0.5) nor for nevus$_{non-irr}$ (P = 1.0). When including patients with measurements available from all 3 visits, CNN scores were not significantly different between timepoints neither for nevus$_{irr}$ (P = 0.449) nor for nevus$_{non-irr}$ (P = 0.420). Finally, including all visits the rate of correct "benign" diagnoses was 94.7%.

### Assessment by Type of Irradiation

Due to varying irradiation protocols a subgroup analysis was performed for the largest group of patients receiving SUP (N = 35). In this analysis mean EIS scores of nevus$_{irr}$ significantly increased from 2.69 (2.21-3.16) at V1 to 3.23 (2.72-3.73) at V2 (P = 0.044) and was 3.13 (2.40-3.84) for the 16 patients attending V3 (Figure 5). In parallel, mean
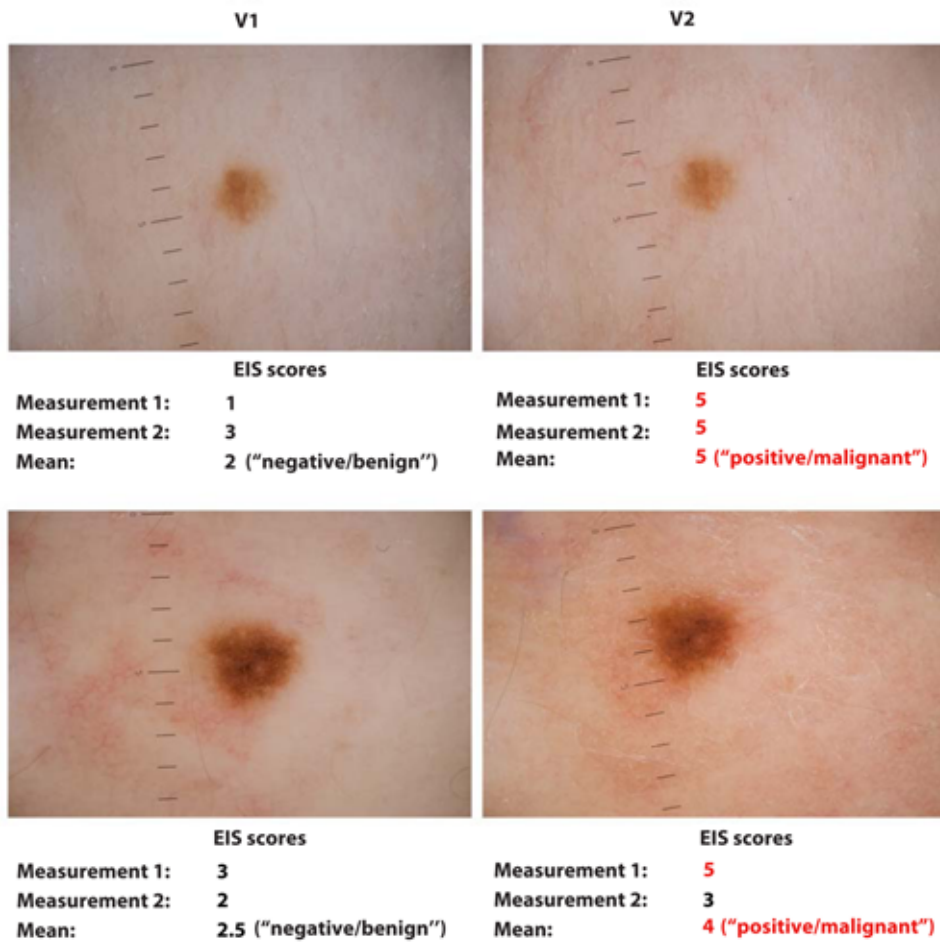
**Figure 3.** Figure shows dermoscopic images of two nevi$_{irr}$ from V1 and V2 with corresponding electrical impedance spectroscopy (EIS) scores. For both lesions and timepoints measurements were repeated and mean values used to define a negative/benign or positive/malignant result. For both lesions mean EIS scores increased from V1 to V2 and lesions were assessed negative/benign at V1 versus positive/malignant at V2.

**Table 3.** A linear mixed-effects model was used to assess the impact of irradiation on the absolute in electrical impedance spectroscopy scores at V1 and V2 (before and after irradiation) by comparing UV-irradiated versus shielded nevi.

| | Estimates | 95% CI | P |
|---|---|---|---|
| (Intercept) | 1.43 | 0.12; 2.74 | 0.037 |
| Age | 0.01 | -0.01; 0.03 | 0.479 |
| Gender (male) | 0.30 | -0.31; 0.91 | 0.347 |
| EIS score at V1 | -0.57 | -0.73; -0.41 | < 0.001 |
| Irradiation (no) | -0.25 | -0.69; 0.18 | 0.254 |

CI = confidence interval; EIS = electrical impedance spectroscopy.

**Table 4.** A linear mixed-effects model was used to assess the impact of irradiation on the relative differences in electrical impedance spectroscopy scores at V1 and V2 (before and after irradiation) by comparing UV-irradiated versus shielded nevi.

| | Estimates | 95% CI | P |
|---|---|---|---|
| (Intercept) | 0.88 | 0.02; 1.74 | 0.050 |
| Age | 0.01 | -0.01; 0.02 | 0.502 |
| Gender (male) | 0.41 | 0.01; 0.81 | 0.053 |
| EIS score at V1 | -0.32 | -0.43; -0.21 | < 0.001 |
| Irradiation (no) | -0.18 | -0.46; 0.10 | 0.221 |

CI = confidence interval; EIS = electrical impedance spectroscopy.

EIS scores of nevus$_{non-irr}$ increased to a slightly lesser but still significant extent from 2.57 (2.07-3.07) at V1 to 3.03 (2.48-3.57) at V2 (P = 0.033) and was 3.09 (2.28-3.91) at V3 (Figure 5). Paired assessments showed no significant differences in the number of nevi labeled "malignant" by EIS

scores at V1versus V2, neither for nevus$_{irr}$ (P = 0.344) nor for nevus$_{non-irr}$ (P = 0.388).

For 30 patients CNN scores were available, there was neither a significant difference in CNN scores between V1 and V2 for nevus$_{irr}$ (P = 0.797) nor nevus$_{non-irr}$ (P = 0.894).
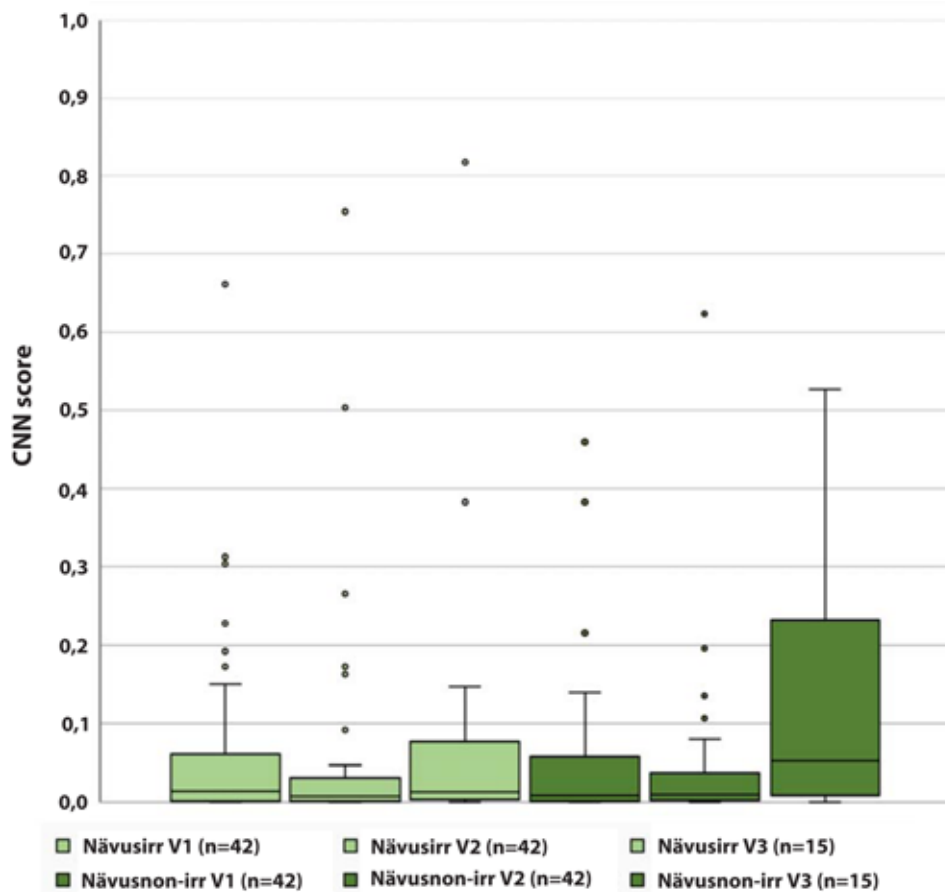
**Figure 4.** Boxplots show convolution neural networks (CNN) scores of irradiated nevus$_{irr}$ and UV-shielded nevus$_{non-irr}$ at all 3 study visits (V1-before UV irradiation; V2-after UV irradiation; V3-not earlier than 4 weeks following the last irradiation). The upper and lower bounds of boxes represent the 25$^{th}$ and 75$^{th}$ percentiles while the median is given by the line intersecting both boxes. Whiskers present the full range of malignancy scores. The a priori cut-off for a malignant classification is indicated by dotted lines (CNN score > 0.5).

## Conclusions

Dermoscopic and histopathologic changes of nevi following UV irradiation have previously been described [12, 14]. Such changes may be of clinical relevance when patients attend skin cancer screenings following sun exposure. Particularly for patients under follow-up by sequential digital dermoscopy subtle changes related to sun exposure, eg increase in the number of dark dots and globules, may result in an increased number of unnecessary excisions. Hence, another short time follow-up examination before biopsy of melanotic lesions has previously been recommended after intense UV exposure [12].

According to our literature search, there is no data available on the performance of assistant devices such as EIS or CNN when used to assess melanocytic lesions after sun exposure. Our study provides first data on EIS and CNN scores of common nevi before and after phototherapy.

Overall, 50patients were included to assess EIS scores of 2 nevi per patient (UV irradiated and UV shielded) before and after phototherapy with different irradiation protocols performed. We found that for the overall group of patients and across all phototherapy regimen EIS scores of both UV irradiated and UV-shielded nevi were not significantly different before and after UV exposure. There may be several explanations for this observation, which are not mutually exclusive. In agreement with others we found a limited reproducibility of EIS measurement [21]. This might have probably interfered with the statistical comparison of EIS scores before and after UV exposure (background analytical noise covering relevant signals). Second, cumulative UV doses until the second visit (V2) might not have been sufficient to induce significant alteration of EIS scores. Yet, morphological changes in nevi have been reported as early as after 2 MED [12]. After two UVB minimal erythema doses marked melanocytic activation was reported, avoided by physical and sunscreen protection [22]. Another study found that even after a single dose of UVB clinical and dermoscopic changes in nevi occurred, partially prevented by physical barriers or sunscreens [23]. Moreover, a positive correlation of the extent of morphological changes with increasing total
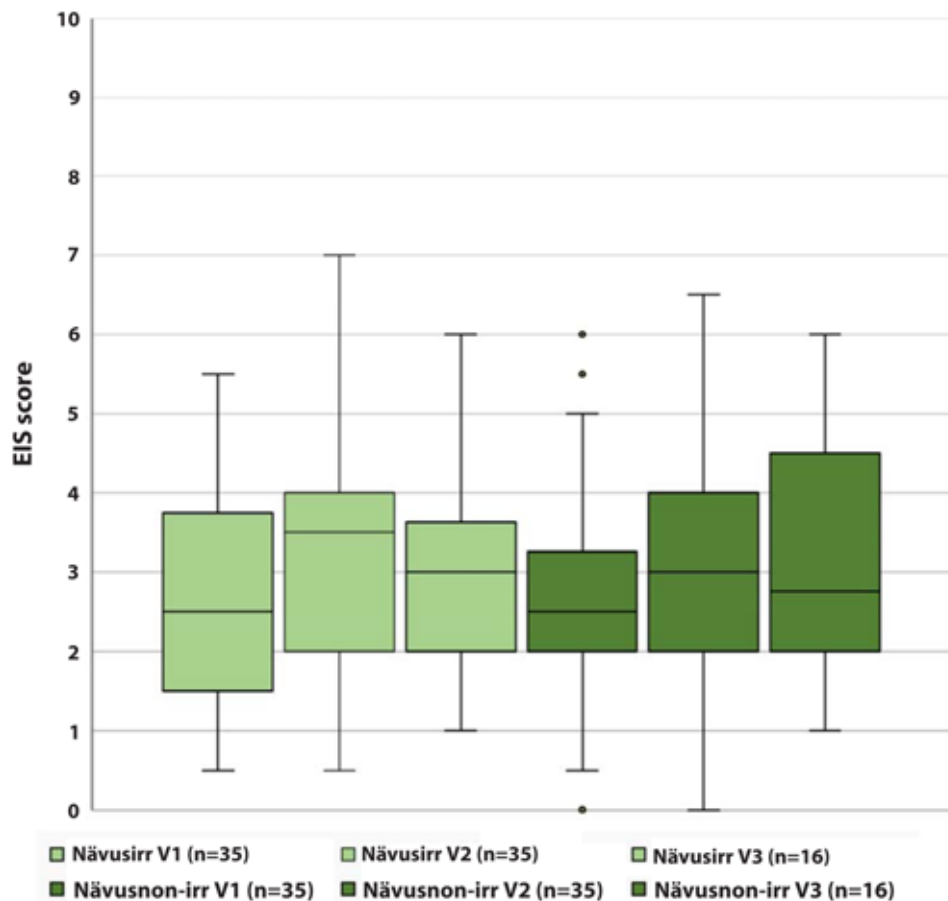
**Figure 5.** Boxplots show electrical impedance spectroscopy (EIS) scores of nevis$_{irr}$ and nevis$_{non-irr}$ at all 3 study visits (V1-3) for the subgroup of patients receiving SUP. The upper and lower bounds of boxes represent the 25$^{th}$ and 75$^{th}$ percentiles while the median is given by the line intersecting both boxes. The a priori cut-off for a diagnosis of malignancy is indicated by a dotted line (EIS score ≥ 4).

cumulative UV dose has also been shown [24]. Finally, it seems well conceivable, that "moderately" UV exposed nevi have been included in the training data of the device [6], which might have attenuated effects on EIS scores, and particularly on class changes (changes from benign to malignant after UV exposure). In contrast, effects of acute sun exposure were not further assessed in pivotal studies since exclusion criteria of the pivotal study included "lesions and/or reference located on acute sunburn". In the future, training sets of devices for the evaluation of melanocytic lesions should consider the influence of UV irradiation. The information that sun-exposed lesions were excluded from studies has to be included in clinical tutorials for users and in the webpage of the device.

In the literature changes of melanocytic lesions have been reported following exposure to UV light of various wavelengths [12,13,25-27]. Although natural sunlight differs from therapeutic irradiation [28], SUP includes both the UVB and UVA component and thus a subgroup analysis was performed for this largest group of patients. SUP patients received a dose of 3-4 MED-UVB over a mean number of 7.7 sessions. In these cases, we found a significantly elevated

EIS scores at V2 for both UV irradiated and shielded nevi. In our study the increase in EIS scores was quite similar for directly versus indirectly (because UV-shielded) irradiated nevi, which is in line with previous studies reporting melanocyte activation and proliferation after irradiation in both UV exposed and shielded human skin [25,27]. It has been postulated that mediators from irradiated skin might spread to neighboring UV protected skin through a paracrine pathway [25,27,29]. In confirmation, our linear effects model assessing EIS scores before and after irradiation did not reveal an impact of direct UV irradiation.

From our results we assessed the rate of nevi correctly labeled as benign by means of EIS scores (true negative rate, specificity). EIS attained a true negative rate of roughly 50%, which appears low in nevi lacking any dermoscopic signs of malignancy. This finding is in line with previous studies on EIS reporting a limited specificity of 34.4% at a high sensitivity of 96.6% [5,6]. Due to the study setting malignant lesions were not included, and thus we could not calculate sensitivity (true positive rate). The specificity of 49.3% obtained in the study is still superior to the 34.4% reported in the pivotal study with the method. This difference might be

explained by the different populations of patients and lesions included within the two studies, since the accuracy of EIS was shown to be correlated with lesion atypia. For a comparison, the ABCD rule of dermoscopy achieves a specificity of 91.2% and a true negative predictive value of 95.8% [30], hence surpassing EIS by far.

We used this prospective clinical study to additionally assess the reproducibility of EIS scores (2 consecutive measurements of the same lesions). One previous publication raised concerns regarding reproducibility, because the authors found that for 45% of benign lesions the difference in EIS scores was ≥2 points and differences up to ± 4 points were observed. Moreover, for one melanoma included in their study a decrease in EIS scores by 2 points was found after repeated measures [4]. According to the correlation coefficient in our study, reproducibility was "good" to "moderate", depending on the thresholds applied [19,20]. Yet, for approximately 30% of repeated measurements a change in the diagnostic category (from benign to malignant or vice versa) was observed, which in our view is an important limitation regarding clinical application of EIS. There are various factors which determine electrical impedance during the EIS procedure, amongst others the amount of saline solution applied to the skin. The intralesional variability of EIS scores may be explained by the intrinsic variability of the method, but possibly also by a modification of the lesion by repeated application of the liquid and electrodes on the skin surface in a short period.

Besides EIS measurements, we assessed dermoscopic images by a deep learning CNN for a second approach based on lesion morphology. Here, we found no relevant changes of CNN scores following UV irradiation, which implies a favorable robustness of the applied CNN. The rate of correctly classified benign lesion was 94.7%, which is in line with its previously published high specificity [8,9]. The CNN was trained with > 150.000 labeled dermoscopic images from around the globe comprising a real-life sample of nevi with or without previous sun exposure. In our study CNN scores of included nevi were quite low, reflecting our study setting with inclusion of clinically clear-cut benign nevi. Since only common nevi were included, we may not draw any conclusions with regard to atypical nevi or melanomas.

Altogether, our study reveals several further limitations. The number of included patients was low and only artificial sources of UV irradiation were assessed [31]. Furthermore, the applied phototherapy protocols varied with regard to UV spectrum, applied dosage and number of sessions.

In conclusion, our study shows that UV exposure may increase EIS scores of nevi. UV shielded nevi surrounded by UV exposed skin showed similar changes as directly irradiated nevi. Physicians should be aware of these interrelations when applying EIS as an assistance system. In contrast, the tested CNN was more robust to the effect of UV exposure with almost unchanged scores.

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