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Clinical performance of a novel hyperspectral imaging device for cutaneous melanoma and pigmented skin lesions in Caucasian skin

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Abstract

Background: The quest for diagnostic tools for the detection of cutaneous malignant melanoma (cMM) is ongoing. A challenge in cMM care is not overlooking cMM at an early stage, while simultaneously avoiding unnecessary biopsies or excisions of benign pigmented skin lesions (PSLs). A novel hyperspectral imaging (HSI) device is shown to have potential for differentiating equivocal PSLs in Asian skin types. Our objective was to assess the accuracy of the HSI device in distinguishing between cMM and benign PSLs in patients with Caucasian skin types.

Methods: Patients with Caucasian skin types (Fitzpatrick I-II), enrolled for excisional biopsies of PSLs were included and examined using the HSI device. The discrimination index (DI) was used to demonstrate the sensitivity (SE) and specificity (SP) in comparison with the re-evaluated histopathology diagnoses.

Results: In 186 patients, 202 pigmented skin lesions were included. The sensitivity to detect cMM was 96.7% (87/90), and the specificity for benign lesions was 42.1% (45/107). The AUC was 0.800 (95% confidence interval (CI): 0.740-0.861).

Conclusions: Our novel HSI device showed a high sensitivity in detecting malignant lesions in patients with Caucasian skin types. Compared with analogous technologies, as multispectral imaging or electrical impedance spectroscopy, our device showed similar or better accuracy in differentiating cMM from benign PSLs. Therefore, it might be a useful clinical tool in skin types I-IV and where further triage of pigmented skin lesions is important.

KEYWORDS

Caucasian skin type, hyperspectral imaging, melanoma, pigmented skin lesions

1 | INTRODUCTION

Early detection of cutaneous malignant melanoma (cMM) is paramount for avoiding morbidity and mortality in the disease.[1,2] Regarding melanoma detection, naked-eye examination can only reach a sensitivity of about 60%, which among trained dermoscopists can be increased to about 80%-95% with the aid of dermoscopy.[3-6] Importantly, the sensitivity is only increased in experienced examiners. Thus, there is a demand for novel non-invasive diagnostic systems that can differentiate between malignant and benign pigmented skin lesions (PSLs), as compared to today´s gold standard invasive diagnostic method: a histopathological examination (PAD) after excision. There is still a long way to go before realising a fully automatic, objective and complete device for skin cancer screening,[7,8] but steady progress has been made with different types of technologies, such as optical and electrical spectroscopies[8-20] and deep neural networks.[21-23] A challenge for all types of diagnostic tools is detecting cMM at the earliest stages and simultaneously helping to reduce unnecessary biopsies or excisions of benign PSLs.[9]

By using a hyperspectral imaging (HSI) technique, it is possible to simultaneously acquire both the position information and the wavelength information of the assessed object. The device captures the light reflected off the object and extracts wavelength information using a spectroscope.[18] Recently, a novel hyperspectral imager was designed to detect cMM among PSLs in Asian skin types. Previous studies have shown that it has potential as a desirable adjunct diagnostic tool in these skin types.[18-20] However, its performance in Caucasian skin, with mainly Fitzpatrick skin types I-II, has not yet been assessed. The aim of this study was to assess the efficiency and accuracy of the HSI device in diagnosing cMM among PSLs in patients with Caucasian skin types.

2 | MATERIALS AND METHODS

2.1 | Clinical facilities, study design and data acquisition

The study was performed in the dermatological department in Skåne University Hospital, Lund, Sweden, from September 2014 to June 2016. It was part of the diagnostic procedures of the established BioMEL biobank project (www.bioMEL.org). The BioMEL project collects clinical and molecular information on suspected PSL, including cMM, before and after excision. Hence, the database and biobank include photos, blood samples, fresh frozen tumour tissue samples and normal skin samples and information about the final histopathologic diagnosis. BioMEL is approved by the Ethical Board of Lund University (2013/101). Potential study participants over 18 years, with equivocal PSLs planned for excision, were consecutively offered to be recruited to the study before the planned excisional biopsy for diagnosis. All patients were Caucasians, corresponding to Fitzpatrick skin types I-II. Exclusion criteria were based on previous studies with HIS[18-20] and on former studies conducted with non-invasive diagnostic devices,[13,16] see Table 1. All included patients provided written informed consent. After study enrolment and dermoscopy, the PSLs were examined with the HSI device and thereafter excised for histopathological examination. All lesions were re-examined by a dermatopathologist specialised in melanocytic lesions.

TABLE 1 Exclusion criteria

Patients not willing to sign the study-specific informed consent form
Amelanotic lesions
Metastases or recurrent lesions
Lesion located on acral volar skin
Longitudinal melanonychia and lesion around nail plate
Lesion on mucosal surface
Lesion on genitalia
Lesion located in an area that has been previously biopsied, excised, or traumatised
Lesion with foreign matter
Lesion on hair-covered areas
Skin surface not measurable (eg lesion on a stalk)
Skin surface not accessible
Skin surface not intact

2.2 | Hyperspectral imager measurements

Hyperspectral data (HSD)[24] from included lesions were collected using a novel HSI device: MSI-03 (Mitaka Kohki Co., Ltd.). The technical specifications of this device can be summarised as follows: a light source of 150 W (halogen lamp), the measurement area 16 × 22 mm, the area resolution of 12.3 μm, a wavelength range of 400-800 nm and a wavelength resolution of 2.4 nm.[20] The time for the accumulation of HSD was about 20 seconds/area of measurement. For lesions smaller than the field of view (16 mm × 20 mm), HSD for the single lesion was accumulated with the field of view set so that the lesion and healthy skin could be measured simultaneously. Lesions that were larger than or equal to the field of view were measured by dividing them into small areas and then observing the peripheral region of each small area as was done for small lesions. Assessing HSD did not affect the lesions or the clinical management of the patients.

The discrimination index (DI) of a lesion was derived from the corresponding HSD as a continuous numerical value that reflected the lesional irregularity and randomness at the pigmented molecular level, through a variety of spectra included in the HSD. A higher DI corresponds to higher randomness of a lesion.[18-20]

Briefly, the variation of spectra was measured, using the spectral angle (SA) between each spectrum in the HSD and a reference spectrum.[25] Healthy skin, without pigmented lesions, is used as the reference spectrum. Although the spectra of healthy skin of Japanese and Caucasians is different, it is mathematically confirmed that differences in the reference spectra do not significantly affect the entropy values (see below).

The spectrum is considered a multidimensional vector. The inner product of the spectrum of each pixel and the reference spectrum is calculated. This is called the spectral angle (SA).[25]

Hence, the entropy value of the SA was reflected in our DI. Typically, cMM is expected to show higher and wider values of SAs.

An upper limit of the frequency distribution of SA, as in the earlier study on Asian PSLs,[20] was introduced in order to enhance the contribution from the frequency distribution in the larger SA region. This means that the contribution from normal skin regions (outside the PSL) to the evaluation of DI is suppressed in a random manner and at a uniform rate that is determined by the upper limit. For example, when a very small melanoma is measured, the value of SA distribution will be concentrated because most pixels of the HSD correspond to the unaffected skin. In this case, applying the upper limit to the SA distribution has the effect of emphasising the diversity of the small melanoma. A typical example of the HSI imaging and analysis of a malignant melanoma and a benign PSL is shown in Figure 1.

After normalising the modified frequency distribution of SA, the DI was defined as the image entropy of the normalised SA frequency distribution.[26] The original reference spectrum was used also in this study, and the cut-off level of the frequency distribution of SA was set to 10 000.[20] The DI was obtained for every lesional HSD. For large lesions, the DI was evaluated for every divided partial region. The highest DI was selected as a representative DI of the lesion. When all patients were enrolled, the HSI data, blinded to the histopatological diagnosis (PAD), were sent to Japan for analysis. After HSI data were completed the PAD, with final histopathological diagnosis, was compared with the DI for all lesions. The DI was used to calculate the sensitivity (SE) and specificity (SP) endpoints.

2.3 | Study objective and endpoint

The general objective of this study was to evaluate the diagnostic accuracy of the novel HSI device in distinguishing between cMM and benign PSLs in patients with Caucasian skin types. Secondary objectives were to find an appropriate cut-off level for DI in patients with Caucasian skin types and to determine a single cut-off value for DI, independent of skin type.

2.4 | Statistical analysis

A receiver operating characteristics (ROC) analysis was used to compare the performance of the HSI device regarding Caucasian PSLs and to determine the DI irrespective of skin types. The cut-off level was evaluated through the sensitivity and specificity. The alpha level was set at 0.05. The 95% confidence interval (CI) was obtained using the Clopper–Pearson exact CI.[27] The PSLs were during statistical analyses divided into two or three groups: malignant melanoma group (MM), the benign PSL group and the malignant non-melanoma skin cancer group (NMSC). All statistical calculations were performed using BellCurve for Excel (Social Survey Research Information Co., Ltd.).

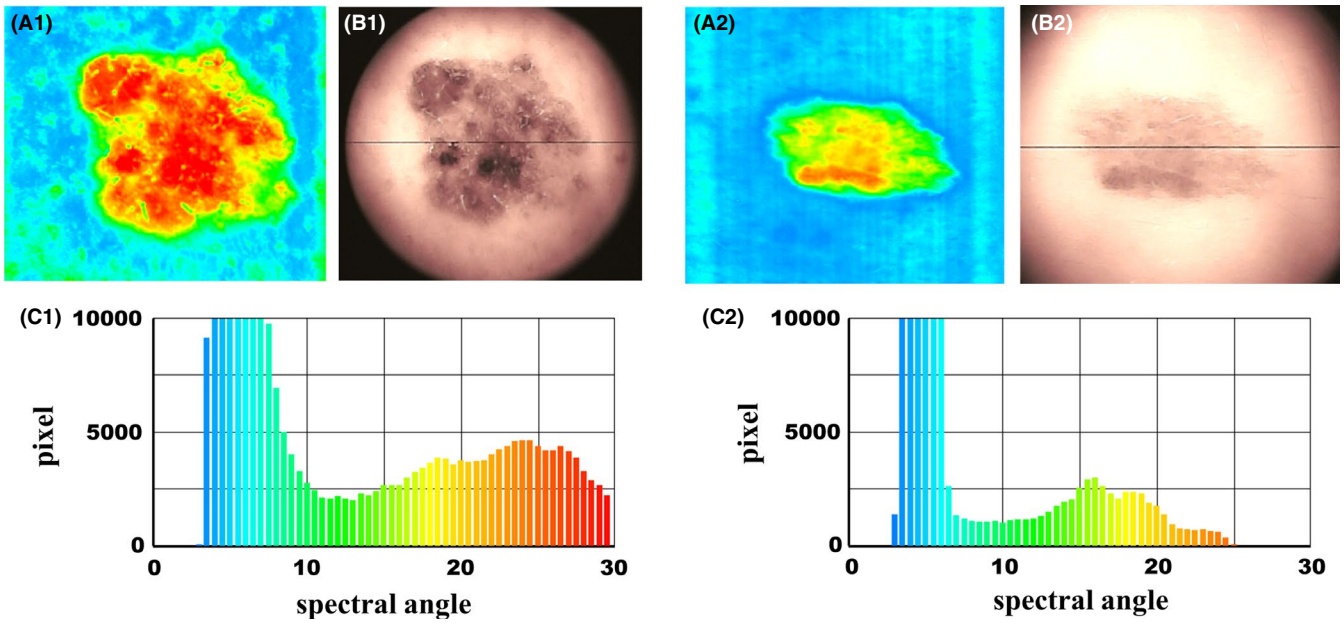

FIGURE 1 Typical analysis example for malignant melanoma (1) and benign (2) lesions with our discrimination index of 5.689 and 4.905, respectively. (A) Spectral angle (SA) map. The warmer colours correspond to a higher spectral angle. (B) Charged Coupled Divice (CCD) monitor image. The image is trimmed to the same size as the spectral angle map. (C) Histogram of spectral angle. The colour of the bar matches the spectral angle map. Distinctive of melanoma is higher and wider spectral angles

3 | RESULTS

3.1 | Study participants and lesions

A total of 186 participants with 207 PSLs were originally enrolled in the study. Median age of participants was 62 years (range: 15-96 years). Most patients had one PSLs included in the study. However, of all 98 males (53%), 14 had two examined PSLs and one had three PSLs. Of the 88 females (47%), five had two examined PSLs. The basic characteristics of the participants are summarised in Table 2.

Of the 207 lesions registered at baseline, 5 lesions were excluded due to non-eligibility because of placement on non-target skin (acral volar skin) for four patients and one patient because of a background other than normal skin. Five PSLs were histopathologically classified as 'non-melanoma skin cancer', including three basal cell carcinomas (BCC) and two squamous cell carcinomas (SCC). These five lesions were excluded in further calculations regarding cMM and PSLs. There were no device-related exclusions.

3.2 | Identification of the cut-off level for DI

We examined the dependence of the cut-off level for DI. The eligible and evaluable PSLs were divided into two groups. The 'malignant group (MM)' consisted of cMM (n = 53), melanoma in situ (n = 34), one case of MELTUMP (melanocytic tumour of uncertain malignant potential) and two cases of SAMPUS (superficial atypical melanocytic proliferations of uncertain significance). The 'benign group' consisted of benign PSLs (n = 107). The non-melanoma skin cancers (n = 5) were excluded in this analysis. Figure 2 shows the distribution of DI from the MM (solid squares) and benign PSL (solid circles) groups. In the panel the median, the 25th percentile and 75th percentile of DI for each group are also indicated by horizontal bars. The difference in DI for the two groups was statistically significant ($P < .001$).

Table 3 shows the dependence of the sensitivity and specificity obtained for the cut-off values. The meanings of the cut-off levels are presented. The cut-off level for cMM was set to 4.669 to fulfil the criteria to include most melanomas and exclude most benign lesions. Hence, the cut-off value was set at the lower limit where the 95% confidence interval for sensitivity exceeded 0.9. Figure 2 indicates that this level is appropriate.

TABLE 2 Characteristics of the study participants

Characteristics	Patients enrolled (n = 186)	Patients with eligible lesions (n = 181)
Sex		
Female	98 (49.7)	97 (53.6)
Male	88 (44.7)	84 (46.4)
Median age in years (range)	62 (15-96)	62 (15-96)

3.3 | Performance of the HSI device

The performance of the HSI device, with the cut-off level of 4.669, is summarised in Table 4 and Figure 2. The MM group comprised n = 90 lesions, the benign PSLs comprised n = 107. The sensitivity for the two groups was 96.7% (95% CI: 90.6%-99.3%), and the specificity was 42.1% (95% CI: 32.6%-52.0%), respectively. Out of

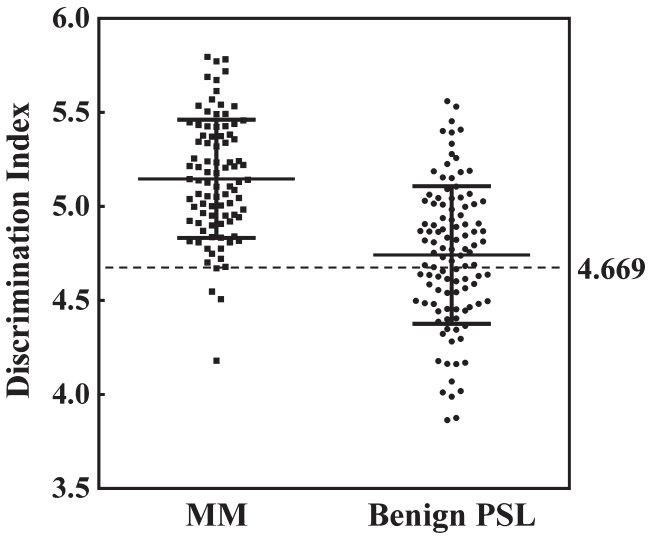

FIGURE 2 Distribution of the discrimination index (DI) for malignant melanoma (MM) and the other benign pigmented skin lesions (Benign PSL) from Caucasian skin types. In the panel, the median, the 25th percentile and 75th percentile of DI, for each group are also indicated by horizontal bars. The difference in DI for the two groups was statistically significant ($P < .001$)

TABLE 3 Dependence of HSI performance on DI cut-off levels for eligible Caucasian PSLs consisting of 90 melanoma and 107 benign pigmented skin lesions

Condition for cut-off level	Cut-off	SE (%) (95% CI)	SP (%) (95% CI)
Max. SP at 100% SE	4.179	100 (96.0-100)	9.3 (4.6-16.5)
Max. OR	4.377	98.9 (94.0-100)	27.1 (19.0-36.6)
Min. BER	4.894	78.9 (69.0-86.8)	69.2 (59.5-77.7)
Lower limit of sensitivity 95% CI > 0.9	4.669	96.6 (90.3-99.3)	43.0 (33.5-52.9)

Abbreviations: BER, balanced error ratio defined by (FNF + FPF)/2; CI, Clopper–Pearson exact confidence interval; FNP, false negative fraction; FPF, false positive fraction; OR, odds ratio defined by (TPF)(TNF)/{(FNF)(FPF)}; SE, sensitivity; SP, specificity; TNF, true negative fraction; TPF, true positive fraction.

TABLE 4 Observed sensitivity, specificity and true and false positive/negative values for pigmented skin lesions (PSLs) of Caucasians

Diagnosis	Total (n)	TP	FN	SE (%)
MM-group	90	87	3	96.7
Invasive melanoma	53	52	1	98.1
In situ melanoma	34	33	1	97.1
MELTUMP/SAMPUS	3	2	1	66.7
Diagnosis	**Total (n)**	**TN**	**FP**	**SP (%)**
Benign PSL[a]	107	45	62	42.1
Benign MN	33	15	18	45.5
MN with severe dysplasia	15	6	9	40.0
MN with moderate dysplasia	22	7	15	31.8
MN with mild dysplasia	19	8	11	42.1
Seborrheic keratosis	9	4	5	44.4
Other benign lesions	9	5	4	55.6
Diagnosis	**Total (n)**	**TP**	**FN**	**SE (%)**
Non-melanoma skin cancer (NMSC)	5	3	2	60.0
Pigmented BCC	3	2	1	66.7
SCC	2	1	1	50.0

Abbreviations: BCC, basal cell carcinoma; FN, false negative; FP, false positive; MELTUMP, melanocytic tumour of uncertain malignant potential; MM, malignant melanoma; MN, melanocytic nevus; SAMPUS, superficial atypical melanocytic proliferations of unknown significance; SCC, squamous cell carcinoma; SE, sensitivity; SP, specificity; TN, true negative; TP, true positive.

[a]Benign PSL = excluding all NMSC and MM.

the 90 lesions in the MM group, the following were by the device classified as false negatives: one case of lentigo maligna on head/neck area, one case of superficial spreading melanoma (SSM) on the frontal trunk (0.3 mm Breslow thickness) and one case of SAMPUS (Superficial Atypical Melanocytic Proliferations of Unknown Significance) on the lower extremities. These cases correspond to the bottom three DI plots in the MM group in Figure 2.

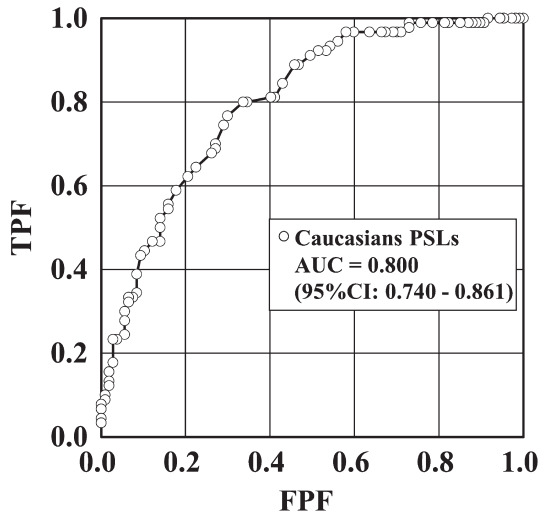

FIGURE 3 Receiver operating characteristics (ROC) curves obtained using DI relative to the histopathological gold standard. The circles represent the ROC curves for Caucasian pigmented skin lesions sets. The area under the curve (AUC) reveals that the evaluated HSI system has practical potential as a clinical adjunct tool. CI, confidence interval; FPF, false positive fraction; TPF, true positive fraction

Figure 3 shows receiver operating characteristics (ROC) curves obtained using DI relative to the histopathological gold standard (PAD). The circles represent the ROC curves for Caucasian pigmented skin lesions sets. The area under the curve (AUC) reveals that the HSI system has practical potential as a clinical adjunct tool, as the AUC was 0.800 (95% confidence interval (CI): 0.740-0.861).

For the small group of NMSC-lesions, including three pigmented basal cell carcinomas (BCCs) and two squamous cell carcinomas (SCCs), the sensitivity was 60.0% (95% CI: 14.7%-94.7%). The lesions in the benign group were presented in Table 4 and Figure 2, the vast majority, 83%, consisted of nevi, either benign or with dysplasia. For seborrheic keratosis, the specificity was 44.4%, with 5 out of 9 cases as false positives.

4 | DISCUSSION

In this study, we evaluated a novel HSI device (MSI-03) for possible use to differentiate melanomas from benign PSLs in Caucasian skin types. Finding and treating a cMM as early as possible is very important.[1,2] In a daily clinical setting, there is often no problem in distinguishing advanced cMM from benign nevi with the help of the naked eye or dermoscopy, while considering the personal medical history and constitution of the patient. However, intermediary or 'early' malignant lesions often have some features of malignancy coupled with

benign hallmarks that make both clinicians and pathologists unsure about whether the lesion is benign or not.[28] There is a delicate balance between the risk of missing cMM and performing unnecessary excisions of benign PSLs. Additional objective assessment tools are both needed and desired. Therefore, there is an ongoing quest to develop an objective superior diagnostic tool for melanoma detection.

The specific HSI device was initially evaluated for melanoma detection/ PSL discrimination in a Japanese population. Japanese patients, and their corresponding reaction to sunshine, also referred as their Fitzpatrick skin type,[29] are presumed to be different compared to Swedish patients with Caucasian skin/lighter skin types. Swedish patients with Caucasian skin are mainly regarded as Fitzpatrick skin types I-II, while Japanese usually are regarded as Fitzpatrick skin types III-IV.[29-31] To be trustworthy, a novel diagnostic device must therefore be tested in different populations. In the present study, we looked at the performance of the MSI-03 device in Caucasian skin. The device achieved a high sensitivity (96.7%) for melanoma detection, which is higher than the level seen in previous studies on dermoscopy, the current gold standard method for non-invasive pre-operative preliminary diagnosis of cMM.[6]

The observed high sensitivity was independent of the pathological stage of assessed cMM and the few cases classified as false negatives by the device were all lesions at a very early malignant stage. These three lesions were one in situ melanoma, one SAMPUS and one cMM with a Breslow thickness of 0.3 mm. It can be assumed that these three lesions were biologically less aggressive and therefore showed a low randomness in the respective lesion. However, it is difficult to speculate about biological aggressiveness as we cannot follow the natural course of events of these specific lesions. Importantly, the results are indicating that it is essential to include more lesional and patient-related facts before a patient with an equivocal PSL is dismissed. In the future, if the HSI device will be used in the clinic and a lesion is judged to be benign and therefore not excised, it is always important to give the examined patients advice about repeated self-examinations and to stress that one must seek medical advice if the examined and/or other PSLs change. This is in line with the advice, we give today after dermoscopy and the following judgement of a lesion being benign.

In a clinical setting, many seborrheic keratosis (SK) can easily be diagnosed with the help of dermoscopy, but occasionally they can mimic cMM. Hence, the 'difficult -to diagnose SKs' today warrant unnecessary excisions. A non-invasive device that could discriminate these from cMM is desirable. Unfortunately, the MSI-03 device classified a great proportion of seborrheic keratosis (SK) as false positives. We can speculate that this probably occurred because such lesions usually include a variety of cutaneous spectra, and thus, they are given high DIs. Misjudgement of SK has repeatedly been pointed out previously, and our findings is unfortunately in line with other established technologies used in the pre-operative detection of melanoma.[13,16] Although this issue poses a remaining challenge, it is not considered to be a serious issue as long as the devices are used clinically as adjunct tools.

The focus of our study was not to assess non-melanoma skin cancers specifically. Our focus was to assess all kind of PSLs, with main focus on differential diagnoses to cMM. In the study, five non-melanoma skin cancers were included and the MSI-03 device classified one out of three of the pigmented BCCs as false negative. The relatively low sensitivity for pigmented BCC may be attributed to their strong cohesive nature, which may reduce a variety of cutaneous spectra included in the corresponding HSD. Importantly, due to low numbers and only three cases of BCC, we can draw no relevant conclusions about the diagnostic accuracy of the HSI device in diagnosing pigmented BCC. The same is true for the two cases of SCC. The results are interesting, and more studies with larger numbers of pigmented NMSC of different kinds are warranted for testing the HSI device further.

One important strength of the study is that the clinical examination data were blinded to the data manager. Another strength is that DI was analytically derived from the corresponding lesional HSD and solely compared with the corresponding histopathological result to determine the performance of the HSI device. Also, all lesions and patients were enrolled in a tertiary dermatology clinic. Hence, the lesions probably mirror more equivocal PSLs in Caucasian skin types, than PSLs in a less selected cohort of patients would have shown, but still the sensitivity was high. Additionally, the AUC for PSLs in Caucasian skin types was high (0.8).

The overall specificity for the HSI device was only 42.1% for the benign PSLs. This is not comparable with for example dermoscopy, where specificity for melanoma detection often reaches about 80%.[6] Nevertheless, the specificity of the studied HSI device is in line with that of other diagnostic adjunct devices that are already established on the market, such as optical scanners[13] and electrical impedance spectroscopy.[16] To be of future superior clinical interest, the MSI-03 device needs to increase its specificity, especially for clinically difficult PSLs. If this will prove to be possible, the device could be an excellent and surpassing non-invasive, fast adjunct tool in clinical practice.

In conclusion, we have shown that the novel HSI device (MSI-03) has a high accuracy in detecting cMM also in patients with Caucasian skin types. Consequently, it might be a useful clinical tool for physicians managing patients not only with Fitzpatrick skin types III and IV, but also I and II and where further triage and examination of PSLs is important.

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DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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