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SIAscopy – a new non-invasive technique of melanoma diagnosis

The majority of the literature reports the relentless world-wide progress of melanoma. There are 130,000 new cases of melanoma diagnosed each year and incidence increases by 5% a year in fair-skinned population (6, 8). Melanoma is a potentially fatal disease, however, there is a chance of complete cure if detected early enough. Unfortunately, as the diagnostic effectiveness is currently insufficient, the mortality is high – 27% of patients who contract the disease, die (6). The probability that primary care doctor identifies a malignant process within the lesion is less than 50%, because the clinical diagnosis of melanoma is difficult and relies on the identification of visual features that are often subtle to detect (6). In an effort to improve diagnostic accuracy of such heterogeneous disease several approaches have been developed of which the most commonly employed is skin surface microscopy. It is a useful technique, which allows visualisation of morphological characteristics at the dermoepidermal junction. However, skin lesions are assessed purely visually by a dermatoscope which is a simple magnifying device, so that the diagnosis is highly subjective and operator-dependent being based on an individual interpretation of colours within a dermatoscopy image. A complication factor of dermatoscopy is that the visual appearance of skin lesion through a dermatoscope is a result of layering of microscopic structures (Fig. 1) and therefore, it is posssible that their different combinations give the same colour within the dermatoscopy view and the possibility of diagnostic error as a result (7). The need to overcome the operator-dependent and subjective nature of dermatoscopy in extracting information regarding the microstructure of a skin lesion led to the development of SIAscopy.

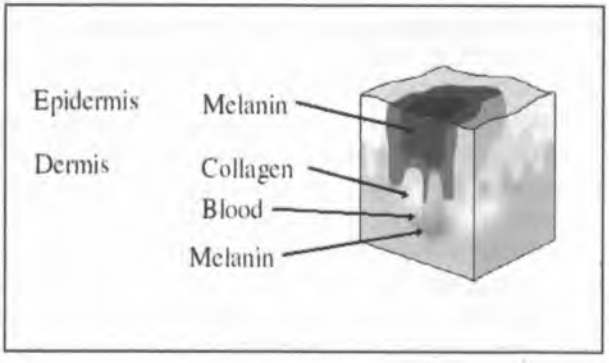

Fig. 1. The layering of skin microscopic structures*

* All figures used with the kind consent of Symon Cotton, Astron Clinica Scientific Director

The SIAscopy (Spectrophotometric Intracutaneous Analysis), a unique and patented imaging technology, is a result of over 10 years of research undertaken at Birmingham University, the Cambridge University Hospital and Astron Clinica, UK (4). The first device employing this technique, termed SIAscope, was launched in the year 2000 (Fig. 2). Since then a series of trials involving the new technique have been either completed or underway at major centers worldwide: UK, Germany, Australia, Switzerland, Sweden and USA (4). Those indepenent clinical trials have shown that SIAscopy is a very useful tool improving the diagnostic accuracy of clinicians, allowing them to correctly identify more cases of melanoma while avoiding unneccesary surgery and has been compared very favourably with dermatoscopy (10).

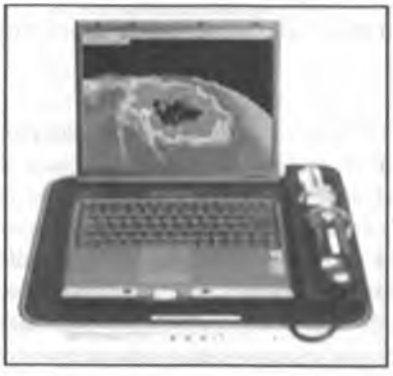

Fig. 2. A SIAscope

SIA is the first of a new generation of "smart multispectral imaging" techniques, where a mathematical model is used to compute tissue structure directly from spectral measurements and to return high-resolution information regarding the skin lesion (9). This technique can be rapidly and easily performed *in vivo*, in a non-invasive manner. SIAscope (or Mole Scan) measures the optical properties of the skin using 8 wavebands of light in the visible and near infrared spectrum, i.e. 400–950 nm (Fig. 3) (7). The device measures the reflectance (it means the quantity of light which is returned from the tissue) of over 350,000 points in an area of skin (3). The reflected light from skin lesion is a complex interaction of melanin, haemoglobin, collagen, keratin and minor pigments (4). It is possible to separate out these individual components of the skin because different microstructures interact with different wavelengths of light in different ways, and the handset is calibrated to record the precise amount of light reflected at each wavelength (11). The data are fed into an optical model of the skin which is calibrated and used as an input to a series of complicated computer algorithms allowing the points within the plane of skin to be transformed onto two-dimensional high-resolution pixelmaps (5, 7). In this way a digital information is converted into its graphical representation. Individual components of the skin are then displayed on the screen of SIAscope along with a colour reference view. These images, called SIAgraphs clearly show the underlying skin microarchitecture *in vivo* with identification of individual components and give information regarding their distribution, position and quantity within a horizontal plane of skin at each of these points (6). In particular they enable to observe the epidermal melanin, the presence, depth and quantity of dermal melanin within the papillary dermis, haemoglobin (i.e. vasculature) and collagen content of the papillary dermis within the lesion (6). Thus images are shown corresponding to colour view, total melanin (SIA-TM), dermal melanin (SIA-DM), dermal papillary colagen (SIA-C) and dermal blood (SIA-B) (7). There is also a possibility to display the 3-dimensional representation of the collagen picture (SIA-3D) (11). The system takes

approximately 5 seconds to acquire the images and further 10 seconds to process the data and display them as a visual information on the monitor (7).

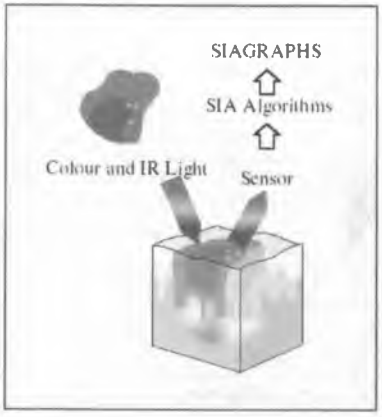

Fig. 3. The base of the spectral imaging technique

An important advantage of SIAscopy is that measurements are relative to the dermoepidermal junction, supplying clinicians with information whether chromophores have crossed this boundary. This is especially useful when applied for the location of melanin – a chromophore that under normal conditions is only found in the epidermis along the basal layer. Its presence beneath the junction can be assessed with great accuracy and is a key piece of diagnostic information regarding melanoma. The accurate extraction of dermal melanin is possible because the effect of other, above-mentioned, chromophores on the wavebands is removed by SIAscope and the spectral remittance of melanin changes with regard to its position in the epidermis or the papillary dermis (7).

The first large study involving the new technique that has been undertaken by Marc Moncrieff, Symon Cotton and their colleagues from Addenbrooke's Hospital in Cambridge, the University of Birmingham and Astron Clinica in the year 2002, yielded very promising results that were published in the British Journal of Dermatology (7). The authors undertook a diagnostic study of patients referred for excional biopsy of pigmented skin lesions. The study was based on a dataset that included 348 lesions taken from 311 patients (200 female and 111 male). The test of interest was the detection of the SIAscopic features suitable for the early identification of melanoma. An appropriate reference test was used in the form of histopathological examination from excisional biopsy of pigmented skin lesions which the results from the SIAscope were compared to. The SIAgraphs, all patient data and photographs were taken before the reference test was performed, and these were stored in a protected computerised database. Researchers had no access to the SIAgraphs prior to the excisional biopsy and the histopathological exam, and were also blinded to the reference test results when evaluating the SIAgraphs. This means that the interpretation of the SIAgraphs could not have been influenced by the results of the reference test, and vice versa (7). The authors identified three SIAscopy features as the most useful in melanoma diagnosis (Table 1): the presence of dermal melanin not due to hair follicles, displacement of blood in the papillary dermis by invasive regions with erythematous blush at the invading margin and tumour punching holes in papillary collagen (6). Two other features were: collagen arranged into rosettes and whorls around invasive nodules, dermal melanin in haphazard arrangements in invasive regions. In contrast, typical of benign naevi is a regular arrangement of dermal and epidermal melanin, a homogeneous vascularity and a homogeneous collagen arrangement (6). A new research undertaken in the year 2002 at Addenbrooke's Hospital identified two new features – dermal melanin

distribution and dermal melanin asymmetry (9). Crucially, the appearance of all those features could be related to underlying histopathological phenomena (7). These are the features that can be seen in the SIAscope screen images of melanoma and benign naevus in figures number four to nine (11).

Table 1. SIAgraphic features definitions used for the analysis and scoring system (1)

Feature	Definition	SIAgraph view
Collagen holes	An area within the lesion demonstrating an absence of collagen not due to hair follicles or sebaceous/sweat ducts	SIA- C
Blood displacement with erythematous blush	A confluent area demonstrating an absence of blood within the lesion with a peripheral increase in blood compared to the surrounding normal skin for ¾ of the circumference of the lesion	SIA- B
Dermal melanin level	The presence of dermal melanin within the lesion (not due to hairs), scored from 1 to 4 depending on the colour seen (green – 1, turquoise – 2, blue – 3, red – 4, black – 5)	SIA- DM
Dermal melanin asymmetry	An uneven and asymmetrical distribution of dermal melanin in relation to the entire lesion	SIA- DM & colour view

* Table used with the kind consent of Symon Cotton, Astron Clinica Scientific Director

Figures 4A and 4B are colour images of the skin lesion which correspond with dermatoscopy view (11). It is the magnified view taken with an alcohol and water based matching fluid between the window of the SIAscope and the skin of the patient, to allow maximum penetration of the light. It provides a good introduction to SIAscopy as it shows three of the key dermatoscopic criteria for melanoma, namely "blue-grey veil, "broadened pigment network" and "radial streaming" as well as the asymmetry of shape and border (Fig. 4B). In contrast, the lesion in the Figure 4A is large, almost homogeneous in colour, quite symmetrical and regular. These features indicate the benign melanocytic skin lesion which is the compound naevus presented in the picture (11).

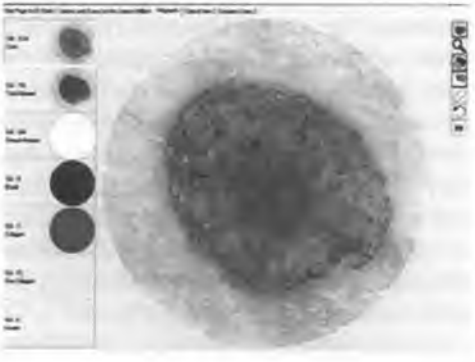

Fig. 4A. Colour SIAgraph of a compound naevus

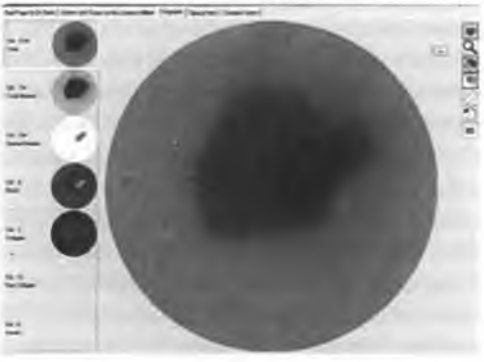

Fig. 4B. Colour SIAgraph of a melanoma

Figures 5A and 5B are total melanin SIAgraphs showing jointly the content of melanin in the epidermis and the dermis (11). They indicate that it is a clearly melanocytic lesion and assist the clinician in the analysis of these features that are due to melanocytes such as "pigmented network", "radial streaming", "branched streaks", "pigmented aggregated globules" and "black dots". In addition,

SIAscopy allows examination of the structural components which are formed from the distribution of the pigment melanin, to be free from the background components of the skin lesion. Thus total melanin SIAgraphs can enhance surface microscopy features. "Pigmented network" is formed by melanin along the basal layer of the epidermis and has a "honey-combed" appearance that is discrete and regular in benign lesions while broadened and distinct in melanomas (2). "Radial streaming" likewise "branched streaks" are formed by the confluent radial nests of melanocytes at the proximity of the dermoepidermal junction and are found at regions of the melanoma radial growth phase. "Black dots" and " pigmented aggregated globules" are determined by a localised accumulation of melanocytes in the stratum corneum and are highly specific for the invasive growth phase if placed peripherally within the lesion (2). In addition, the total melanin SIAgraphs provide good means of segmenting the lesion in terms of its melanin containing regions. That allows the lesion to be analysed for its border asymmetry and variations in distribution of a pigment. Besides an accurate and repeatable measurement of the maximum diameter of the lesion can be obtained. Figure 5B, that is the SIA-TM of melanoma, shows areas of increased pigment (i.e.melanin) in darker colours and melanin-based dermatoscopy features such as radial streaming (11). In contrast, in the total melanin SIAgraph of benign naevus (which is a compound naevus) its symmetry can be seen, a clear-cut border and the regularity of pigment distribution which provides, as a result, homogeneity of colour within the lesion (Fig. 5A) (11).

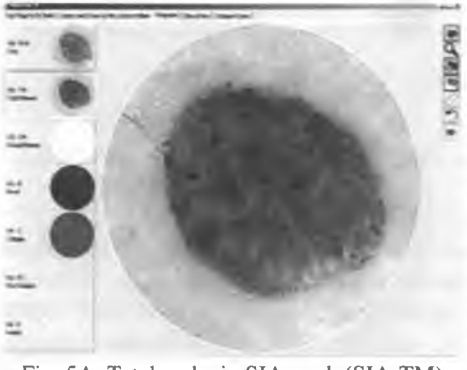

Fig. 5A. Total melanin SIAgraph (SIA-TM) of the compound naevus

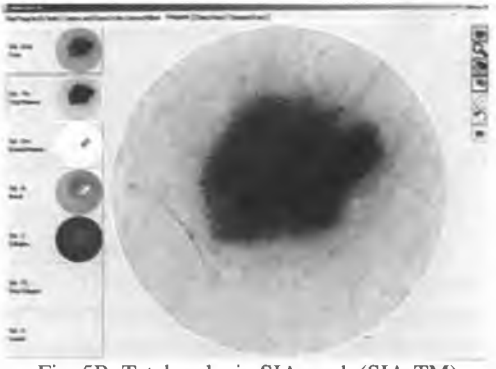

Fig. 5B. Total melanin SIAgraph (SIA-TM) of the melanoma

Figures 6A and 6B are dermal melanin SIAgraphs (11). SIAscopy is able to detect melanin in the dermis even when the depth of tumor penetration beneath the dermoepidermal junction is small (0.01mm) (9). It is also possible to determine an amount, distribution and depth of dermal melanin present. Melanin within most benign lesions should primarily be found in the superficial dermis; conversely within melanoma, pigment should be found deeper in the dermis. The detected dermal melanin is divided into five levels – each level is a function of the depth and concentration of melanin within the papillary dermis, and corresponds to a different colour in the SIAgraph images going from the least (green) to the most (black) ivolvement of dermis (Fig. 10) (9). In addition, information on the depth of melanin within the papillary dermis can also be returned in the form of a Clark's level (6). The dermal melanin SIAgraphs are especially useful in objective identification of blue-grey areas, which is stated to be the single most significant surface microscopic finding of invasive melanoma (7). This feature represents fibrosis with melanophages and / or malignant cells in a thickened papillary dermis (2). However, dermatoscopic identification of this feature is highly subjective because the same appearance may arise either from a reduction in the thickness of the papillary dermis or overlying layer of hyperkeratosis or haematoma (6). It can also be masked by excessive epidermal melanin. The blue-

grey areas can be clearly reconstructed by superimposition of SIAgraphs that display dermal melanin and collagen content within a lesion. The result accurately places the areas within the lesion. For instance, an eccentric focus of dermal melanin may indicate an invasive melanoma whereas in case of benign compound or blue naevus dermal melanin should be uniformly distributed filling the entire lesion (6). Comparison of the dermal melanin content to the total melanin content may also yield important diagnostic information that will help to distinguish an invasive melanoma from a compond naevus. While compound naevi have melanocytes in the dermis, it is much less common for them to have melanin in the dermis because the dermal melanocytes begin to atrophy and cease to produce melanin (7). The SIA-DM view of the compound naevus presented in Figure 6A confirms that the lesion has no dermal melanin while SIA-DM in Figure 6B shows areas where melanin is found in the dermis of the lesion clearly indicating melanoma (11).

Fig. 6A. Dermal melanin SIAgraph (SIA-DM) of the compound naevus

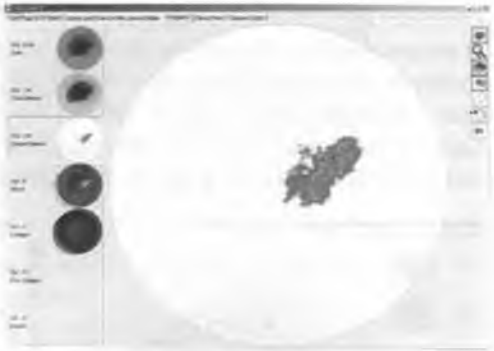

Fig. 6B. Dermal melanin SIAgraph (SIA-DM) of the melanoma

SIAgraphs in Figures 7A and 7B show blood view of the same lesions which correspond with the vasculature within the papillary dermis (11). The darker red colour arises from the areas of increased haemoglobin concetration while the white areas indicate decrease in blood. This can be clearly seen in Figure 7B presenting the blood SIAgraph of melanoma. An invasive nodule or nest of melanoma cells will displace the blood supply (i.e. blood vessels) from the papillary dermis and promote a strong immunocytic reaction characterised by local vasodilatation (7). This pathophysiological process is revealed by SIAgraphs as blood displacement (the white area near the centre of the lesion) with erythematous blush seen as the darker red area at the invading margin of the lesion. In opposite, the SIA-B view of the compound naevus (Fig. 7A) shows the blood vessels in very high resolution and in

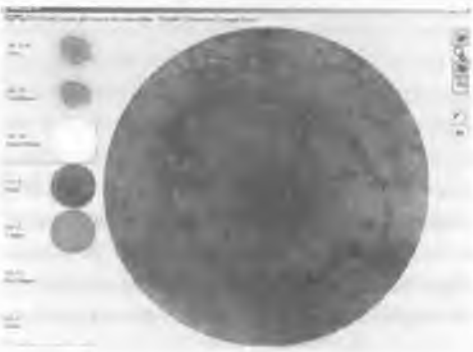

Fig. 7A. Blood SIAgraph (SIA-B) of the compound naevus

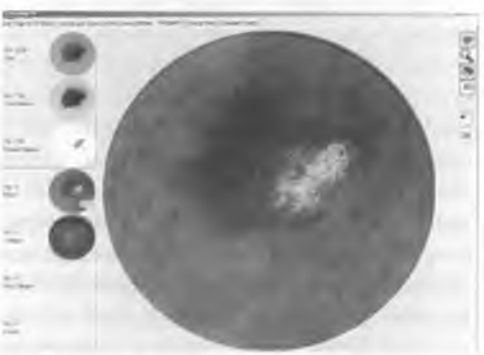

Fig. 7B. Blood SIAgraph (SIA-B) of the melanoma

uniform arrangement within the entire lesion (11). An important advantage of SIAscopy is a reliable identification of "red, blue-red and red-black lagoons" formed of blood and typical of haemangioma and angiokeratoma. The structures like these can be clearly seen in the blood SIAgraphs. It allows their differentiation from a melanocytic lesion (6).

Figures 8A and 8B are SIAgraphs of collagen content and distribution within the papillary dermis of the lesion. Note the darker area near the centre of the lesion in the SIA-C of melanoma (Fig. 8B) (11). This is a typical SIAscopic pattern for the invasive tumor that is Clark's level III or a greater one which, by definition, has areas where the papillary dermis is replaced by invasion of melanoma cell nests (7). In other words, the invasive nodul punches a "hole" in the collagen layer. These areas can be seen in collagen SIAgraphs as a contiguous absence of the collagen, termed by the research group as "black holes". They are the result of invasive melanoma optical properties. The melanoma nests in the dermis absorb the light which therefore does not return to the handset of the device and gives almost black colour in the SIAscopy view (7). Note also the lighter, almost white, areas surrounding the black hole in Figure 8B (11). They correspond with high collagen concentration peripherally to the invasive region. The fibrosis is produced by the immunocytic response to the melanoma cells invading papillary dermis and can also be seen as changes in collagen arrangement, in the form of whorls and rosettes (6). The SIA-C view of compound naevus shows an increase in collagen, too (Fig. 8A). However, this is homogenous over the whole area of the lesion and the arrangement of collagen is uniform (11).

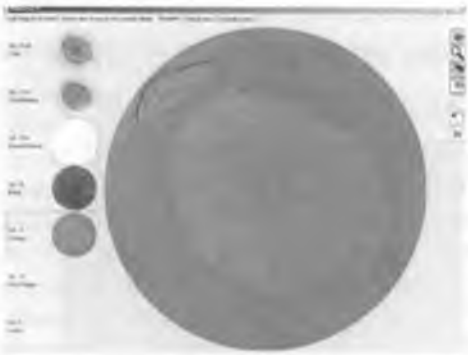

Fig. 8A. Collagen SIAgraph (SIA-C) of the compound naevus

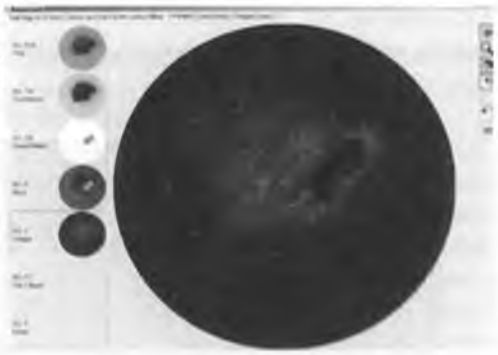

Fig. 8B. Collagen SIAgraph (SIA-C) of the melanoma

In Figure 9 a three-dimensional representation of the collagen view is presented (11). Here a "hole" in collagen is clearly visible, surrounded by higher points (i.e."peaks") showing areas where fibrosis is occuring. Using SIAscope there is a possibility to select an appropriate angle and height of view which is shown at the window on the left of the screen (11). In addition, during the research,the

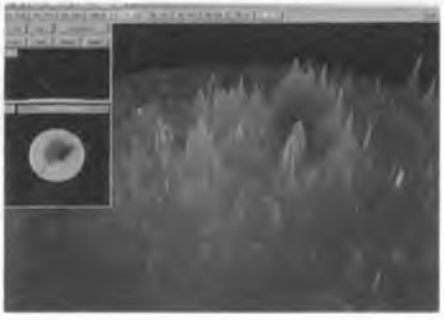

Fig. 9. Three-dimensional representation of the melanoma collagen view (SIA-3D)

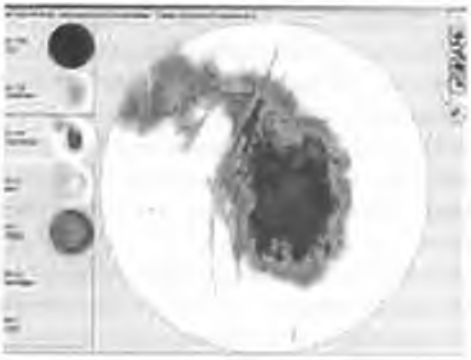

Fig. 10. Colours corresponding with levels of the dermal melanin detected

statistical analysis was performed on the data set using a suitable software on a personal computer (7). The sensitivity and specificity of these features for diagnosing melanoma have been described and shown to have a high degree of reliability (i.e. how often two clinicians agree at the same time) and reproducibility (i.e. how often the same clinician agrees at different times) in their identification. However, as expected no single feature was both highly specific and sensitive (7). Some of them show high sensitivity, e.g. the presence of dermal melanin whilst others high specificity (Table 2) (4). That was the reason why the authors decided to analyse those data for combinations of features using

Table 2. Sensitivity and specifity data for SIAscopic features of melanoma (1)

Feature	Sensitivity (%)	Specificity (%)
Dermal melanin	**96.2**	56.8
Collagen holes	78.8	74.0
Blood displacement with blush	63.5	**83.8**

* Table used with the kind consent of Symon Cotton, Astron Clinica Scientific Director

multiple logistic regression analysis (7). The study showed that the combination of dermal melanin presence which is the most sensitive for melanoma and the feature of the highest specificity, namely blood displacement with blush is consistently useful and specific. Next, the inclusion of the presence of collagen holes as a further feature was shown to increase the sensivity of the test (7). Furthermore, the combination of SIAscopy features with standard clinical data was established to be superior in predicting melanoma to the model that used SIAscopy features alone (10).This made it possible to devise a very simple scoring system based on the lesion diameter, patient age, dermal melanin and blood displacement with blush that is highly specific (74%) and sensitive (90.4%) in diagnosing melanoma (Table 3) (4, 10).

Table 3. Combined SIAscopic scoring system (2)

Feature	Score
Dermal melanin	3
Blood displacement with blush	1
Diameter (maximum diameter > 6 mm)	1
Patient age (in years)	1 For every completed 15 years
The score is calculated by simple addition. A **total score > 5** is indicative of **melanoma**	

* Table used with the kind consent of Symon Cotton, Astron Clinica Scientific Director

However, SIAscopy is not just the best for naevi examination but also a complete tool for dermatology. There is evidence that it can be used to assist in diagnosis and management of other dermatological conditions (11). Some of the possibilities are as follows:

1. Identifying margins and the extent of infiltration of basal cell carcinoma (BCC) that allows to minimise healthy tissue removal (4). BCC is one of the most common cancers in fair-skinned populations and mostly occurs on cosmetically important areas, such as a face. Thus it needs to be removed with the minimum of surrounding healthy tissue. Unfortunately, the peripheral margin of the tumor often extends beyond the region that can be seen by the naked eye meaning that a surgeon needs to take a substantial rim of normal skin to be sure of adequate clearance. Furthermore, the tumor may extend deeper than it clinically appears at the time of excision. Trials have shown that SIAscope can detect the extent of tumor by producing three-dimensional topographical maps of the collagen distribution and, as a result allows doctors to minimise the cosmetic impact of surgery (1).

2. Management of basal cell carcinoma in photodynamic therapy (PDT) which is widely used as a method that gives good cure rates without the need of surgery. However, it only works on certain types of BCCs. Currently, some trials are underway to show usefulness of SIA in predicting which skin cancer will respond well to PDT (1).

3. Diagnosis and management of psoriasis (1). SIAscopy may be especially helpful in a differentiation between psoriasis and dermatitis allowing an accurate treatment to be applied. Using SIAscope, the minimum effective dose for phototherapy can also be determined (1).

4. Monitoring the progress of wound healing (1). As SIA can produce the image of the vascularity around wounds, the SIAscope is used to measure the effectiveness of new methods to accelerate wound healing, particularly diabetic wounds, and has potential to predict what intervention is necessary to promote effective wound healing. Some diabetic ulcerations can be slow to heal and are often referred to vascular surgeons for expensive treatment. Blood SIAgraphs can give an indication of whether a wound is likely to heal without a surgical intervention (1, 11).

5. Management of lentigo maligna that can be a real challenge (11). Thus, in some cases, a punch biopsy performing is needed to confirm a diagnosis. It should be taken from the correct part of the

lesion but finding this area by a naked eye or with a dermatoscope can be difficult. Dermal melanin SIAgraph highlights the areas of pigment presence in the dermis which are likely to be the best ones to sample in order to confirm the diagnosis in the least invasive and most reliable way (11). Above--mentioned possible applications of the SIAscopy have shown early promise in their development.

So far SIA for medical diagnosis has been proven only on human skin but research is ongoing into its application in other, especially epithelial tissues including linings of the lung, gastrointestinal tract and linings of the genital tract (11). As the early SIAscopic features of pigmented skin lesions are very simple to learn and use, it would be reasonable to evaluate the SIAscope in the setting of general practice where there is a possibility to screen patients before being referred to the dermatologist. It would be also useful to assess SIAscopy as a tool for monitoring patients with pigmented skin lesion especially those with dysplastic naevus syndrome or lentigo maligna.

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SUMMARY

Spectrophotometric Intracutaneous Analysis (SIA) is a fast, non-invasive and completely safe method of pigmented skin lesions differentiation with distinct advantages over clinical and dermatoscopic diagnosis of melanoma. It is easy to perform and allows to examine the skin lesions with great accuracy and in a highly objective manner. The sensitivity of the method reaches the value of 96%. It has also been shown that SIAscopy is the most reliable and reproducible of melanoma non-invasive diagnostic techniques. The device, termed SIAscope operates by emission of harmless radiation ranging from 400 to 950 nm into the skin and next, by a measurement of the reflected light quantity for each wavelengths. It is possible because individual components of the skin vary in their optical properties. They absorb and/or reflect light to a various degree and interact preferentially with particular wavelengths

of light. From the spectral measurements SIAscope extracts information regarding location, quantity and distribution of melanin, collagen and haemoglobin (i.e. vascularity) within the layers of the skin. The data are then displayed on the screen as the SIAgraphs, which are graphical representations of digital information. It has been established that melanoma displays a characteristic SIAscopic image. It allows doctors to diagnose the tumor early enough even without much experience.

SIAskopia – nowa nieinwazyjna metoda diagnostyki czerniaka

Śródskórna Analiza Spektrofotometryczna jest metodą umożliwiającą szybkie, łatwe i całkowicie bezpieczne obrazowanie zmian skórnych *in vivo* oraz ich wysoce obiektywną ocenę. Jest metodą o udowodnionej przewadze nad badaniem klinicznym i dermatoskopowym w różnicowaniu zmian barwnikowych skóry i diagnostyce czerniaka. Wykazano również, że jest badaniem o najwyższej czułości, sięgającej 96%, oraz największej wiarygodności i odtwarzalności spośród wymienionych metod nieinwazyjnych. Urządzenie zwane SIAskopem emituje nieszkodliwe promieniowanie w zakresie światła widzialnego i bliskiej podczerwieni (400–950 nm), a następnie mierzy ilość światła odbitego przez komponenty skóry w zakresie każdej długości fali. Wykorzystuje różnice we właściwościach optycznych poszczególnych mikrostruktur skóry, które w różnym stopniu pochłaniają i/lub odbijają światło, oddziałując preferencyjnie z określoną długością fali. Aparat określa położenie, ilość i rozmieszczenie melaniny i kolagenu w obrębie badanej zmiany oraz jej unaczynienie. Obraz cyfrowy jest wyświetlany na monitorze w formie graficznej (SIAgrafy). Czerniak posiada charakterystyczny obraz SIAskopowy, co umożliwia jego wczesne rozpoznanie nawet mało doświadczonemu lekarzowi.