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Strategies for early recognition of cutaneous melanoma—present and future

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ABSTRACT Cutaneous melanoma is a highly aggressive malignant tumor of skin melanocytes with an increasing incidence in most countries of the world, especially in the fair-skinned populations. Despite all preventive and therapeutic efforts, malignant melanoma is still the most lethal skin cancer. A delayed diagnosis results in an advanced stage and worsened prognosis. Once distant metastases are present, the five-year survival rate is less than 10 percent. At the same time, patients may be cured by an early diagnosis of cutaneous melanoma followed by a wide excision. Therefore, the early detection of melanoma at curable stages is crucial for the patients' survival. Besides the investigation of pigmented lesions with the unaided eye, a wide range of examination techniques for improved diagnostic accuracy have been developed and validated in clinical trials. However, none of these techniques are able to provide a definite and final diagnosis or to replace an excisional biopsy of suspicious lesions followed by histological analysis. This review provides a concise overview of general principles as well as current and future strategies for an improved early diagnosis of cutaneous melanoma

Introduction

Cutaneous melanoma is a highly aggressive malignant tumor of melanocytic origin with increasing incidence in most countries of the world over the last few decades. In Caucasian populations the incidence rates for cutaneous melanoma have risen faster than those for any other malignant entity over the last 30 years [1]. The individual risk for developing melanoma depends on intrinsic and environmental factors. Intrinsic factors include the inherited degree of skin pigmentation (skin type I-V) or mutations of tumor-suppressor genes (e.g., *CDKN2A*, encoding for Cyclin-dependent kinase inhibitor 2A), which might be reflected by a positive family history of melanoma. The most relevant environmental factor is the exposure to ultraviolet radiation. When a patient's risk for melanoma needs to be assessed during daily clinical routine, the personal and family history of melanoma, number of common

and atypical nevi, skin type, presence of freckles, eye color, hair color, and the presence of non-melanoma skin cancer lesions should be considered [2]. The overall number of nevi induced by ultraviolet radiation in early infancy was shown to be an especially important predisposing risk factor for the development of melanoma [3]. Individuals with a high nevus count are endangered notably, whereby the risk of melanoma development increases almost linearly with rising numbers of melanocytic nevi on the whole body [4]. Although cutaneous melanoma is less common than other skin cancers, it causes the majority (approximately 90 percent) of deaths related to skin cancer. An advanced tumor thickness (Breslow's depth) is strongly associated with an increased mortality. Therefore, the early detection of melanoma at early and curable stages is critical for the patients' survival. In contrast to many other tumor entities, cutaneous melanoma may already develop metastases at a low tumor volume. Once distant metastases have occurred, the median survival is approximately nine months and the five-year survival rate is less than 10 percent. On the contrary, for thin melanomas with a tumor thickness of less than 0.76 mm, the ten year survival rate is 99.5 percent. These rates markedly decrease to 48 percent for lesions with more than 3 mm tumor thickness [5].

Until today, the most common method for detecting melanoma is visual diagnosis. To make a correct diagnosis, knowledge about the different melanoma subtypes is essential. The most frequent form of cutaneous melanoma is superficial spreading melanoma (SSM, Figure 1). It grows slowly and initially in a horizontal plane and subsequently, in more advanced cases, it will reach a vertical growth phase. With naked eye examination, lesions are often sharply demarcated, polycyclic and multicolored. In contrast, nodular melanoma (NM), a much more aggressive form, exhibits an early vertical growth phase. NM emerges primarily and is then often detected late, at an advanced tumor thickness, or it develops secondarily within a SSM (Figure 2). The nodes often grow rapidly, are vulnerable with a tendency to ulceration and bleeding, or might appear non-pigmented. Lentigo maligna melanoma (LMM, Figure 3) characteristically occurs at older age and is localized in areas of chronically sun-exposed skin, like the face or dorsa of the hands. Similar to SSM, it appears polycyclic, sharp-bounded and often shows multiple brown spots. A rare growth variant of cutaneous melanoma, the acral-lentiginous melanoma (ALM, Figure 4) is localized in palmoplantar skin but may also involve the nail unit. ALM represents the most common growth variant in dark-skinned (e.g., Asian) populations. Due to the architecture of palmoplantar skin with parallel ridges and furrows, the margins are often not clearly defined and the pigmentation is incoherent.

Further melanoma subtypes are not classifiable or represent hybrid forms. Moreover, special forms like mucosal and ocular malignant melanoma exist.

In summary, the most effective approach to improve the prognosis of cutaneous melanoma is early recognition and surgical excision at curable stages. The identification and the screening of high-risk patients is an important prerequisite to further enhance efforts to lower the mean tumor-thickness at the time of diagnosis. Excisional biopsies of suspicious lesions with subsequent histopathologic examination of specimens will allow for a definite classification.

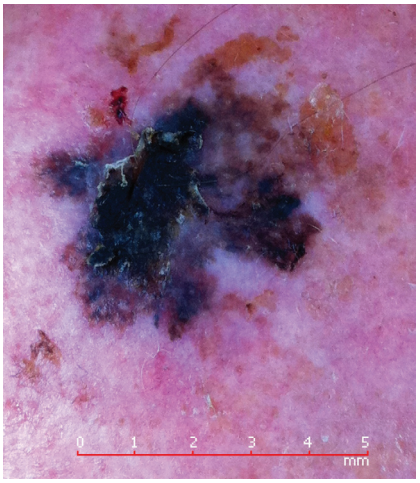

Figure 1. Superficial spreading melanoma of the scalp (SSM, Breslow thickness 1.2 mm). Note the sharply demarcated borders of the lesion, a central ulceration, and the multiple colors (black, brown, white). The surrounding skin shows actinic damage. [Copyright: ©2012 Brehmer et al.]

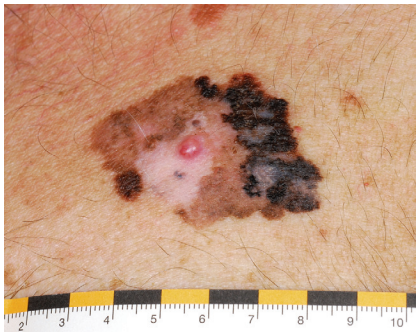

Figure 2. A nodular melanoma (NM) that developed secondarily within a superficial spreading melanoma on the back (Breslow thickness 3.5 mm). The SSM portion shows pink and black-brown colors, while the nodular portion appears homogeneously pink. [Copyright: ©2012 Brehmer et al.]

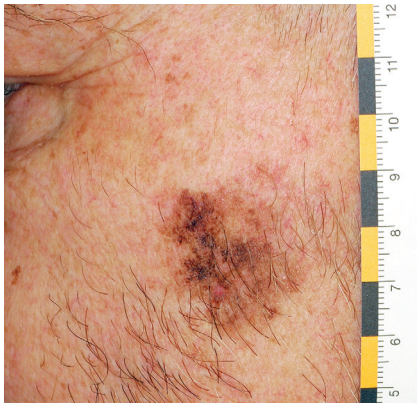

Figure 3. Early lentigo maligna melanoma (LMM, Breslow thickness 0.2 mm) on the left cheek. This LMM shows the typical localization in areas of chronically sun-exposed skin. Note the macroscopically visible granular appearance of light brown to black colors. [Copyright: ©2012 Brehmer et al.]

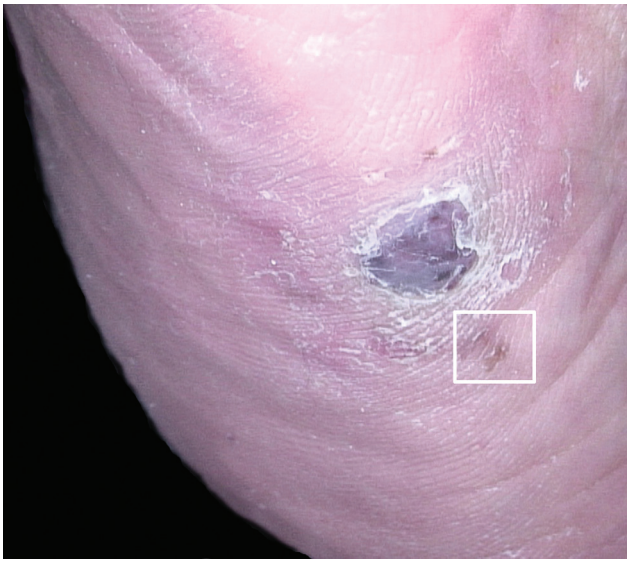

Figure 4. Nodular acral lentiginous melanoma (ALM) on the left lateral plantar foot (Breslow thickness 2.1 mm). Note the small pigmented area (white box) at the periphery of the otherwise amelanotic lesion. [Copyright: ©2012 Brehmer et al.]

Clinical examination with the unaided eye

The application of the clinical *ABCD rule* (Table 1) devised by Friedman et al in 1985 is a common method for the clinical diagnostics of cutaneous melanoma [6]. The criteria asymmetry, irregular margin, multiple colors and a diameter over 6 mm, cutaneous melanoma has to be considered. However, the *ABCD rule* is characterized by a low specificity as other benign skin lesions such as seborrheic keratosis may also fulfill the aforementioned criteria. Moreover, it is not applicable for pigmented lesions on the palms, soles or face due to the particular skin anatomy at these sites [7]. Small melanomas with a diameter of 6 mm or less or rare non-pigmented subtypes of melanoma will also not be detected by the *ABCD rule*. Certain dynamic changes within melanocytic lesions are also suggestive of cutaneous melanoma, for instance, asymmetrical changes in size, shape or color, or itching and bleeding. In consequence, the acronym was extended by the letter "E" for evolving or evolution to the *ABCDE rule* [8].

Before examination of selected nevi in more detail, it is useful to get an overview of recurrent and predominant patterns of a patient's nevi. Nevi in the same individual tend to resemble one another, so-called "signature lesions," indicating benign nevi on a regular basis. In contrast, melanomas often deviate from the individual's nevus pattern, so-called "ugly duckling sign" [9]. Recently, a high sensitivity for the early detection of melanoma with the help of the "ugly duckling sign" could be demonstrated [10].

Medical total body photography is often used in dermatology to support the clinical surveillance of high-risk patients. One method is the total body photography in standardized and reproducible positions. Photographically assisted follow-up images help clinicians and patients to detect new and changing pigmented lesions with the unaided eye [11,12]. In contrast to digital dermoscopy, which allows for monitoring of a few lesions only, full body photography permits monitoring of all lesions of a patient. Therefore, full body photography is a useful supplement to dermoscopy.

Dermoscopy

Dermoscopy (also known as epiluminescence microscopy, dermatoscopy, or amplified surface microscopy) allows for a significant improvement in the preoperative diagnostic accuracy of pigmented skin lesions. Dermoscopy is a non-invasive technique for the in vivo examination of melanocytic and non-melanocytic skin lesions. The handheld dermo-

TABLE 1. ABCD-rule. The ABCD criteria were intended as a simple tool to alert nondermatologists to the clinical features of melanoma. The criteria were not meant to provide a comprehensive list of all melanoma characteristics.

A	Asymmetry	Benign nevi are symmetric, their shape is round or oval. In contrast, cutaneous melanomas grow faster in several areas and are consequently asymmetric.
B	Border irregularity	Common nevi are bounded regularly to normal skin, whereas cutaneous melanomas often exhibit ragged and dull margins.
C	Color variegation	Benign nevi usually show homogeneous brown shade of color, whereas cutaneous melanomas exhibit different colors like black, brown, red or slate blue.
D	Diameter > 6 mm	After a growth period in infancy and adolescence, common nevi remain stable in size, whereas melanomas often grow rapidly. A diameter more than 6 mm is considered to be suspicious.

TABLE 2. The 7-point checklist of dermoscopy.
With the addition of criteria scores, a score of 3 or more points is suspicious for melanoma.
The odds ratio is a measure to describe the strength of association between two variables, in this case between a dermoscopic structure and the possibility of malignancy.

Major Criteria	7-point score	Odds Ratio
Atypical pigment network	2	5.19
Grey blue areas	2	11.1
Atypical vascular pattern	2	7.42
Minor Criteria		
Irregular streaks	1	3.01
Irregular diffuse pigmentation (blotches)	1	4.90
Irregular dots and globules	1	2.93
Regression structures	1	3.89

scope traditionally consists of a magnifier, a non-polarized light source and a transparent plate. A liquid medium, for instance, immersion oil or spray for skin disinfection, is needed between the instruments contact plate and the skin to reduce the reflection of light. With the help of dermoscopy further information about the architecture, e.g., the pigmented network, the vascular pattern and the distribution of color of a single lesion is obtained [13]. Today, many different dermoscopes are commercially available (e.g., Dermatoscope™ by Heine Optotechnik; Episcope™ by Welch Allyn; DermoGenius™ by Rodenstock Präzisionsoptik). More recently dermoscopes that emit polarized light to eliminate skin surface reflection entered the market. These instruments do not require skin contact and a liquid medium can be omitted (e.g., Dermlite™ 3 Gen).

The dermoscopic evaluation of a lesion is performed in two steps. This procedure for classification of pigmented skin lesions was agreed on at an international consensus meeting [14]. In the first step it has to be determined whether a melanocytic or non-melanocytic tumor is present. In case of a melanocytic lesion, the differentiation between benign or malignant/suspicious lesions follows in a second step. For this second step various algorithms were established and validated in clinical trials. Most algorithms (e.g., the *ABCD rule* of dermoscopy [15], the 7-point checklist of dermoscopy [16], or Menzies' scroring method [17]) use a number of criteria associated with the presence of melanoma as first described for the pattern analysis by Pehamberger et al [18]. Especially, three algorithmic methods (qualitative pattern analysis, the *ABCD rule* of dermoscopy, and the 7-point checklist) were shown to be valid and reliable in distinguishing benign and malignant melanocytic tumors. The pattern analysis is based on a detailed, qualitative assessment of numerous dermoscopic criteria, and a high rate of diagnostic accuracy could be obtained by experienced investigators after a significant degree of formal training (19). The *ABCD-rule* of dermoscopy uses a semiquantitative scoring system based on a complex evaluation of asymmetry, border, color, and different dermoscopic structures within the lesion [15]. The 7-point checklist (Table 2) was developed as a quantitative scoring system with three major criteria (score of 2 points) and four minor criteria (score of 1 point). A minimum total score of 3 is required for the diagnosis of melanoma [16]. The 7-point checklist can be learned and applied more easily and in comparative studies allowed the best sensitivity in the hands of non-experts [20,21]. Two unsuspicious melanocytic nevi are shown in Figures 5 and 6, while three superficial spreading melanomas with their typical criteria for malignancy are demonstrated in Figures 7-9.

A systematic overview of Medline publications between 1983 and 1997 showed that dermoscopy leads to a 10–27% increase in sensitivity as compared to the clinical diagnosis with the unaided eye [22]. Dermoscopy not only allows for an earlier detection of melanoma but was also shown to avoid unnecessary excisions of benign nevi. Depending on the individual experience of the clinician, a sensitivity of up to 92%and a specificity of up to 99% were documented for the detection of cutaneous melanoma by dermoscopy [23]. Among dermatologists, dermoscopy has become a routine examination technique in Europe and is with gaining acceptance worldwide.

When computer hardware became more and more available and affordable, digital dermoscopy devices were devel-

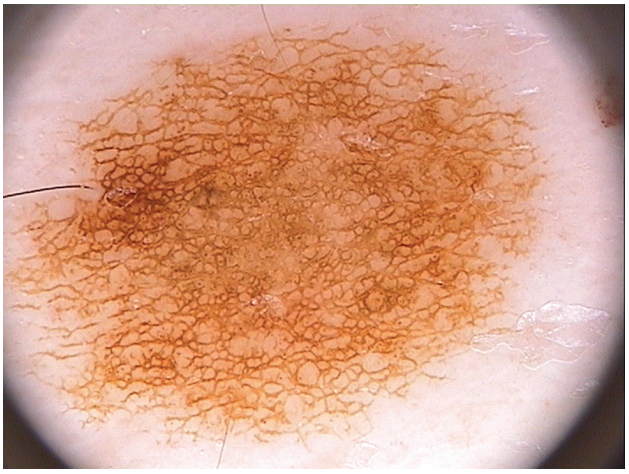

Figure 5. Common nevus. The pigment network is homogenous light brown with predominantly regular meshes and thick lines. The pigment network is thinning towards the periphery. [Copyright: ©2012 Brehmer et al.]

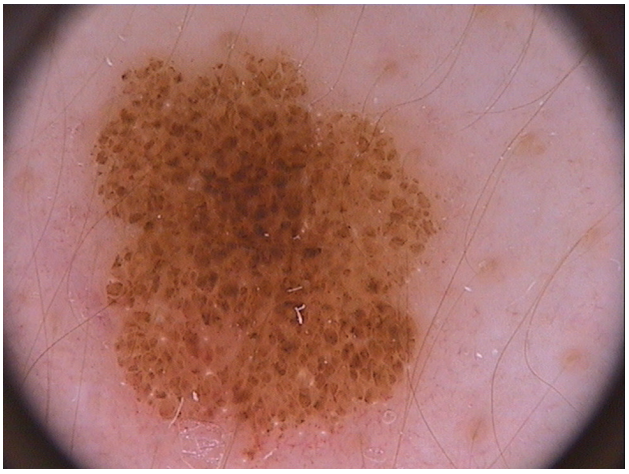

Figure 6. Common nevus with globular pattern. The brown, round-to-oval structures are distributed regularly within the lesion. [Copyright: ©2012 Brehmer et al.]

oped and rapidly integrated into the clinical setting. Digital overview and dermoscopic images offer the advantage of computer storage and retrieval during later examinations of patients [13]. Some digital dermoscopy devices even offer a computer-assisted diagnosis [24-26].

Despite a higher impact on financial and personnel resources, the sequential digital dermoscopic examination offers a number of advantages for patients with a high number of atypical nevi and a personal and/or family history of melanoma [2,27]. Due to the multitude of atypical pigmented lesions in these high-risk patients, it is often difficult to detect melanoma at an early stage without excising hundreds of benign nevi (Figure 10). By comparison of dermoscopic follow-up images with baseline images subtle intralesional changes can be detected and assessed. A range of studies have proven that digital dermoscopy follow-up of high-risk patients allows for the early detection of melanomas that have not yet acquired melanoma-typical dermoscopic features, thus increasing the sensitivity [27-29]. With the help of sequential digital dermoscopy, incipient melanomas can be identified by detection of intralesional changes, for instance asymmetrically enlargement or architectural changes (Fig-

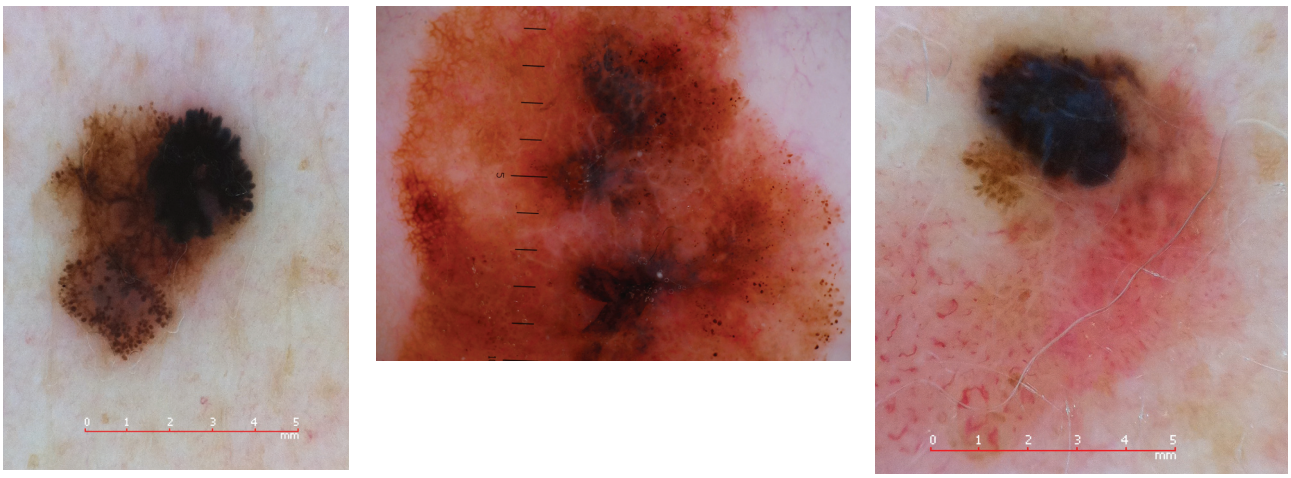

Figure 7. (left) Superficial spreading melanoma (SSM, Breslow thickness 0.7 mm). Note the macroscopically visible appearance of light brown to black colors. Besides the atypical pigment network with irregular meshes and different thick lines and multiple, irregularly distributed dots the melanoma shows deep black, irregular, linear structures not clearly combined with pigment network lines (streaks). [Copyright: ©2012 Brehmer et al.]

Figure 8. (center) The superficial spreading melanoma (SSM, Breslow thickness 0.9 mm) shows irregular diffuse black and gray-blue pigmentation in the center of the lesion. Note the multiple colors. The dots are distributed irregularly. [Copyright: ©2012 Brehmer et al.]

Figure 9. (right) Superficial spreading melanoma (SSM, Breslow thickness 1.05 mm). Note the multiple colors (gray-blue, brown, red). A sharply bounded gray-blue pigmentation and multiple linear irregular as well as dotted vessels due to neovascularization can be detected. The linear vessels of thicker melanomas are often twisted and curved. [Copyright: ©2012 Brehmer et al.]

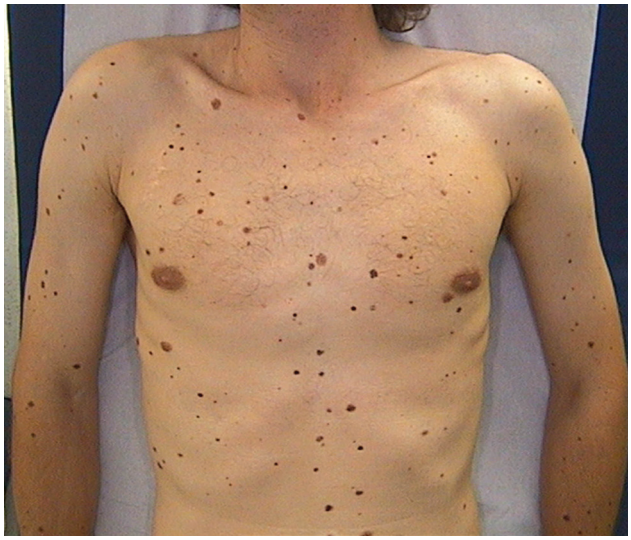

Figure 10. Patient at increased risk for cutaneous melanoma with history of previous melanoma, hundreds of nevi, and multiple atypical nevi (e.g., asymmetry, color variegation). A long-term surveillance for early detection of melanoma is indicated. [Copyright: ©2012 Brehmer et al.]

ure 11 A-C) [30,31]. This applies especially for melanomas without suspicious dermoscopic features, so-called "featureless melanoma." Another strategy of sequential dermoscopic follow-up is the short-term follow-up (three-month interval), which targets a restricted number of highly atypical

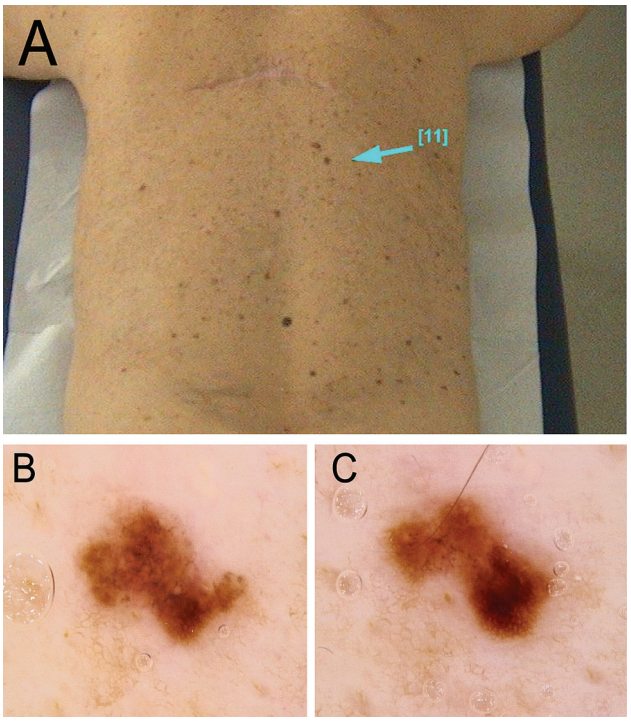

Figure 11A-C. Subtle lesional changes over time (6 month interval between B and C). An excisional biopsy in this high-risk patient with previous melanoma (scar over left scapula) was triggered by an asymmetrical enlargement, accompanied by an excentric hyperpigmentation and an increasing prominent network. Histologic diagnosis: early superficial spreading melanoma (SSM, Breslow thickness 0.2 mm). [Copyright: ©2012 Brehmer et al.]

nevi, which should be removed whenever dynamic changes become apparent [29,32]. Numerous systems for sequential digital dermoscopy imaging are commercially available (e.g., Molemax™, Fotofinder™, SolarScan™).

New innovative applications

The need for a further improved diagnostic accuracy for the assessment of skin tumors has led to the development and investigation of new imaging tools. An innovative technique is the ***in-vivo confocal laser scanning microscopy (CLSM)***, which represents a relatively novel imaging tool allowing for non-invasive examination of skin morphology in real time and at a near-histopathologic resolution. Multiple studies have evaluated the use of reflectance mode CLSM for the diagnosis of melanoma in the past decade. In this regard, two different algorithms for melanoma diagnosis have been developed by two independent groups from Modena and Barcelona, showing similar sensitivity and specificity values for several CLSM criteria [33,34]. The relative simple two-step method developed by Segura et al [33] uses protective, as well as risk factors, whereby the presence of two risk factors results in a sensitivity of 86.1% and a specificity of 95.3% for the diagnosis of melanoma. Pellacani et al identified six criteria, two major and four minor criteria, as independently correlated with a melanoma diagnosis [34]. The two major criteria corresponded to the presence of atypical melanocytic cells within the epidermal basal layer and the papillary dermis or within the basal layer of non-edged papillae. The four minor criteria were represented by the presence of roundish cells in superficial layers spreading upward in a pagetoid fashion, pagetoid cells widespread throughout the lesion, cerebriform clusters within the papillary dermis and bright nucleated cells in the upper dermis. The presence of at least two features, one major and one minor criterion, was essential for melanoma diagnosis. On the other hand, regular dermo-epidermal architecture and absence of pagetoid infiltration and atypical cells were indicative of benign lesions.

The evaluation of skin lesions by CLSM is based on illumination of the tissue by a point laser light source and reflectance of individual skin structures, of which melanin is providing the strongest contrast [35-37]. Specific morphological pattern can be observed by CLSM in nevi and melanoma allowing for differentiation of benign and malignant, but also for differentiating melanocytic from non-melanocytic lesions such as pigmented basal cell carcinoma (Figure 12). Due to scanning mode of CLSM an area of up to 8 x 8 mm may be evaluated on horizontal sections and on different skin levels (e.g., stratum corneum, stratum spinosum, dermo-epidermal junction, dermis). Thereby, the great advantage of CLSM lies in the immediate diagnosis that may guide the

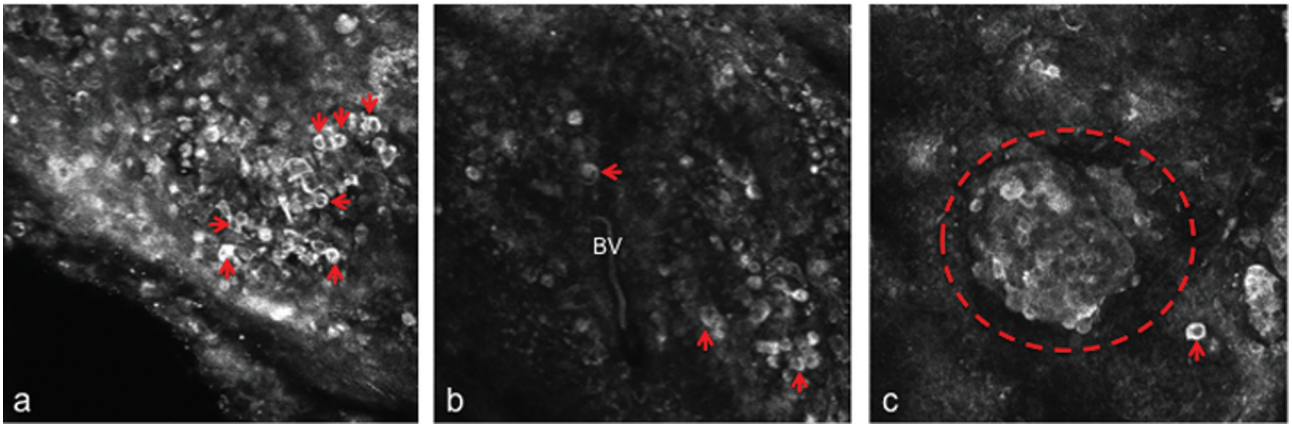

Figure 12A-C. In-vivo reflectance laser scanning microscopy (CLSM) images (500 x 500 µm) of a melanoma. (A) Obtained at the level of the granular/spinous layer of the epidermis showing multiple large round nucleated cells (red arrowheads), which correspond histologically to pagetoid spread of atypical melanocytes. (B) Obtained at the level of the dermo-epidermal junction showing the presence of large, nucleated cells (red arrows) corresponding to atypical melanocytes which are arranged in clusters around a dilated blood vessel (BV). The papillae are not clearly outlined, which results in so-called "non-edged papillae." (C) CLSM image at the superficial dermis with a large nest of melanocytes (dashed red circle). Within the nest large atypical melanocytes with dark central nucleus are seen. Furthermore, single atypical melanocytes are seen (red arrow). [Copyright: ©2012 Brehmer et al.]

clinician's decision for further management of a lesion. Furthermore, CLSM provides the clinician and the researcher with the possibility of monitoring of pigmented lesions over time and may change the way we evaluate melanocytic lesions in the future.

To implement the CLSM in the clinical setting, a consensus conducted as an online meeting for terminology in CLSM has been published [38].

The multispectral digital dermoscopy, a new development of conventional dermoscopy, has recently entered the European market (MelaFind™) and offers a fully automated differentiation of melanoma from atypical melanocytic nevi. Light of different wavelengths is transmitted and the degree of reflection or absorption by the different components of human skin (e.g., collagen, melanocytes, and blood vessels) is analyzed by a computer algorithm. A diagnosis is made by the assessment of the distribution of melanin, collagen and hemoglobin in a given lesion. A prospective multicenter trial, which led to the approval by the European agencies, showed a high sensitivity of 98.4%, but a low specificity of approximately 10%. However, as reported in the study by Monheit et al, the specificity was superior to that of clinicians formally trained in the use of dermoscopy [39].

Another novel non-invasive optical biomedical imaging technique is ***the optical coherence tomography (OCT)***. The basic principle relies on low-coherence interferometry enabling high resolution, two- or three-dimensional, cross-sectional imaging of microstructural morphology in biological tissue [40]. Using conventional OCT, the stratum corneum, the epidermis, and upper dermis and blood vessels can be visualized. However, with most of the present devices, it is not possible to investigate skin tissue on the cellular level, whereas the architecture of a pigmented lesion and the distribution of blood vessels can be assessed. Significant micromorphologic differences between benign and malignant tissues visualized by OCT were described. Cutaneous melanomas often show marked architectural disarray, the dermo-epidermal border is blurred and exhibits finger-shaped elongated rete ridges [41]. More precise data concerning sensitivity and specificity of OCT for the diagnosis of cutaneous melanoma are missing. Of note, for the diagnosis of intraocular tumors, optical coherence tomography was shown to provide valuable information [42].

Conclusion

Early detection of cutaneous melanoma is one of the most effective ways of reducing mortality rates from this disease. In addition to the clinical assessment with the unaided eye, dermoscopy has become a standard examination technique throughout most European countries, as it was shown to significantly improve the diagnostic accuracy of the clinical examination. Total body photography notably facilitates the detection of newly developed pigmented lesions in patients with a high nevi count. With the help of sequential digital dermoscopy imaging, even subtle dynamic changes are detectable, which is shown to improve the differentiation of atypical nevi and early melanomas in high-risk patients. A novel imaging tool is the confocal laser scanning microscopy, allowing examination of skin tumor morphology on a cellular level in real time. In the near future the recently approved MelaFind™ device will probably be applied for difficult-to-diagnose melanocytic lesions in selected centers.

Above all, it has to be emphasized that none of the aforementioned examination techniques are currently able to

provide a definite and final diagnosis or to replace excisional biopsy of suspicious lesions followed by histological analysis.

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