Recent advances in diagnosing cutaneous melanomas

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Abstract

Early detection of lesions while minimising the unnecessary removal of benign lesions is the clinical aim in melanoma diagnosis. In this context, several non-invasive diagnostic modalities, such as dermoscopy, total body photography, and reflectance confocal microscopy have emerged in recent years aiming at increasing diagnostic accuracy. The main developments in this field are the integration of dermoscopy and digital photography into clinical practice.

Introduction and context

Successful treatment of melanoma, by surgical removal, is reliant on the early detection of the lesion. The challenge is to diagnose and remove all malignant lesions at an early stage while minimising the unnecessary removal of benign lesions. Visual inspection with the naked eye has a relatively low sensitivity in detecting early melanoma [1-3]. In this context, several non-invasive diagnostic modalities, such as dermoscopy, total body photography, and reflectance confocal microscopy (RCM), have emerged in recent years that are aimed at increasing diagnostic accuracy and raising the threshold for surgical procedures.

Recent advances

Dermoscopy

Dermoscopy (also known as dermatoscopy or epilumi-nescence microscopy) allows for the visualization of anatomical structures within the epidermis and papillary dermis that would otherwise not be able to be visualised by the naked eye [4]. This is achieved with the use of a hand held dermatoscope to magnify the skin surface and reduce the refraction of light by the corneal layer. Various diagnostic algorithms (pattern analysis, ABCD rule, Menzies method, seven-point checklist, and three-point check list) have been proposed to help assess the structures and patterns seen in dermoscopy. Recently, criteria for amelanotic/hypomelanotic melanoma have been described (Table 1).

There are two different types of dermatoscopes: the original, non-polarised version requires an immersion medium (oil, alcohol) and is superior in visualising blue-white areas (often associated with regression), milia-like cysts, and comedo-like openings (features of seborrheic keratosis). The alternative dermatoscope uses polarised light and has been found to be better for assessing vascular structures and shiny white streaks that could be a sign of fibrosis [5]. It has been proposed that using the two different dermatoscopes in conjunction with each other may help to increase the sensitivity and specificity of detecting melanoma [6].

Various studies and three meta-analyses of the literature have validated the ability of dermoscopy to increase diagnostic accuracy. Dermoscopy was shown to be superior to naked-eye examination performed by specialists in two meta-analyses [1,3]. Recently, a meta-analysis by Vestergaard *et al.* [2], which focused exclusively on trials that were performed in a clinical setting, found that the relative diagnostic odds ratio was 15.6 for the use of dermoscopy to diagnose melanoma compared with naked-eye examination.

Furthermore, it has been reported that dermoscopic training for primary care physicians can improve their ability to correctly refer individuals with suspicious lesions and decrease the rate of excision or referral in

Table 1. Melanoma features in dermoscopy

Menzies method [38]	7-point checklist [39]	Amelanotic and hypomelanotic melanoma [40]
Positive features 1. Blue-white veil 2. Multiple brown dots 3. Pseudopods 4. Radial streaming 5. Scar-like depigmentation 6. Peripheral black dots/globules 7. Multiple colors 8. Multiple blue/gray dots 9. Broadened network	**Major criteria** *Score: +2* 1. Atypical pigment network 2. Blue-whitish veil 3. Atypical vascular pattern	**Positive features** 1. Irregularly sized or distributed brown dots/globules 2. Multiple blue/gray dots 3. Irregularly shaped depigmentation 4. Blue-white veil 5. More than one shade of pink 6. Predominant central vessels 7. Dotted and linear irregular vessels
Negative features 1. Symmetry of pattern 2. Presence of a single color	**Minor criteria** *Score: +1* 1. Irregular streaks 2. Irregular pigmentation 3. Irregular dots/globules 4. Regression structures	**Negative features** 1. More than three milia-like cysts
Absence of negative features and presence of ≥1 positive feature is diagnostic of melanoma	Score ≥3 is diagnostic of melanoma	Absence of negative features and presence of ≥1 positive feature is diagnostic of melanoma

For more details on dermoscopic diagnosis, including ABCD rule and pattern analysis, see [41].

benign skin lesions [7-9]. A complete skin examination with the aid of dermoscopy requires less than 3 minutes [10]. Haenssle and colleagues [11] performed a prospective long-term study with patients at high risk for melanoma in a real-life clinical setting using the seven-point checklist to dermoscopically score melanocytic lesions. A sensitivity of 62% for lesions scoring more than 3 points and specificity of 97% was found. Of the melanomas that were false negatives on dermoscopic evaluation, 25% were detected by dermoscopic follow-up and 13% by complementary patient history and the 'ugly duckling' sign. Regression pattern, radial streaming, and atypical vascular pattern were found to be the criteria associated with the highest relative risk for melanoma.

Overall, there is strong scientific evidence that clinical examination, including detailed anamnesis for identifying melanoma risk factors (family and personal history of melanoma, total number of nevi, including number of atypical nevi, skin type, presence of ephelides, hair and eye colour, non-melanoma skin cancer history, history of intermittent sun exposure) [12], and full body clinical inspection with detection of any lesions that are dissimilar to the rest ('ugly ducklings' [13]) aided by dermoscopy, is the gold-standard in non-invasive diagnosis of melanoma.

Total body photography and sequential dermoscopic follow-up
Photography enables documentation of lesions and has the ability to track and compare any changes over time. Macroscopic digital pictures of standardised body positions and digital dermoscopic images of lesions of concern enable nearly the entire body surface to be recorded and referred to in follow-up examinations.

This technique is particularly helpful in the surveillance of individuals with numerous nevi with a family history of melanoma (so-called dysplastic nevus syndrome). Photographic monitoring aids in identifying stable lesions and early detection of any concerning changes [14]. Theoretically, any photographic equipment can be used for total body photography but there are now specific digital skin photography systems available.

Technologic advances have led to the development of devices for sequential digital dermoscopy. Digital dermoscopic (and clinical) images are taken and linked to the body site via a computer. At follow-up visits the same lesion is re-photographed for comparison. This method has helped to detect a subgroup of slow-growing melanomas that lack suspicious features at baseline examination but exhibit detectable changes on follow-up [15].

However, due to the increased time expenditure and cost of follow-up for every melanocytic lesion in a given patient, there is a need to correctly identify those that benefit most from digital dermoscopic follow-up. Haenssle *et al.* [16] performed a prospective long-term study including patients at risk for development of melanoma to identify those who benefit most from sequential dermoscopy follow-up. According to the results, the authors suggested a follow-up plan as follows: (a) short-term follow-up of 3 months for patients with familial atypical mole and melanoma syndrome and (b) long-term follow-up of 6-12 months for those with atypical mole syndrome. Patients with multiple common nevi and no additional risk factors were found to have low benefit from sequential digital dermoscopy.

Some of the drawbacks of sequential dermoscopy include the potential for loss to follow-up [17]. Only preselected lesions are dermoscopically monitored and changes in a previously unsuspicious lesion or a *de novo* lesion might therefore be missed. Of note, suspicious nodular lesions should be excised immediately rather than observed over time as they are at higher risk of rapid change and spread if malignant.

The use of digital imaging has the added benefit of enabling teledermatologic applications. Teledermoscopy is defined as the transmission of digital dermoscopic images over a distance for specialist consultation, allowing primary care physicians to forward dermoscopic images to dermatologists for second opinion [18]. Good interobserver agreement between face-to-face diagnosis and diagnosis based on digital images has been demonstrated in several studies [19]. Furthermore, digital dermoscopic and clinical still images with complementary clinical data have been shown to increase confidence and interobserver agreement [20]. The feasibility of teledermoscopy using mobile devices has been recently demonstrated, highlighting the potential of mobile teledermoscopy as a screening and triage tool [21]. Teledermoscopy is particularly useful in remote areas where referral to a specialist is financially demanding and time consuming for the patient.

Reflectance confocal microscopy
RCM is a non-invasive imaging technique that uses a near infrared laser beam to create black and white images in a horizontal plane. The images are able to define cellular structures and morphology and can obtain images, with good resolution, of the epidermis, dermoepidermal junction, and the superficial dermis. RCM images are created from the difference in reflectivity of different tissue structures. Melanin and melanosomes are strongly reflective, making RCM a suitable modality for examining melanocytic lesions [22].

Several recent studies have identified RCM features of melanoma and nevi and have found key differences between the two. In short, features most suggestive of melanoma as found by Pellacani *et al.* [23,24] are displayed in Table 2. Other diagnostic algorithms for melanoma diagnosis have been proposed [25-27]. Gerger and colleagues [26] developed a decision tree analysis based on three RCM features (monomorphic melanocytic cells, keratinocyte borders, and polymorphic melanocytic cells). Segura and colleagues [27] recently presented a two-step algorithm for differentiation between melanocytic lesions and non-melanocytic lesions in the first step and between nevi and melanoma in the second step. A recent focus of interest is the value of RCM in diagnosis and pre-operative mapping of surgical margins in lentigo maligna (melanoma *in situ* in severely sun-damaged skin) [28,29]. A recently developed algorithm for diagnosis of lentigo maligna of the face is displayed in Table 2. Furthermore, a glossary of commonly used RCM terms has been published [30]. RCM is a promising potential clinical tool; however, large-scale clinical studies are required to be able to determine the entirety of its benefit.

Other non-invasive diagnostic tools
Other non-invasive diagnostic techniques currently in the process of being developed include multispectral image analysis, multiphoton laser scanning microscopy (MPM), optical coherence tomography, high frequency ultrasound, computer-assisted diagnosis, and molecular profiling.

Table 2. Features of melanoma in reflectance confocal microscopy (RCM)

Features of melanoma in RCM	Features of facial lentigo maligna in RCM
2 major criteria	**2 major criteria**
Score: +2	*Score: +2*
1. Cell atypia at the DEJ	1. Round large pagetoid cells >20 µm
2. Non-edged papillae	2. Non-edged papillae
4 minor criteria	**4 minor criteria**
Score: +1	*Positive features, Score: +1*
1. Roundish pagetoid cells	1. Three or more atypical cells at the DEJ in five fields of 500 × 500 µm
2. Widespread pagetoid infiltration	2. Follicular localization of atypical cells
3. Cerebriform nests	3. Nucleated cells within dermal papillae
4. Nucleated cells within dermal papillae	*Negative feature, Score: -1*
	4. Broadened honeycomb pattern in epidermis
Score ≥3 diagnostic for melanoma (sensitivity 97%; specificity 72%)	Score ≥2 diagnostic for lentigo maligna (sensivity 85%; specifity 76%)

The algorithm for melanoma diagnosis displayed above has been described by Pellacani *et al.* [42] and features of facial lentigo maligna have been described by Guitera *et al.* [29]. DEJ, dermal-epidermal junction.

Multispectral image analysis relies on the principle that different wavelengths of light penetrate the skin to different depths, enabling computer-aided visualization of criteria invisible to macroscopic and dermoscopic techniques.

High frequency ultrasound provides limited resolution images of the skin in the vertical plane. When used alone it is not reliable for diagnostic purposes. It can be used, however, as a tool for assessing tumour thickness and vascularity, which can assist in planning management preoperatively [31].

Optical coherence tomography is comparable to ultrasound but uses light instead of sound waves; it reaches a lower depth, providing a better resolution than ultrasound, but does not reach the resolution capabilities of RCM. Although there are studies regarding the various features of skin cancer, reports of diagnostic accuracy are lacking [32].

MPM utilizes non-linear excitation by a near-infrared laser source. Like RCM, the MPM allows imaging of horizontal sections of the skin, allowing visualization of cellular and subcellular structures. To date it is mainly used as a research tool [33].

Computer-assisted diagnosis uses automated diagnostic systems that extract and analyse criteria of skin lesions to provide a diagnosis without subjective human interpretation bias. It has been shown to reach levels of diagnostic accuracy similar to that of expert dermatologists [34,35]. However, in order not to miss a melanoma, there is a tendency for these tools to overdiagnose melanoma. A recent meta-analysis showed a slightly higher sensitivity for computer-aided dermoscopic diagnosis compared to expert diagnosis, but significantly lower specificity [36]. To date, a few fully automated systems are available, some of which are integrated in the software of videodermoscopy devices. MelaFind® uses multispectral imaging and the DB-MIPS system extracts information from dermoscopic images. The MelaFind system is currently in the final stages of being granted US Food and Drug Administration approval.

Molecular profiling for the diagnosis of melanoma is an emerging development. A method that uses RNA acquired from the cornified layer of a lesion gathered by tape stripping [37] is currently being investigated.

Implications for clinical practice

To date, the current standard method for melanoma diagnosis is naked-eye inspection with closer dermoscopic examination of suspicious lesions to determine which should be excised and sent for histopathological confirmation. The use of digital photography to track changes has been shown to be effective and is now integrated into practice. It is difficult to predict how clinical practice will be affected and if the new emerging imaging modalities, such as RCM, MPM, and computer-assisted diagnosis, will prevail, or if molecular analysis will substitute morphology. Further large-scale studies will determine their importance. Despite emerging technologies, it remains crucial to evaluate lesions in the context of the examination of the individual patient. Only those lesions that are considered suspicious can be further evaluated due to time expenditure, and, therefore, careful clinical examination and pre-selection is still irreplaceable.

Abbreviations

MPM, multiphoton microscopy; RCM, reflectance confocal microscopy.

Competing interests

HPS is co-founder and share holder of e-derm-consult GmbH, a spin-off company of the Medical University of Graz (Graz, Austria) with emphasis on holistic solutions for teledermatology. He is also share-holder and consultant for MoleMap Australia by Dermatologists Pty Ltd. EMTW and CESC declare that they have no competing interests.

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