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Noninvasive Imaging Technologies in the Diagnosis of Melanoma

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The incidence of melanoma has increased during the last few years. Melanoma care and survival can be improved by early diagnosis, which can be facilitated by the use of noninvasive imaging modalities. Here we review 5 modalities available in clinical practice. Total body photography is used to follow patients at high risk for melanoma by detecting new lesions or subtle changes in existing lesions. Dermoscopy is an effective noninvasive technique for the early recognition of melanoma by allowing clinicians to visualize subsurface structures. Computer-assisted diagnostic devices are fully automated analysis systems with the capacity to classify lesions as benign or malignant with limited involvement from clinicians. Confocal scanning laser microscopy is an in vivo and noninvasive technology that examines the skin at a resolution comparable to that of histology. High-resolution ultrasound is an adjunct diagnostic aid mainly for the early detection of lymph node metastasis. Applications and limitations of each technology are discussed.
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In the United States, the incidence of melanoma has risen dramatically during the past 5 decades for both men and women across all categories of tumor thickness. The lifetime risk of developing invasive melanoma was 1 in 1500 in 1930; it is at present 1 in 74.[1] The most worrisome trend is the annual 3.86% increase in the thickest tumor (>4 mm) category.[2] Currently, there is no cure for advanced cutaneous melanoma; only early diagnosis followed by prompt excision ensures a good prognosis. However, clinical diagnosis of melanoma is a challenging task, and the process can be subjective and is prone to inaccuracies and misdiagnosis.[3,4]

The need for improved diagnostic accuracy in melanocytic skin lesions has led to the development of a variety of noninvasive imaging modalities that can be used to complement naked-eye examination and facilitate the early detection of melanoma. Although significant progress has been made in the effort to incorporate noninvasive imaging technology in the clinical setting, the nature of dermatology, with its readiness of visual inspection and ease of skin biopsy, may deter physicians from adopting these technologies widely in daily practice. Furthermore, there is no consensus on the optimal strategy to appropriately use these tools in clinical practice.[5]

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In this article, we review the most clinically relevant imaging modalities and discuss their advantages and limitations.

Total Body Photography

Total body photography (TBP) is an effective method for detection of early melanomas and can be an aid in the clinical surveillance of high-risk patients.[6] It was first described by Kopf and Slue at New York University in 1988[7] as a method for monitoring high-risk patients with a personal history of melanoma and for following patients with a large number of atypical nevi. In the course of the last 2 decades, the basic principles of TBP have not changed, but medical photographers and clinicians today enjoy the benefit of having superior technical equipment.

Patients with many atypical melanocytic nevi are selected for photographic documentation of the skin of their whole body. A digital single lens reflex (SLR) camera with an attached flash and studio lighting is set up to carry out the photographic session. SLR cameras with high-resolution image quality are preferred over point-and-shoot digital cameras. Under the instruction of a medical photographer, patients position themselves for a set of 20 or more recommended poses (Fig. 1).[7-9] The poses are designed to capture targeted anatomic sites (eg, face, chest, abdomen, and arms) with minimal overlap. Also, the poses are created to display specific areas of the body, such as axillae and plantar surface of the feet that are often overlooked.[10] Often, close-up clinical and dermoscopic images of concerning lesions are also taken for

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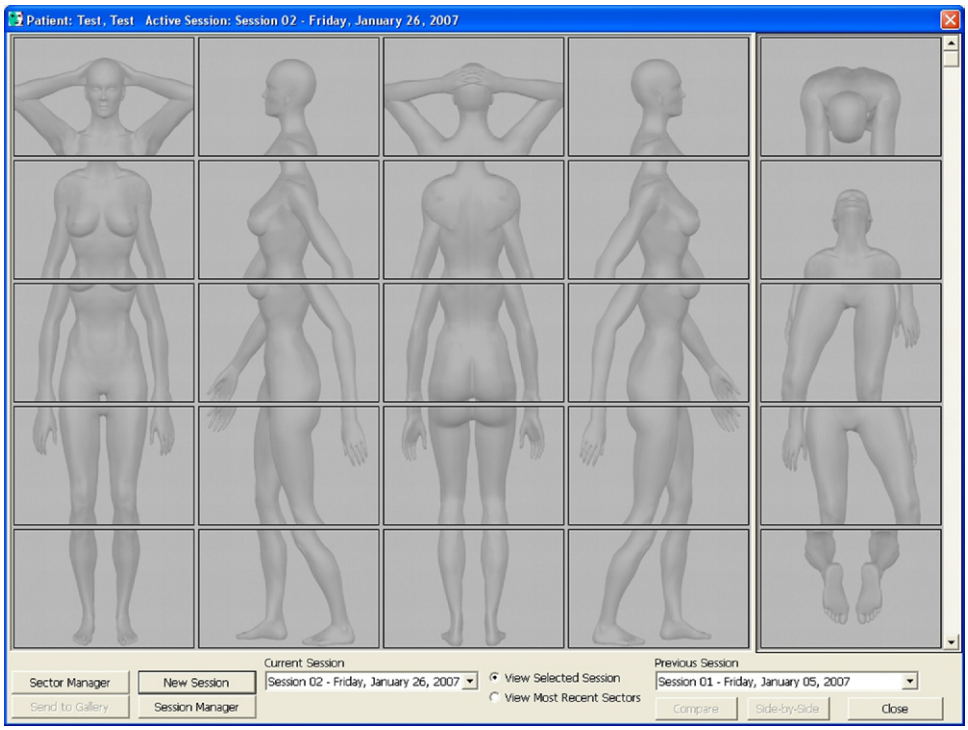

Figure 1 Standardized set of poses designed to image targeted anatomic sites.

future follow up. Many types of imaging software (eg, Mirror, Canfield, NJ) are available on the market and permit the photographer to upload and store the images in a secured database. Furthermore, there are options that allow the photographers to tag the close up clinical and dermoscopic photos of particular lesions to their designated anatomic site. This feature permits the detection of early and subtle changes in many atypical lesions. It is common practice to give a duplicate set of images, either in prints or digital CD, to patients.[11] With these images, patients are empowered to perform self-examination, because they have baseline photos to track suspicious changes in the appearance of their moles.[10]

The clinical utility of TBP in following patients with a high risk for melanoma has been well demonstrated.[6,12-14] In each visit, clinicians can perform a total-body examination while using the baseline photos for comparisons. This approach works exceedingly well to document the stability of lesions and track subtle changes in existing moles that may otherwise be missed by the unaided eye.[7,10] The element of change is a valuable clue.[15,16] In fact, the letter "E," signifying evolution or change, has been added to the well-known "ABCD" acronym for diagnosing melanoma. Hence, it is understandable that the majority of melanomas diagnosed with the aid of TBP are in situ and thin lesions[13,17,18] and that many do not have the classical "ABCD" melanoma features.[6] Aside from early detection of melanoma, TBP also decreases the number of medically unnecessary biospies.[6,13,14] In patients with classic atypical mole syndrome, decreasing the numbers of unnecessary biopsies helps to decrease the number of scars and also helps to reduce psychological stress.

Despite its clinical utility, only a small percentage of dermatologists use TBP in their daily practices. Logistical and financial constraints remain major obstacles to the diffusion of this technology into clinical practice.[19] With the recent introduction of a Current Procedural Terminology Code for use of TBP in patients with dysplastic nevi,[20] decreasing cost of digital photo technology, and improved software for image storage and retrieval, it is anticipated that TBP may become more popular, particularly in academic medical centers.[17,19]

Dermoscopy

Dermoscopy (also called dermatoscopy, epiluminescence microscopy, in vivo cutaneous surface microscopy) is an effective noninvasive technique for the early recognition of melanoma (Fig. 2). Since its introduction in 1971,[21,22] clinicians and researchers have worked in concert to establish dermoscopic and histologic correlations. More importantly, several diagnostic algorithms for diagnosing melanoma have been described.[23-27] As the field matures, there is an increasing acceptance of the use of dermoscopy in clinical practice. The number of clinicians who use dermoscopy has increased at a dramatic rate from 5% in 1995 to 50% in 2001 in the United States.[28] This trend is observed internationally.

Two types of dermoscopes are available. The standard, so-called nonpolarized dermoscope (NPD) uses a liquid interface, such as oil or alcohol that has a refraction index similar to that of the skin, to optically link the stratum corneum with the glass plate of the dermoscope. This interface allows more light to penetrate the skin, and its deep structures can be visualized. The second type of device is the

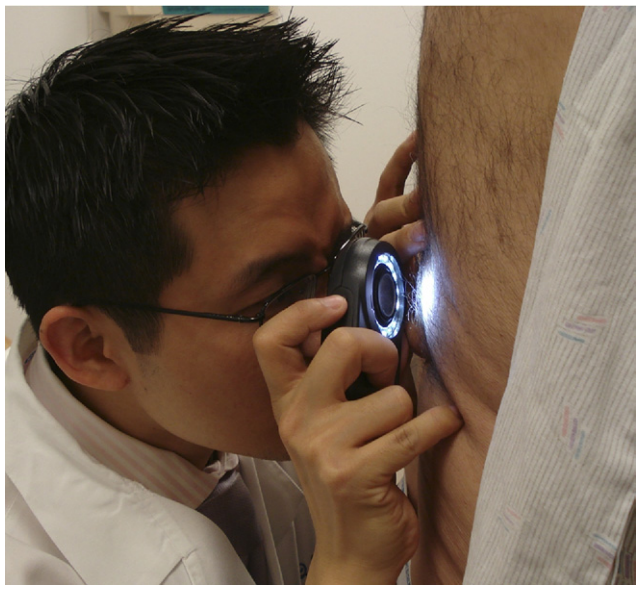

Figure 2 Gross examination of the skin with a polarized dermoscope.

polarized dermoscope (PD), which is equipped with a polarized light filter that preferentially captures the backscattered light from the deeper levels of the skin, obviating the need for fluid or direct contact with the skin. In general, the dermoscopic image qualities from PD and NPD are relatively similar. The major difference is that surface dermoscopic structures (eg, comedone-like openings, milia-like cysts and blue white veil) are better observed with NPD. In contrast, deep structures (eg, vessels) are better seen with PD.[29]

The clinical utility of dermoscopy in aiding the diagnosis of melanoma is well documented. A list of these benefits are described in Table 1.[30] Among these benefits, increased diagnostic accuracy is the most important feature. In the hands of experienced users, dermoscopy increases the diagnostic accuracy by more than 40%.[31] This improvement has been verified by several meta-analyses.[23,32,33] For patients, the improvement in diagnostic accuracy directly translates into an improvement of the benign/malignant biopsy ratio.[34] Terushkin et al[35] have shown that a group of clinicians performed fewer biopsies as their dermoscopic acumen increased. Increasing diagnostic confidence is another valuable benefit that appeals to practitioners.[36] By seeing subsurface structures, clinicians have more assurance when they inform their patients about the diagnosis of benign lesions. Finally, dermoscopy also helps the clinician determine the type of biopsy needed to accurately sample the lesion of concern. For pigmented basal cell cancer, small shave biopsy is adequate. If a physician has high suspicion of melanoma, excisional biopsies are a better choice. Also, for large lesions, dermoscopy can guide the clinicians to perform small incisional biopsies at the most atypical portion of a lesion, if such an approach is chosen.[30]

Table 1 Clinical Benefits of Dermoscopy

Increase diagnostic accuracy
Improve diagnostic confidence
Decrease the number of medically unnecessary biopsies
Assist in the clinical follow-up of patients with a large number of atypical nevi
Help to differentiate melanocytic and nonmelanocytic lesions
Determine the appropriate types of biopsy (eg, shave, incisional, or excisional biopsy)
Select suspicious area for biopsies in large lesion
Determine tumor margins before surgical excision

Table 2 Comparison of Sensitivity and Specificity of Dermoscopy Algorithms

Dermoscopy Diagnostic Algorithm	Sensitivity, %	Specificity, %
Pattern analysis*[27]	100	87.7
ABCD*[27]	96.3	70.4
Seven-point checklist*[27]	96.3	72.8
CASH[25]	98	68
Menzies*[27]	96.3	72.8

*Sensitivity and specificity results from the 2003 Internet Consensus Meeting.

A number of diagnostic algorithms and approaches have been described with the aim of teaching novices to correctly diagnose melanoma (see Table 2 for the sensitivity and specificity of each algorithm). In general, the algorithms can be classified as score-based (eg, ABCD rule of dermoscopy,[23] CASH (ie color, architecture, symmetry, and homogeneity), or 7-point check list[24,25]) or gestalt-based (eg, pattern analysis).[37] Full description on each of the methodologies is beyond the scope of this discussion. We will focus mainly on pattern analysis because it is the method most frequently used by clinicians in daily practice.[27,31]

Classic dermoscopic patterns of melanoma tend to have multiple colors (>3) and many dermoscopic structures. Most classic melanomas display asymmetry in at least 1 axis, and many have 2 axes of asymmetry. It is important to emphasize that symmetry is judged by shape, color, and dermoscopic structures. If a lesion is symmetric in shape and asymmetric in the distribution of dermoscopic structures, this lesion should still be ranked as asymmetric. In contrast to benign nevi, the shape and size of the dermoscopic structures in melanoma are not uniform, and the structures are arranged in a haphazard distribution. With regards to architectural order, the dermoscopic patterns of melanoma are chaotic and disorganized. The presence of specific dermoscopic structures is associated with melanoma (Table 3). Figures 3-6 illustrate examples of dermoscopic patterns of frank melanomas.

Despite its clinical efficacy, dermoscopy has several shortcomings. As mentioned previously, extensive training in the interpretation and analysis of dermoscopic structures and patterns is needed. A steep learning curve often discourages many clinicians from routinely using the device in daily practice. Also, some subset of melanomas (MMs), such as amelanotic/hypomelanotic MMs that lack pigmentations and dermoscopic structures, are exceedingly difficult to diagnose with dermoscopy. Moreover, its role in detecting MMs < 6 mm remains in debate.[38,39] Nevertheless, for these difficult

Table 3 Dermoscopic Structures Commonly Seen in Melanomas

Structures	Descriptions
Atypical network (including branched streaks)	• Black, brown, or gray network with focal irregular mesh with thick lines and different sized holes. • The lines represent the melanocytes and melanin along the rete ridges, and the holes represent the dermal papillae. • Branched streaks represent remnants of pigmented rete ridges resulting from bridging of nests of melanocytes at the dermal-epidermal junction.
Streaks (includes pseudopods and radial streaming)	• Linear pigmented projections at the periphery of the lesion. • When these linear structures terminate with a bulbous projection they are called pseudopods. • Histologically, they represent confluent junctional nests of melanocytes.
Atypical dots and globules	• Black, brown, or gray dots or globules varied in size and distributed haphazardly within the lesions. • They frequently occur at the periphery of the lesion and are not associated with the network. • Histologically, black dots represent melanin in the stratum corneum, gray dots represent melanin free in dermis or within melanophages, and brown dots represent small nevomelanocytic nests at the tips of the rete ridges. • Brown globules represent larger nevomelanocytic nests along the dermoepidermal junction or in the dermis.
Negative or reverse pigment network	• The lines of the network appear lighter (almost white) in color compared with the holes which are darker in color. • Histologically, this probably represents narrow and hypopigmented rete ridges accompanied by the presence of large melanocytic nests within a widened papillary dermis.
Off-center blotch	• A blotch is a darkly pigmented area in which one cannot discern any structures. • Histologically, it represents large concentrations of melanin in the epidermis and/or dermis.
Blue white veil overlying flat (macular) areas and/or the presence of blue-gray granules (peppering)	• Irregular, confluent, gray-blue to whitish blue pigmentation overlying flat areas within the lesion. • Histologically, this represents regression. One can also see peppering which represents melanin or melanophages in the papillary dermis. • If the regression is complete then one will see a white scar like area instead.
Blue white veil overlying raised areas	• Irregular, confluent, blue-white hazy pigmentation overlying raised areas within the lesion. Histologically, it represents melanocytes in the dermis together with compact orthokeratosis.
Vascular structures	• Presence of different shaped blood vessels can be seen in melanoma. • The most common are dotted, linear irregular and polymorphous vessels.

lesions, clinicians can perform short-term mole monitoring by taking dermoscopic photos of the concerning lesions.[30,40]

Computer-Assisted Diagnostic Systems

The combination of TBP and dermoscopy has improved diagnostic accuracy, but there are still significant numbers of pigmented lesions that pose a diagnostic challenge. To further improve diagnostic accuracy, various research groups in the world have been engaged in developing equipment and analytical software that can provide objective evaluations and even diagnoses of pigmented skin lesions, especially melanoma.[41-43] The ultimate goal is to develop an end-to-end, fully automatic analysis system with a capacity to classify lesions as benign or malignant with a limited involvement from clinicians.[44,45]

To achieve this goal, the computer-assisted diagnostic devices need to perform a series of sequential steps: image acquisition, lesion segmentation, feature extraction, and lesion classification. Image acquisition nearly always involves taking digital images of lesions. These images can be taken with both as gross images and by dermoscopic methods. Segmentation is achieved by mathematical algorithms that demarcate the borders between the lesion and surrounding skin. Feature extraction involves analyzing morphologic features that have the potential for differentiating benign vs. malignant pigmented lesions (eg, asymmetry, border irregularities, blotchiness, color variation and dermoscopic structures). The value of selected features is integrated into a mathematical score, which is compared with a threshold value. This process converts the qualitative interpretation of dermoscopic structures and patterns into quantitative values, thus providing objectivity. A large number of features are often identified, but only a small subset is incorporated into the final classifier. In the final step, a classifier or neural network is devised by combining a subset of features that can best differentiate benign

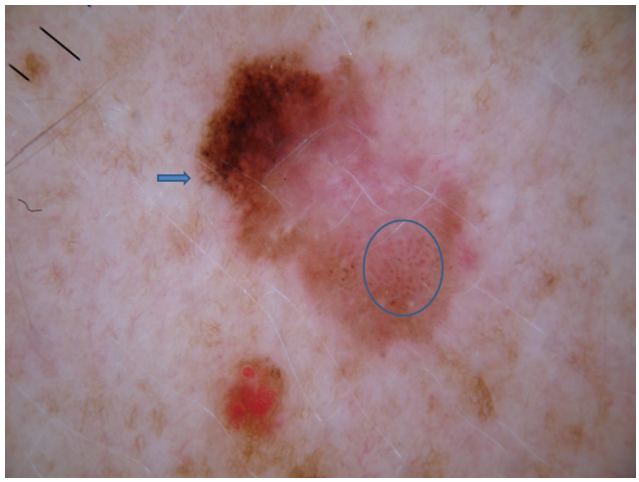

Figure 3 Dermoscopy image of a melanoma showing asymmetric pseudopods (→), atypical network and a focal area of dotted vessels (○). The lesion is asymmetric in 2 axes, disorganized in pattern and has irregular border and multiple colors.

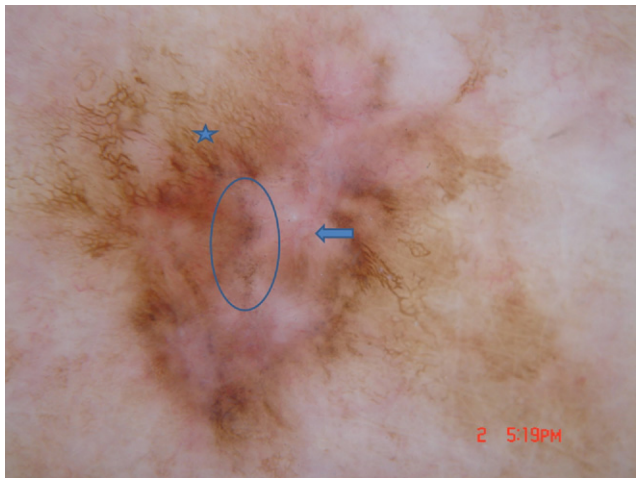

Figure 5 This invasive melanoma (Breslow thickness 0.6 mm) has peripheral branched network (*), atypical linear vessels (→), and regression (○). The lesion has multiple colors and disorganized pattern.

vs. malignant lesions with histopathologic diagnosis as the gold standard.

A number of computer-assisted analysis systems are available (Table 4). MelaFind (MELA Sciences, Inc, Irvington, NY) and SIA scope (Biocompaibles, Surrey, UK) are slightly different from the other systems because both systems use multispectral narrow band light ranging from 400 to 1000 nm. MelaFind uses a multispectral digital imaging probe and automatic software for image acquisition, processing and analysis. Ten distinct spectral bands, from 430 to 950 nm, are used to capture a sequence of 10 images from each lesion. The imaging process takes <5 seconds to complete. Each sequence of multispectral images is analyzed for asymmetry, color variation, and texture changes allowing objective determination of lesion parameters. The images are then compared with a databank of biopsy-proven images, using a set of algorithms to determine whether the lesion should be biopsied.[44,46] In a multicenter study[44] evaluating the feasibility of distinguishing melanoma from benign melanocytic lesions, MelaFind was reported to have a sensitivity of 100% and specificity of 85% with a 13-parameter classifier and a sensitivity of 100% and specificity of 73% with a 12-parameter nonlinear classifier. In 2008, MelaFind was demonstrated to have a greater sensitivity (74%) than expert dermoscopists (39%) in diagnosing melanomas that are <6 mm in size, but the system had significantly lower specificity.[47]

SIAscopy is based on the premise that individual skin components vary in their optical properties.[48] A SIA scope illuminates light ranging from 400 to 1000 nm into 24 × 24-mm area of skin and measures the reflected light quantity for each wavelength. This device permits the examination of distribution, positions, and quantity of melanin, blood, and collagen within epidermis and papillary dermis. The images are calibrated and entered into a series of algorithms to determine the microarchitecture of the underlying skin.[49] However, un-

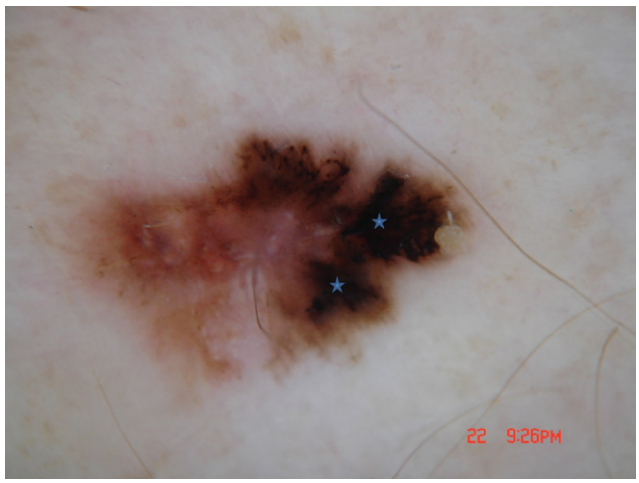

Figure 4 This melanoma has off center blotches (*), peripheral atypical network, and a faint structureless area. There are also irregular dots/globules.

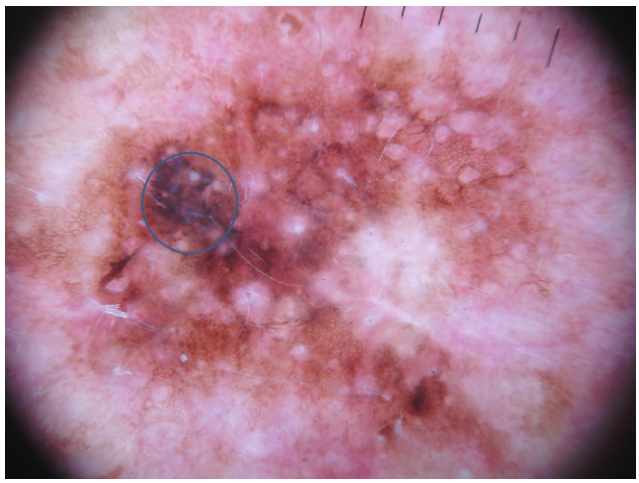

Figure 6 The dermoscopy image of this melanoma reveals focal blue white veil area (circle) and central scar-like depigmentation.

Table 4 Computerized Image Analysis Systems Available on the Market and/or Under Development

Device Names	Company	Web Sites
DyaGenius der	BIOCAM, GmbH	http://www.biocam.de/index.php?id=72&L=1
MelaFind	MELA Sciences, Inc.	http://www.eosciences.com/
SIAscope	Biocompatibles International Plc	http://siascopy.biocompatibles.com/
NevuScan	Vista Medical, Inc.	http://www.vistamedical.com/Romedix/RomedixProducts.htm
DBDermo-mips	University of Siena	http://www.skinlesions.net

like other systems it does not have the analysis software that automatically identifies the features and builds classifiers to categorize pigmented lesions. Instead, clinicians need to recognize the important diagnostic features on the monitor. In 2002, Moncrieff et al reported 82.7% sensitivity and 80% specificity for melanoma detection in a dataset of 348 pigmented lesions.[50] However, Haniffa et al failed to demonstrate the utility of the system in improving melanoma diagnosis.[51]

Computer-assisted diagnostic system is a promising field with significant limitations. First, most of the current diagnostic algorithms in these systems are created based on a database of clinically difficult lesions (eg, melanoma and dysplastic nevi) preselected by expert dermoscopists. In essence, the "machines" may not have had adequate training to build a "mental" database of benign lesions, such as seborrhic keratosis. The potential possibility of the "machines" failing to recognize benign and common lesions can be a disservice when these systems are used by nonexpert dermoscopists and nondermatologists. Second, when faced with difficult lesions, clinical experts often examine surrounding lesions for comparison before making a diagnostic or treatment decision. A lesion with an atypical pattern may be removed if it is significantly different from its neighbors, but the same lesion may only need to be monitored if its surrounding neighbors have similar patterns. This is the concept of the ugly duckling, a very useful way to discriminate between most atypical nevi and early melanoma.[52,53] Unfortunately, these "machines" will not have the comparative analytical capabilities. They can only image one lesion and make a diagnostic judgment for that lesion alone without the comparative knowledge of its neighboring lesions. Furthermore, none of the machines currently factors in the history of the lesion or the patient, which are important factors in clinical assessment. In summary, computer assisted diagnostic devices have the potential to improve the clinical care of high risk melanoma patients. However, to date, the true benefits of these systems for experienced dermoscopists[53] and nonexperts remain in question. Future studies in real clinical settings are needed to answer these questions.

Confocal Scanning Laser Microscopy

Confocal scanning laser microscopy (CSLM) is an in vivo and noninvasive technology that examines the skin at a resolution comparable to that of histology.[54] Typical CSLM has a lateral resolution of 0.5 to 1 μm and axial resolution of 3 to 5 μm. Its high-resolution optics allows the physicians to clearly visualize tissue morphology to the level of cellular details[55,56] in a real-time setting. With a maximum penetration of 350 μm in normal skin, it is not infrequent to find red blood cells tumbling along within the vessels in the papillary dermis.

To deliver these optical images, CSLM requires a set of components, including light source, condenser, objective lenses, and photodetector. CSLM illuminates a small volume of a laser light in the visible or near infrared wavelengths on a small point within the skin tissue. Reflected light from the focal point is collected by objective lenses, which then focus it into a small pinhole-sized spatial filter positioned in front of the photodetector. The pinhole-sized filter collects light emanating only from the focus and prevents any scattered and reflected light from elsewhere, enabling optical sectioning of a horizontal tissue plane. Received light by photodetector is converted to generate images for display. Horizontal movements of the laser light permit scanning of the selected area of skin, while axial movement allows the generation of an array of *en-face* sections from stratum corneum to the upper papillary dermis.[56-58]

CSLM with an 830-nm light source is ideal for detecting melanoma because melanin serves as an endogenous contrast agent. Its presence in melanocytic nevi and melanoma provides strong contrast, thereby permitting the clear visualization of the architecture and outlines of cells in the *en face* section.[54,57] Even amelanotic melanoma can be recognized by CSLM because of the presence of melanosomes and melanin granules in their cytoplasm.[59] A large number of studies have demonstrated the feasibility of using CSLM to diagnose melanocytic lesions,[60-66] specifically MMs. Like the "2-step diagnostic procedure" in dermoscopy, a 2-step guideline has recently been created for analysis of MM with CSLM. In the first step, melanocytic and non-melanocytic lesions are differentiated with 4 CSLM features: cobblestone pattern, pagetoid spread, mesh appearance of the dermoepidermal junction, and the presence of dermal nests. Within the melanocytic lesions, the presence of typical basal cells and edged papillae are considered positive features associated with benign nevi and the presence of roundish pagetoid cells and atypical dermal nucleated cells are associated with melanoma (Table 5; Figs. 7-10).[67]

To further differentiate melanomas from benign nevi, several authors have identified CSLM criteria proven to be valuable.[62,63,68,69] Pellacani et al[63] have proposed a diagnostic algorithm that uses 2 major (ie, nonedged dermal papillae and cytologic atypia at the basal layer) and 4 minor criteria (ie, roundish pagetoid cells, widespread pagetoid infiltration in

Table 5 Definition of CSLM Features Described in the Text

CSLM Features	Description
Cobblestone pattern	Aggregates of small polygonal cells with bright cytoplasm separated by a less refractive outline in the epidermis
Pagetoid infiltration	Presence of cells with a dark nucleus and bright cytoplasm, twice the size of keratinocytes, in the superficial layers of the epidermis
Atypical cells	Roundish-polygonal single cells or in small nests
Dermal nests	Oval to round bright aggregates with well-defined borders
Edged papillare	Dermal papillae surrounded by a ring of small bright basal cells
Nonedged papillae	Dermal papillae without a demarcated rim of bright cells
Mesh appearance at dermoepidermal junction	Predominance of junctional thickenings corresponding to enlargements of interpapillary space formed by aggregated cells and/or clusters bulging within dermal papilla in contiguity with basal layer
Broadened honeycomb pattern	Honeycombed pattern with bright elongated and broadened intercellular spaces

CSLM, confocal scanning laser microscopy.

the epidermis, nucleated cells within dermal papillae, and cerebriform cell clusters in the dermis). The presence of at least 2 features, 1 major and 1 minor criterion, are required for melanoma diagnosis. Gerger et al[62] identified melanocyte cytomorphology, melanocytic architecture, and keratinocyte cell borders as important features. With these features, the investigators achieved an overall sensitivity of 88% and specificity of 98% for melanoma diagnosis.

CSLM can also be used to identify subsets of MMs, ie, specifically lentigo maligna and hypomelanotic/amelanotic melanoma[70,71] that are difficult to diagnose under clinical and dermoscopic examination, even by experts.[72-74] The lack of

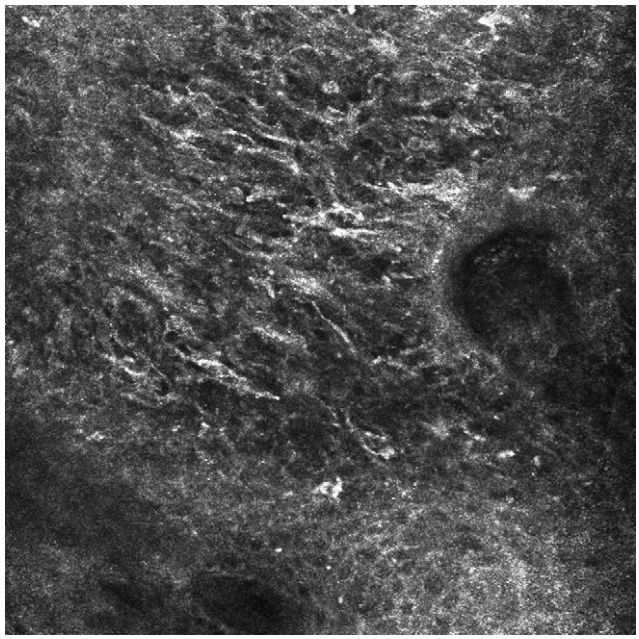

Figure 7 Basic CSLM image (0.5 × 0.5 mm) reveals multiple dendritic-shaped pagetoid cells in spinous layer.

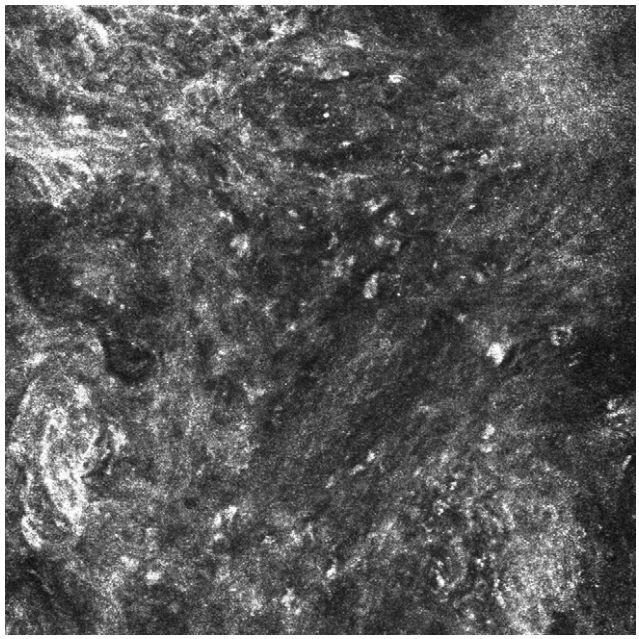

Figure 8 Basic CSLM image (0.5 × 0.5 mm) of this melanoma shows architectural disarrangement along with scattered bright pleomorphic structures within the dermoepidermal junction (DEJ).

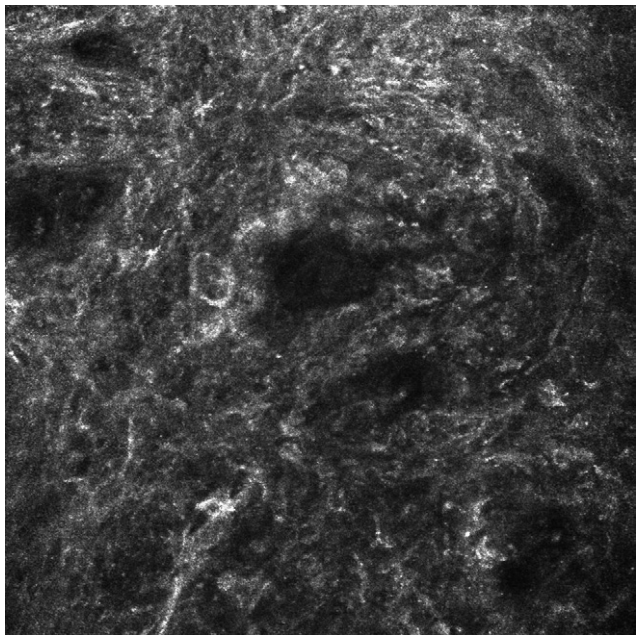

Figure 9 Basic CSLM image (0.5 × 0.5 mm) of this melanoma depicts severe architectural disarray with multiple bright pleomorphic structures associated with numerous smaller less refractile inflammatory cells at DEJ and within the dermis.

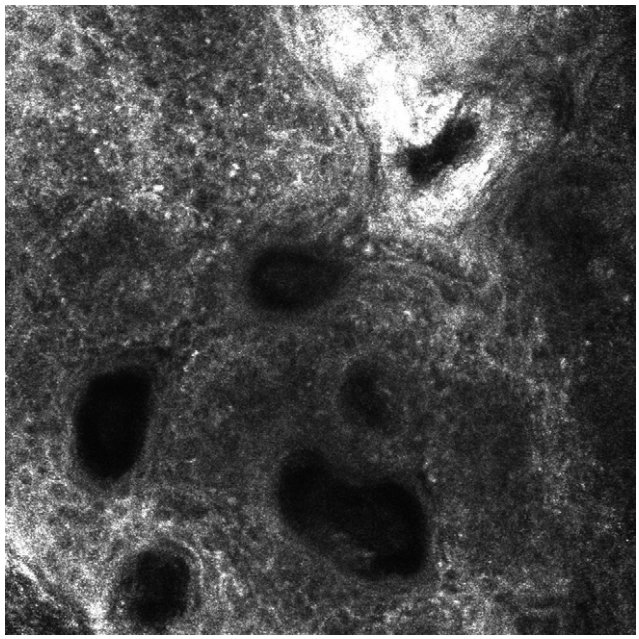

Figure 10 Basic CSLM image (0.5 × 0.5 mm) of this melanoma reveals several nonedged papillae not uniform in size and shape and some atypical nucleated bright cells infiltrating the rete ridges at the DEJ.

pigmentation in hypomelanotic/amenlanotic MMs yields a paucity of dermoscopic structures as diagnostic clues. However, the aforementioned CSLM features are still visible under CSLM inspection, thereby providing clinicians an added view to verify the initial clinical suspicion. Indeed, the diagnostic accuracy of the CSLM is superior for hypomelanotic/amelanotic MMs compared with pigmented lesions.[71,72]

Lentigo maligna may be difficult to distinguish from benign lesions, such as solar lentigo, pigmented actinic keratosis and lichen planus like keratosis. With CSLM, clinicians can visualize clues, such as the confluence of dendritic, large and bright cells in the suprabasal layers or around the hair follicles.[70,75] Histologically, these correspond to the presence of atypical melanocytes or MM cells centered on the hair follicles or present as pagetoid spread. In 2010, Guitera et al[71] described a diagnostic algorithm relying on 2 major features (ie, nonedged papillae and round large pagetoid cells $>$ 20 μm) and 4 minor features (ie, 3 or more atypical cells at the junction in 5 images, follicular localization of pagetoid cells, nucleated cells in the dermal papillae and single negative feature of broadened honeycomb pattern of the epidermis) to differentiate lentigo maligna from other benign macules. The algorithm achieved a sensitivity of 85% and specificity of 76% for the diagnosis of LM and was shown to be equally effective in the diagnosis of amelanotic lesions. Aside from diagnostic utility, studies[76,77] have also demonstrated the feasibility of using CSLM in preoperative and intraoperative surgical margin assessment of indistinct lesions, and in response follow-up to noninvasive therapy.

Currently, the technology has moved from bench research to the clinical arena. However, the application of CSLM in clinical care is mainly restricted to academic centers and select numbers of pigmented lesion clinics around the world. As with many novel technologies, the high cost and bulky design of current CSLM devices are considered to be major barriers. Efforts, such as miniaturizing the device and lowering the cost of production can facilitate wider adoption. In addition, extensive training in both the acquisition and the interpretation of CSLM images is needed. Like dermoscopy, there is a steep learning curve to master the interpretation of CSLM images. Lastly, the technology has intrinsic limitations where CSLM evaluation can give rise to false-positive or false-negative results.[64,78,79]

High-Resolution Ultrasound

Medical ultrasonography is an ultrasound-based diagnostic imaging modality used to visualize body tissue in real time. Modern ultrasound devices are both portable and relatively inexpensive when compared with other imaging modalities. The ultrasound technology is based on pulse-echo systems in which acoustic pulses are generated by a transducer and propagated to the body tissue. The return waves (echo) from the tissue are detected and converted into images for visual inspection. The resolution of the image and depth of tissue penetration is largely dependent on the frequency of the ultrasound transducer. High-frequency (ie, short wavelength) scanners offer greater resolution (eg, axial resolution of 10 μm and lateral resolution of 30 μm) but poorer tissue penetration (eg, $<$2 mm). In dermatology, high-frequency (eg, $>$20 MHz) ultrasound is used to evaluate lesions near the skin surface. For assessment of melanocytic lesions, 50- to 100-MHz ultrasound is needed.[48,80,81]

The application of ultrasound in the clinical management of melanoma is limited. The technology is useful to aid the detection of lymph node metastasis in patients with cutaneous melanoma.[82-84] Physical examination alone often fails to detect locoregional metastases or cannot unambiguously classify palpable lymph nodes. High-resolution ultrasound has been shown to have remarkable superiority over physical examination. The authors of a number of studies[84,85] have reported high sensitivity and specificity ($>$90%) for detection of locoregional metastasis with the aid of ultrasound. In addition, ultrasound can be used to differentiate reactive and malignant lymph nodes based on size, shape, border, and echo density of the lymph node. Solid, round shaped lymph nodes with hypoechogenic centers and cortical widening[81,86] are signs of a malignant lymph node. With the introduction of color Doppler ultrasound, the added information regarding the vascular structure of lymph nodes provides further detail about the involved nodes.[86] The noninvasive detection of malignant lymph nodes has the potential to improve the triage of surgical management for sentinel lymph node biopsy or dissesction.[81]

Aside from determining the lymph node status, several feasibility studies have demonstrated the use of ultrasound to evaluate the Breslow thickness of melanoma.[87-92] When visualized with ultrasound, melanoma cells are seen as homogeneously hypoechoic and the surrounding normal dermis are hyperechoic.[90] This difference makes it feasible to demarcate

the boundaries between the tumor and its surrounding normal tissue. Theoretically, when combined with other imaging modalities, such as dermoscopy and CSLM, a clinician can accurately diagnose melanoma and measure the thickness of the lesion in a noninvasive fashion. Knowing both the diagnosis and thickness, only a single surgical procedure with the appropriate margin is needed for thin and intermediate thickness lesions.[93,94] However, currently, ultrasound has not demonstrated an adequate level of consistency and reliability. It is not uncommon to overestimate melanoma thickness in the presence of lymphocytic infiltrates and nevus remnants, or to underestimate thickness if small clusters of melanoma cells are located deep in the dermis.[88,95]

The value of ultrasound in diagnosing melanoma is limited, but it is useful for assessing lymph node status. Despite being safe and relatively inexpensive, this technology is largely unused by dermatologists in the United States.[96] The major barrier to adopting this technology is that most clinicians are not formally trained to use and interpret the information.

Conclusions

Attempts to reduce melanoma mortality have been focused on prevention and early detection. To this end, several imaging modalities have been developed to aid in the early diagnosis and screening of a high–risk population. To date, TBP and dermoscopy are proven technologies that are relatively inexpensive and easily accessible to practicing physicians. Both technologies can dramatically improve the clinical care of patients at high risk for melanoma. Computer-assisted diagnostic systems are a promising technology currently employed in a limited number of academic settings and specialty clinics. It should be viewed as an adjunctive tool, not a first line of diagnostic technology. CSLM is perhaps the most significant advance in optical microscopy during the past decade. It provides physicians with an unprecedented capability to visualize a lesion at a detail comparable to histology. However, many obstacles, especially the high cost, need to be resolved before it can be widely adopted for clinical care. The value of high resolution ultrasound in diagnosis is limited, but it can aid the early detection of regional lymph node involvement. Lastly, it is important to remember that all these tools should not be used in isolation in the management of patients with suspicious skin lesions. Clinical presentation, personal and family history, and even other clinically seemingly unrelated elements must all be factored into the overall diagnostic decision process.

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