Update and Clinical Use of Imaging Technologies for Pigmented Lesions of the Skin

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The incidence of melanoma is on the rise, and early detection of disease is imperative to reduce mortality. Dermatologists are key players in the early detection of melanoma; however, some clinicians rely on their clinical examination without any additional diagnostic tools to make this important diagnosis. Certain patients, such as atypical nevus patients, have more complicated mole examinations, making the diagnosis of melanoma difficult, whereas some melanomas, such as amelanotic melanomas, can be diagnostically challenging. The goal of the clinician is to detect melanoma with the highest accuracy, while avoiding unnecessary biopsies. Using diagnostic melanoma tools as an adjunct to the clinical examination, dermatologists have the opportunity to increase both their sensitivity and specificity for melanoma detection. This article will review current imaging technologies and those in development for pigmented lesions, updating the clinician on basic principals of such modalities and clinical use of such technologies in practice.
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Melanoma's propensity to metastasize and poor prognosis once the disease is widespread underscores the importance of early detection. From 2004 to 2008, the age-adjusted incidence rate of melanoma among men and women in the United States (US) was 20.8 per 100,000 persons per year.[1] Based on patient deaths between 2003 and 2007, the age-adjusted mortality rate for melanoma was 2.7 per 100,000 men and women per year. Dermatologists currently have only a few tools to assist with the diagnosis of melanoma and must rely largely on their clinical judgment to determine whether to perform biopsy of a pigmented lesion. Using clinical judgment alone to detect melanoma, dermatologists have been reported to have a sensitivity of 58%-90% and a specificity of 77%-99%.[2-4] Noninvasive diagnostic tools may increase the clinical accuracy of dermatologists,[5] but dermatologists also must be willing to learn and adopt new technology in their clinical practice. Rather than replacing the dermatologist, such technologies could play an important role in enhancing their clinical decision making. In this update, we will review current technologies used in the US, including dermoscopy and total body digital photography (TBP), as well as those used outside of the US and technologies in development, such as multispectral imaging, optical coherence tomography (OCT), reflectance confocal microscopy (RCM), ultrasound, magnetic resonance imaging (MRI), dynamic infrared imaging (DIRI), and photoacoustic microscopy. We will discuss basic principles of these technologies, review studies using the technologies in evaluation of pigmented lesions (Table 1), and discuss how the technology may be implemented into one's practice.

Dermoscopy

Dermoscopy (also known as dermatoscopy, epiluminescence microscopy) is the most-accepted diagnostic tool for melanoma detection that provides physicians with the ability to view deeper pigment and vascular structures in the skin in vivo to help a clinician decide whether a melanocytic lesion is benign or malignant. There are 2 types of dermoscopes that are currently available: (1) nonpolarized light dermoscopes and (2) polarized light dermoscopes.[6] The nonpolarized light dermoscope uses an oil or gel interface with direct skin contact to allow more light to penetrate the skin, allowing for deeper viewing of skin structures below the surface, whereas polarized light dermoscope uses a polarized light filter, which preferentially captures backscattered light from

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Table 1 Reported Detection Rates of Melanoma Based on Studies in the Literature

	Sensitivity (%)	Specificity (%)
Clinical eye	58%-90%	77%-99%
+ Dermoscopy	70%-95%	
SIAscope	82.7% (70.3%-90.6%)	80.1% (75.1%-84.2%)
MelaFind	98.4% (92%-100%)	9.9% $P = 0.75$
OCT	Unknown	Unknown
Confocal microscopy	97.3%	83%
DIRI	100% (40%-100%)	80% (56%-94%)

DIRI, dynamic infrared imaging; OCT, optical coherence tomography; SIAscope, spectrophotometric intracutaneous analysis.

deeper skin levels, allowing for viewing of subsurface skin structures without a liquid interface or skin contact.[7] Multiple algorithms have been developed to determine if a lesion is benign versus malignant, such as the ABCD rule (Stolz method), pattern analysis, Menzies method, 7-point checklist (Argenziano method), modified ABC-point list, and CASH method (Kopf et al).[8-13] Traditional dermoscopes have been heavy and unwieldy devices, but today's versions are lightweight, smaller, can easily be stored in a clinician's examination coat pocket, thus readily available for use in any patient's full skin examination to improve diagnostic accuracy.[14]

Multiple studies have shown that dermoscopy can improve a clinician's performance when screening for melanoma. When used by a clinican trained in dermoscopy, sensitivity for melanoma detection has been shown to be increased above clinical examination alone from 58%-90% to 70%-95%.[5] Multiple studies have corroborated this improvement.[8,15,16] An improvement of the benign/malignant biopsy ratio has also been shown.[17] However, without training, clinicians may have a decreased accuracy of melanoma detection, emphasizing the need for training and education before clinical use.[18]

In the US, use of dermoscopy has increased in the past 9 years from an estimated 23% to 48%.[19,20] Reasons for use of dermoscopy among those surveyed in studies included usefulness in detecting melanoma and decreasing patient anxiety. Reasons for not using dermoscopy included a lack of interest and/or training and concerns about the time needed to conduct a dermoscopic clinical examination. Interestingly, a 2008 randomized multicenter study by Zalaudek et al[21] demonstrated that the median time needed to complete a skin examination increased by 72 seconds with dermoscopy, which argued that using a dermoscope should increase one's examination modestly. In contrast, in Australia, a 2008 survey revealed that 98% of respondents used dermoscopy, and 95% had been trained in dermoscopy.[22] More widespread dermoscopy training of US dermatologists could encourage its use.

In clinical practice, the dermoscope can be helpful in several ways. With proper training and experience, dermoscopy can be used to increase one's accuracy for melanoma detection. Dermoscopy can be used both to take a closer look at nevi, which look clinically suspicious to the naked eye, and also to examine underlying benign mole patterns in patients with numerous or atypical nevi to then help delineate a der-

moscopic "ugly duckling."[23,24] Dermoscopy can decrease the number of unnecessary biopsies, help clinical follow-up of atypical nevi, and help with the selection of the most suspicious areas within larger pigmented lesions for biopsy. Challenges to the use of dermoscopy include variability in interpretation by physician, based on the need for experience and training for more accuracy,[25-28] and the challenge of using dermoscopy on very early melanomas, featureless melanomas, and amelanotic lesions.[29-31] Despite these challenges, the clinical value of dermoscopy for melanoma detection has been well established, and the use of dermoscopy should strongly be considered for any clinical practice screening patients for melanoma.

Total Body Digital Photography

TBP allows clinicians to have complete photographic documentation of patients' skin examinations. These photographs are taken in a series of standard poses,[32] with the possibility of adding close-up dermoscopy photos by a photographer. A copy of the digital photos may be given to the patient to use for reference. The baseline photographs allow clinicians and patients to determine de novo, changing, and stable nevi by comparing the current skin examination with the photographs to help with clinical follow-up and early detection of melanoma.[33] TBP has particular clinical value in patients at higher risk for melanoma with complex mole patterns and patients with multiple nevi.

TBP has been shown to detect early melanomas, reduce the number of lesions excised, and to reduce patient anxiety surrounding their nevi and risk of melanoma.[34] A recent study examined how successful TBP followed by dermoscopy imaging as a 2-step process would be in diagnosing early melanoma compared with traditional diagnostic rates in the New Zealand Cancer Registry, and it showed that use of TBP and dermoscopy imaging allowed clinicians to diagnose thinner melanomas.[35] Of these, 69% of melanomas diagnosed using the 2-step process had a Breslow depth of <0.75 mm, compared with 52% of the Registry's melanomas ($P = .0216$). Among patients who had the 2-step process for diagnosis, 1.9% of melanomas were thicker than 3 mm versus 10.8% of melanomas in the Registry ($P = .0.67$). A 2011 study found that use of the 2-step process of TBP and dermoscopy allowed for early melanoma detection and low biopsy rates for patients.[36] Similarly, a recent study by Goodson et al[37] revealed that the TBP biopsy rate per patient was 0.59

biopsies versus 1.1 found using serial digital epiluminescence microscopy photography in a previous cohort of patients. Further studies need to be performed to verify this decrease in biopsy rate in TBP patients. Additionally, a 2008 survey study in patients with atypical moles revealed that patients had less anxiety after TBP was taken, measured by the Modified Breast Cancer Worry Scale and Revised Impact of Events Scale.

Current available TBP modalities include Canfield Scientific's MIRROR TBP software (Fairfield, NJ) and DigitalDerm, Inc's MoleMapCD program (Columbia, SC) . Canfield Scientific's TBP software has an average cost of $4500, and there is a need for accessing and training a professional photographer to take the photographs in standard positions, having staff available to handle billing, download onto the software, and ensure proper computer security. In contrast, DigitalDerm, Inc's MoleMapCD program requires a written referral from the clinician, which is sent to DigitalDerm. The company then schedules patients for an imaging session in one of their photography locations, located in 10 states, and produces 2 MoleMapCDs for a patient cost of $349-$395. Physicians can use this compact disc (CD) to view the skin images when the patient returns for follow-up appointments.

Challenges of TBP include the cost of TBP to both the clinic and patient and possible increased time to perform a full skin examination with TBP. In addition, younger patients are known to continue to develop new nevi, and therefore, change does not always signify malignancy.[38] In the future, computer systems may be able to aid the clinician using TBP to automatically detect changing lesions with serial TBP imaging for interpretation. Despite these challenges, TBP has been shown to be effective in dermatology patients and should be considered an option for high risk patients.

Multispectral Imaging and Computer-Based Analysis

Multispectral imaging provides sequences of images from one area taken at different wavelengths of light (400-1000 nm), allowing for different images of a pigmented lesion at different depths of the skin up to 2 mm deep within seconds. Computer algorithms are then used to analyze this information to give a clinician data to help interpret a pigmented lesion as benign or malignant. There are 2 multispectral imaging technologies currently in development: spectrophotometric intracutaneous analysis (SIAscope) (developed by Astron Clinica, Toft, United Kingdom, and marketed by Biocompatibles since 2009) and MelaFind (MELASciences, Inc, Irvington, NY).

SIAscope provides 8 different spectrally filtered wavelengths ranging from 400 to 1000 nm. The clinician is provided with different windows (color, melanin, dermal melanin, blood, collagen) corresponding to lesion appearance with different wavelength peaks, which must be interpreted by the user. A preliminary investigation found that the presence of dermal melanin, collagen holes, and blood displacement with erythematous blush correlated with an 83% sen-

sitivity and 80% specificity for melanoma detection in a study performed by Moncrieff et al.[39] More recently, Glud et al[40] performed a prospective study examining SIAscope's use in diagnosing melanoma compared with dermoscopy in 2009. The authors found that sensitivity of dermoscopy was 92% compared with 100% for SIAscopy, whereas the dermoscopy specificity was 81% compared with 59% for SIAscopy. The authors concluded that overall, dermoscopy remains the best approach to diagnosing pigmented lesions, but SIAscope could produce dermoscopic images and help with training of clinicians. MoleMate (Biocompatibles; Surrey, UK), currently marketed in the United Kingdom, Ireland, Australia, and New Zealand, uses SIAscopy with a diagnostic algorithm designed to assist dermatologists and general practitioners, with interpretation of a lesion based on a 12-point system with >6 points being suspicious for melanoma.[41-43] MoleMate is marketed to assist with triage of patients with suspicious lesions, decisions to perform biopsy of lesions reducing unnecessary excisions of seborrheic keratoses, and reassuring patients. MoleMate currently retails for $4000.

MelaFind uses 10 different wavelengths of light (430-940 nm) and can capture features of pigmented lesions 2.5 mm below the skin surface. In contrast to SIAscope, MelaFind provides a binary output recommending either a biopsy or clinical follow-up of the lesion. To provide this decision, MelaFind compares the lesion's features with a pigmented lesion database and uses a lesion classification algorithm, which has most recently shown a sensitivity of >95% for melanoma detection.[44] Of note, severely atypical nevi/high-grade dysplastic nevi and melanoma, both yield a MelaFind "positive" result. MelaFind is not currently designed to evaluate amelanotic lesions, lesions on certain anatomical sites (acral, mucosal, subungal), lesions within areas of scarring, and pigmented lesions <2 mm in diameter. It has not been used in clinical trials for clinically obvious melanomas.

Preliminary studies using MelaFind for melanoma diagnosis found that MelaFind had a sensitivity ranging from 98% to 100% and specificity ranging from 44% to 85%.[45,46] Most recently, a 2010 prospective, multicenter, blinded study comparing MelaFind with clinician performance in detecting melanoma found that MelaFind had a biopsy sensitivity of 98.4%, whereas clinicians' biopsy sensitivity was 78%.[44] MelaFind's biopsy specificity was 9.9% compared with the clinician specificity of 3.7%. The authors concluded that MelaFind would be a useful device for dermatologists evaluating pigmented lesions. MelaFind is currently undergoing Food and Drug Administration (FDA) review under a Premarket Approval (PMA) application submitted in June 2009. In November 2010, the FDA General and Plastic Surgery Devices Advisory Committee Panel voted in favor of the device in a vote of 8-7, and after an amendment application to the PMA, limiting the device's indication of use to dermatologists, the FDA approved MelaFind's PMA application in November 2011. MelaFind is not yet commercially available in the US. MelaFind had also received the CE (European Conformity) Mark approval.

Given that both SIAscopy and MelaFind devices are designed to evaluate a single lesion, in practice, a clinician

would need to preselect the suspicious lesion or lesions. Rather than functioning as an overall melanoma screening device, both would need to be used as an adjunct to the clinical examination. Therefore, this technology could potentially be used in the clinic on borderline suspicious pigmented lesions to help with the decision to biopsy. Lesions already identified by the clinician as concerning for melanoma and requiring biopsy would not need to be evaluated by such devices. Further studies to evaluate clinical use in pigmented lesion patients need to be performed.

Optical Coherence Tomography

OCT is a noninvasive technique similar to ultrasound, except that it uses infrared light instead of ultrasound waves to generate micronscale cross-sectional vertical images of tissue in real time.[47] OCT measures echo time delay and intensity of backscattered light using an interferometer to generate the images. It is based on the Michaelson interferometer, using a low-coherence length broadband light source. This system creates a 2-dimensional cross-sectional image, built up by lateral scanning across the tissue, with axial and lateral resolution of approximately 15 μm and penetration depth of up to 1 mm.[48] The difference in reflection from various tissue components provides contrast in the image. Although resolution is not to the level of cellular structures, the basic architecture of the tissue can be evaluated.

A 2007 study examined the difference in micromorphologic features of benign nevi versus melanoma using OCT in vivo.[49] Benign features included a clearly demarcated dermoepidermal junction zone, whereas malignant features included architectural disarray, a lack of clear dermoepidermal border, and large, vertical, icicle-shaped structures. The differences between benign and malignant nevi and real-time imaging could be useful for clinicians assessing pigmented lesions in a clinical setting, but further testing needs to be performed. No studies examining the sensitivity and specificity of OCT for detection of melanoma have been performed to date. OCT devices are available commercially through 18 manufacturers, mostly for use in the ophthalmology field. Its use in dermatology is currently in research settings. Potential applications for OCT in dermatology in the future could include real-time margin delineation of nonmelanoma skin cancers for treatment planning[50,51]; however, clinicians would have to be trained to interpret OCT imaging. The practical utility for OCT use in pigmented lesion analysis needs further study.

Reflectance Confocal Microscopy

RCM is a noninvasive imaging system that allows for real-time in vivo examination of the skin with high-resolution cellular detail in horizontal planes, described as "quasi-histological" imaging.[52] RCM focuses a low-power laser beam in the near- or infrared range on a specific point in the skin. Backscattered light is detected from the focal point through a pinhole-sized spatial filter. This form of microscopy relies on

natural variations in refractive indices of tissue microstructures for contrast. The microscope images a series of horizontal planes, with an axial thickness of 2-5 nm and lateral resolution of 0.5-1.0 nm and a depth of 300-400 nm to the level of the papillary dermis. RCM uses a video monitor with grayscale footage, showing nuclear, cellular, and architectural detail. When RCM is used to scan pigmented lesions, differences between benign and dysplastic melanocytes versus melanoma cells have been observed.[53] Benign melanocytes appear as round-oval, bright, monomorphic cells. Dysplastic melanocytes appear as larger round-oval bright cells with dark nuclei, with more variation in size than benign melanocytes. Melanoma cells have been described as bright polymorphous cells that can appear as stellate cells. The nesting in melanoma nevi is poorly defined, and there is a disarray of the natural honeycomb pattern of the cells. Bright, granular, highly refractile particles have been described, along with pagetoid cells.

Studies performed to test the diagnostic accuracy of RCM on pigmented lesions found that device sensitivity was 88.2% to 91.9% and specificity was 69.3% to 97.6%.[54-56] However, these studies were retrospective in nature and had preselected confocal images. In 2007, Langley et al[57] performed a prospective study comparing RCM with dermoscopy. RCM had a higher sensitivity than dermoscopy, and both imaging techniques had similar specificity; however, this was a study of a single clinician performing both techniques. A 2010 study found that a computer algorithm could identify pagetoid melanocytes and disruptions at the dermal–epidermal junction, which could be useful in automated diagnosis of superficial spreading melanomas (SSMs) using RCM,[58] and a 2011 study also examined automated analysis of melanoma versus nevi, with a classification identifying 93.6% of melanomas and 90.40% of nevi in a learning set.[59] Automated RCM image analysis will require further investigations to show utility.

RCM is commercially available as a clinical imaging tool through Lucid, Inc (Rochester, NY). The device can be purchased for $80,000 or leased for $750 per month. It is available in the US, Germany, and Australia. Current RCM entails bedside imaging of a suspicious lesion selected by the clinician and transmission of this image to a dedicated dermatopathologist for interpretation within 24 hours. For a clinician trained in RCM, the technology could also be used in real time to help delineate margins of nonmelanoma skin cancers before biopsy or excision.[60] Limitations of the currently available RCM include the delay in interpretation of image, the need for training of the clinician in RCM, and high cost of the device.

Ultrasound

Ultrasound has been researched as a possible method of melanoma detection. In 2008, Schmid-Wendtner and Dill-Müller[61] found that melanomas, benign nevi, and other skin lesions appeared as solid homogenous hypoechoic lesions, suggesting ultrasound would not be useful in the diagnosis of primary melanoma. Ultrasound has also been investigated in

the detection of sentinel lymph node (SLN) melanoma metastases, but there is some controversy over its effectiveness. Sanki et al[62] looked at its use in detecting metastatic disease in 871 lymph nodes in 716 patients from 2001 to 2005 before SLN biopsy. The sensitivity of ultrasound in detecting metastases was 24.3% (19.5%-28.7%) and the specificity was 96.8% (95.9%-97.7%), indicating that ultrasound should not replace SLN biopsy for identifying metastatic disease, but can be useful in assessing preoperative lymph nodes. Hinz et al[63] combined ultrasound with powerful Doppler sonography and found a sensitivity of lymph node metastasis detection of 22.2% and a specificity of 100%. A 2011 study used lymph node ultrasound in concert with clinical examination on 433 melanoma patients and found that the combined ultrasound and clinical examinations resulted in a sensitivity of 93.94% (79.77%-99.26%) and a specificity of 98.08% (97.17%-98.75%). These results indicate that high-frequency sonography could be a valuable part of melanoma follow-up when used in conjunction with clinical examination[64]; however, SLN biopsy still remains the most accurate method of regional node staging.

Magnetic Resonance Imaging

MRI machines were investigated to determine whether MRI images could help clinicians diagnose pigmented lesions in vivo. Tested the use of MR microscopy to examine skin tumors was tested by el Gammal et al[65] in 1996. Based on the MRI images, researchers could not reliably discriminate benign from malignant skin lesions. However, MRI could prove to be useful to measure thickness or volume of skin tumors for treatment planning.

Dynamic Infrared Imaging

DIRI is a noninvasive imaging technique that passively records natural infrared radiation from living tissues.[66] Infrared radiation intensity is directly proportional to the temperature of the tissue and indirectly proportional to the degree of tissue perfusion. DIRI can sensitively detect changes in tissue surface perfusion and temperature changes (resolution of 0.006°C) and has a depth resolution of approximately 200 mm (papillary dermis). In 2009, Gomez et al[67] did a pilot study examining the use of DIRI in the detection of melanoma in 20 patients/24 lesions and found the device had a sensitivity of 100% and a specificity of 80%. DIRI imaging allowed the researchers to distinguish between melanoma and benign/dysplastic nevi. More recently, a DIRI study found that when a lesion was air cooled by 15°C for 30-60 seconds, benign lesions and normal skin recovered similarly, but malignant lesions had a higher temperature during the thermal recovery process.[68] Although DIRI is still in a research phase and not marketed, the concept of thermal imaging of nevi may be a promising technology for continued future investigation.

Photoacoustic Microscopy

Photoacoustic microscopy delivers nonionizing laser pulses into tissues.[69] Some of the energy is absorbed and converted into heat, leading to transient thermoelastic expansion and wideband emission. Ultrasonic waves are detected by ultrasonic transducers to form images. Optical absorption is associated with physiological properties, such as hemoglobin concentration and oxygen saturation. Researchers at Washington University in St. Louis used the photoacoustic microscope to examine a nevus and identify melanoma cells.[70,71] The photoacoustic microscope was also able to show contrast between melanin and hemoglobin and was used to image melanoma cells in bovine blood. Research on photoacoustic microscopy is still ongoing, but it is another imaging modality that may show future promise.

Conclusions

There have been great advances in imaging technology for the detection of melanoma in the past 15 years. From widely used technologies like the dermoscope to new frontiers of imaging, such as photoacoustic microscopy, these new tools can aid clinicians in diagnosing difficult lesions. Such advances could be most useful for high-risk melanoma patients, including those with numerous and atypical nevi, and in identifying subtle melanomas, such as amelanotic or nevoid subtypes. Dermatologists will need to understand and adopt such new imaging modalities to improve the clinical accuracy of melanoma detection. In the hands of a trained clinician, such technologies could be used in concert with the patient history and the rest of the clinical examination to enhance the ability to diagnose melanoma while avoiding unnecessary biopsies.

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