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Current and emerging technologies in melanoma diagnosis: the state of the art

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Abstract

Relative to other specialties, dermatologists have been slow to adopt advanced technologic diagnostic aids. After all, most skin disease can be diagnosed by simple visual inspection, and the skin is readily accessible for a diagnostic biopsy. Diagnostic aids such as total body photography and dermoscopy improve the clinician's ability to diagnose melanoma beyond unaided visual inspection, however, and are now considered mainstream methods for early detection. Emerging technologies such as in vivo reflectance confocal microscopy are currently being investigated to determine their utility for noninvasive diagnosis of melanoma. This review summarizes the currently available cutaneous imaging devices and new frontiers in noninvasive diagnosis of skin disease. We anticipate that multimodal systems that combine different imaging technologies will further improve our ability to detect, at the bedside, melanoma at an earlier stage.

Introduction

Last year, more than 60,000 people in the United States were diagnosed with invasive melanoma and more than 8000 Americans died of the disease.¹ The single most promising strategy to acutely cut the mortality rate from melanoma is early detection. Attempts to improve the diagnostic accuracy of melanoma diagnosis have spurred the development of innovative in vivo imaging modalities, including total body photography, dermoscopy, automated diagnostic systems, and reflectance confocal microscopy. These are now being harnessed to improve early detection.

The role of imaging in routine screening or as part of the initial evaluation of suspected disease is well established in many areas of clinical medicine, including gastroenterology, cardiology, and neurology. The introduction of computed tomography (CT) imaging for patients with symptoms suggestive of appendicitis in the mid-1990s led to a dramatic increase in diagnostic accuracy. Today it is difficult to believe that in the era before widespread diagnostic CTscanning, one in five patients empirically diagnosed with appendicitis would receive an unnecessary surgery.² By 2000 appendiceal CT was being used to evaluate most patients in whom appendicitis was suspected and was frequently requested by surgeons and emergency room physicians before deciding to admit the patient. By 2005 the reported negative appendectomy rate dropped to less than 5%.³

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Dermatologists have only recently begun to incorporate novel imaging techniques into diagnostic algorithms, not only for skin cancer but also for diagnosing other diseases. Dermoscopy is the fastest growing method to image skin. During the last decade, the dermoscopic lexicon and algorithms for dermoscopic assessment were rigorously developed and disseminated (Fig. 1), such that dermoscopy is now part of the initial examination for many patients. Reflectance confocal microscopy is a tool that can image skin in vivo with near-histologic resolution. Emerging technologies are advancing the scope and diagnostic power of confocal microscopy and are sure to increase its portability and user-friendliness. Here we summarize the most important current and emerging diagnostic aids. These technologic aids serve to complement the traditional naked-eye examination, which continues to remain the basis for diagnosis and detection.

Total-body photography

The use of total-body photography (TBP) to monitor patients with many dysplastic nevi and facilitate their skin examination has been well documented.⁴⁻⁸ Clinical photographs improve the malignant to benign ratio among biopsied dysplastic nevi.⁹ Serial images may be used for comparison to find changes that may be suggestive of malignancy, notably a change in size, shape, or color. Photographically assisted follow-up relies on the premise that *relative* change is a sensitive marker for early melanoma. Studies have shown that up to 35% of prospectively diagnosed melanomas were identified solely on the basis of change.⁹⁻¹¹

Relative change refers to those changes that are unique to one or several lesions, above and beyond the changes found in the entire set of nevi, which thus distinguishes a small subset of nevi that need to be further evaluated.

Some data suggest that reliance on photographic follow-up may lead clinicians to raise their threshold for excision at the time of initial evaluation,¹² potentially resulting in failure to diagnose melanoma in patients who are noncompliant with follow-up.¹³ A short-term retrospective study, however, found that baseline photography did not affect biopsy rates in the first year of follow-up, but that only positive patient history of melanoma or presence of severe dysplastic nevi, or both, lowered the threshold for biopsy.¹⁴ Prospective studies of the effect of photographically assisted follow-up on biopsy rates are needed.

Implementing TBP in clinical practice requires multiple considerations. First, one must choose a camera system, decide on a standardized set of poses that will be used, and decide how the images will be stored. Second, one should consider additional features such as digital dermoscopy (described later), providing patient photo books or CDs for self-monitoring, and, importantly, the role of TBP in practice (ie, which patients get TBP and how the images will be used).¹⁵

Computerized systems for image acquisition and storage are commercially available. Digital images may be used to document pigmented lesions, detect changes, and be included in a referral note when a patient is sent to a colleague for consultation or surgery. Newer systems that capture clinical and dermoscopic images have been developed, enabling viewing in tandem. Some have raised concerns about images being a liability issue in the event of a malpractice suit, but these concerns have not materialized to date.

Three-dimensional TBP

Although current commercially available TBP systems rely on 2-dimensional (2D) images, the advent of 3D imaging systems holds great promise. Having a 3D representation of the patient's entire cutaneous surface on a screen may reduce work time, clarify documentation, and facilitate automated detection of changed lesions. The VECTRA facial imaging line by Canfield Imaging Systems (Fairfield, NJ), for example, provides a geometric resolution of 1.8 mm, a rapid capture time of 2 milliseconds, 360° navigation, and computer software for image analysis. To date, 3D photography of large body surface areas is being used mostly by plastic surgeons. These systems primarily address body contours, with limited skin surface resolution. Because there are no inherent technical barriers to combining the high-resolution facial and low-resolution body approaches, 3D photography promises to play a future role in general dermatology practices.

Dermoscopy

The science underlying dermoscopy has been understood for at least 300 years. The first detailed reports of its use in imaging surface structures which, at the time, referred primarily to capillaries, date back to early 20th century Europe.¹⁶ In 1971 dermoscopy was used to evaluate pigmented lesions.¹⁷ In the 1980s and 1990s, rigorous studies, primarily in Europe and Australia, established dermoscopic/histologic correlates and algorithms for dermoscopic diagnosis of melanoma. Although adopted more slowly in the United States, by 2001 approximately 50% of academic dermatology programs and 23% of general dermatologists used dermoscopy.^{18,19} These numbers are sure to grow as more clinicians realize the benefit of dermoscopy and patients at high risk for melanoma request its availability. For a detailed discussion of dermoscopy, see the article "Dermoscopy: what's new" in this issue of *Clinics in Dermatology*.

A large meta-analysis found that dermoscopy used in conjunction with clinical examination and patient history results in a 50% improvement in diagnostic accuracy.²⁰ Its power to detect melanoma in small (<6 mm) or featureless lesions, however, remains questionable.²¹⁻²⁴ Complete reliance on dermoscopy may be a liability in the case of ambiguous melanoma, particularly when trying to determine whether to perform an excision. One study showed that 30% of ambiguous melanomas are improperly managed when evaluated solely by clinical and dermoscopic images without patient contact.²⁵ This is because some lesions are appreciated as being suspicious only when viewed in the context of the surrounding skin and with information about the patient's history.

A myriad of dermoscopic structures have been identified that help the clinician determine whether a given lesion is melanocytic or nonmelanocytic and benign or malignant.^{26,27} Nevi tend to be symmetric, uniform, display fewer than three colors, and possess an orderly, perhaps even aesthetically pleasing, architecture. Malignant melanomas are deviant, and under dermoscopy they appear asymmetric in color and structures and display marked architectural disorder. Most melanomas possess at least one of the following nine specific dermoscopic structures: atypical network, peripheral streaks, atypical dots or globules,

negative pigment network, off-center pigmented blotches, blue-white veil over raised or flat areas, atypical vascular structures, and peripheral brown structureless areas.

Polarized and nonpolarized dermatoscopes are available, and although comparable in their imaging power, certain structures are better seen under different systems. A myriad of dermoscopic algorithms have been created, from scoring systems to the less mathematic “patternanalysis” method.

The evolution of competing dermoscopic algorithms with variable definitions of specific attributes complicates dermoscopic diagnosis. In an attempt at simplification, the International Dermoscopy Society recently initiated a study aimed at creating a unified dermoscopy algorithm (UDA) by using the most popular and widely accepted algorithms developed by the leading dermoscopists. The UDA Study is a multicenter, World Wide Web-based study that will track the ratings and scores of hundreds of histologically confirmed melanocytic lesions, nevi, and melanomas by dermatologists around the world. Lesions will be evaluated according to the asymmetry, border irregularity, color, diameter (ABCD) system; 7-point score; 3-point score; Menzies method; color, architecture, symmetry, and homogeneity (CASH) system; and pattern analysis each of which has been shown to have good diagnostic accuracy (Table 1).^{26,28,29} The study is designed to identify features that are the most reproducible and diagnostically significant and formulate them into a single algorithm. More information can be found on the International Dermoscopy Society Web site at www.dermoscopy-ids.org, and a link to the study is at <http://uda.dermoscopy-ids.org/>.

Teledermoscopy

A growing workforce shortage of dermatologists is manifest in the long wait times for patients seeking evaluation of concerning moles.³⁰ The shortage of expert dermoscopists is even more pronounced. Although dermoscopy has entered the mainstream of dermatologic practice, a minority of US dermatologists regularly use the technology in their practices. Some believe that dermoscopy is too difficult to learn. Yet numerous educational guides are available that can be used to teach oneself how to use dermoscopy (Appendix A). Others are skeptical about its clinical utility.

In New Zealand an even more striking disparity between the dermatology workforce and demand for melanoma screening has led to commercialization of “teledermoscopy” by a company called MoleMap NZ. A patient arrives at a center to have pictures taken by a nurse or medical photographer who is trained by a dermatologist on how best to capture the images. The MoleMap procedure obtains a detailed description of each lesion at both the clinical and dermoscopic levels. To make up for loss of patient contact, the nurse is trained to ask the patient a series of questions about his or her skin and use a low imaging threshold to avoid missing important lesions. Images and data are sent electronically to expert dermoscopists in a store-and-forward fashion.

Store-and-forward teledermoscopy permits the consultant, who may reside in a different time zone, to access and read images at his or her own convenience. In this paradigm, the

consultant may look at many more moles with dermoscopy than the dermatologist would have in the clinic. Further, it enables serial visualization of lesions so that they may be evaluated for change and, for lesions that are worrisome, may prevent unnecessary biopsies. The dermoscopist's report, with provisional diagnosis and recommendations, is returned to the patient for self-monitoring purposes or to the patient's primary care providers, or both, for referral for excision. Some programs offer a feature that enables the referring physician and dermoscopist to consult in real time, a great learning opportunity for the referring physician. Patients who would otherwise need to wait several months before getting an appointment are assured that an expert will be examining their skin within days and without the need to travel long distances.

The MoleMap database has records of approximately 50,000 patients and slightly more than a million lesions. Thus far, about 1850 lesions have been recommended to undergo excision on the ground of suspicion for melanoma, and 3500 nonmelanoma skin cancers have been diagnosed. A comparison of MoleMap with the general New Zealand Cancer Registry indicates that the melanoma incidence is 25-times greater in MoleMap, and the average Breslow depth is 0.75 mm compared with 1.51 mm. Most (55%) are found in situ, and 33% are thinner than 1 mm (A. Bowling, chief executive MoleMap NZ, personal communication, April 2, 2008). The company has migrated this paradigm to Australia and plans to expand to the United States.

Total body dermoscopic imaging, as in MoleMap, also enables individual nevi to be evaluated in relation to the patient's entire collection of nevi. Contextual comparison has two advantages. First, it is known that roughly 80% of people have moles that fall into one of four predominant global dermoscopic patterns, with the reticular (network) pattern found half the time.³¹ Further, global dermoscopic patterning varies with skin type and age in white patients, so that any lesion that defies the expected, or global, pattern according to the patient's skin type and age may also warrant investigation.³² Clinical images can be used to compare nevi and identify "ugly ducklings," as one small study recently showed that the ugly duckling sign had a 90% sensitivity for melanoma detection.³³

The role of dermoscopy in melanoma risk stratification

Dermoscopy provides a unique visual perspective, and the dermoscopic patterns offer morphologic information above and beyond clinical morphology. This information can be used to characterize nevi and may prove helpful to stratify a patient's risk for melanoma according to some highly preliminary data that indicate that dermoscopy may be useful in risk stratification for melanoma. A small case-control study observed a complex dermoscopic pattern (ie, with both reticular and globular elements) more frequently in melanoma patients with clinically dysplastic nevi compared with age-matched controls with dysplastic nevi but no personal history of melanoma.³⁴ If corroborated in a larger, more rigorous study, a complex dermoscopic pattern within individual nevi may constitute a robust marker of melanoma risk. In addition, a greater risk might be implied by variability in mole pattern within an individual, such as a patient with dark moles containing a reticular pattern, other pink moles with homogenous pattern, and some brown moles with globular pattern.

Computer-assisted diagnosis of pigmented lesions

In the early 1990s, multiple groups began to study the utility of machine vision and computerized analysis in melanoma diagnosis.^{35,36} Since that time, advances in computer technology, digital imaging, and software programming have made computers figure more prominently as potential aids in the evaluation of melanocytic lesions.^{37,38} A recent trial comparing three commercially available systems for diagnostic accuracy found that each one tended to overdiagnose suspect melanocytic lesions as melanoma and questioned whether they were ready to be used in clinical practice.³⁹ Nonetheless, logic dictates that with proficient training and programming, automated systems will eventually match, if not exceed, clinical diagnostic accuracy.

Digitized pigmented lesion images can be analyzed in a variety of ways. Most approaches begin with algorithms for lesion segmentation to determine the boundaries between the lesion and the surrounding skin. The lesion is then analyzed for various diagnostic features such as color, hue, texture, asymmetry, border irregularity, and dimensions. Some systems provide quantification of such features for physician assessment, whereas others analyze the full constellation of features and provide a provisional diagnosis.⁴⁰⁻⁴⁵ Some have achieved a degree of sensitivity and specificity approaching expert dermoscopists.^{37,43,45-48} On the basis of these encouraging results, scientists are working to develop fully automated diagnosis systems.^{38,43,49}

Multispectral imaging

Light of different wavelengths penetrates the skin to variable depths. Multispectral images are sequences of images taken at different wavelengths of light. Spectral images, ranging from 400 to 1000 nm, provide information on the distribution of collagen, melanin content, and blood vessel distribution within skin lesions.⁵⁰⁻⁵² A fully automated system using 15 spectral bands between 483 nm (blue) through 951 nm (near-infrared) has been reported to achieve a 97% contour accuracy in a sample of 1856 pigmented lesions.⁵³ A follow-up study using multispectral analysis and an artificial neural network showed that it could recapitulate clinicians' assessments with 88% sensitivity and 80% specificity.⁴¹ Spectrophotometry has also been used in the preoperative evaluation of melanoma thickness, with sensitivity and specificity values ranging from 75% to 90%.⁵⁴

MelaFind (Electro-Optical Sciences Inc, Irvington, NY) is a hand-held imaging device that uses visible and infrared light to capture images of suspicious pigmented skin lesions, which are then analyzed against a proprietary database of melanomas and benign lesions.⁵⁵ In contrast to dermoscopic analysis, which is qualitative and potentially subjective, spectral imaging is quantitative and more objective. A study of MelaFind's accuracy for distinguishing melanomas from benign nevi found perfect sensitivity and 85% specificity using a 13-parameter linear classifier and perfect sensitivity and 73% specificity with a 12-parameter nonlinear classifier.³⁸ Further research is needed to determine how this technology might be incorporated into clinical practice.

Confocal scanning laser microscopy

Reflectance confocal microscopy (RCM) is a noninvasive imaging modality that permits in vivo examination of the epidermis and papillary dermis at a spatial resolution comparable with histology.⁵⁶⁻⁵⁸ Confocal microscopy is an emerging technology for melanoma diagnosis,^{59,60} preoperative and intraoperative margin assessment,⁶¹ and follow-up for response to medical treatment.⁶¹⁻⁶⁹ Compared with histology, RCM technology produces images noninvasively, in real time, and at a lower cost. Because scanning is done directly on the patient, large volumes of tissue within one lesion, as well as multiple lesions, may be examined at the bedside during a single office visit. Images may be easily stored or sent electronically for referral or consultation. Reflectance confocal microscopy technology may be used adjunctively with other imaging modalities, including photography and dermoscopy.⁷⁰ Scientists have worked to make RCM a clinically useful tool and have successfully decreased the confocal microscope from the size of a table down to a handheld device (Fig. 2).

A confocal microscope consists of a light source such as a collimated and focused laser beam that illuminates a “point” within an object. The backscattered light is imaged onto a detector through a “point” aperture such as a pinhole. The size of the pinhole aperture determines the size of the illuminated voxel. The detector thus receives light only from the illuminated voxel that is in focus, and light from out-of-focus regions is rejected or spatially filtered by the detector aperture. By scanning the illuminated voxels in 2D, a thin slice or a section may be imaged within an object as long as the object is optically transparent or translucent. This is known as optical sectioning. The confocal microscope noninvasively images thin optical sections within turbid scattering objects, such as skin, without the need to physically cut the object into thin sections. Commercial instruments have been developed that image with lateral resolution of 0.5 to 1.0 μm and an optical sectioning thickness of 1.0 to 5.0 μm , to a depth of 200 to 300 μm in human skin (depth of papillary dermis). Confocal imaging, being entirely noninvasive, preserves the natural architecture of the tissue, cellular hydration, tonicity, and contrast of structures. Melanin and melanosomes provide strong contrast for confocal microscopy, which renders melanocytes and melanoma cells amenable for viewing at near-histologic detail, including some amelanotic melanomas.^{61,71}

Confocal scanning laser microscopy may be used in either reflectance or fluorescence modes. Reflectance mode relies on inherent differences in the refractive index of structures. Free cytoplasmic melanin pigment and pigmented and nonpigmented melanosomes provide strong contrast. As a result, even amelanotic melanomas appear bright on RCM, thus allowing for their detection.

Fluorescence confocal microscopy is based on the same optical principles as its reflectance counterpart (see above). Fluorescence, however, uses fluorescent dyes such as fluorescein, toluidine blue, methylene blue, or Yaroslavsky stains⁷² to provide highly specific contrast. A laser light source, at an appropriate wavelength, is used to excite the fluorophore. The excited fluorophore emits fluorescence at a longer wavelength that is detected and displayed according to the fluorescence intensity. Some of these dyes distribute selectively to specific

tissue elements (eg, nucleus, cytoplasm, stroma), and others can be chemically or immunologically targeted to specific molecular ligands.

Fluorescence imaging can target multiple specific sub-cellular structures or proteins of interest, depending on the combination of wavelength of light and fluorophores used. In the future, it may be possible to noninvasively reproduce the staining methods that pathologists commonly use on excised tissue. Recent studies on dual-mode reflectance and fluorescence confocal scanning microscopy in murine models have yielded promising results for tracking melanoma progression.^{73,74} The two modes may one day be used clinically in tandem.

Confocal point scanners continue to evolve into successful laboratory, clinical, and commercial instruments with increasing utility among researchers and dermatologists. Point scanners are relatively complex in terms of the optics and electronics, however, and remain relatively expensive and not yet widespread. For confocal microscopy to succeed in clinical settings, the scanners must be made simple to manufacture, low-cost, with repeatable performance and image quality, and easy to use. Line scanning, as opposed to point scanning, offers the opportunity to simplify the optics, electronics, and mechanics of in vivo confocal microscopy.^{75,76} An illuminated line source and a line detector are used instead of a point source and point detector. Line scanning offers the key advantage of simplicity compared with point scanning: the need for one less scanner and the use of linear array detection technology significantly reduces the required optics and electronics. The optical section thickness achieved is 1.7 μm , and the lateral resolution is 1 μm . The axial sectioning is 1.2-times thicker than that achieved with point scanning, which is adequate for imaging epidermis but limited in its ability to clearly image the deeper dermis.⁷⁶ Commercially available designs include the high speed line scanner (5-Live, Carl Zeiss, Göttingen, Germany) and a combined point and line scanner (Live Scan, Nikon, Tokyo, Japan).

A second emerging technology is spectrally encoded confocal microscopy (SECM).⁷⁷ This highly creative technology exploits broad bandwidth light (white light) rather than narrowband light, in a line scanning fashion, with various points along the line represented by a spectrum of colors. Each point along the line is decoded by a spectral filter, resulting in point-level resolution along the line. The spectral information is translated into spatially resolved points, where the resolution is determined by the bandwidth at each wavelength. Because it images tissue point-by-point, SECM is closer to true confocal microscopy than regular line scanning. The technique provides a 1.4- μm lateral resolution and a 6- μm optical sectioning, in addition to superior contrast compared with regular line scanning.⁷⁷ In addition, SECM may be performed using a small probe such as a catheter or endoscope.⁷⁸

Clinical aspects of confocal microscopy

In 2001, two separate groups pioneered the earliest work using RCM to characterize the cellular morphology of melanocytic cells and the growth patterns of melanocytic lesions.^{61,71,79} They showed very clearly that pigmented keratinocytes, melanocytes, and melanophages could be recognized using RCM and that once a lesion is determined to be melanocytic in origin, various growth patterns could be used as evidence for or against the need to biopsy. A glossary of the terms commonly used in confocal microscopy has been

compiled.⁸⁰ The characteristic findings of cutaneous neoplasms under confocal microscopy have been documented in the first atlas of cutaneous RCM.⁸¹

The first large study to test the accuracy of RCM in distinguishing benign nevi from melanomas was published in 2005.⁵⁹ Using a moderately sized sample of 90 benign nevi and 27 melanomas, the authors reported an overall sensitivity of 88% and specificity of 97% achieved by five observers who had no prior training in confocal microscopy.⁵⁹ In a follow-up study that included nonmelanocytic lesions (90 nevi, 27 melanomas, and 45 nonmelanocytic lesions), this group found an overall 91% sensitivity and 99% specificity of confocal imaging for melanoma diagnosis.⁸² Pagetoid melanocytosis, or diffuse bright round or dendritic cells in the spinous or granular layer, was shown to be highly suggestive of melanoma.⁸³

An algorithm for melanoma diagnosis was proposed consisting of two major and four minor criteria.⁸⁴ The two major criteria are presence of non-edged dermal papillae and cytologic atypia at the basal layer. The four minor criteria include roundish cells in superficial layers spreading upwards in a pagetoid fashion, pagetoid cells widespread in the lesion, nucleated cells within dermal papillae, and cerebriform cell clusters in the dermis.⁸⁴ A diagnostic challenge cited by the group was the Spitz/Reed nevus, which displays many of the features found in melanomas.

A follow-up study used 37 confocal features to score 351 ambiguous melanocytic lesions (215 nevi, 136 melanomas). Certain features could adequately distinguish early melanomas from highly atypical nevi above and beyond visual examination.⁸⁵ A more recent analysis of only confocal images of 50 nevi and 20 melanomas, without clinical or dermoscopic information, found that three features were sufficient in identifying 95% of tumor images: monomorphic melanocytic cells, polymorphic melanocytic cells, and easily identified keratinocyte cell borders. Finally, another study compared RCM with dermoscopy in the evaluation of 125 lesions (88 nevi, 37 melanomas) and showed the latter to be more sensitive (97% versus 89%) but both were equally specific for melanoma.⁸⁶ Results of these major studies on the use of confocal microscopy for diagnosing melanoma are summarized in Table 2.⁸⁴⁻⁸⁷

Biopsies are susceptible to sampling error, which presents a special concern for large or complex pigmented lesions. Reflectance confocal microscopy can be used to scan an entire lesion in the horizontal plane, or en face, and hence may be used to identify areas of atypia within a lesion. This may prove very beneficial for diagnosing some lentigo maligna melanomas that have skip areas or distinct foci of invasion. It is also a promising tool for lateral margin mapping of indistinct lesions (eg, amelanotic and lentigo maligna melanomas) and may be used as an adjunct to Mohs surgery.⁸⁸ With the current imaging depth of 350 μm , RCM cannot assess deep margins of invasive melanomas.) Reflectance confocal microscopy may prove effective for intraoperative assessment of the undersurface of excised specimens in real time, obviating the need for frozen sectioning and streamlining the surgical process.

With the introduction of topical agents such as imiquimod for cutaneous malignancies, a noninvasive method to evaluate response to therapy is highly desirable. It is not uncommon for physicians to misinterpret posttopical therapy-induced erythema as evidence of cancer persistence or to clinically fail to appreciate persistent tumor. Confocal microscopy may prove helpful in monitoring patient progress or detecting persistent or recurrent malignant lesions.

Ultrasound imaging

Melanocytic lesions have been examined with 20-MHz ultrasound and more recently higher-frequency (50- to 100-MHz) ultrasound. Melanomas generally appear as echolucent areas on ultrasound images. Modern scanners provide an axial resolution of 10 μm and a lateral resolution of less than 30 μm . Although ultrasound imaging cannot be used to make a diagnosis of melanoma, it can provide information about perfusion patterns of lymph nodes and other soft tissues that can be used to stage the tumor.⁸⁹ Ultrasound imaging may overestimate tumor thickness if there are infiltrating lymphocytes or nevus remnants present, or underestimate thickness if small clusters of melanoma cells are found in the deep dermis.⁹⁰⁻⁹³

Magnetic resonance imaging

Magnetic resonance imaging also has been studied as a way to evaluate melanocytic lesions. Although magnetic resonance imaging cannot yet reliably discriminate benign from malignant skin lesions,^{94,95} it may be used to measure melanoma thickness or volume in the future.⁹⁶⁻⁹⁸

Optical coherence tomography

Confocal microscopy provides subcellular resolution but is limited to a 300- μm penetration depth, which is adequate for imaging the epidermis. Optical coherence tomography is an interferometry technique that uses a high bandwidth light source to provide good optical sectioning. The broadband source leads to a small coherence length and achieves an axial and lateral resolution of approximately 15 μm and a penetration depth of 500 to 1000 μm .^{99,100} This level of resolution enables visualization of the gross architecture of the epidermis and superficial dermis.¹⁰¹⁻¹⁰³ Optical coherence tomography has been used to examine the retina and as aid in diagnosing certain gastrointestinal and cardiovascular disease. Preliminary data suggest that optical coherence tomography may help detect nonmelanoma skin cancer,^{100,104} contact dermatitis and psoriasis,⁹⁹ and corticosteroid-induced atrophy.¹⁰⁵ Much more work is needed on its utility for cancer detection. The emerging technology of optical coherence microscopy may prove to have superior lateral resolution by virtue of using a higher numeric aperture of the lens.¹⁰⁶

Molecular profiling

Finally, a highly preliminary but exciting development in noninvasive melanoma diagnosis is the tape stripping method using the Epidermal Genetic Information Retrieval System (DermTech, La Jolla, CA) that was presented in 2007 at the Society of Investigative

Dermatology.^{107,108} A piece of adherent tape touched to the patient's skin retrieves RNA from the stratum corneum that may subsequently be sent for genetic profiling. Specific mutations or polymorphisms may identify a suspicious lesion as a nevus or melanoma. At the annual meeting of the American Association for Cancer Research in April 2008, the group presented preliminary data showing that the assay has 100% sensitivity and 90.6% specificity for melanoma in a test set of 18 melanomas and 48 atypical nevi.¹⁰⁹

Conclusions

The accessibility of the skin to simple visual inspection and the relative ease of skin biopsy have retarded the adoption of high-tech diagnostic aids by dermatology relative to other specialties. These same attributes of visually distinct lesions and easy accessibility make the skin an excellent target for a myriad of noninvasive diagnostic technologies. The imperative to decrease melanoma deaths through early detection has prompted varied technologic approaches to improve diagnostic sensitivity while avoiding unnecessary excisions. Among these, total body photography and dermoscopy have been the first to attain significant diffusion into clinical practice. Of the numerous evolving technologies, the optical-based approaches hold the greatest promise in the near-term. Eventually, it can be anticipated that multimodal systems will significantly improve the accuracy and reduce the trauma of dermatologic diagnosis.

Drugs names

Imiquimod (Aldara and Beselna).

Appendix 1. Dermoscopy educational resources

Books

Marghoob AA, Braun R, Kopf AW, editors. Atlas of dermoscopy. London: Parthenon Publishing, 2004.

Malvey J, Puig S, Braun, RP, Marghoob, AA, Kopf AW. Handbook of dermoscopy. London: Taylor & Francis, 2006.

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Tosti A. Dermoscopy of hair and scalp disorders with clinical and pathological correlations. London: Informa Healthcare, 2008.

Compact Discs

Marghoob A, Braun R, Kopf A. Interactive CD-ROM of dermoscopy. London: Informa Healthcare, 2007.

Argenziano G, Soyer HP, De Giorgi V, et al. Interactive atlas of dermoscopy. [Book and CD-ROM] Milan: Edra Medical Publishing and New Media, 2000.

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Online resources

International Dermoscopy Society: www.dermoscopy-ids.org

Skin Cancer Society of Australia: www.dermoscopyatlas.com

French Federation in Dermatology and Venereology: www.dermatoscopie.org

Live courses

See the International Dermoscopy Society Web site: www.dermoscopy-ids.org

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Fig. 1. Cumulative increase in the number of dermoscopy-related PubMed citations. Once considered an area of high specialization, dermoscopy is a growing field within dermatology. Much research has been done to develop and refine dermoscopic assessment of the skin so that it can help diagnose dermatologic diseases, especially, but not exclusively, skin cancer.

Fig. 2.
Confocal microscopy from (A) benchtop (B) to bedside.

Table 1
Current dermoscopic algorithms and their diagnostic accuracy for melanoma^{26,28,29,a}

Method	Sensitivity, %	Specificity, %	Features, No.	Evaluated by consensus net meeting
ABCD	83	70	9	Yes
Pattern analysis	84	83	15	Yes
7-point	84	72	7	Yes
Menzies	86	71	10	Yes
3-point	86	71	3	No
CASH	98	68	10	No
Range	83-98	68-83	3-15	

ABCD, asymmetry, border irregularity, color, diameter; CASH, color, architecture, symmetry, and homogeneity.

^aThis table shows the dermoscopic algorithms that have been shown to have good diagnostic accuracy for melanoma, the reported sensitivity and specificity values, and the number of features evaluated by each system.

Table 2
Current studies of confocal microscopy for the diagnostic accuracy for melanoma

Study	Sample size		Evaluation technique	Threshold score	Sensitivity, %	Specificity, %	Features, No.
	Melanoma, No.	Nevi, No.					
Pellacani, 2005	37	65	Major (2 points) and minor (1 point) criteria	3	97.3	72.3	6 (4 major, 2 minor)
Pellacani, 2007	136	215	Major and minor criteria	2	96	52	6
				3	92	69	
Langley, 2007	37	88	Overall evaluation	NS	97.3	83	7
Gerger, 2008	20	50	Overall evaluation	NS	97.5	99	NS
			Decision tree	>1	97.6	92.4	2

NS, not specified.