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Imaging Techniques for the In Vivo Diagnosis of Melanoma

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The ability to detect early melanoma remains of paramount importance in our efforts to curtail deaths related to this malignancy. Fortunately, our clinical skills at recognizing the varied clinical presentation of early melanomas are continuously improving. Our enhanced clinical acumen together with improved awareness of the danger signs of melanoma has resulted in a greater proportion of thin melanomas being diagnosed today as compared to the past. The implementation and utilization of *in vivo* imaging technologies in clinical practice promises to further enhance our ability to detect melanoma while this cancer is still thin and easily curable. This article describes the utility and application of the *in vivo* imaging technologies that are currently in clinical use today including dermoscopy, total body photography, individual lesion photography, and reflectance confocal microscopy.

KEYWORDS melanoma, dermoscopy, total body photography, confocal, short term mole monitoring

The past century has witnessed an increase in survival among patients with newly diagnosed melanoma (MM), despite escalating incidence rates and lack of effective therapy for advanced disease. These seemingly conflicting data have but one explanation—the earlier diagnosis of surgically resectable primary MM. Our ability to recognize the varied clinical "faces" of MM, including those of thin, featureless, and amelanotic MM continues to evolve and improve with each passing day. The improved clinical acumen for recognizing MM is in large part a result of the implementation of imaging technologies in dermatology. The simple act of obtaining images of lesions, which can be viewed retrospectively once the biological nature of the lesion has been revealed, is a tremendously powerful tool that has contributed significantly toward our understanding of the varied clinical primary morphology features of MM. Needless to say, the ultimate aim of screening efforts for MM is early detection and removal of MM (sensitivity) while at the same time avoiding the removal of as many benign lesions as possible (specificity). This seemingly difficult aim is being addressed and imaging technologies are once again leading the way. These technologies include but are not limited to digital photography, dermoscopy, and reflectance confocal microscopy (RCM).

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Digital Photography (Total Cutaneus and Individual Lesion)

One of the most sensitive signs of early MM is the detection of appreciable change in the color, shape, size, or emergence of symptoms such as itch and tenderness within a preexisting melanocytic lesion. However, there are several challenges that clinicians face in the diagnosis of MM. One challenge is that benign nevi are very common such that on average most individuals have between 20 to 40 nevi by the third to fourth decade of life. Furthermore, approximately 6% of population has the atypical mole syndrome (dysplastic nevus syndrome).[1] These dysplastic nevi often appear suspicious by the ABCD criteria and, thus, they frequently are biopsied unnecessarily. Another challenge is that the change in a lesion can be gradual and escape notice by the patient or physician or MM may be overlooked in the background of many dysplastic nevi.[2] It is therefore difficult for the patient and physician to recall from memory the precise morphology of an individual lesion to appreciate whether change has occurred over time. The technique of photographically assisted follow-up was developed in recent decades to assist in this regard.

Baseline imaging can be used to obtain overview photographs as well as supplemental close up photos of all lesions

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or selected lesions. Methods for obtaining reliable total cutaneous photography have been described.[2] The 3 basic criteria that are essential for the success of this technique are ease and standardization (reproducibility) in image acquisition, good quality of photographs, and availability of the photographs for clinical use.[3] A standard set of poses for total cutaneous photography facilitates reproducibility both in terms of image acquisition and in use of the pictures during skin examination.[2] Fundamental to the usefulness of this series of photographs is that nearly the entire skin surface is visualized. Additional "close-up" images of individual lesions may also be obtained. These images are used for side-by-side comparison with the patient's current mole status during follow-up examinations.

In 1992, Shriner and coworkers,[3] reported that 41% of U.S. residency programs use photography in management of DN. By year 2002, of 105 residency programs 63% used TBP and 75% used photography of individual lesions.[4] Furthermore, programs with specialized pigmented lesion clinics were more likely to use total body photography than programs without it (83% versus 49%, $P = 0.001$).[4]

Photographically assisted follow-up is indicated for patients at high risk for MM such as those with dysplastic nevi, familial MM, patients with dysplastic nevi in conjunction with personal history of MM, as well as those patients with very complex skin examinations (eg, patients with many nevi) or those undergoing numerous nevus excision. A baseline set of total cutaneous photographs is obtained in these patients and used for comparison in future self-examinations and in professional examinations. On follow-up visits, innately concerning lesions as well as any new or changed lesions are identified (Fig. 1). These lesions are evaluated with dermoscopy or compared with baseline close-up/dermoscopy photos and a decision to biopsy, excise, or continue with short-term or long term follow up is rendered.[3] Those lesions that are stable on follow up are considered biologically senescent.

Many studies have touted the advantage of baseline cutaneous photography in facilitating early detection of new and subtly changing MM, while they are thin and before they exhibit the classical clinical "ABCD" features of MM, in high-risk patients (increased sensitivity).[5] Banky and coworkers,[6] used baseline clinical photography in the follow-up of 309 high-risk patients for median time of 34 months. Of the diagnosed MM during the study period, 44% were in situ as compared with 35% for the general population in the same geographical region. The median thickness of the invasive MM was 0.39 mm as compared with 0.6 mm for that geographical region in general. Wang and coworkers[7] performed a similar study in which they used baseline clinical photography for the long-term follow-up of high risk patients. A total of 42% of the diagnosed MMs were in situ, and the mean thicknesses of invasive MMs were 0.55 mm. All the MMs were less than 1 mm in thickness, and there were no metastases or deaths attributable to MM. These studies in addition to others are evidence that baseline clinical photography improves sensitivity in diagnosis of MM.[8]

One potential pitfall to photographic-assisted follow-up is a decrease in sensitivity at baseline caused by a reliance on monitoring for the decision whether to excise a lesion. In patients that have not yet proven themselves as compliant with the follow-up regimen, the clinician should excise suspicious lesions at the baseline visit. However, in the long run, the use of TBP allows for increased specificity (avoiding unnecessary biopsies) of lesions that have proven to be stable over time.[9,10] Kelly and coworkers[11] used baseline cutaneous photography in the long-term follow-up of 278 patients with dysplastic nevi. Their group described two-thirds of the detected new MMs arose de novo; therefore, prophylactic excision of atypical (dysplastic) nevi in their cohort would not have provided a satisfactory alternative to meticulous follow-up. In this regard, photographically assisted follow-up provides the clinician with knowledge of the stability of atypical (dysplastic) nevi that would otherwise likely have been subjected to excisional biopsies.[6]

Patients also may be given the total body picture set for use in the monthly skin self-examination (SSE). SSE aids in the detection of thin MMs and reduces mortality from MM by 63%.[12] Oliveria and coworkers[13] observed that the addition of baseline clinical photography to SSE leads to an increase in sensitivity for detecting changing or new nevi from 60% to 72% and increase in specificity from 96% to 98%. Feit NE and coworkers[14] noted that 30% of MM identified during follow-up were identified by the patients who were comparing their skin to baseline TBP during monthly SSE sessions. Furthermore, studies indicated that, when patients were provided with baseline cutaneous photography, they were more compliant at performing SSE as compared with those patients that were not provided with their TBP (61% versus 37%, respectively).[13]

Although SSE is a powerful method for early detection, changes in MM can still escape detection by even the most vigilant of patients. Photography-assisted follow-up can help bridge that gap. Banky and coworkers[6] used baseline clinical photography for the long-term follow up of high-risk patients in their clinic. During the study period, only 5% of the diagnosed MMs were found by the patient. Malvehy and coworkers[15] studied 290 patients with multiple atypical moles that were followed with the use of digital imaging. Eight of the patients (3%) developed MM. None of the patients noted change in the lesions before diagnosis. In one study, 278 patients who had greater than 5 dysplastic nevi were followed for a mean of 42 months using base line clinical photography. Twenty of the patients (7%) developed MM. Eleven of them (55%) had not noted a change before diagnosis.[11]

Dermoscopy

Dermoscopy has become a key diagnostic tool in the armamentarium of physicians that screen patients for skin cancer. Dermoscopy is a technique that uses a handheld magnification device similar in appearance to an otoscope that is placed on the skin after application of a liquid interface (ie, nonpolarized dermoscopy). In recent years, a smaller portable cross-polarized instrument that does not require an immer-

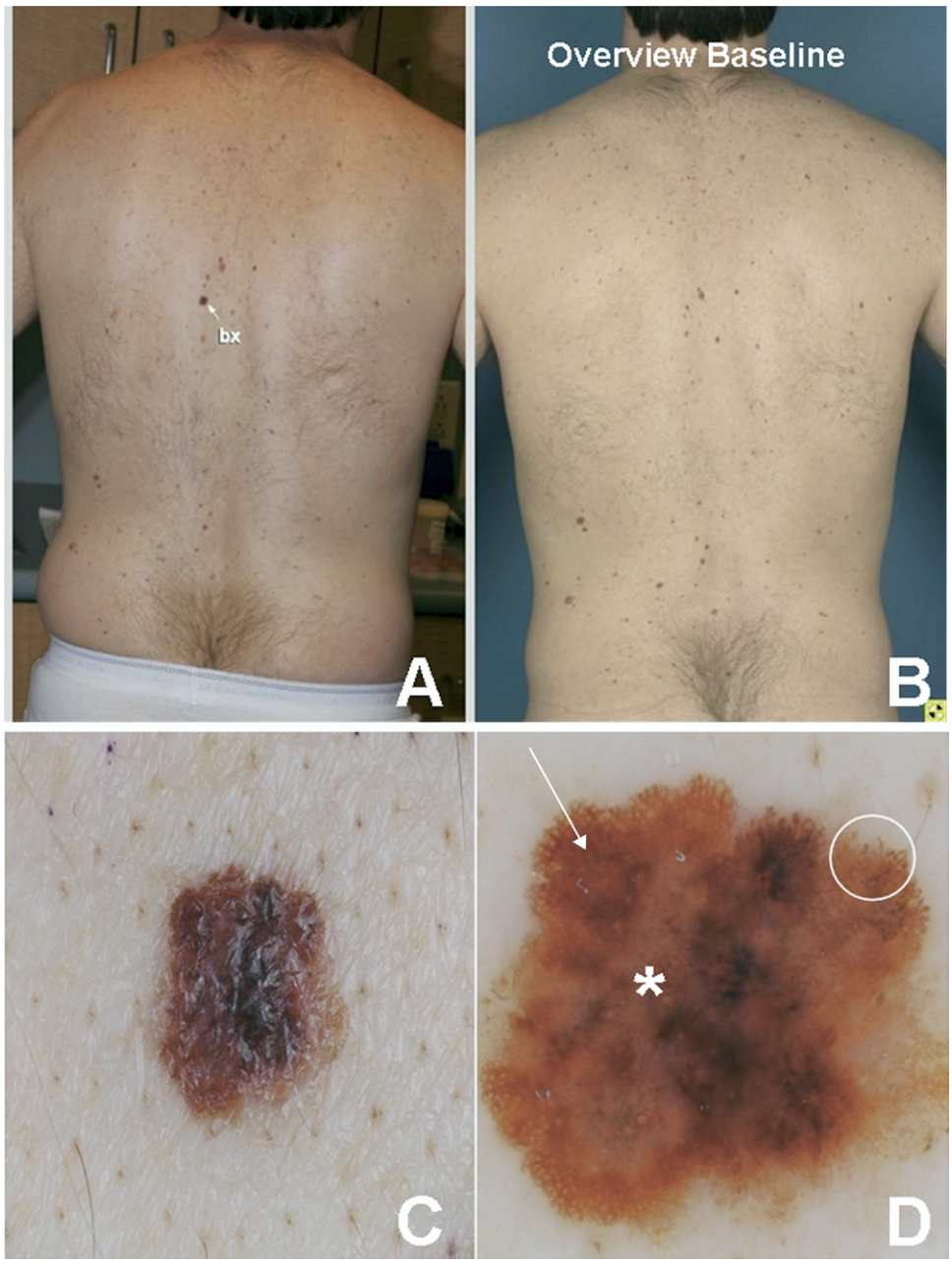

Figure 1 This patient presented with many nevi and a history of MM. Baseline TBP were obtained and used for comparison during his routine SSE and office visits. After 3 years of undergoing periodic cancer screening, the patient was lost to follow-up for 2 years. However, during that period, he continued to perform periodic SSE. The patient noted a change in a lesion on his back, which prompted him to return to the clinic. On examination, it was obvious to all that he had an "ugly duckling" lesion that was highly suspicious for MM (A, arrow). In comparison, his baseline images revealed that his nevi initially resembled each other (B). The "ugly duckling" lesion was a 1-cm reddish-black papule (C) that showed on dermoscopy a complex pattern with atypical network (D, arrow), peripheral streaks (D, circle) and irregular globules and blue–white structures (D, asterisk), highly suggestive for MM. This proved to be a 0.5-mm MM, which arose from a banal-appearing preexisting nevus. This case also illustrates that superficial spreading MM, which is the most common type of MM, is relatively slow growing and thus affords us a window of opportunity for its timely detection. (Color version of figure is available online.)

sion liquid (ie, polarized dermoscopy) has been introduced. Both devices greatly reduce defraction of light by the corneal layer, allowing for visualization of subsurface anatomic structures of the epidermis and papillary dermis that are otherwise not discernible to unaided eye. The observer can now appreciate morphological alterations in skin lesions as dermoscopic structures of different shapes and colors. Most dermoscopic colors and structures have been correlated with histopathologic findings.[16,17] Hence, dermoscopy can be considered a form of bedside in vivo gross tissue inspection that can help to predict tissue pathology.

The accuracy of clinical unaided diagnosis by experienced

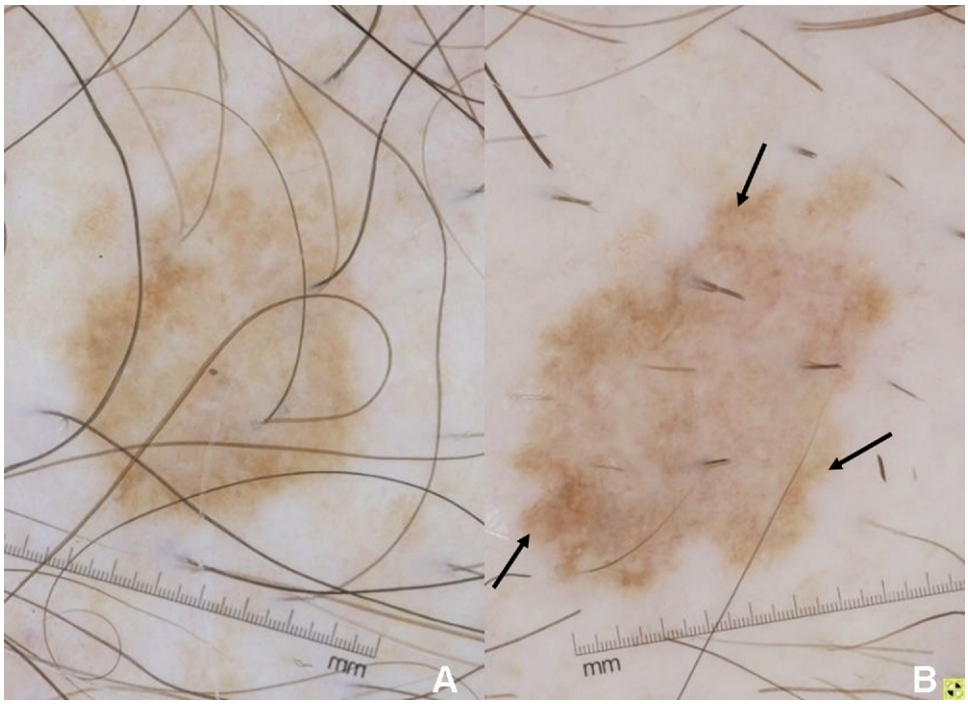

Figure 2 Digital dermoscopic monitoring of melanocytic lesions in high-risk patients results in early detection of thin tumors, while they still lack the classic clinical and dermoscopic features of MM. This patient has many atypical nevi and a personal history of MM. This lesion on his chest was imaged at baseline (A). During the 5-month follow-up examination, it was noted that this lesion had changed in size in an asymmetric fashion (B, arrows). It did not reveal any MM specific features, however, because of the observed change the lesion was excised and proved to be a 0.4-mm MM. (Color version of figure is available online.)

dermatologist's eye is only about 60%.[18] Dermoscopy enhances the diagnostic accuracy[18,19] and helps triage which pigmented lesions require biopsy. A large meta-analysis of dermoscopy studies showed that diagnostic accuracy was significantly increased by 49% with dermoscopy compared with unaided examination, with mean sensitivity increasing by 19% (83% versus 70%) and mean specificity by 6% (81% versus 86%).[18-20] The increase in specificity by dermoscopy impacts excision rates of pigmented lesions. Carli and coworkers[21] conducted a randomized trial of MM screening that showed a 42% reduction in the number of patients referred for biopsy when using dermoscopy (15.6%) compared with naked-eye examination (9%).[21] This result is consistent with a retrospective analysis that showed a significant reduction in the benign/malignant ratio of excised melanocytic lesions from 18:1 in the predermoscopy era to 4:1 after dermoscopic use was implemented by trained clinicians.[22] Of note, there was no improvement in the benign/malignant ratio for physicians who did not use dermoscopy during this period (12:1 versus 14:1). In addition, the benefit of using dermoscopy greatly depends on experience, and reliance on dermoscopy by untrained or less-experienced examiners was found to be no better than clinical inspection without dermoscopy.[18] Pagnanelli and coworkers[23] demonstrated that a web-based training course improves diagnostic performance of nonexperts, in MM diagnosis by dermoscopy. This observation is further supported by a study conducted by Benvenuto-Andrade and coworkers,[24] which indicated that short training in dermoscopy increases confidence in the correct diagnosis when evaluating pigmented lesions.[24]

Pushing the boundaries on MM diagnosis entails recognizing the tumor at an earlier and earlier stage of development—enter the era of diagnosing dermoscopic "featureless" MMs with the use of sequential dermoscopic imaging. Monitoring a lesion for change using baseline and follow-up dermoscopic images is aimed at increasing the specificity of diagnosis of MM (Fig. 2). It is usually restricted to patients with multiple atypical nevi because it is often more practical to simply remove a single atypical mole on a patient with few to no additional nevi then it is to follow them. For individuals possessing many nevi, the removal of all of their atypical moles would be impractical. In such patients, sequential dermoscopic imaging may prove to be more humane way of management. The principle is that if a lesion is found to be stable, the patient can be reassured that the lesion is biologically indolent at that moment in time and thus can be followed routinely.

Menzies and coworkers introduced the concept of short-term mole monitoring, which involves sequential reexamination of the same lesion during a 3- to 4-month period.[9] Short-term dermoscopic monitoring is aimed at increasing specificity of evaluation of equivocal melanocytic lesions. It is used to evaluate melanocytic lesions that lack dermoscopic features of MM, yet appear somewhat atypical to the examiner or have a history of change. In this setting, any morphologic change during the 3-month period warrants an excision. The exception to this is an overall increase or decrease

in pigmentation without architectural change and the loss or appearance of milialike cysts. The majority (81%) of the lesions followed up in Menzies study did not change and thus were "spared" from undergoing unnecessary removal. Of the lesions that did reveal change, 11% were found to be MM, all of which were thin and none revealed any of the classic dermoscopic findings of MM. The specificity for the diagnosis of MM by means of short-term digital monitoring of dermoscopically equivocal lesions was reported to be 83%.

Long-term surveillance is reserved for evaluating melanocytic lesions in patients at high risk for MM such as those with atypical mole syndrome. The aim once again is at early detection of MM whereas at the same time lowering the rate of unnecessary excisions of benign nevi. In patients with multiple atypical moles, it is quite a challenge to spot an early MM in the "forest" of atypical nevi, as well as to recognize a MM arising in an atypical nevus. Excision of all atypical lesions is often impractical and is associated with significant disfigurement, morbidity and cost. Bauer and coworkers,[25] evaluated dermoscopic changes and the rates of excision of nevi and MM in a long-term follow up of high-risk patients using digital dermoscopy. During a median follow-up time of 25 months, 128 (6.0%) of all lesions showed changes in size or architecture. However, excisions were only performed in cases of asymmetrical growth, asymmetrical changes of pigmentation, or development of dermoscopic features indicative of MM. Thus, only 33 lesions showing suspicious changes were excised, of which 2 were MM in situ and the rest nevi. In another study, Kittler and coworkers[26] followed suspicious lesions lacking MM-specific features at baseline for over the course of 8 months. In their study, after follow up of 1.5 to 4.5 months, only 38.2% of the MMs showed specific dermoscopic features for MM. This value increased to 55% after 4.5 to 8.0 months and to 64.9% after more than 8.0 months. The observed changes in MM lesions included asymmetrical enlargement, focal changes in pigmentation and structure, regression features, or change in color. Some insignificant change included a darker or lighter overall appearance, changes in the number or distribution of brown globules or disappearance of parts of the pigment network and replacement by diffuse brown pigmentation. The conclusion of the study was that MM specific dermoscopic criteria in featureless MM become readily apparent as the length of follow-up increases. However, MMs that lack any specific features can in fact be detected via the short-term monitoring process. Thus, MM lacking MM-specific dermoscopic features can now be detected based on observing their dynamic evolution over time, which is a proclamation to all of its malignant biology.[26,27]

One of the possible risks of dermoscopic monitoring of melanocytic lesion involves patient noncompliance. Twelve percent of patients offered monitoring did not return for follow-up imaging.[9] Because a proportion of patients subjected to mole monitoring are found to have a MM, these would be missed in noncompliant patients. Another risk of monitoring involves rapidly growing MM that will significantly progress during follow-up. Liu and coworkers,[28] studied the dynamics of MM growth and recognized a subset of MM (i.e., nodular MM) with very rapid growth (0.5 mm increase in thickness per month or more).[28] Interestingly, these rapidly growing MM usually manifest clinical features of symmetry, elevation, border regularity and lack of pigmentation. Thus, clinicians may fail to excise them at baseline and opt for follow-up due to the banal appearance of many of these nodular MM. These MM occur more in male patients of older age, the very population that still suffers from increase in MM mortality.[29] To avoid missing a nodular MM, the golden rule is NEVER to monitor lesions that are nodular or rapidly changing.[30,31] Furthermore, patients who develop aggressive tumors seem to lack the most important risk factors for MM, particularly the presence of a large number of nevi and freckles,[28] again emphasizing another golden rule that a suspicious lesion in patients with few nevi are better removed.

Another method of recognizing early MM that were previously considered featureless is by appreciation of new dermoscopic structures. One type of dermoscopic finding that has received increasing attention in recent years is the vascular component (Fig. 3). Different morphologic types of vessels are associated with different melanocytic or nonmelano-

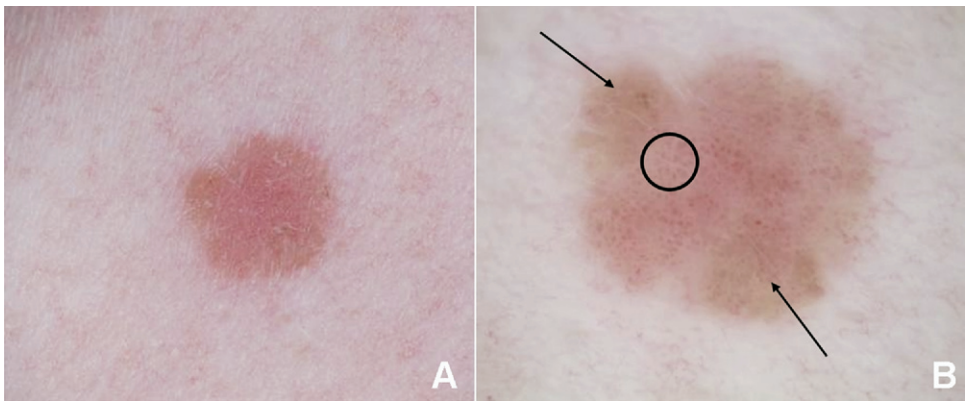

Figure 3 This patient has many nevi and a previous history of MM. This lesion on his lateral abdomen was different from the surrounding nevi in that it was lighter in color and had a hint of pink color in it (A). Dermoscopy revealed multiple dotted vessels (B, circle) and tan structureless areas at the periphery (B, arrows), both features common to MM. The lesion was biopsied and histopathology disclosed that it was indeed a micro-invasive MM. (Color version of figure is available online.)

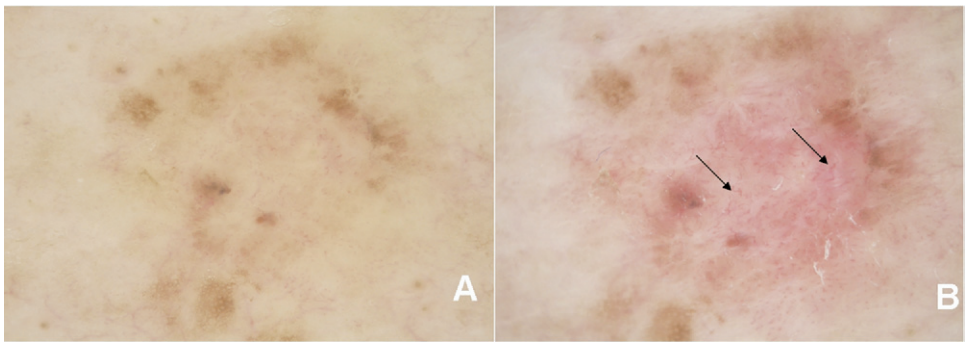

Figure 4 Nonpolarized dermoscopy (A) demonstrates that pressure from skin contact with the dermoscope and superficial back scatter of light makes it difficult to appreciate the vessels in the dermis. However, on noncontact polarized dermoscopy (B), linear-irregular vessels can be clearly seen (arrows) in this 0.4-mm hypomelanotic melanoma. (Color version of figure is available online.)

cytic skin tumors. Therefore, the recognition of distinctive vascular structures may be helpful for diagnostic purposes, especially when the classic pigmented dermoscopic structures are lacking. Argenziano and coworkers,[32] observed that linear-irregular type vessels were the most common vascular pattern seen in MM followed by dotted vessels and polymorphous/atypical vessels. Although rarely seen, milky-red globules/areas showed the highest predictive value for MM (77.8% of lesions with this feature were MM). In this study, dotted vessels were highly predictive for a melanocytic lesion (90% of lesions with dotted vessels were melanocytic). In this context, dotted vessels were the most common vascular pattern in Spitz nevi,[32] although more than one third of lesions exhibiting dotted vessels were MM. Therefore, lesions with dotted vessels should be viewed with caution.[32] This is especially important in hypopigmented and amelanotic MM, in which dotted vessels can often be the only clue to the correct diagnosis of MM.[33]

Until recently, dermoscopes used only nonpolarized light sources to illuminate the skin. However, new commercially available dermoscopes that employ the properties of cross-polarized light have been recently introduced.[34] Benvenuto-Andrade and coworkers,[35] compared dermoscopic features and patterns of skin lesions by using conventional and polarized light dermoscopy (PD). They noticed that vascular structures are better appreciated under PD. This was explained by the better visualization of deep structures by PD because of its ability to reject superficially reflected light more efficiently than nonpolarized dermoscopy.[35] In addition, PD unlike non-polarized dermoscopy does not require direct skin contact, hence preventing the blanching of the vasculature, which occurs due to the pressure placed on the skin when it is viewed with a contact dermoscopy device (Fig. 4).[35] The use of PD should thus improve our ability to identify early and amelanotic MM based on the vascular pattern.[35] On the other hand, nonpolarized dermoscopy was superior in visualization of blue-white areas, such as seen in regression areas (Fig. 5).[35] If the dermoscopic techniques were to be used simultaneously, their complementary nature may generate more sensitive and specific criteria for dermoscopic diagnosis of melanocytic lesions.

Reflectance-Mode Confocal Microscopy (RCM)

In vivo RCM is a noninvasive imaging technique that allows for the en face (horizontal plane) visualization of microscopic structures and cellular detail of the epidermis, dermoepider-

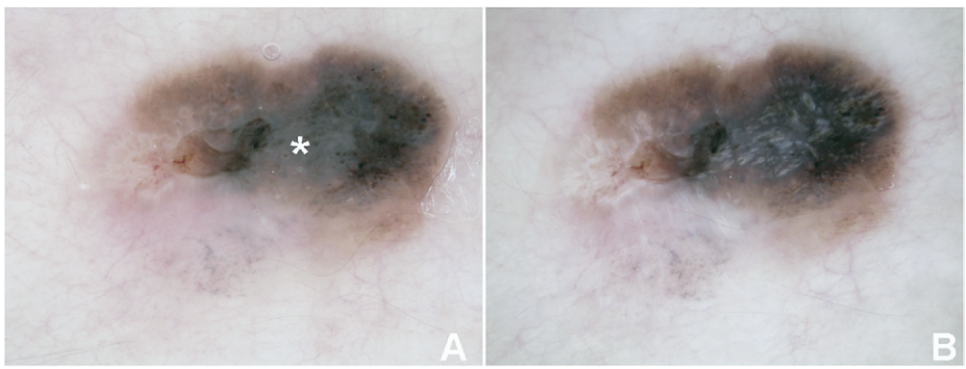

Figure 5 Nonpolarized dermoscopy shows a blue-whitish veil (A, asterisk), which probably represents melanin in melanocytes and melanophages in the dermis and overlying compact orthokeratosis. However, on polarized dermoscopy (B), the blue–whitish veil is not as apparent, due to deeper penetration of the polarized light, and due to its inability to 'visualize' the orthokeratotic layer. (Color version of figure is available online.)

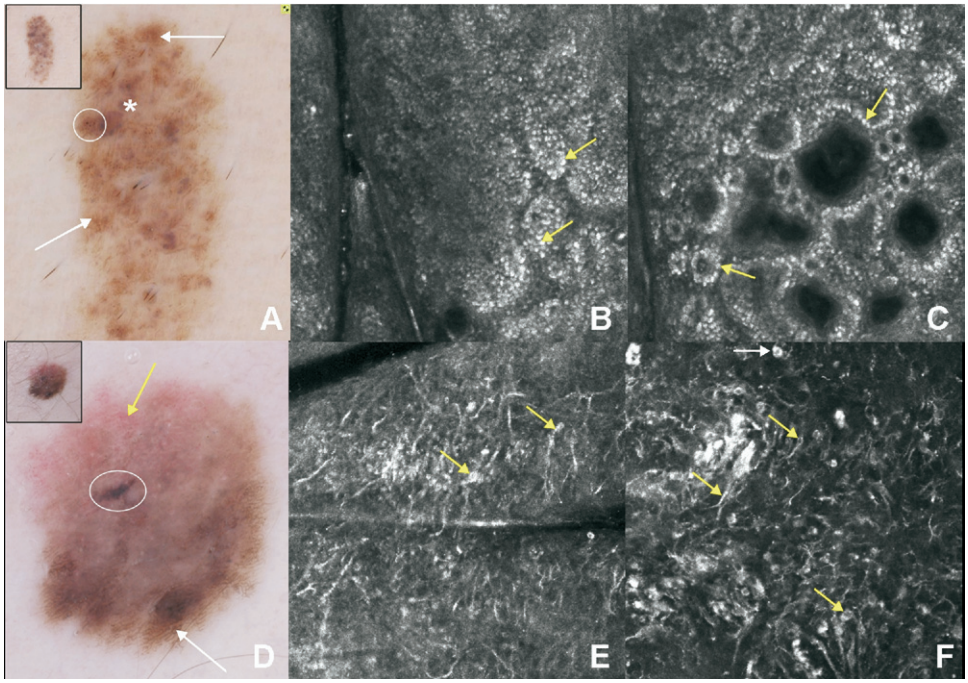

Figure 6 This 13 × 4-mm pigmented lesion (A, inset) was found at baseline examination on the popliteal fossa of a 60-year-old patient with a history of basal cell carcinoma. Dermoscopy (A) showed a patchy network (A, arrow), irregular dots and globules (A, circle) and bluish areas (A, asterisk). However, on RCM at the level of the epidermis, round, monomorphic bright cells (B, arrows) were viewed, compatible with pigmented keratinocytes. Similarly, similar bright keratinocytes were observed on RCM as regular rims around dermal papillae ("edged dermal papillae") at the dermal-epidermal junction (C, arrows). These findings are compatible with a benign nevus, and indeed, this was a lentiginous compound nevus. In contrast, the second lesion, a 12 mm papule (D, inset) on the back of a 54 year old patient without skin cancer history, was noted by the patient due to change in size and color. Dermoscopy (D) revealed a complex lesion with atypical network (D, white arrow), blue-white structures, dark blotch (D, circle) and dotted vessels (D, yellow arrow). On RCM at the level of the suprabasal epidermis (E), multiple dendritic cells are seen (arrows), suggesting pagetoid spread. On RCM at the level of the dermal-epidermal junction, there is a marked density of round (white arrows) and dendritic (yellow arrows) atypical cells. These findings were suggestive of malignancy, and indeed this was a melanoma 0.3 mm in depth. (Color version of figure is available online.)

mal junction and superficial dermis at histopathological resolution.[36-39] RCM works by the operator tightly focusing a low power laser beam (near-infrared wavelength) on a specific point in the skin and detecting only the light reflected from that focal point through a pinhole-size spatial filter. This beam is then scanned horizontally over a 2-dimensional grid to obtain a horizontal microscopic section.[37-39] The imaging depth in normal skin is 200 to 300 μm, to the level of papillary dermis, secondary to limited penetration of the near-infrared light through the skin. Adjustments can be made in the focal length of the beam, allowing the microscope to image a series of horizontal planes stacked vertically, with an axial thickness of 2 to 5 μm.[36-38] This in vivo axial section thickness correlates closely with the axial thickness of excised histological sections.[38,39] The contrast in RCM images relies on differences in the reflectivity of tissue structures. Melanin in the cytoplasm or melanosomes is strongly reflective, and thus melanocytic lesions are suitable for RCM evaluation.[40] In addition, in contradiction to histology, RCM imaging preserves the natural architecture of the tissue, including cellular hydration, natural tonicity and the natural contrast of structures,[36-40] and enables the assessment of details in the same tissue over time.[41]

There are studies that have identified several distinguishing RCM features between MM and nevi (Fig. 6).[42-44] Pellacani and coworkers[42] applied RCM to characterize cytological and architectural aspects of cell clusters in melanocytic lesions. They noted that nests appeared denser in benign lesions, whereas in MM they were less cohesive (described as "sparse clusters"). In addition, cerebriforms nests were only seen in MM. Similarly, in benign lesions the basal layer formed a bright ring around the dermal papillae ("edged papillae"), whereas in dysplastic nevi and MM there was a higher frequency of lack of that rim ("nonedged papillae"). Also, in MM pagetoid melanocytosis was usually extensive and diffuse, characterized by marked cellular atypia, whereas in benign lesions, where pagetoid spread of melanocytes was infrequently seen, it was focal and without cellular atypia.[43] Marghoob and coworkers,[44] applied RCM to assess congenital nevi that have features in common with MM on both clinical and dermoscopic examination, thus making in vivo diagnosis difficult. RCM examination of CMN revealed normal epidermal and dermoepidermal architecture and did not identify increased number of atypical or dendritic melanocytes, abnormal single cells (pagetoid), or an irregularly nested melanocytic proliferation at the dermoepidermal

junction, thus helping to rule out the diagnosis of MM developing within the CMN. However, like on histopathology, Spitz/Reed nevi represent a pitfall in RCM diagnosis, owing to the frequent observation of pagetoid infiltration in superficial layers, architectural disarray, cytologic atypia at basal layers, and nucleated cells within dermal papillae.[45] Thus, the diagnostic significance of these features is context dependent and correlation with other histologic features and the clinical presentation is critical for a correct diagnosis.

On the basis of RCM features that distinguish MM from nevi, 3 studies preliminarily analyzed the potential of RCM in diagnosis of melanocytic lesion.[45-47] Pellacani and coworkers[46] concluded that characterization of RCM features of MM and nevi improves diagnostic accuracy for melanocytic lesions that are difficult to diagnose. Cellular atypia was the most sensitive feature for MM diagnosis, whereas the presence of nucleated cells infiltrating dermal papillae was the most specific.[45] Gerger and coworkers,[47] examined 117 melanocytic skin lesions and 45 nonmelanocytic skin lesions using RCM. In their study, differentiating between MM and all other lesions based solely on RCM features was achieved with a positive predictive value of 94%.[47]

In addition, RCM allows for scanning of the entire area of the lesion in question in the horizontal plane; hence areas that show cellular or architectural atypia can be identified to direct biopsy site selection. This may prove useful for improved sensitivity in diagnosing some lentigo maligna MM that may display skip areas and foci of invasion.[48] In addition, most biopsy specimens undergo limited sectioning before histologic evaluation, and sampling errors may occur in large, complex pigmented lesions, as well as MM arising in precursor nevi which may permit small foci of MM to go undetected. To that end, RCM can be done at patient's bedside to examine the melanocytic lesions and mark the foci of concern with ink or a suture to direct pathological sectioning. RCM may also have the potential to noninvasively delineate MM margins, thus improving the presurgical and intraoperative assessment of extent of excision needed to clear tumors that lack good clinical delineation, such as amelanotic MM and lentigo MM.[49]

Another area in which confocal microscopy may be of benefit is the evaluation and monitoring of persistent or recurrent malignant lesions. With the introduction of topical agents such as imiquimod, many cutaneous malignancies may be treated topically without posttreatment biopsy to confirm cancer clearance. However, it is not uncommon for physicians to misinterpret post-topical therapy-induced erythema as evidence of cancer persistence. RCM may potentially allow for the ability to perform virtual biopsies to diagnose the existence of cancer and to confirm whether the cancer has been successfully "cured" on completion of topical therapy.[39] In addition, in cases where cutaneous malignancies have been excised, it is recommended that the scars be followed for the detection of local recurrence.[50] However, there are some malignancies, such as amelanotic or lentigo maligna, in which detection of recurrence can be challenging. This is another scenario in which RCM may assist in the follow-up of these patients by allowing for the periodic and noninvasive scanning of the skin surrounding the excision scars for the detection of recurrence.

In summary, the technologies presented in this review can help the clinician identify MM at an earlier, curable stage, while avoiding excessive scarring from removal of benign lesions. With further technological improvements, these diagnostic devices are expected to be less expensive and possibly easier to use (such as by increase automation of the process). Without doubt, making these technologies more accessible to dermatologists, primary health care professionals, and patients may further lower the mortality from this lethal tumor.

References

1. Halpern AC, Guerry D, Elder DE, et al: Natural history of dysplastic nevi. J Am Acad Dermatol 29:51-57, 1993
2. Halpern AC, Marghoob AA, Bialoglow TW, et al: Standardized positioning of patients (poses) for whole body cutaneous photography. J Am Acad Dermatol 49:593-598, 2003
3. Shriner DL, Wagner RF Jr., Glowczwski JR: Photography for the early diagnosis of malignant MM in patients with atypical moles. Cutis 50: 358-362, 1992
4. Nehal K, Oliveria SA, Marghoob AA, et al: Use of and beliefs about dermoscopy in the management of patients with pigmented lesions: A survey of dermatology residency programs in the United States. Mel Res 12:601-605, 2002
5. Feit NE, Dusza SW, Marghoob AA: MM detected with the aid of total cutaneous photography. Br J Dermatol 150:706-714, 2004
6. Banky JP, Kelly JW, English DR, et al: Incidence of new and changed nevi and MM detected using baseline images and dermoscopy in patients at high risk for MM. Arch Dermatol 141:998-1006, 2005
7. Wang SQ, Kopf AW, Koenig K, et al: Detection of melanomas in patients followed up with total cutaneous examinations, total cutaneous photography, and dermoscopy. J Am Acad Dermatol 50:15-20, 2004
8. Tucker MA, Fraser MC, Goldstein AM, et al: A natural history of MM and dysplastic nevi: An atlas of lesions in MM-prone families. Cancer 94:3192-209, 2002
9. Menzies SW, Gutenev A, Avramidis M, et al: Short-term digital surface microscopic monitoring of atypical or changing melanocytic lesions. Arch Dermatol 137:1583-1589, 2001
10. Kittler H, Binder M: Risks and benefits of sequential imaging of melanocytic skin lesions in patients with multiple atypical nevi. Arch Dermatol 137:1590-1595, 2001
11. Kelly JW, Yeatman JM, Regalia C, et al: A high incidence of MM found in patients with multiple dysplastic naevi by photographic surveillance. Med J Aust 167:191-194, 1997
12. Berwick M, Begg CB, Fine JA, et al: Screening for cutaneous MM by skin self-examination. J Natl Cancer Inst 88:17-23, 1996
13. Oliveria SA, Chau D, Christos PJ, et al: diagnostic accuracy of patients in performing skin self-examination and the impact of photography. Arch Dermatol 140:57-62, 2004
14. Feit NE, Dusza SW, Marghoob AA: MM detected with the aid of total cutaneous photography. Br J Dermatol 150:706-714, 2004
15. Malvehy J, Puig S: Follow-up of melanocytic lesions with digital total-body photography and digital dermoscopy: A two-step method. Clin Dermatol 20:297-304, 2002
16. Argenziano G, Puig S, Zalaudek L, et al: Dermoscopy improves accuracy of primary care physicians to triage lesions suggestive of skin tumors. J Clin Oncol 24:1877-1882, 2006
17. Scope A, Benvenuto-Andrade C, Agero AC, et al: Correlation of dermoscopic structures of melanocytic lesions to reflectance confocal microscopy. Arch Dermatol 143:176-185, 2007
18. Kittler H, Pehamberger H, Wolff K, et al: Diagnostic accuracy of dermoscopy. Lancet Oncol 3:159-165, 2002
19. Bafounta ML, Beauchet A, Aegerter P, et al: Is dermoscopy useful for the diagnosis of MM? Results of a meta-analysis using techniques adapted

to the evaluation of diagnostic tests. Arch Dermatol 137:1343-1350, 2001
20. Menzies SW, Zalaudek I: Why perform dermoscopy? The evidence for its role in the routine management of pigmented skin lesions. Arch Dermatol 142:1211-1212, 2006
21. Carli P, de Giorgi V, Chiarugi A, et al: Addition of dermoscopy to conventional naked-eye examination in MM screening: A randomized study. J Am Acad Dermatol 50:683-689, 2004
22. Carli P, De Giorgi V, Crocetti E, et al: Improvement of malignant/benign ratio in excised melanocytic lesions in the 'dermoscopy era': A retrospective study 1997-2001. Br J Dermatol 150:687-692, 2004
23. Pagnanellli G, Soyer HP, Argenziano G, et al: Diagnosis of pigmented skin lesions by dermoscopy: Web-based training improves diagnostic performance of non-experts. Br J Dermatol 148:698-702, 2003
24. Benvenuto-Andrade C, Dusza S, Hay J, et al: Level of confidence in diagnosis: Clinical examination versus dermoscopy examination. Dermatol Surg 32:738-744, 2006
25. Bauer J, Metzler G, Rassner G, et al: Dermascopy turn histopathologist's attention to the suspicious area in melanocytic lesions. Arch Dermatol 137:1338-1340, 2001
26. Kittler H, Guitera P, Riedl E, et al: Identification of clinically featureless incipient MM using sequential dermoscopy imaging. Arch Dermatol 142:1113-1119, 2006
27. Haenssle HA, Krueger U, Vente C, et al: Results from an observational trial: Digital epiluminescnce microscopy follow up of atypical nevi increases the sensitivity and the chance of success of conventional dermoscopy in detecting MM. J Invest Dermatol 126:980-985, 2006
28. Liu W, Dowling JP, Murray WK, et al: Rate of gowth in MM. Arch Dermatol 142:1551-1558, 2006
29. Golger A, Young DS, Ghazarian D, et al: Epidemiological features and prognostic factors of cutaneous head and neck MM: A population-based study. Arch Otolaryngol Head Neck Surg 133:442-447, 2007
30. Argenziano G, Zalaudek I, Ferrara G, et al: Dermoscopy features of melanoma incognito: Indications for biopsy. J Am Acad Dermatol 56: 508-513, 2007
31. Argenziano G, Scalvenzi M, Staibano S, et al: Dermatoscopic pitfalls in differentiating pigmented Spitz nevi from cutaneous melanomas. Br J Dermatol 141:788-793, 1999
32. Argenziano G, Zalaudek I, Corona R, et al: Vascular structures in skin tumors. Arch Dermatol 140:1485-1489, 2004
33. Bono A, Maurichi A, Moglia D, et al: Clinical and dermatoscopic diagnosis of early amelanotic MM. MM Res 11:491-494, 2001
34. Arrazola P, Mullani NA, Abamovits W: Dermlite II: An innovative portable instrument for dermoscopy without the need to immersion fluids. Skinmed 4:78-83, 2005
35. Benvenuto-Andrade C, Dusza SW, Agero CA, et al: Differences between polarized light dermoscopy and immersion contact dermoscopy for the evaluation of skin lesions. Arch Dermatol 143:329-338, 2007
36. Rajadhyaksha M, Gonzalez S, Zavislan JM, et al: In vivo confocal scanning laser microscopy of human skin, II: Advances in instrumentation and comparison with histology. J Invest Dermatol 113:293-303, 1999
37. Gonzalez S, Sackstein R, Anderson RR, et al: Real-time evidence in vivo leukocyte trafficking in human skin by reflectance confocal microscopy. J Invest Dermatol 117:384-386, 2001
38. New KC, Petroll WM, Boyde A, et al: In vivo imaging of human teeth and skin using real-time confocal microscopy. Scanning 13:369-372, 1991
39. Rajadhyaksha M: Confocal reflectance microscopy: diagnosis of skin cancer without biopsy? in Frontiers of Engineering. Washington, DC, National Academies Press, 1999, pp 24-33
40. Rajadhyaksha M, Grossman M, Esterowitz D, et al: In vivo confocal scanning laser microscopy of human Skin: Melanin provides strong contrast. J Invest Dermatol 104:946-952, 1995
41. Agasshi D, Anderson RR, Gonzalez S: Time-sequence histologic imaging of laser treated cherry angiomas using in vivo confocal microscopy. J Am Acad Dermatol 43:37-41, 2000
42. Pellacani G, Cesinaro AM, Seidenari S: In vivo assessment of melanocytic nests in nevi and MM by reflectance confocal microscopy. Mod Pathol 18:469-474, 2005
43. Pellecani G, Cesinaro AM, Seidenari S: Reflectance-mode confocal microscopy of the in vivo characterization of pagetoid melanocytosis in MM and nevi. J Invest Dermatol 25:532-537, 2005
44. Marghoob AA, Charles CA, Busam KJ, et al: In vivo confocal scanning laser microscopy of a series of congential melanocytic nevi suggestive of having developed malignant MM. Arch Dermatol 141:1401-1412, 2005
45. Pellacani G, Cesinaro A, Seidenari S: Reflectance-mode confocal microscopy of pigmented skin lesions-improvement in MM diagnostic specificity. J Am Acad Dermatol 53:979-985, 2005
46. Pellacani G, Cesinaro AM, Longo C, et al: Microscopic in vivo description of cellular architecture of dermoscopic pigment network in nevi and MM. Arch Dermatol 141:147-154, 2005
47. Greger A, Koller S, Weger W, et al: Sensitivity and specificity of confocal laser-scanning microscopy for in vivo diagnosis of malignant skin tumors. Cancer 107:193-200, 2006
48. Tannous ZS, Mihm MC, Flotte TJ, et al: In vivo examination of lentigo maligna and malignant MM in situ, lentigo maligna type, by near-infrared reflectance confocal microscopy: Comparison of in vivo confocal images with histologic sections. J Am Acad Dermatol 46:260-263, 2002
49. Busam KJ, Hester K, Charles C, et al: Detection of clinically amelanotic malignant MM and assessment of its margins by in vivo confocal scanning laser microscopy. Arch Dermatol 137:923-929, 2001
50. Curiel-Lewandrowski C, Williams CM, Swindells KJ, et al: Use of in vivo confocal microscopy in malignant MM: An aid in diagnosis and assessment of surgical and nonsurgical therapeutic approaches. Arch Dermatol 140: 1132-1227, 2004