Non-Invasive Imaging Techniques: Dermatoscopy and Confocal Microscopy Before a Biopsy

Relatively new tools can provide helpful information to support diagnosis and guide management strategies.

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Noninvasive imaging devices have emerged as powerful tools which increase clinical diagnostic accuracy and aid in the management of skin cancer. These tools allow for visualization of superficial and deep components of skin lesions. For a more superficial evaluation, the most widely used technique is dermatoscopy. Dermatoscopy involves the use of a dermatoscope, which is a magnifying device that illuminates and enlarges images in its view, allowing for the visualization of ultrastructural features not seen by the naked eye. For a deeper look into the skin, reflectance confocal microscopy (RCM) or confocal microscopy (CM) is an innovative tool that optically sections and illuminates skin based upon the refractive indices of cell structures, relying on melanin for contrast. CM images have cellular resolution and are comparable to histological sections.

When used together, dermatoscopy and CM can provide a more comprehensive understanding of lesions in the skin through both gross and cellular findings.

METHODS
A literature review was conducted on PubMed using the search term “confocal microscopy skin”, “dermoscopy”, and “dermatoscopy.” Related citations suggested by the search engine and citations from the suggested articles were also considered. Articles of all dates were considered but searches were limited to articles written in English.

RESULTS
Dermatoscopy. Dermatoscopy is a noninvasive technique that uses light and magnification to visualize morphological structures of the skin, from the epidermis to the superficial papillary dermis, that are not otherwise visible with the naked eye. Dermatoscopy is used as a diagnostic tool at the first level of clinical evaluation. Traditional dermatoscopes use nonpolarized light sources and are applied directly against the skin, using a fluid interface to make the skin surface more transparent. This allows the viewer to see both surface and subsurface structures in the skin. There are now commercially available dermatoscopes that use cross-polarized light, which allows visualization of subsurface structures without a liquid interface or direct skin contact.

Confocal microscopy. Reflectance confocal microscopy utilizes a laser and captures images at the cellular level throughout different layers of the skin. When used together, dermatoscopy and confocal microscopy have been shown to increase the sensitivity and specificity of diagnoses of pigmented lesions, thereby reducing biopsy and excision rates of benign lesions. These noninvasive tools have also been used to provide valuable information about the gross morphological and cellular features of a wide variety of skin diseases, in addition to skin cancer.

TAKE HOME TIPS
Dermatoscopy and confocal microscopy are noninvasive imaging techniques that have been developed to increase the clinical diagnostic accuracy in the management of pigmented skin lesions. Dermatoscopy, which utilizes a magnifying device, allows for the visualization of morphological structures of the skin from the epidermis to the papillary dermis. Reflectance confocal microscopy utilizes a laser and captures images at the cellular level throughout different layers of the skin. When used together, dermatoscopy and confocal microscopy have been shown to increase the sensitivity and specificity of diagnoses of pigmented lesions, thereby reducing biopsy and excision rates of benign lesions. These noninvasive tools have also been used to provide valuable information about the gross morphological and cellular features of a wide variety of skin diseases, in addition to skin cancer.
The original purpose of dermatoscopy was to assist in the evaluation of pigmented skin lesions, especially in the diagnosis of early melanoma. However, dermatoscopy is a valuable tool in the diagnosis of both pigmented and nonpigmented skin lesions, increasing the clinical diagnostic accuracy and improving physicians’ confidence in their diagnosis. Studies have shown that dermatoscopy is better than naked eye examination (NEE) alone at visualizing diagnostic submacroscopic morphological features of both pigmented and nonpigmented lesions. Dermatoscopy can improve the diagnosis of almost all pigmented lesions, including early melanoma, as well as an expanding variety of other lesions located in challenging sites, such as the nail apparatus and acral skin. Among nonmelanoma skin cancers (NMSCs), dermatoscopic features, such as vascular patterns, have been defined in the literature for nodular basal cell carcinomas (BCC), squamous cell carcinomas (SCC) and keratoacanthomas, which aid in the differentiation of equivocal lesions. The examination of vascular patterns is also useful in differentiating scalp psoriasis from seborrheic dermatitis and differentiating seborrheic keratoses from melanocytic lesions. In addition, dermatoscopy has improved the recognition of a growing number of skin conditions in general dermatology, including skin infections and infestations such as scabies, pediculosis, molluscum contagiosum, tungeniasis, and Tinea nigra.

Currently, dermatoscopy has different patterns of use by dermatologists in the United States and abroad. In a cross-sectional survey of all US fellows of the American Academy of Dermatology, 3,238 surveys were completed and returned from 8,501 eligible recipients. Less than half of respondents reported using dermatoscopy (48 percent). The remaining 52 percent of respondents reported a lack of training, a lack of interest, additional time required for examination, and a belief that it would not affect clinical decisions as the top reasons for not using dermatoscopy. Worldwide, approximately 3,500 clinicians from 110 different countries were members of the International Dermoscopy Society in 2009.

The most compelling evidence for the efficacy of dermatoscopy has been the documented improvement in diagnostic accuracy, sensitivity, and specificity in identifying melanomas. With higher specificity, there is an accompanying decrease in excision rates of benign lesions. In a meta-analysis of eight original studies, 328 melanomas and 1,865 mostly melanocytic benign pigmented skin lesions were examined with NEE and dermatoscopy. The sensitivity for dermatoscopic diagnosis of melanoma ranged from 0.75 to 0.96, and the specificity ranged from 0.79 to 0.98. Compared to NEE, dermatoscopy had a significantly higher discriminating power, with an estimated odds ratio of 76 (16 for NEE), and an estimated positive likelihood ratio of 9 (4 for NEE). In an analysis of 27 studies including 9,821 pigmented skin lesions, the diagnostic accuracy for melanoma improved by 49 percent compared to diagnoses made based on naked eye examination alone (log odds ratio of 4.0 vs. 2.7). However, the degree of experience of the observing physician had a significant effect on the diagnostic accuracy. Dermatoscopic examination by untrained observers was equivalent to clinical examination with an unaided eye.

Dermatoscopy also influences clinical practice by guiding management decisions. Ultimately, dermatoscopy can improve the ability to determine whether or not a lesion should undergo biopsy. In a randomized study of combined examination (naked eye and dermatoscopy) compared to naked eye examination alone, the combined approach resulted in a significant reduction in the percentage of patients referred for operation. In a study by van der Rhee, et al., 209 suspicious pigmented lesions in general dermatology clinics were studied to assess the impact of dermatoscopy on clinical management. Pre- and post-dermatoscopy diagnoses and management decisions of the lesions were made by dermatologists with experience using dermatoscopy. Fourteen of 209 lesions were histologically proven to be melanoma, which were all intended to be excised based on NEE alone. In all other lesions, dermatoscopy resulted in a nine percent reduction in the number of excisions. In another study assessing the impact of dermatoscopy on the diagnosis and management of suspicious lesions in high-risk patients (i.e. relatives from melanoma families), dermatoscopy was performed on 40 suspicious pigmented lesions, and pre- and post-dermatoscopy diagnoses and management decisions were compared. Dermatoscopy did not lead to any changes in diagnoses from melanoma to non-melanoma or vice versa. However, the use of dermatoscopy resulted in a change of management decisions in 37 percent of lesions. Before dermatoscopy, 24 lesions (49 percent) were intended for excision. However, in 14 cases, excision was abandoned and in four cases, excision was decided on after dermatoscopy. The use of dermatoscopy in high risk patients resulted in 42 percent fewer excisions, which increased diagnostic specificity significantly from 0.53 to 0.74.

Dermatoscopy also has important potential uses in teledermatology. Dermatoscopes can be used to capture images that can be shared by primary care physicians or physicians in rural settings through telemedicine with less time and lower costs. Teledermatoscopes have been demonstrated to result in...
relatively high concordance (91 percent) between face-to-face diagnoses and remote diagnoses. The accuracy of diagnosis was independent of the quality of the image, and was influenced by the difficulty of the lesion evaluated.14 In a multicenter study, 11 physicians with varying degrees of experience with dermatoscopy (six dermatologists, two dermatology residents, one oncologist, one internist, and one general practitioner) evaluated digital and dermatoscopic images of skin lesions. Forty-three pigmented skin lesions were evaluated, which included melanomas, melanocytic nevi, basal cell carcinomas, lentigines, seborrheic keratoses, and an angio-keratoma. Using teledermatoscopy, 85 percent of the diagnoses were correct, ranging from 77 percent to 95 percent. In comparison, face-to-face diagnosis is dependent on the expertise of the observing physician.15

The utility of dermatoscopy is dependent on the training and experience of the physician. Dermatoscopy is a technique that has grown to be accepted and incorporated into most dermatology training programs in the United States. In a survey of all accredited dermatology residency programs in 2002, 51 percent of respondents reported using dermatoscopy, for the specific purpose of examining skin lesions. The number of biopsies performed, and reducing patient anxiety. Thirty-eight percent of the chief residents reported receiving training in dermatoscopy during the residency program, and 45 percent anticipated that the use of dermatoscopy would continue to increase over the next five years.16 Beyond the specialty of dermatology, dermatoscopy may have particular potential clinical use for primary care physicians. Primary care physicians (PCP) are second to dermatologists in providing care for skin conditions. They continue to perform a significant proportion of skin-related procedures such as excisions and biopsies in the United States, or are required to appropriately triage suspicious lesions. Studies have shown that primary care physicians identify melanomas with less accuracy than dermatologists. However, one day of training in dermatoscopy can significantly increase the referral sensitivity without reducing the specificity when dermatoscopy is used to examine skin lesions. Histopathologic examination of equivocal lesions in one study reported that 23 malignant skin tumors were missed by PCPs performing naked eye examinations alone, whereas only six were missed by PCPs using dermatoscopy.17

There are several limitations to the use of dermatoscopy that should be considered. First, the use of dermatoscopy is limited to the identification of known, “classic” features. Early melanomas have been documented to be one of the more difficult types of skin lesions to identify. They may lack specific dermatoscopic features, and thus may be difficult to diagnose even with dermatoscopy. In a study comparing dermatoscopic features of melanocytic lesions, no dermatoscopic feature or pattern of features could be identified that could reliably differentiate between early melanomas and melanocytic nevi at the time of first presentation.18 However, other studies have shown that even among melanomas that are difficult to diagnose, dermatoscopy can still reveal subtle dermatoscopic clues that can help identify these lesions as melanomas.19

Additionally, more time is required to utilize this tool. In a study comparing skin examinations performed with and without dermatoscopy, skin examinations without dermatoscopy took an average of 70 seconds, while the use of dermatoscopy significantly increased the duration of the examination to 142 seconds. The additional time for dermatoscopy was directly proportional to the patient’s total lesion count. However, the entire exam did not exceed three minutes, which is a reasonable amount of time, considering that surveys of patient satisfaction have shown that the additional time spent may impart a positive effect on the patient satisfaction with their health care.20

Dermatoscopy is a valuable and convenient tool in routine clinical examinations. It allows trained physicians to quickly visualize submacroscopic features of the skin. However, Argenziano, et al. stress that even with dermatoscopy, patients must be evaluated as a whole rather than solely on morphological features observed with dermatoscopy. In a study of the management recommendations for patients with multiple atypical nevi, six experienced dermatoscopists provided management recommendations for a series of lesions based on dermatoscopic images alone, and then in the context of other nevi from the same patient (the comparative approach). In the first step of this study, morphological features alone were studied and excision recommendation rates ranged from 40-70 percent. In the second step, using the comparative approach, excision recommendation rates ranged from five to 29 percent. Two melanomas were included in the study and were correctly judged in both steps. The study concluded that, especially among patients with multiple nevi, evaluating equivocal lesions using the comparative approach resulted in a lower rate of excision recommendations compared to evaluating the lesion based on morphological structure alone.21

Confocal Microscopy. Reflectance confocal microscopy is a noninvasive imaging tool that captures cellular images of the skin. It offers the ability to view skin and its cellular structures in vivo, penetrating up to a depth of 200 μm.22 The mechanism behind the reflectance mode involves the emission of an infrared laser light through a lens onto the desired skin section. Various structures reflect the laser light back through an aperture and confocal planes of images are analyzed and assembled into digital black and white images.22 Melanin is the most refractive component of the skin and provides the bright white contrast seen in confocal images.2 Confocal microscopy shows
horizontal sections of skin at different depths beneath the surface (Figure 1), as well as vertical stacks, which allows for a three-dimensional analysis of skin lesions.23

The applications of CM in dermatology are far-reaching, ranging from its heavily-researched use in skin cancer diagnosis as well as many other novel uses. In the study of skin cancer, CM has considerable diagnostic accuracy. In a study of 42 consecutive patients, 50 lesions that were previously scheduled for excision were imaged using CM to assess the diagnostic accuracy. Of the 50 lesions, 13 were melanomas, 22 were benign nevi, nine were basal cell carcinomas, and 6 were squamous cell carcinomas. CM correctly identified 12 of the 13 melanomas with a sensitivity of 92 percent and a specificity of 75 percent, 19 of the 22 benign nevi with a sensitivity of 86 percent and a specificity of 95 percent, six of the nine BCCs with a sensitivity of 67 percent and a specificity of 100 percent, and correctly identified all six SCCs with a sensitivity of 100 percent and a specificity of 75 percent.23

Larger studies have been conducted to confirm the diagnostic accuracy of CM, particularly with melanocytic tumors. In a study of 117 melanocytic tumors, 27 were melanomas and 90 were benign. Five confocal observers had an average sensitivity of 88 percent and an overall sensitivity of 98 percent.24 In a study of 351 melanocytic lesions, 136 were melanomas and 215 were benign nevi. Two observers achieved a sensitivity of 92 percent and a specificity of 69 percent.25 A third study evaluating 125 melanocytic lesions composed of 88 melanocytic nevi and 37 melanomas which were all previously scheduled for excisions, confocal microscopy diagnosis yielded a sensitivity of 97 percent and a specificity of 83 percent. When confocal microscopy was combined with dermoscopy in this study,

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Figure 1. Confocal images at different depths of the skin. (A) Image of the stratum corneum layer of the epidermis (0-15 μm). (B) Image of the stratum granulosum of the epidermis (10-20 μm). (C) Image of the stratum basalis layer of the epidermis (40-130 μm). (D) Image of the papillary dermis (50-150 μm).
there were no misdiagnosed cases of melanoma when both tools were used.26

Confocal microscopy is also useful in the evaluation of non-melanoma skin cancer. In a study of 152 lesions, 100 percent sensitivity for the detection was basal cell carcinoma was achieved when two or more diagnostic criteria were present. When four or more of these criteria were present, sensitivity was 83 percent and specificity was 96 percent.27 In a study of the diagnostic accuracy of CM in the identification of actinic keratoses, 46 actinic keratoses and 10 control sites were imaged with confocal microscopy and analyzed by two observers. Upon analysis, the first observer identified 45 of 46 actinic keratoses accurately and the second observer identified all of the actinic keratoses accurately. Both observers identified all control sections of normal skin correctly.28 A study of 30 actinic keratoses and 30 control sites demonstrated an overall sensitivity of 93 percent and specificity of 88 percent in two observers.29

Novel uses for confocal microscopy have emerged in general dermatology. Confocal microscopy has recently been used to study burn healing. Twenty-four burn patients were imaged with confocal microscopy at 12, 36, and 72 hours after the burn. Based upon their activity within the first 72 hours after the burn, 18 burns were identified as healing, and six burns were identified as non-healing. Notable differences under confocal microscopy were seen between healing and non-healing burns. Microcirculation increased by 80 percent within the first 12 hours in healing burns, but only increased by 50 percent for non-healing burns. By 72 hours, microcirculation had decreased in the non-healing burns. Inflammatory cells were seen 72 hours post-burn in the non-healing group, while few were observed in the healing group. Information about burns within 72 hours from confocal microscopy may be a valuable tool for clinicians when determining treatment options.30 Confocal microscopy has also been used to study the efficacy of dermatologic treatments. In a study of the efficacy of cryotherapy, 10 superficial basal carcinomas were treated with two rounds of cryotherapy and imaged before treatment and then five hours, 24 hours, and three months after treatment. Five hours after treatment, all of the lesions showed signs of necrosis and blistering on confocal microscopy. Eight of the lesions in particular showed necrosis in the upper dermis. Twenty-four hours after treatment, all of the lesions showed signs of necrosis underneath the collagen bundles. After three months, tumor clearance was confirmed only in the eight lesions that demonstrated necrosis at the upper dermis five hours post-treatment.31

Like dermatoscopy, the interpretation of confocal microscopy images requires training. Studies have demonstrated that a brief educational intervention may have a significant impact on the diagnostic accuracy of unexperienced physicians. In one study assessing the accuracy of CM in the detection of basal cell carcinoma, four unexperienced readers (two dermatology residents and two dermatopathologists) evaluated the images. Readers had no prior experience in analysis of confocal images but received training in a 30-minute oral presentation in which 10 examples of normal skin and BCC were compared. To test diagnostic accuracy, each reader assessed three normal skin images and three images of BCC. One dermatopathologist and one resident also studied the various features of BCC in 120 images. When presented with 60 confocal images pairs of normal and cancerous skin, one resident and one dermatopathologist correctly identified all of the morphological features in the set, while the other resident and dermatopathologists only misidentified one set each.24,32

The applications of confocal microscopy in skin disease provide dermatologists with insight into cellular features of various lesions and conditions that have been previously undetected without invasive procedures. The multipurpose applications support the use of confocal microscopy as a tool in the evaluation of suspicious lesions and other skin conditions. While more studies are currently exploring novel uses of CM, many reports already support the diagnostic accuracy of confocal microscopy in skin cancer.25-29,32

CONCLUSION

Noninvasive imaging tools such as dermatoscopy and confocal microscopy aid physicians in the diagnosis and management of skin conditions. With an expanding aging population, skin disease is highly prevalent in the United States, with approximately one out of three people having one or more skin disease at any given time. The incidence of skin cancer has been climbing in recent years, which has led to higher levels of awareness among physicians and in the public alike. Although histologic examination remains the gold standard in the evaluation of skin pathology, there is a need for noninvasive imaging tools that can help detect melanoma early and also reduce the number of unnecessary excisions. With the combined use of both dermatoscopy and confocal microscopy, the goal is not only to prevent missing the diagnosis of skin cancer, but to identify it as early as possible.

Dermatoscopy and confocal microscopy are links between clinical examination and histopathological examination. Figure 2 demonstrates Dr. Rao’s approach to incorporate noninvasive tools in the management of pigmented lesions. Upon clinical presentation, single lesions that are atypical, have a history of change, or are particularly worrisome to the patient can be immediately indicated for biopsy. In patient presentations where there are either multiple lesions, the lesions are located in aesthetically significant areas, or biopsy is otherwise contraindicated, dermatoscopy should be utilized. Thus, on the first level of clinical examination, naked eye examination and dermatoscopy allow the physician to observe the morphological features of the lesion in vivo. On dermatoscopy, identify-
ing known malignant or benign patterns further refines the decision to biopsy or not. For equivocal lesions with unknown dermatoscopic patterns, confocal microscopy is a second-level approach to enhance the diagnostic accuracy of difficult melanocytic neoplasms before excision. Similarly, identifying known malignant and benign features guide the physician, while indeterminate patterns can be watched closely through short-term follow-up (Figure 2). In its current form, RCM is best suited as an adjuvant tool after initial dermatoscopic screening, rather than a primary diagnostic tool.25

When used together by clinicians with appropriate knowledge, training, and experience, dermatoscopy and confocal microscopy are noninvasive tools that allow dermatologists to gather pertinent information about the gross morphological and cellular features of the lesion, thus improving diagnostic accuracy before deciding to biopsy. 

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