DERMATOLOGY PRACTICAL & CONCEPTUAL
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Abstracts from the Joint Meeting of the International Society for Digital Imaging of the Skin (ISDIS), the International Confocal Group (ICG), and the International Dermoscopy Society (IDS) in conjunction with the 2014 American Academy of Dermatology, March 22, 2014, Denver, CO, USA

Citation: Abstracts from the Joint Meeting of the International Society for Digital Imaging of the Skin (ISDIS), the International Confocal Group (ICG), and the International Dermoscopy Society (IDS) in conjunction with the 2014 American Academy of Dermatology, March 22, 2014, Denver, CO, USA. Dermatol Pract Concept. 2014;4(3):23. http://dx.doi.org/10.5826/dpc.0403a23

Published: July 31, 2014

Impact of in vivo reflectance confocal microscopy on the number needed to treat melanoma in doubtful lesions

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Dermoscopy is a non-invasive imaging technique that improves accuracy in the diagnosis of melanoma. It has been associated with a reduction in the false-positive detection rate and a subsequent decrease in unnecessary excisions. *In vivo* confocal microscopy is also a non-invasive technique which allows the examination of the skin at cellular resolution; its diagnostic accuracy has been evaluated by several studies concluding that the use of this novel technique provides a significant improvement in melanoma detection.

The number-needed-to-treat (NNT) ratio is an effective method for measuring accuracy in melanoma detection. The aim of the present study was to assess the impact of RCM analysis on the number of dermoscopically equivocal pigmented lesions excised for every melanoma, in a clinical setting.

Three hundred and forty-three consecutive patients presenting with dermoscopically equivocal lesions, assumed to be melanocytic neoplasms based on clinical and dermoscopic features, were prospectively enrolled. Dermoscopy and confocal microscopy diagnosis were made by dermatologists with expertise in both techniques. Histopathological assessment was considered as the reference standard. The main outcome was NNT, calculated as the proportion of dermoscopically and RCM equivocal lesions excised for every melanoma. Secondary outcomes included sensitivity, specificity, positive predictive value and negative predictive value of each technique for diagnosing melanoma.

Results: Dermoscopy alone obtained a hypothetical NNT of 3.73; the combination of dermoscopy and RCM identified 264 equivocal lesions that qualified for excision, 92 of which were confirmed to be a melanoma, resulting in an NNT of 2.87, whereas the analysis of RCM images classified 103 lesions as melanoma, with a consequent NNT of 1.12. The difference in NNT was statistically significant between the three groups ($P < 00001$). There was no significant improvement in sensitivity when comparing the combination of dermoscopy and RCM with RCM alone (94.6% vs. 97.8%; $P = 0.043$). However, the differences between specificities were statistically significant ($P < 1x10^{6}$), favouring RCM alone.

Conclusions: The addition of RCM analysis to dermoscopy reduces unnecessary excisions with high diagnostic accuracy and could be a mean for reducing the economic impact associated with the management of skin cancer.

Eruptive facial post inflammatory lentigo-like reaction: clinical and dermatoscopic features

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We present 8 cases of an unusual presentation of a fixed drug eruption (FDE) mimicking a clinical lentigo on the face. Since Brocq's first and very detailed description of FDE, we have not found any description in the literature of the special form of FDE described herein. The sudden appearance of a lentigo on the face after the ingestion of NSAIDs can mimic other forms of lentigo and can easily be misdiagnosed. Most of our patients presenting with this form of post inflammatory lentigo-like reaction (PILLR) have a clinical lentigo like appearance on the face from the beginning. The appearance of these PILLR usually lack strong local symptoms such as burning and itching, demonstrating that this is mainly a subclinical form of FDE that later became a clinical PILLR. Only after specific questioning about mild burning or itching, required for the medical records, did patients remember having these symptoms.

All of them had a history of previous NSAIDs intake, specifically of ibuprofen or ketoprofen.

The majority of the patients had a PILLR with different intensities of brown clinical color upon first clinical examination; with the exception of two patients whose PILLR had also a pink color in the acute phase (Fig 1). The clinical appearance of a PILLR generally persisted for more than six months.

Under dermatoscopy, the lesions were generally asymmetric and the borders were ill-defined. All cases presented a brown uniform background color of different shades—from light brown to dark brown—that produced a pseudonetwork. In all patients a light pink area due to vessels arranged as red dots or short telangiectatic vessels accompanied the brown pseudonetwork. Brown and/or brown-gray dots also distributed randomly or in focal areas of the lesion generated a dermatoscopic granular pattern. In those patients with darker skin, an annular granular pattern was observed in focal areas along symmetric follicular openings.

The pink color present under dermoscopy (as the result of vessels associated with inflammation) is a strong indicator for a PILLR diagnosis and is not found in the dermatoscopy of other forms of lentigo. The histopathologic analysis of PILLR displays features of a mild form of FDE.

Deconstructing Skin: RCM and FCM interpretation with quantitative image analysis tools

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Most skin cancers originate at and spread from the dermal epidermal junction. Currently, biopsy followed by histology is the "gold standard." However, this is an invasive procedure, which is painful, costly and time consuming. Moreover, statistics show that, depending on the setting, up to 80% of these biopsies may turn out to be benign. With the aid of new imaging technologies, lesions may be diagnosed non-invasively and the number of the biopsies reduced [1]. Reflectance Confocal Microscopy (RCM) is one these technologies, which is proven to be highly sensitive and specific in non-invasive diagnoses of melanomas [2,3] and basal cell carcinomas [4,5] with cellular-level resolution (0.5-1 um) and optical sectioning (1-3 um) capabilities. RCM provides images of enface sections down to the papillary dermis, which is often the depth that clinicians wish to examine. However, the current practice in RCM based diagnosis relies on visual examination, and therefore is subjective. In many cases, visually analyzing RCM images is more challenging compared to hematoxylin and eosin (H&E) stained histology, since the only source of contrast is reflectance (leading to gray scale images) contrary to the color contrast (purple and pink colors) in histology. Moreover, due to speckle noise and optical aberrations, the image quality decreases as the depth increases. Therefore, recognition tasks that are simple in histology can be challenging in RCM images. Currently, only a relatively small group of "early adopter" clinicians can read and analyze these images reliably. Training novice readers requires substantial effort and time and is currently a barrier against wider adoption of this technology. In order to address this need, machine learning based methods for quantitative analyses may be utilized.

In this study, the development of tools such as automated dermal epidermal junction delineation and video-mosaicing are reported. In the first scenario, the problem of finding the dermal epidermal junction (DEJ), which is a trivial task in H&E stained histology but not in RCM images is addressed. This problem is particularly important because, most of the time, clinicians make their diagnostic decision using mosaics of RCM images collected at or around the DEJ level. In current practice, DEJ level is determined by the clinicians in a subjective manner, by going back and forth between the RCM images collected at different depths and examining

them. Standardization of this procedure by automatically delineating the DEJ level in a quantitative manner will lead to the accuracy and repeatability of both image acquisition procedure and RCM based diagnosis. In order to automate DEJ delineation, we developed 2 algorithms, one for highly-pigmented (type > III) and another for lightly pigmented (type < III) skin types, as they have different reflectance characteristics due to their varying melanin content. In stacks of dark skin, the algorithm aims to locate highly reflective basal cells at the DEJ level using an order statistics based filtering approach. In lightly pigmented skin, as the pigmentation level is lower, the basal cells are not bright enough to the detected reliably. In this case, we benefit from the fact that, blurring occurs in RCM images of deeper levels of skin, especially below the DEJ (due to optical aberrations). We model this phenomenon using a multi scale entropy filtering based method, and delineate the DEJ using this model. We tested the proposed DEJ delineation algorithms on 16 highly pigmented and 12 lightly pigmented skin stacks and compared our results against manual segmentation of expert readers. The algorithms can delineate DEJ with a mean ±std of 7.5±5 um in highly pigmented skin and 29±5.4 um in lightly pigmented skin.

In another scenario, we showed the feasibility of creating mosaics out of RCM videos collected at a given level of skin, so called video-mosaicing[6]. Video-mosaicing provides a tool for rapidly and adaptively imaging over large areas of skin which can be useful for examination of larger areas around dermal-epidermal and various other application such as delineating margins of lentigo maligna melanoma to guide surgical excision or non-melanoma skin cancer margins to guide Mohs surgery. In our study, we showed that if (i) there is 25-50% overlap between consecutive frames and (ii) the imaging depth is kept constant, it is possible to convert these videos into high-quality mosaics of the imaged area. For this purpose we developed a computer program that can first find the identification tag in the video, crop out that region automatically and extract individual frames of the RCM video. Then, we use freely available software (ICE, Microsoft) to stitch and blend the consecutive frames into a mosaic. We evaluated the proposed algorithm on videos of non-melanoma margins in Mohs surgical wounds, lentigo maligna margins, malignant melanoma in situ, seborrheic keratosis, and benign lesions. A sample case of "malignant melanoma in situ" is presented in Figure 1. Several diagnostically-significant structures, such as atypical epidermal cells, epidermal disarray, perifollicular infiltration, roundish, dendritic, and pleomorphic pagetoid cells, dilated blood vessels and meshwork pattern with atypical cells can be clearly be identified in the resulting videomosaic. The results of this study suggest that in principle, a coverage rate of ~240-360 mm^2/min is within reach for any confocal microscope with configuration similar to that (1 mm x 1mm FOV, ~ 8 frames/second) of the Vivascope 3000. Thus, video-mosaicing technology has the potential for much faster imaging of large areas compared to the current commercially-available RCM mosaicing approach, which typically images at ~14 mm2/min. Moreover, it enables the clinician to cover areas with any desired shape and along any desired path that may be determined real-time during acquisition.

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Management of BCC: is there a place for dermoscopy?

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Following the first descriptions of the dermatoscopic pattern of basal cell carcinoma (BCC) that go back to the very early years of dermatoscopy, the list of dermatoscopic criteria associated with BCC has been several times updated and renewed. Up to date, the usefulness of dermatoscopy in differentiating pigmented and non-pigmented BCC from other skin tumors has been extensively demonstrated. In addition to its well-documented value in improving the diagnosis, dermatoscopy continuously gains an essential role in the management of BCC.

Dermatoscopy for choosing the appropriate treatment modality

In our era, the therapeutic armamentarium of clinicians for BCC includes several surgical methods as well as non-surgical modalities. The choice of the appropriate treatment depends on several factors including the histopathologic subtype, the presence of pigmentation or ulceration, the tumor depth, the anatomical site and the presence of residual disease or recurrence. Dermatoscopy has been shown to provide valuable information for several of the aforementioned parameters.

The histopathologic subtype is the most crucial factor influencing the treatment choice for BCC. In the recent years, sBCC has been shown to respond perfectly to non-ablative treatments such as imiquimod or photodynamic therapy, prompting experts to recommend the latter modalities as first-line therapeutic options for this subtype. In contrast, conventional or Mohs surgery is considered the choice treatment for nodular, infiltrative and sclerodermiform subtypes, while non-surgical treatments are much less effective.

A recent study investigated the accuracy of dermatoscopic criteria for discriminating superficial from the other subtypes of BCC. This is particularly relevant in clinical practice, since the possible misinterpretation of a nodular or infiltrate tumor as superficial BCC could lead the clinician to the inappropriate choice of a non-surgical treatment modality. According to the results of the latter study, the presence of short fine telangiectasia, multiple small erosions and structures corresponding to dermo-epidermal pigmentation predict the superficial subtype. In contrast, detection of ovoid nests should lead clinicians to exclude the diagnosis of superficial BCC, while arborizing vessels and large ulcerations are also suggestive of nodular, sclerodermiform or infiltrative tumors.

The presence of pigmentation is not routinely reported in histopathologic reports, since in the past it was not considered to influence the management and prognosis of the tumor. However, the use of PDT in BCC treatment restored the importance of pigmentation, since its presence was shown to influence the tumor's response. In detail, case series studies reported a poor response of pigmented BCC to PDT, compared to non-pigmented variants (14% versus 62-100%). The low efficacy of PDT in pigmented tumors has been attributed to melanin, which appears to act as a competitive light-absorbing pigment, decreasing response rates.

Effectively, the presence of clinically undetectable pigmentation might represent a diagnostic pitfall for clinicians, forcing them to apply an ineffective treatment on a subset of BCCs. This problem seems to be, at least partially, solved by the application of dermatoscopy, which was recently shown to reveal clinically undetectable pigmentation in approximately 30% of macroscopically non-pigmented BCCs, enhancing clinicians to better select tumors potentially sensitive to PDT and minimizing treatment failures.

Dermatoscopy for assessing excision margins

Dermatoscopy, by providing a more accurate assessment of the true extension of the tumor, allows a more precise estimation of the required surgical margins, helping to minimize the recurrence rate. The discrimination of BCC vessels from the dermal plexus vasculature of the surrounding healthy skin can be based on the blurred appearance and dark red-to-purple color of the surrounding sun-damaged skin, in contrast to the bright-red and focused vessels of the tumor. However, while the diagnostic significance of pigmented structures is unquestionable, the usefulness of vascular structures in defining the surgical margins is controversial. It has been suggested that arborizing vessels do not directly correspond to BCC cells, but represent feeding vessels of the tumor and may extend also to the perilesional skin. Subsequently, if the extension of vessels is used to define the excision margins, there is the risk of unnecessarily removing healthy skin surrounding the BCC. Although the latter hypothesis seems reasonable, it was supported by only one published case and, accordingly, the question whether vascular structures should be considered for defining surgical margins of BCC remains to be further elucidated.

Dermatoscopy for monitoring response to non-ablative treatments

A common problem associated with non-ablative modalities is the post-treatment evaluation, since at the end of a treatment cycle, the clinical morphology of the lesion often does not allow a reliable estimation of the possible presence of residual disease.

Dermatoscopy has the potential to improve the post-treatment evaluation of BCC following non-ablative procedures, minimizing therefore the risks of under- or over-treatment of BCC. Specifically, the disappearance of the dermatoscopic criteria of BCC after treatment has been shown to accurately predict histopathologic clearance, while the persistence of some BCC criteria correlates well with the presence of residual disease. According to the results of a recent study, the presence of arborizing vessels, ulceration or pigmented structures (e.g., blue-gray ovoid nests and maple leaf-like areas) accurately predicts residual disease, and should prompt the clinician to continue the treatment. Instead, red/white structureless areas and/or superficial fine telangiectasia might represent equivocal features, since they do not always correspond to residual disease. Effectively, detection of the latter criteria warrants close monitoring to recognize a possible recurrence of the BCC.

Diagnosis of basal cell carcinoma with dermoscopy and reflectance confocal microscopy as the basis for direct referral to definitive surgery

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Background: In usual practice, the diagnosis of a suspected basal cell carcinoma (BCC) is typically confirmed by biopsy of the suspected lesion, followed by the histopathologic evaluation of tissue specimens via light microscopy, prior to referral to surgery. A physician's presumptive diagnosis of BCC can be enhanced by identifying dermoscopic features typical for BCC. Reflectance confocal microscopy (RCM) is also useful for diagnosis of BCC. It is conceivable a presumptive diagnosis of BCC supported by dermoscopic and RCM features could circumvent the need for biopsy prior to surgery, with confirmation of the diagnosis performed on the surgical specimen.

Objective: To investigate the feasibility of bypassing biopsy of suspected BCC and proceeding directly to excision or Mohs surgery based on dermoscopic features alone, as well as when combined with RCM. In addition, we sought to compare the diagnostic accuracy for BCC based on prior RCM experience.

Methods: Potential study subjects were identified during the routine office visit by the presence of one or more lesions for which BCC was suspected, thus warranting a biopsy. Clinical, dermoscopic and RCM images were obtained prior to biopsy. Eight clinicians with varying levels of expertise, each blinded to the histopathologic findings, individually interpreted the clinical, dermoscopic and RCM images. Based on these interpretations, the clinicians chose between 4 hypothetical options: definite BCC (willing to send for definitive treatment without biopsy), other malignancy (perform biopsy for diagnosis), uncertain diagnosis (perform biopsy), and benign (do not biopsy). The choice decisions were made based on dermoscopy alone and subsequently on dermoscopy supplemented by RCM.

Results: Of the 100 suspected lesions enrolled, 90 were verified as BCC on histopathology. The pooled sensitivity for direct referral to definitive surgery without biopsy was 67.59% for dermoscopy alone. Adding RCM imaging increased the pooled sensitivity for direct referral to surgery to 76.53%. For the diagnostic decision to refer for treatment without biopsy, the pooled positive predictive value was 96.97% for dermoscopy alone and 98.64% for dermoscopy plus RCM. The sensitivities were generally higher for dermoscopy alone as the level of experience increased, although with a sacrifice to specificity.

Limitations: Actual patient management was not affected in this study. Physician behavior might be different if bona fide referrals were actually being made. The interpretations were made on image evaluation alone rather than at bedside, which might enhance accuracy.

Conclusions: Dermoscopy provides a high positive predictive value for BCC diagnosis. The addition of RCM to dermoscopy increases diagnostic sensitivity. Based on this study, from the standpoint of cost-effectiveness and patient convenience, dermoscopy and dermoscopy with RCM could be acceptable for direct-referral-to-surgery clinical decisions.

What's new in the diagnosis of LM?

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The term lentigo maligna (LM) refers to melanoma in situ arising on chronically sun-damaged skin with a flattened dermal-epidermal junction. It most commonly arises on the face although it is not limited to this anatomic region. Little is currently known about the influence of age, gender and topography on the clinical and dermoscopic variability of LM. Therefore, we retrospectively collected all consecutive cases of histopathologically proven facial and extra-facial LM diagnosed between January 2012 and January 2013 at 4 academic skin cancer clinics in France, Italy, Serbia and USA. The frequency of clinical and dermoscopic features of 201 cases of LM from 200 patients were assessed in correlation to specific anatomic sub-sites, patient's age and gender. Most cases were located on the face, with the cheeks being the most commonly affected sub-site. Location on the cheek was significantly associated with female gender compared to all other sub-sites. Dermoscopically, gray color irrespective of a specific pattern, was the most prevalent finding. The knowledge about the age, gender and site-related clinical features of LM associated with dermoscopic-gray colour may enhance the clinical recognition of LM.

The elephant study

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Background: Teaching dermatoscopy, or any other morphologic method, relies on two different approaches: a logical and a heuristic method. With the first, single elements are evaluated and results deducted to reach a decision; with the second, overall appearance is being rated and compared to other instances observed before. Previous studies in the field of dermatology imply that a heuristic method may perform better when compared to strict algorithms such as the ABCD-rule when applied by lay people. It is not known whether in dermatoscopy comparing a heuristic to a more detailed logic teaching for medical students has any difference.

Aim: To compare the efficacy of two different teaching methods in regard to dermatoscopy.

Methods: Medical students without prior contact to dermatoscopy were shown 50 lesions consisting of melanomas, nevi, basal cell carcinomas, seborrheic keratoses, dermatofibromas and benign vascular lesions and asked to diagnose and rate for chance of malignancy every lesion. Afterwards the students were split into two groups and received either a logic or heuristic teaching within one hour. Afterwards they were asked to do the same assessment of 50 lesions as in the beginning. Diagnostic values as well as diagnostic accuracy (for malignancy) as measured by the AUC of ROC curves were compared.

Results: Diagnostic accuracy improved by 0.21 ($p<0.001$) and 0.19 ($p<0.001$) in the heuristic and logic group respectively after the teaching, there was no difference between the two groups ($p=0.585$). Percent of correct diagnoses increased similarly by +32.9% ($p<0.001$) and +35.7% ($p<0.001$) without difference between the groups ($p=0.451$).

Conclusion: Only one hour of teaching is sufficient to largely improve diagnostic-dermatoscopic abilities of medical students. There is no significant difference in increase of diagnostic accuracy between teaching logic or heuristic when assessing classic dermatoscopic appearances of common lesions.