Recognizing the benefits and pitfalls of reflectance confocal microscopy in melanoma diagnosis

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The incidence of melanoma has been on the rise for the last several decades, with a current US lifetime risk of developing melanoma estimated as 1 in every 60 individuals [1]. The key to preventing death from melanoma is the early detection of this cancer, at a stage where surgical excision is curative. However, in attempt to diagnose melanoma early, physicians are also removing many benign lesions, most of these being melanocytic nevi. Recognizing the benefits and pitfalls of reflectance confocal microscopy in melanoma diagnosis

The pursuit to improve our clinical sensitivity for melanoma diagnosis, while minimizing unnecessary skin biopsies, has led to the development of skin imaging techniques. Among recent non-invasive imaging modalities, reflectance confocal microscopy (RCM) stands out as particularly promising since it offers bedside imaging at cellular-level resolution. Stevenson and coauthors [2] have reported in Dermatology Practical & Conceptual on a systematic review of the diagnostic accuracy of RCM for melanoma diagnosis. They have identified five publications, including a total of about 900 lesions, a third of which were melanomas; most of these lesions were reportedly equivocal for diagnosis, clinically and dermatoscopically. Based on these studies, the pooled sensitivity for melanoma diagnosis using RCM is 93% (range 91%-97%) and specificity is 76% (range 68%-86%). While the study by Stevenson et al [2] did not address the exact contribution of RCM as an add-on test to dermatoscopy, the aforementioned data suggests that RCM can indeed increase diagnostic accuracy beyond clinical and dermatoscopic examination.

To simulate the added contribution of RCM to dermatoscopy, Stevenson et al [2] took a hypothetical case of 1000 dermatoscopically equivocal skin lesions, and based on the previously reported benign to malignant ratio of 4:1 for experts' diagnosis of melanoma [3], they assume a ratio of 800 benign lesions to 200 melanomas. They estimate that RCM will prevent the unnecessary excision of 608 benign lesions that would be diagnosed as benign based on RCM, reflecting the specificity of 76%. If we were to formulate the best indications for using RCM as an add-on test to dermatoscopy, we would need to better point-out which lesions are included in this group of 608 benign lesions that would be diagnosed as benign based on RCM, reflecting the specificity of 76%. If we were to formulate the best indications for using RCM as an add-on test to dermatoscopy, we would need to better point-out which lesions are included in this group of 608 benign lesions that are dermatoscopically equivocal, but RCM negative. In this editorial, we can only attest to our own impression and experience, as well as some literature reports, that this group of lesions could encompass the following examples:
(1) nevi with irregular pigment pattern (e.g., irregular network, complex pattern) on dermatoscopy showing a regular pattern (e.g., ringed or meshwork patterns) on RCM (Figures 1, 2);

(2) nevi with a hyperpigmented structureless pattern on dermatoscopy that display on RCM a cobblestone pattern of the epidermis (reflecting pigmented keratinocytes at the basal and suprabasal epidermis) or a dense infiltrate of melanophages in the dermis;

(3) a dermatoscopically-equivocal lesion on sun-damaged skin with a differential diagnosis between solar lentigo and melanoma on sun-damaged skin, that presents a straightforward pattern of solar lentigo on RCM, without any findings concerning for melanoma;

(4) a pink macule revealing only a vascular pattern on dermatoscopy, while RCM demonstrates a straightforward pattern of nevus;

(5) a macule or patch displaying granularity or blue-gray hue on dermatoscopy, while showing on RCM features of lichen planus-like keratosis with melanophages and remnants of solar lentigo, in the absence of suspicious findings for melanoma [4];

(6) recurrent pigmentation in a scar, whereby RCM helps discriminate between a benign reactive pigmentation and an atypical melanocytic proliferation which would require a biopsy to exclude melanoma [5].

However, there is also a “price” associated with overriding dermatoscopic concern with RCM-based diagnosis. In the
still be strongly considered for digital dermatoscopic monitoring. In contrast, for nodular lesions a dichotomous decision, biopsy or not, should always be obtained; nodular lesions that do not show clear-cut benign findings on RCM in a way that correlates well and accounts for the dermatoscopically-concerning findings, should be strongly considered for biopsy. Finally, in the simulated scenario discussed by Stevenson et al [2] among the 200 melanomas that are deemed for excision based on the dermatoscopic impression, 14 melanomas may be misdiagnosed as benign based on the RCM findings, reflecting an imperfect sensitivity of 93%. If we were to improve in recognizing the pitfalls of RCM, we would need to identify recurring patterns among these 14 melanomas. Again, based on personal experience and literature reports, here are some potential examples of RCM-false negative melanomas: (1) nodular melanoma associated with hyperkeratosis or ulceration [6]; (2) fully ulcerated melanoma, a scenario where RCM should not be used, since secondary surface changes (e.g., blood, scale-crust) can obscure diagnostic findings; (3) nevoid type melanoma consisting cytologically of mostly of small-melanocytes [7]; and (4) melanoma in situ showing on RCM only focally suspicious findings for melanoma, while displaying equivocal reticular pattern on dermatoscopy (Figure 3). We also need to develop strategies to minimize the rate of RCM false-negative melanomas. As a general rule, good agreement between clinical, dermatoscopic and RCM findings should be reached to minimize the risk of missing melanomas. We need to remember that RCM is an adjunct test that should be integrated with other diagnostic data. In this regard, there is a difference between flat and nodular equivocal lesions. Flat lesions with significant clinical and dermatoscopic suspicion that are diagnosed as benign based on RCM imaging, should estimation by Stevenson et al [2] among the 200 melanomas that are deemed for excision based on the dermatoscopic impression, 14 melanomas may be misdiagnosed as benign based on the RCM findings, reflecting an imperfect sensitivity of 93%. If we were to improve in recognizing the pitfalls of RCM, we would need to identify recurring patterns among these 14 melanomas. Again, based on personal experience and literature reports, here are some potential examples of RCM-false negative melanomas: (1) nodular melanoma associated with hyperkeratosis or ulceration [6]; (2) fully ulcerated melanoma, a scenario where RCM should not be used, since secondary surface changes (e.g., blood, scale-crust) can obscure diagnostic findings; (3) nevoid type melanoma consisting cytologically of mostly of small-melanocytes [7]; and (4) melanoma in situ showing on RCM only focally suspicious findings for melanoma, while displaying equivocal reticular pattern on dermatoscopy (Figure 3). We also need to develop strategies to minimize the rate of RCM false-negative melanomas. As a general rule, good agreement between clinical, dermatoscopic and RCM findings should be reached to minimize the risk of missing melanomas. We need to remember that RCM is an adjunct test that should be integrated with other diagnostic data. In this regard, there is a difference between flat and nodular equivocal lesions. Flat lesions with significant clinical and dermatoscopic suspicion that are diagnosed as benign based on RCM imaging, should
RCM shows features that are highly suspicious for melanoma (Figure 5) [10].

In conclusion, RCM is rapidly becoming an important add-on tool in the armamentarium of dermatologists who screen patients for skin cancer. Incorporating RCM as a diagnostic adjunct can increase specificity of melanoma diagnosis. However, we need to study more extensively the indications for using RCM, and equally importantly, the limitations of RCM.
References