Diagnostic Accuracy of Reflectance Confocal Microscopy for Diagnosis of Skin Lesions

An Update

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Context.—Histopathology is the current standard to diagnose skin disease. However, biopsy may not always be feasible, such as in patients with multiple nevi, a patient with a lesion on an aesthetically significant site, or in children. Recently, noninvasive techniques, including reflectance confocal microscopy (RCM), optical coherence tomography, and Raman spectroscopy, have enabled dermatologists to manage skin lesions in real time without the need for biopsy.

Objective.—To report the updated diagnostic accuracy of RCM for equivocal skin lesions.

Design.—In this study, we retrospectively reviewed our data of clinically suspicious lesions from 2010 to 2017 that were evaluated by RCM.

Results.—Our results showed an overall sensitivity of 98.2% and specificity of 99.8%.

Conclusions.—In conclusion, RCM is a noninvasive real-time tool with the potential to diagnose skin lesions with high accuracy and without biopsy.

Histopathology is the current standard to diagnose skin disease. However, biopsy may not always be feasible, such as in patients with multiple nevi, a patient with a lesion on an aesthetically significant site, or in children. Biopsy also has associated complications, including bleeding, infection, or scarring. Recently, noninvasive techniques, including reflectance confocal microscopy (RCM), optical coherence tomography (OCT), and Raman spectroscopy, have enabled dermatologists to manage skin lesions in real time without the need for biopsy. Reflectance confocal microscopy and OCT are already in use in clinical practice. Optical coherence tomography has been used for the diagnosis, treatment, delineation, and monitoring of nonmelanoma skin cancer, specifically basal cell carcinoma.

Moreover, recent substantial technical advances in Raman spectroscopy have enabled the in vivo application of this technique. Reflectance confocal microscopy is a US Food and Drug Administration (FDA)–approved device (since 2008) that is used to supplement the bedside management of skin lesions, such as skin cancers and inflammatory processes. More recently, RCM has proven beneficial in distinguishing benign from malignant melanocytic lesions, lentigo, basal cell carcinoma, and squamous cell carcinoma. Reflectance confocal microscopy may also help in monitoring treatment response for skin inflammation in lupus erythematosus, lichen planus, psoriasis, herpes, and more. Reflectance confocal microscopy, because of its high cellular resolution and ease of use in practice, has gained more popularity than other in vivo devices.

Reflectance confocal microscopy is a laser device (830 nm) that enables visualization of skin layers to a depth of 250 to 300 μm. The black-and-white confocal images have almost the same resolution as traditional hematoxylin-eosin histology slides. The aim of this study is to report the updated diagnostic accuracy of RCM for equivocal skin lesions.

MATERIALS AND METHODS

We retrospectively reviewed our data of clinically suspicious lesions from 2010 to 2017 that were evaluated by RCM. These data were stored and transferred via Vivianet (Balwyn, Australia), a Health Insurance Portability and Accountability Act (HIPAA)–compliant, cloud-based secure server.

The patient data included in this study were from 3 private general dermatology clinics based in New York, New Jersey, and California. The confocal expert reader in this study used a Vivianet reading station in the New York office. The expert reader is a physician and a fellow of the American Academy of Dermatology. Patient age, location of lesion, clinical impression, confocal microscopy diagnosis by a trained confocal specialist (confocal training of more than 10 years), histology diagnosis, and patient follow-up of lesions determined to be benign were recorded. In all cases, confocal microscopy was performed by a confocal scanning laser microscope (Vivascope 1500i, CaliberID, Rochester, New York). A preliminary diagnosis was based on the dermoscopic image and confocal microscopy evaluation. Patients included in

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this study had skin types I to VI according to the Fitzpatrick classification scale. An increased number of melanosomes in dark skin corresponds to increased brightness on RCM when compared to fair skin. However, the brightness of interpapillary spinous and upper spinous keratinocytes is not necessarily influenced by skin type. Diagnosis should not be affected by phototype when interpreted by an expert reader.

Lesions were excluded from the data if the patient was lost to follow-up after RCM diagnosis, if the lesion was determined to be atypical on RCM but not removed because of patient preference, and if RCM was not performed on a given lesion. A true-positive was defined as RCM diagnosis of malignancy or atypia with histologic confirmation; a false-positive was defined as RCM diagnosis of malignancy or atypia with contradicting histologic outcomes; a true-negative was defined as RCM diagnosis of benign lesion with the lesion remaining the same during at least 1 year; and a false-negative was determined as RCM diagnosis of benign lesion with the lesion changing within 1 year and requiring biopsy or histology showing malignancy or atypia.

**Statistics**

Statistical analysis was performed to calculate sensitivity and specificity using SPSS (IBM, Armonk, New York). The sensitivity numerator included the total number of malignant lesions (malignant melanoma, lentigo maligna, squamous cell carcinoma, and basal cell carcinoma) and severely atypical lesions (nevus with severe atypia) that RCM diagnosis recommended for excision. The specificity numerator corresponded to the total number of benign lesions (benign melanocytic nevi, solar lentigos, seborrheic keratoses, and other benign diagnoses) that were recommended to undergo routine follow-up after confocal microscopy evaluation.

**RESULTS**

A total of 1189 clinically suspicious lesions were included in the analysis. Of the included lesions, 25.9% (308 lesions) were located on the face and neck, 41.7% (496 lesions) were located on the trunk, 28.5% (339 lesions) were located on the extremities, and 3.8% (46 lesions) were located on the hands and feet. Overall, 155 lesions were determined to be positive for malignancy or atypia on RCM diagnosis, and 1034 lesions were determined to be benign. A total of 109 lesions were considered true positives, 46 lesions were considered false positives, 1032 lesions were considered true negatives, and 2 lesions were considered false negatives (Figure 1). Of the 155 lesions positive for malignancy, the diagnoses included malignant melanoma in 6 cases, severely dysplastic nevus in 127 cases, squamous cell carcinoma in 7 cases, and basal cell carcinoma in 15 cases. Of the 1032 true-negative lesions, the diagnoses included seborrheic keratosis/solar lentigo in 120 cases and benign melanocytic nevus in 912 cases. Overall sensitivity and specificity were calculated as 98.2% and 99.8%, respectively. Positive and negative predictive values were 70.3% and 99.8%, respectively (Table).

**DISCUSSION**

Although the FDA approved RCM nearly a decade ago, it has not been adopted as a routine diagnostic tool in US dermatology clinics. In contrast, RCM has gained popularity in many European countries such as Italy and Germany. The diagnostic accuracy of RCM has been investigated in the past to report the real-time efficacy of RCM. Pellacani et al,11 pioneers and experts in the field of RCM, have established criteria to distinguish benign lesions from malignant lesions. Benign melanocytic nevi (Figure 2, A) show a cobblestone pattern of epidermis and ring pattern, with edged papillae at the dermoeidermal junction (Figure 2, B).11 The cobblestone pattern represents the regular arrangement of pigmented, and therefore refractile, keratinocytes within the epidermis found in melanocytic lesions. The ring pattern

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**Figure 1.** A total of 1189 clinically suspicious lesions were evaluated by using reflectance confocal microscopy (RCM). Of these, 155 lesions were determined to be malignant or severely atypical; 1034 lesions were determined to be benign.
refers to large, dark, oval areas that are circumscribed by small, bright cells. Histologically, this represents a horizontal section of the dermal papillae, lined by melanocytes and pigment-rich keratinocytes. The presence of severe cytologic atypia and nonedged papillae at the dermoepidermal junction constitute the major criteria to diagnose malignant melanoma (Figure 3).\(^{11}\)

A retrospective analysis of 143 cases of squamous cell carcinoma using RCM by Manfredini et al\(^ {12}\) showed characteristic RCM features of polymorphic vessels, erosion/ulceration, architectural disarrangement, speckled nucleated cells in the dermis, irregularly dilated vessels, and absence of hyperkeratosis in poorly differentiated tumors. For seborrheic keratoses, RCM features include normal honeycomb pattern with pseudo horn cysts and an increase in interpapillary areas. When following these criteria, RCM shows high diagnostic sensitivity and specificity.

Rao et al,\(^ {13}\) in collaboration with Pellacani et al, performed an extensive study on the comparison and concurrence of bedside diagnosis by a trained physician and distant diagnosis by an expert reader. Both confocal readers evaluated a total of 334 confocal cases. All the cases were collected from the US patient population only. The confocal diagnoses were then compared with the histologic diagnoses. Sensitivity of a confocal expert was reported as 97.4\% and specificity as 80.5\%; sensitivity and specificity of confocal trainee were reported as 93.1\% and 64.1\%, respectively. It was concluded that a lower rate of specificity may be due to differences in the level of image-reading experience.\(^ {13}\)

After 5 years of confocal training and experience, Giambrone et al\(^ {14}\) retrospectively reviewed 748 clinically suspicious lesions that were evaluated by RCM in clinics. Statistical analysis revealed a sensitivity of 100\% and specificity of 92.6\%.

**Figure 2.** Benign melanocytic nevus: (A) dermoscopy and (B) reflectance confocal microscopy mosaic shows ring pattern with edged papillae and no atypical cells.

**Figure 3.** Malignant melanoma: (A) dermoscopy and (B) reflectance confocal microscopy mosaic shows nonedged papillae and numerous atypical cells.
In this study, we are reporting an update on retrospective analysis of RCM cases from 2010 to 2017. Our results showed an overall sensitivity of 98.2% and specificity of 99.8%. Specificity of our confocal reader improved from 64.1% to 99.8% with further experience in reading RCM images.

In our current study, 6 cases were diagnosed as basal cell carcinoma on RCM; however, biopsy showed angiofibroma in 4 cases, sebaceous gland hyperplasia in 1 case, and inflamed seborrheic keratosis in 1 case. Peppelman et al. in a recent study described the RCM features of basal cell carcinoma and its subtypes. Tumor nests with peripheral palisading, fibrotic septa, and increase in vascular diameter were characteristic RCM features of nodular and micronodular basal cell carcinoma (Figure 4). We propose that angiofibroma should be considered as the most common differential diagnosis for an increase in vascular diameter with fibrotic septa and irregular honeycomb pattern of epidermis in the absence of tumor islands.

In conclusion, RCM is a noninvasive real-time tool with the potential to diagnose skin lesions with high accuracy and without biopsy. This, however, is dependent on the confocal reader’s training and experience, which is currently an obstacle for RCM to be used in daily practice. In our opinion, dermatopathologists will be the most qualified readers of RCM in the future because of their familiarity with skin pathology.

References

Figure 4. Basal cell carcinoma: (A) dermoscopy and (B) reflectance confocal microscopy mosaic shows tumor nodules with peripheral palisading, clefting, and streaming.