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# Clinical Indications for Use of Reflectance Confocal Microscopy for Skin Cancer Diagnosis

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**IMPORTANCE** Reflectance confocal microscopy (RCM) improves diagnostic accuracy in skin cancer detection when combined with dermoscopy; however, little evidence has been gathered regarding its real impact on routine clinical workflow, and, to our knowledge, no studies have defined the terms for its optimal application.

**OBJECTIVE** To identify lesions on which RCM performs better in terms of diagnostic accuracy and consequently to outline the best indications for use of RCM.

**DESIGN, SETTING, AND PARTICIPANTS** Prospectively acquired and evaluated RCM images from consecutive patients with at least 1 clinically and/or dermoscopically equivocal skin lesion referred to RCM imaging, from January 2012 to October 2014, carried out in a tertiary referral academic center.

**MAIN OUTCOMES AND MEASURES** A total of 1279 equivocal skin lesions were sent for RCM imaging. Spearman correlation, univariate, and multivariate regression models were performed to find features significantly correlated with RCM outcome.

**RESULTS** In a total of 1279 lesions in 1147 patients, RCM sensitivity and specificity were 95.3% and 83.9%, respectively. The number of lesions needed to excise to rule out a melanoma was 2.4. After univariate and multivariate regression analysis, head and neck resulted as the most appropriate body location for confocal examination; RCM showed a high diagnostic accuracy for lesions located on sun-damaged skin (adjusted odds ratio [aOR], 2.13; 95% CI, 1.37-3.30; *P*=.001) and typified by dermoscopic regression (aOR, 2.13; 95% CI, 1.31-3.47; *P*=.002) or basal-cell carcinoma specific criteria (aOR, 9.35; 95% CI, 1.28-68.58; *P*=.03).

**CONCLUSIONS AND RELEVANCE** Lesions located on the head and neck, damaged by chronic sun-exposure, and dermoscopically typified by regression represent best indications for the use of RCM.

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In recent decades, the dermatoscope has been thought to be an essential tool for skin cancer diagnosis, and it is currently referred as the "dermatologist's stethoscope."[1-3] However, in some cases the diagnosis of malignant abnormalities is still challenging in a subset of difficult-to-diagnose melanomas (MMs) and nonmelanoma skin cancers. To narrow this gray zone, reflectance confocal microscopy (RCM), a second-level in vivo imaging technique, has proven to be a useful tool in saving unnecessary excisions of benign lesions that can look dermoscopically suspicious for skin cancer while catching MMs that are dermoscopically inconspicuous.[4-8] Reflectance confocal microscopy provides a horizontal visualization of the skin at a nearly histological resolution and is currently a validated instrument for noninvasive diagnosis of skin tumors, already counting over 600 indexed articles.[4-15]

Up-to-date, retrospective analyses[4-8,11-15] have demonstrated the capability of RCM to improve the diagnostic accuracy in skin cancer detection when combined with dermoscopy, but, to our knowledge, only 2 studies[16,17] have evaluated prospectively the real impact of RCM in the routine clinical workflow. These 2 articles assessed the reduction in number of lesions needed to excise to diagnose an MM achievable through RCM: lesions considered for the analysis were defined under the umbrella of "clinically and/or dermoscopically equivocal." However, this term encompasses a wide group of clinical and dermoscopic situations and does not provide clinicians with the best indications for referring patients to a tertiary center equipped with confocal microscopy for confocal analysis.

To define the best indications for the use of RCM in daily practice, we prospectively evaluated the clinical and



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dermoscopic aspects as well as the outcomes of the RCM examination of lesions referred to the confocal examination during a 3-year study of a daily work routine.

## Key Points

**Questions** When is reflectance confocal microscopy (RCM) most useful in clinical practice?

**Findings** In this study of 1279 equivocal skin tumors referred for RCM consultation, we obtained a diagnostic sensitivity of RCM was 95.3% and specificity was 83.9%. Reflectance confocal microscopy was most useful for lesions located on the head and neck, lesions with clinical evidence of sun damage, and those with evidence of regression on dermoscopy.

**Meaning** Reflectance confocal microscopy is a useful tool for the diagnosis of challenging lesions suspicious for malignant abnormalities.

## Methods

Consecutive patients referred to the Skin Cancer Unit of the Santa Maria Nuova Hospital of Reggio Emilia, Italy, from January 2012 to October 2014, with at least 1 clinically and/or dermoscopically equivocal skin lesion were recruited.

All clinical investigations were conducted according to the Declaration of Helsinki principles.[18] Institutional review board approval was waived and participants were not compensated because participation was part of routine patient care. Consent of patients was collected only prior to excision or biopsy of a skin lesion.

### Clinical Workup

Dermoscopy experts (G.A., C.L., E.M., A.L., I.Z.) visited all patients referred to our skin cancer unit by general practitioners or other dermatologists, patients were examined by using a handheld dermatoscope according to our routine workup. Study inclusion required the presence of 1 or more atypical lesions not meeting the clear-cut clinical and dermoscopic criteria for malignant abnormalities. Those patients were referred to RCM for further evaluation. Patients with lesions located on acral sites or in areas not accessible by the wide confocal probe were excluded.

Confocal investigators with 10 years of experience in RCM (C.L., E.M.) were asked to give a treatment recommendation (ie, surgical excision or digital monitoring), or were consulted on noninvasive, nonmelanoma skin cancers for a diagnostic reassurance before performing nonsurgical treatments.

For each lesion, clinical features were reported in dedicated software (DermoSun, version 2.1; Aliseo): palpability (nodular or flat/palpable), pigmentation (amelanotic, partially pigmented, or pigmented), superficial erosions, diameter (>6 mm), and presence of sun damage on perilesional skin. Pigmentation and erosions were first assessed clinically and subsequently confirmed with the dermoscopic examination. Dermoscopic features suggestive of MM or nonmelanoma skin cancer were also assessed and recorded (eTable in the Supplement).

Exclusion criteria for RCM imaging were lesions located on acral sites and in skin folds difficult to explore with a confocal wide probe, and fully ulcerated or markedly hyperkeratotic lesions.[19] For those lesions, diagnosis was based solely on clinical and dermoscopic examination.

Histopathologic analysis was considered the gold standard. Lesions that were not excised were scheduled for sequential digital follow-up at 3 and/or 6 months, and 1 year after the baseline visit. Lesions with clinically significant changes identified at digital dermoscopic follow-up were excised and their histopathologic diagnoses were collected.

Subsequently, after surgical removal or adequate follow-up (≥1 year), each lesion was classified as benign or malignant. On the basis of the agreement between this final outcome and the result of the confocal examination, lesions were classified as correctly or incorrectly diagnosed according to RCM result.

### Imaging Instruments

Dermoscopic examinations were conducted using the Dermlite HR (3Gen LLC). Dermoscopic images of lesions considered suspicious were acquired by means of Dermlite Photo (3Gen LLC) equipped with a Canon G16 camera (Canon Inc).

Confocal imaging was performed with near-infrared reflectance-mode confocal laser scanning microscope (Vivascope 1500; MAVIG GmbH). Instrument and acquisition procedures have been described elsewhere.[9,10]

### Statistical Analysis

Absolute and relative frequencies for clinical characteristics and dermoscopic criteria were obtained. Reflectance confocal microscopy sensitivity and specificity in diagnosing skin tumors were calculated.

To analyze clinical and dermoscopic factors influencing the RCM diagnostic accuracy, we used Spearman ρ coefficient to flag significant correlations, which were subsequently quantified via univariate logistic regression (calculation of odds ratios [ORs] and corresponding 95% CIs). Furthermore, a logistic multivariate regression model with forward stepwise variable selection was constructed to identify major independent factors (calculation of adjusted ORs [aORs]) among the descriptors that showed a significant difference ($P < .10$) on univariate analysis, together with the notable intervariable interactions. The α level was set at .05. Statistical analyses were performed using the statistical package for social sciences statistical software (version 22.0, IBM SPSS Inc).

## Results

### Study Population

A total of 1279 lesions (in 1147 patients) from 16 000 visits conducted in our skin cancer unit over the course of a 3-year period were sent for RCM analysis. Of these lesions, 668 (52.2%) were excised after RCM evaluation to rule out skin cancer. Histopathologic analysis of those excised lesions identified 239 MMs (35.8%) (mean [SD] Breslow thickness 0.7 [0.7] mm), including 138 in situ MMs (57.7% of all MMs) and 3 cutaneous MM metastases; 61 basal cell carcinomas (BCCs) (9.1%); 16 squamous cell carcinomas (SCCs) (2.4%) and Bowen diseases; 214 Clark nevi (32.1%); and 79 Spitz/Reed nevi (11.8%). The remaining 59 lesions (8.8%)



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Table 1. Clinical Characteristics of Study Population

| Characteristic | MMs (n = 246) | BCCs/SCCs/ Bowen Diseases (n = 134) | Clark Nevi (n = 503) | Spitz/ Reed Nevi (n = 93) | AKs (n = 42) | Other Benign Lesions (n = 238)[a] | All Lesions (n = 1279) |
|---|---|---|---|---|---|---|---|
| Sex, No. (%) | | | | | | | |
| Male | 117 (51.3) | 65 (48.9) | 206 (44.8) | 30 (33.3) | 21 (50.0) | 99 (42.5) | 520 (45.3) |
| Female | 111 (48.7) | 68 (51.1) | 254 (55.2) | 60 (66.7) | 21 (50.0) | 134 (57.5) | 627 (54.7) |
| Age, mean (SD), y | 60.8 (15.3) | 61.5 (16.6) | 42.3 (14.7) | 35.9 (11.0) | 71.6 (11.6) | 60.9 (14.3) | 52.1 (18.1) |
| Body site, No. (%) | | | | | | | |
| Head/neck | 58 (23.6) | 51 (38.1) | 35 (7.0) | 4 (4.3) | 35 (83.3) | 133 (55.9) | 326 (25.5) |
| Chest | 25 (10.2) | 16 (11.9) | 56 (11.1) | 5 (5.4) | 1 (2.4) | 25 (10.5) | 133 (10.4) |
| Abdomen | 12 (4.9) | 12 (9.0) | 62 (12.3) | 4 (4.3) | ... | 15 (6.3) | 107 (8.4) |
| Back | 67 (27.2) | 28 (20.9) | 220 (43.7) | 23 (24.7) | 2 (4.8) | 30 (12.6) | 371 (29.0) |
| Upper limbs | 44 (17.9) | 8 (6.0) | 39 (7.8) | 12 (12.9) | 4 (9.5) | 16 (6.7) | 123 (9.6) |
| Lower limbs | 40 (16.3) | 19 (14.2) | 91 (18.1) | 45 (48.4) | ... | 19 (8.0) | 219 (17.1) |
| Palpability, No. (%) | | | | | | | |
| Nodular | 12 (4.9) | 8 (6.0) | 10 (2.0) | 10 (10.8) | ... | 15 (6.3) | 57 (4.5) |
| Flat/palpable | 234 (95.1) | 126 (94.0) | 493 (98.0) | 83 (89.2) | 42 (100.0) | 223 (93.7) | 1222 (95.5) |
| Pigmentation, No. (%) | | | | | | | |
| Amelanotic | 7 (2.8) | 93 (69.4) | 14 (2.8) | 8 (8.6) | 18 (42.9) | 44 (18.5) | 188 (14.7) |
| Partially pigmented | 48 (19.5) | 25 (18.7) | 82 (16.3) | 13 (14.0) | 19 (45.2) | 107 (45.0) | 300 (23.5) |
| Pigmented | 191 (77.6) | 16 (11.9) | 407 (80.9) | 72 (77.4) | 5 (11.9) | 87 (36.6) | 791 (61.8) |
| Ulceration, No. (%) | 7 (2.8) | 51 (38.1) | 4 (0.8) | ... | 7 (16.7) | 17 (7.1) | 89 (7.0) |
| Diameter >6 mm, No. (%) | 187 (76) | 94 (70.1) | 287 (57.1) | 38 (40.9) | 34 (81.0) | 171 (71.8) | 824 (64.4) |
| Sun-damaged skin, No. (%) | 131 (53.3) | 80 (59.7) | 113 (22.5) | 4 (4.3) | 31 (73.8) | 128 (53.8) | 492 (38.5) |

Abbreviations: AKs, actinic keratoses; BCC, basal cell carcinoma; MM, melanoma; SCC, squamous cell carcinoma.

[a]This group includes benign nonmelanocytic lesions other than AKs (eg, seborrhoeic keratoses, solar lentigos, lichen planuslike keratoses, dermatofibromas), scars, or healthy skin.

were found to be other benign nonmelanocytic lesions (seborrheic keratosis, solar lentigos, lichen planus-like keratosis, actinic keratosis); in 3 cases the pathologist found scar or healthy skin, and in 2 cases fully regressed lesions were found that could not be identified. Considering that the total number of MMs excised in our clinic was 805 in the same time frame, nearly 1 MM out of 3 was referred to RCM for further examination.

Twenty-one lesions (1.6%) were defined as "missing" because patients did not attend the appointment scheduled for surgery. Only 1 case was considered not fully evaluable on RCM because imaging was taken up to the epidermal level: the lesion, clinically nodular, was histologically diagnosed as a basosquamous carcinoma.

The 590 lesions not excised at baseline visit (46.1%) were scheduled for sequential digital dermoscopic follow-up at 3 and/or 6 months, and 1 year after the baseline visit.

After a mean (SD) follow-up of 9.6 (9.5) months, 29 of the lesions (4.7%) were finally removed owing to the onset of morphological changes suggestive of malignant abnormalities. Histopathological examination of these lesions revealed 5 in situ MMs, and 2 microinvasive MMs (mean [SD] Breslow thickness, 0.4 [0.1] mm), 17 Clark nevi, 3 Spitz/Reed nevi, 2 other benign nonmelanocytic lesions. Regarding melanomas removed after follow-up, 5 lesions were excised because they revealed asymmetric enlargement of both structures and colors on dermoscopy: RCM in those lesions after digital follow-up revealed melanoma-specific criteria such as pagetoid spread and disrupted dermoepidermal junction. One lesion was spitzoid at baseline in a man aged 21 years, and excised owing to increased diameter at follow-up: RCM showed features of MM, but the overall appearance on clinical and dermoscopic examination was of a Spitz nevus. The last case is a nondescript macule of the face that on RCM imaging at the first visit revealed few dendritic cells. A punch biopsy was performed, and the result was of an atypical lesion not meeting criteria for lentigo maligna (LM). Thus, a follow-up was performed and RCM again was in favor of an LM. A second biopsy finally diagnosed the lesion as an MM, which has been treated with imiquimod.

Table 2. Univariate Analysis

| Factors Predicting RCM Performance | OR (95% CI) | *P* Value |
|---|---|---|
| Body site | | |
| Head/neck | Reference | Reference |
| Chest | 0.49 (0.22-1.12) | .09 |
| Abdomen | 0.33 (1.5-0.72) | .006 |
| Back | 0.30 (0.16-0.55) | <.001 |
| Upper limbs | 0.19 (0.09-0.38) | <.001 |
| Lower limbs | 0.17 (0.09-0.32) | <.001 |
| Sun-damaged skin | 2.90 (1.93-4.38) | <.001 |
| Lesion diameter >6 mm | 1.62 (1.16-2.28) | .005 |
| Ulceration/erosions | 3.11 (1.12-8.61) | .03 |
| Peripheral streaks | 0.44 (0.27-0.73) | .001 |
| Regression | 2.22 (1.39-3.55) | .001 |
| BCC specific criteria | 11.36 (1.57-82.28) | .02 |

Abbreviations: BCC, basal cell carcinoma; OR, odds ratio; RCM, reflectance confocal microscopy.

A total of 561 lesions were not excised at follow-up and have been declared benign after 1 year of no change (eFigure in the Supplement).

Clinical features of the study population according to histological categories are reported in **Table 1**.



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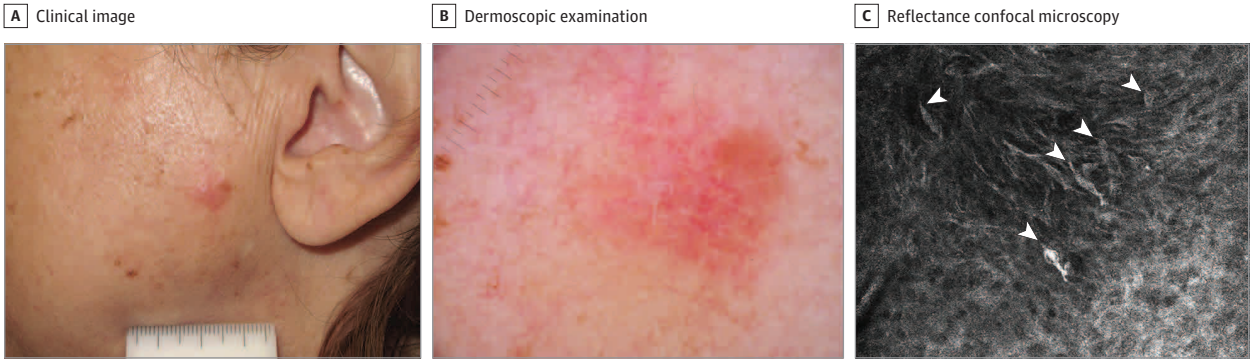
Figure 1. A Lesion Located on the Face




A, Pink facial plaque in a woman in her 70s. B, On dermoscopic examination the lesion revealed fine vasculature and chrysalis. C, Reflectance confocal microscopy (magnification 0.5 × 0.5 mm) showed nucleated dendritic pagetoid cells (arrowheads) suggestive for the diagnosis of melanoma that was confirmed by histologic examination.

Table 3. Multivariate Analysis[a]

| Factors Predicting RCM Performance | Adjusted OR (95% CI) | *P* Value |
|---|---|---|
| Body site | | |
| Head/neck | Reference | Reference |
| Chest | 0.46 (0.20-1.07) | .07 |
| Abdomen | 0.43 (0.19-0.98) | .04 |
| Back | 0.29 (0.16-0.55) | <.001 |
| Upper limbs | 0.20 (0.10-0.41) | <.001 |
| Lower limbs | 0.24 (0.12-0.45) | <.001 |
| Sun-damaged skin | 2.13 (1.37-3.30) | .001 |
| Regression | 2.13 (1.31-3.47) | .002 |
| BCC specific criteria | 9.35 (1.28-68.58) | .03 |

Abbreviations: BCC, basal cell carcinoma; OR, odds ratio; RCM, reflectance confocal microscopy.

[a] Logistic forward stepwise multivariate regression model. Reported ORs were mutually adjusted for all variables in the model.

## RCM Outcomes

The diagnostic performance of RCM has been evaluated for 1256 of the 1279 clinically and dermoscopically equivocal lesions, because fully regressed lesions (n = 2) and lesions whose final outcome was "missing" (n = 21) were not considered.

Regarding our RCM diagnostic accuracy in skin cancers, sensitivity and specificity were 95.3% and 83.9%, respectively. Considering lesions excised or biopsied to rule out an MM, the aid of the confocal microscope allowed us to achieve a number needed to excise of 2.4 to detect 1 lesion.

Surgical removal or incisional biopsy was recommended in 668 cases (53.2%) after clinical dermoscopic examination and confocal consultation. Excision was recommended based on RCM in 229 of 243 cases of MMs; 7 MMs (5 in situ) were excised after the first visit per patient's request or because of clinical features (only 1 pigmented lesion needed follow-up; a recent-onset melanocytic lesion in an elderly patient). The remaining 7 MMs not excised at baseline were excised during the follow-up because of the onset of dermoscopically significant changes. Excision or medical treatment (eg, topical imiquimod, photodynamic therapy, or cryotherapy) was recommended in 131 of 134 cases of nonmelanoma skin cancer. The remaining 3 cases were treated in private settings and not in our skin cancer unit.

## Spearman Correlation

Spearman analysis showed that the RCM performance significantly correlated with several clinical and dermoscopic factors: sun-damaged skin ($\rho = 0.149$; $P < .001$), lesion diameter ($\rho = 0.080$; $P = .004$), erosions ($\rho = 0.021$; $P = .06$), dermoscopically observed regression ($\rho = 0.096$; $P = .001$), and BCC specific criteria ($\rho = 0.086$; $P = .002$) positively correlated; body site ($\rho = -0.182$; $P < .001$), and peripheral streaks ($\rho = -0.094$; $P = .001$) negatively correlated.

## Univariate Analysis

The univariate logistic regression confirmed that the factors highlighted by Spearman correlation were all good predictors of RCM accuracy (**Table 2**). More specifically, the head and neck localization was significantly associated with a true RCM outcome (**Figure 1**). In the presence of sun damage or erosions, it was almost 3 times more likely that the RCM diagnosis was true (sun damage: OR, 2.90; 95% CI, 1.93-4.38; $P < .001$; erosions: OR, 3.11; 95% CI, 1.12-8.61; $P = .03$), while lesions with a diameter of more than 6 mm were more likely to be correctly diagnosed by RCM (OR, 1.62; 95% CI, 1.16-2.28; $P = .005$) (Figure 2). The presence of regression or BCC-specific criteria conferred a 2- and 11-times higher risk of a true confocal outcome, respectively (regression: OR, 2.22; 95% CI, 1.39-3.55; $P = .001$; BCC-specific criteria: OR, 11.36; 95% CI, 1.57-82.28; $P = .02$).

## Multivariate Regression Analysis

In the logistic forward stepwise multivariate regression model (**Table 3**), the head and neck localization, the presence of sun-damaged skin, and the dermoscopic observation of regression and BCC features were independent predictors for a true RCM status. In particular, body sites other than head and neck were from 53.6% to 80.0% less likely to be associated with a true RCM status, compared with the head and neck. Sun damage and regression were almost 2 times more likely to be associated with a correct confocal diagnosis (sun damage: aOR, 2.13; 95% CI, 1.37-3.30; $P = .001$; regression: aOR, 2.13; 95% CI, 1.31-3.47; $P = .002$); finally, the presence of BCC dermoscopic criteria was the highest predicting factor, with a 9-times increased risk of a true RCM status (aOR, 9.35; 95% CI, 1.28-68.58; $P = .03$).



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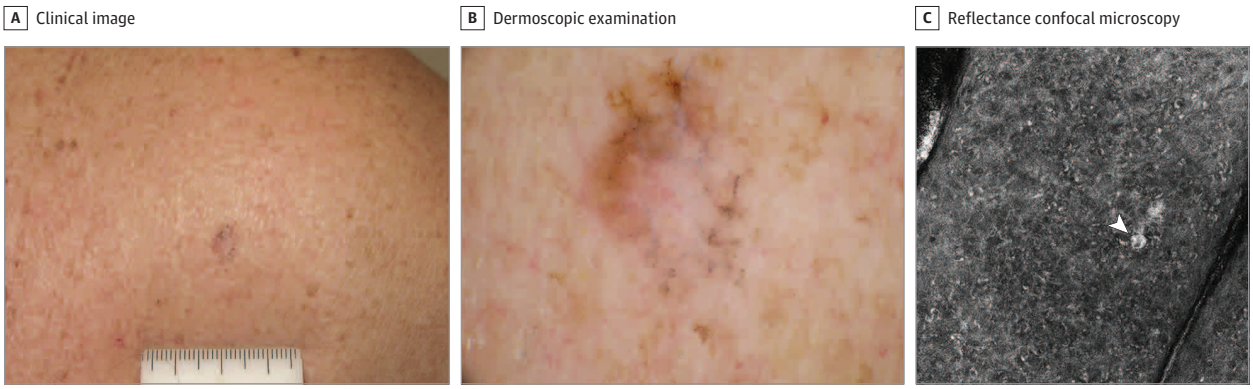
Figure 2. An In Situ Melanoma Dermoscopically Typified by Regression




A, The lesion, located on the sun-damaged chest of a man in his 80s, is clinically inconspicuous. B, Dermoscopic regression; original magnification ×20. C, Reflectance microscopic examination was able to highlight roundish pagetoid melanocytes (arrowhead) that were diagnostic for melanoma.

## Discussion

A growing body of literature[4-17,19,20] has demonstrated that RCM is an add-on tool to dermoscopy that increases accuracy in the diagnosis of skin cancer. In the current study, performed in a tertiary referral center, we aimed to identify the best clinical indications to use RCM in a clinical setting.

Sensitivity of 95.3% and specificity of 83.9% for RCM diagnostic accuracy for skin cancer diagnosis were obtained, in line with previously published retrospective studies.[4-8,11-15] The number of lesions needed to excise to diagnose an MM was 2.4: this number needed to excise overlaps with the data shown by Alarcon and colleagues[17] in 2014, supporting the concept that RCM used in similar clinical settings is a reliable diagnostic technique.

The most favorable clinical indications for use of RCM in a clinical setting were the following: first, lesions located on the head and neck area (Figure 1). This is partly because facial lesions are easily explorable by RCM owing to their thin epidermis and, also to the fact that dermoscopic findings could be ambiguous in this clinical instance. Furthermore, RCM is also useful in the diagnosis of amelanotic lesions even if our population did not have enough of these lesions to be significant. Our results on lesions located on head and neck areas confirm those determined retrospectively by Guitera et al,[21] indicating that RCM is remarkably useful in the differentiation of pigmented macules of the face, allowing skin biopsies that can be disfiguring in cosmetically sensitive areas to be avoided.

Second, presence of sun damage was the only clinical aspect significantly influencing the RCM outcome in terms of improved diagnostic accuracy (**Figure 2**).[22-24] The possible explanation for the good RCM performance on sun-damaged skin is related to the fact that the epidermal atrophy and the flattening of the dermoepidermal junction that might result in bland aspects on dermoscopy make these lesions easily explorable with RCM, which has an excellent resolution for flat lesions.

Third, another favorable indication for the use of RCM is in cases of regressive lesions and lesions presenting BCC dermoscopic criteria (which are not clear-cut on dermoscopic grounds). While the latter is an expected result, because the RCM diagnostic potential on BCCs has been extensively described,[6,25,26] the former is a novel finding. When evaluating lesions characterized by dermoscopic regression, their interpretation could be problematic (sometimes even histologically, in the case of a fully regressed lesion), especially when no other additional dermoscopic clues can be recognized.[27-29] Reflectance confocal microscopy can be of help because it can highlight the presence of remnant melanocytic features within an extensively regressed area that has many melanophages (Figure 2).

Finally, our study confirms that the presence of peripheral streaks (usually identifying Spitz/Reed nevi) is related to low likelihood for an RCM true outcome, and so, as previously outlined,[30] this parameter does not represent a good indication for RCM consultation.

### Limitations

In the current study the main application of RCM is in deciding whether a given lesion should be biopsied. However, other indications of RCM, such as monitoring of response to treatment (surgical and nonsurgical in melanoma and nonmelanoma skin cancer), documentation of skin cancer, or the research use of RCM, have not been considered. Furthermore, it should be considered that the present study has been conducted by experienced confocalists and thus this would be a limitation. Studies designed on a multicentric basis would serve to better define and expand possible clinical indications for RCM. An additional limitation is represented by the limited time frame of 3 years considered in the present study. Longer longitudinal studies on 10 years basis would add more information on possible expanded RCM clinical indications.



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## Conclusion

The current study demonstrates that RCM is an add-on imaging tool for the diagnosis of dermoscopically challenging lesions located on sun-damaged skin, lesions located on head and neck area, or dermoscopically typified by regression.

Our results are relevant not only for dermatologists who regularly deal with confocal microscopy but also for clinicians who desire to refer patients to tertiary centers equipped with RCM for further examinations.


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**Author Contributions:** Drs Borsari and Longo had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design*: Pellacani, Longo.
*Acquisition, analysis, or interpretation of data*: All authors.
*Drafting of the manuscript*: Borsari, Pampena, Raucci, Longo.
*Critical revision of the manuscript for important intellectual content*: Lallas, Kyrgidis, Moscarella, Benati, Pellacani, Zalaudek, Argenziano, Longo.
*Statistical analysis*: Kyrgidis.
*Obtained funding*: Longo.
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*Study supervision*: Argenziano, Longo.

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