



Submitted: 25.6.2018

Accepted: 7.9.2018

Conflict of interest

None.

DOI: 10.1111/ddg.13748

# Diagnostic impact of reflectance confocal microscopy as a second-level examination for facial skin lesions

**Verena Ahlgrimm-Siess<sup>1</sup>,**  
**Friedrich Weitzer<sup>2</sup>,**  
**Edith Arzberger<sup>2</sup>,**  
**Martin Laimer<sup>1</sup>,**  
**Rainer Hofmann-Wellenhof<sup>2</sup>**

(1) Department of Dermatology, Paracelsus Private Medical University Salzburg, Salzburg, Austria

(2) Department of Dermatology, Medical University of Graz, Graz, Austria

## Summary

**Background and objective:** Benign and malignant facial skin lesions may be difficult to differentiate clinically and with dermoscopy. The present study aimed to evaluate the potential utility of in vivo reflectance confocal microscopy (RCM) as a second-level examination for facial skin neoplasms.

**Patients and Methods:** Retrospective and blinded evaluation of 160 consecutive facial lesions was carried out in two separate steps. Clinical and dermoscopic images were assessed first, followed by combined evaluation of clinical/dermoscopic and RCM images. Our study included 60 % malignant lesions, comprising 43 % melanomas, 9 % basal cell carcinomas, 5 % in situ squamous cell carcinomas and 3 % lymphomas.

**Results:** Ancillary RCM significantly improved diagnostic specificity for the detection of malignancy compared to clinical/dermoscopic evaluation alone (58 % vs 28 %). However, sensitivity was slightly lower for RCM-based image evaluation (93 % vs 95 %) due to misclassification of one in situ SCC and one lymphoma. In terms of melanoma diagnosis, RCM-based image evaluation was generally superior; sensitivity was only slightly increased (88 % vs 87 %), but melanoma specificity was significantly higher (84 % vs 58 %).

**Conclusion:** RCM is a valuable diagnostic adjunct for facial skin lesions; unnecessary biopsies in this cosmetically sensitive area could be reduced by one third without missing a melanoma.

## Introduction

Clinical differentiation between benign and malignant skin neoplasms can be difficult even for experienced dermatologists, and biopsies are required in clinically equivocal cases. Facial lesions are an even greater diagnostic challenge because of overlapping, site-specific clinical and dermoscopic features that reflect the unique histomorphology of facial skin, and because of the limitations of biopsy in this cosmetically and functionally sensitive area [1–4]. Non-invasive measures to improve the detection rate of malignant skin lesions include the use of in vivo reflectance confocal microscopy (RCM) as a promising new imaging technique [5].

RCM makes it possible to visualize cytomorphological substrates of equivocal dermoscopic structures at the cellular level [6–10]. As in dermoscopy, flattening of the dermo-epidermal junction (DEJ) in sun-damaged facial skin and the peculiar growth pattern of lentigo maligna (LM) result in differences between the RCM appearance [11]. In addition, the main differential diagnoses of LM are non-melanocytic skin lesions, especially solar lentiginos, seborrheic keratoses or pigmented actinic keratoses – but not nevi, as found with superficial spreading melanoma. In this context, other confounders may hinder the non-invasive diagnosis of facial melanoma with RCM, such as the presence of bright dendritic Langerhans cells in epidermal layers, or pigmented atypical

keratinocytes in non-melanocytic facial lesions, both of which may mimic atypical melanocytes.

Few RCM studies in the literature have included equivocal facial skin lesions to demonstrate the benefit of this technology in this area of the body. Guitera et al. developed a diagnostic RCM algorithm to differentiate lentigo maligna from benign facial macules, and achieved high sensitivity and specificity (93 % and 82 %, respectively) in a study of 29 cases of lentigo maligna (LMs) and 44 benign macules [12]. In addition, RCM proved to be especially helpful for diagnosing solitary hypopigmented or non-pigmented lesions, which often lack reliable clinical and dermoscopic criteria [13, 14]. In a prospective series of 70 pigmented facial macules, Wurm and colleagues achieved similar sensitivity (95 %) and specificity (84 % for dermoscopy vs 82 % for RCM) in a separate and blinded evaluation of RCM images when compared with clinical/dermoscopic examination [15]. A recent multicenter study compared the diagnostic accuracy of RCM and dermoscopy in a larger series of 223 facial skin lesions, and found higher sensitivity for RCM (80 % vs 61 %) but lower specificity (81 % vs 92 %) than dermoscopy for lentigo maligna/lentigo maligna melanoma (LMM) diagnosis [16]. Despite the different results, these studies confirmed the high diagnostic accuracy of RCM if applied to facial skin.

Unlike dermoscopy, RCM is not suitable as a screening method due to time constraints, but has the potential to increase diagnostic accuracy as an adjunct to clinical/dermoscopic evaluation of equivocal lesions, especially in cosmetically and functionally sensitive areas.

The aim of the present study was to demonstrate the diagnostic value of RCM as a second-level examination in facial skin neoplasms, simulating a real-life workflow.

## Patients and methods

We included 160 consecutive facial skin lesions that were imaged in a university hospital setting (Department of Dermatology, University Hospital of Graz, Austria) in 148 patients. Patients were aged from 5 to 93 years (median age 69 years); 42 patients (28 %) were male and 106 (72 %) were female. Of all skin lesions included, 75 % (120/160) appeared clinically flat and 85 % (136/160) were pigmented; 8 % (12/160) were labial lesions. A total of 60 % (96/160) of all lesions were malignant and 40 % (64/160) were benign, comprising 43 % (69/160) melanomas (including 5 recurrent melanomas and 2 melanoma metastases); 9 % (14/160) basal cell carcinomas (BCC); 5 % (8/160) in situ squamous cell carcinomas (in situ SCCs, Bowen's disease); 3 % (5/160) lymphomas; 18 % (28/160) solar lentigines/seborrheic keratoses (SL/SK); 8 % (13/160) nevi (including 4 atypical nevi); 8 % (13/160) post-inflammatory hyperpigmentation (PIH), and 6 % (10/160) "others" (miscellaneous benign disorders, e.g. scars, sarcoidosis, sebaceous gland hyperplasia). A biopsy was performed in 82 % (131/160) of cases, including 98 % (94/96) malignant lesions and 58 % (37/64) benign lesions (including 5 nevi; 15 SL/SK; 9 PIH, and 8 "others"). Two definite BCCs were treated non-invasively without previous biopsy, and the remaining skin lesions were clinically and dermoscopically unequivocal (Table 1).

Conventional clinical images (Nikon D200 digital camera, Nikon Corporation, Tokyo, Japan), dermoscopic images (Dermlite Foto, 3Gen LLC, San Juan Capistrano, CA, USA attached to a Nikon Coolpix 4500 camera, Nikon Corporation, Tokyo, Japan) or dermoscopic Vivacam® images as well as RCM images (Vivascope 1500®, MAVIG GmbH, Munich, Germany) were available for all skin lesions included in the study. Unlike

**Table 1** Diagnoses and frequencies of evaluated skin lesions.

	Malignant lesions 96 (60 %)				Benign lesions 64 (40 %)			
	MM	BCC	In situ SCC	Lymphoma	SL/SK	Nevus	PIH	Others
Included lesions n = 160 (100 %)	69/160 (43 %)	14/160 (9 %)	8/160 (5 %)	5/160 (3 %)	28/160 (18 %)	13/160 (8 %)	13/160 (8 %)	10/160 (6 %)
Flat lesions n = 120/160 (75 %)	58/120 (48 %)	5/120 (4 %)	7/120 (6 %)	1/120 (1 %)	25/120 (21 %)	7/120 (6 %)	13/120 (11 %)	3/120 (3 %)
Pigmented lesions n = 136/160 (85 %)	66/136 (48 %)	6/136 (4 %)	7/136 (5 %)	1/136 (1 %)	28/136 (21 %)	13/136 (10 %)	13/136 (10 %)	2/136 (1 %)
Biopsied lesions n = 131/160 (82 %)	69/131 (53 %)	12/131 (9 %)	8/131 (6 %)	5/131 (4 %)	16/131 (12 %)	5/131 (4 %)	9/131 (7 %)	7/131 (5 %)

*Abbr.:* MM, melanoma; BCC, basal cell carcinoma; in situ SCC, in situ squamous cell carcinoma; SL, solar lentigo; SK, seborrheic keratosis; PIH, post-inflammatory hyperpigmentation.

the handheld RCM device (Vivascope 3000®, MAVIG GmbH, Munich, Germany), the Vivascope 1500® makes it possible to assess large areas of skin (up to 8 mm x 8 mm field of view) in direct correlation with the dermoscopic image and was therefore the imaging method of choice, even though fixation of the imaging probe to the skin can be demanding in uneven areas of the face (e.g. tip of the nose, labial lesion). Skin lesions in facial areas that were inaccessible with the Vivascope 1500® (e.g. inner canthus of the eye) were not included in the study.

Image evaluation was performed retrospectively by two blinded experts in RCM (RHW and EA) in a “double reader concordance” approach in two consecutive steps. Clinical and dermoscopic images were assessed first; clinical and dermoscopic images were then evaluated together with the RCM images. All patient images were anonymized before analysis.

After each step of image evaluation, the observers selected the suspected diagnosis and, if applicable, a differential diagnosis from a drop-down menu. Proposed diagnoses included nevus, melanoma, basal cell carcinoma, in situ squamous cell carcinoma (Bowen’s disease), solar lentigo/seborrheic keratosis, lymphoma, post-inflammatory hyperpigmentation and “others”. In addition, the observers were asked to state whether or not they would recommend a subsequent biopsy.

The diagnostic RCM criteria applied were selected from previously published data on melanoma and non-melanoma

skin neoplasms [17–24]. Specific LM criteria summarized in our previous paper (i.e. predominance of dendritic cells at epidermal layers, localization of atypical melanocytes/melanocytic nests around adnexal structures, presence of cord-like rete ridges at the dermo-epidermal junction instead of a ringed pattern, descent of atypical melanocytes along adnexal structures) were considered together with general cytomorphologic RCM criteria for melanoma, such as presence of melanocyte atypia in basal and suprabasal layers with consecutive loss of the epidermal and dermo-epidermal junction (DEJ) architecture.

All patients gave written consent for RCM examination of their skin lesions. The study was not registered in a public trial registry or approved by a research ethics committee, since data were evaluated retrospectively, and patient management was not modified. The principles expressed in the Declaration of Helsinki were strictly followed.

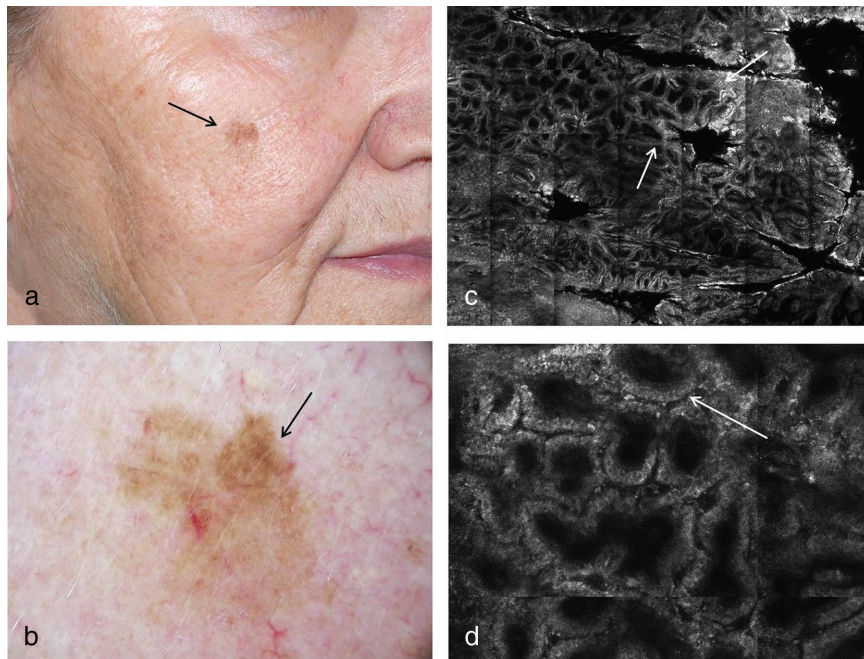
## Results

In the first step of image evaluation (clinical/dermoscopic images), 86 % (137/160) of skin lesions were suspected of malignancy and destined for biopsy, including 95 % (91/96) of malignant skin lesions and 72 % (46/64) of benign lesions. Of the 69 melanomas included in the study, 96 % (66) were considered malignant and recommended for biopsy (Table 2).

**Table 2** Diagnoses and frequencies of skin lesions excised due to suspicion of malignancy or melanoma.

	Number	Excisions due to suspicion of malignancy		Excisions due to suspicion of melanoma (PD or DD)	
		Clinical Exam/ Dermoscopy	Clinical Exam/ Dermoscopy and RCM	Clinical Exam/ Dermoscopy	Clinical Exam/ Dermoscopy and RCM
MM	69	66	66	60 (46 PD)	61 (55 PD)
BCC	14	12	12	1 (DD)	1 (DD)
In situ SCC	8	8	7	5 (1 PD)	4 (3 PD)
Lymphoma	5	5	4	1 (DD)	0
<i>Total malignant</i>	<i>96</i>	<i>91</i>	<i>89</i>	<i>67</i>	<i>66</i>
SL/SK	28	15	7	14 (DD)	4 (DD)
Nevus	13	13	3	6 (1 PD)	1 (DD)
PIH	13	11	11	9 (6 PD)	4 (PD)
Others	10	7	6	2 (1 PD)	1 (DD)
<i>Total benign</i>	<i>64</i>	<i>46</i>	<i>27</i>	<i>31</i>	<i>10</i>
<i>Total</i>	<i>160</i>	<i>137</i>	<i>116</i>	<i>98</i>	<i>76</i>

*Abbr.:* MM, melanoma; BCC, basal cell carcinoma; in situ SCC, in situ squamous cell carcinoma; SL, solar lentigo; SK, seborrheic keratosis; PIH, post-inflammatory hyperpigmentation; RCM, reflectance confocal microscopy; PD, primary diagnosis; DD, differential diagnosis.



**Figure 1** Clinical, dermoscopic, and RCM images of a solar lentigo, destined for biopsy based on clinical/dermoscopic examination to rule out melanoma. An irregularly shaped, tan to dark-brown macule is seen on the right cheek (a; arrow). Dermoscopy shows an ill-defined macule with tan to dark-brown pseudonetwork. A few gray-brown dots (arrow) are observed in an area with eccentric hyperpigmentation, raising suspicion of malignancy (b). Confocal microscopy of the dermo-epidermal junction (approximately 3 mm x 2.5 mm field of view) displays densely packed and well-defined, round to polycyclic, edged dermal papillae (c; arrows). At higher magnification (approximately 0.5 mm x 0.5 mm field-of-view), bright

monomorphic cells aligned around dermal papillae are seen (arrow); the interpapillary spaces appear dark. The RCM findings are characteristic of a solar lentigo (d).

In the second step of image evaluation (clinical/dermoscopic and RCM images together), only 73 % (116/160) of lesions were classified as malignant, comprising 93 % (89/96) of malignant lesions and 42 % (27/64) of benign lesions; one in situ SCC and one lymphoma, which were considered malignant in the first step of image evaluation, were missed if RCM images were also assessed. However, the same percentage of melanomas (96 %; 66/69) was classified as malignant and destined for biopsy.

With additional RCM, the number of incorrectly classified benign skin lesions and subsequent recommendations for biopsy in this cosmetically sensitive area was reduced by 30 % (19/64) (Figure 1).

However, three melanomas (4 %; 3/69) were missed in both steps of image evaluation, including two in situ melanomas and one invasive melanoma (Breslow's depth of 0.5 mm). Despite an unequivocal clinical and dermoscopic appearance, these skin lesions were originally biopsied due to relevant patient history indicative of malignant growth (e.g. new lesion, repigmentation after previous melanoma surgery) (Table 2). Unblinded re-evaluation of corresponding RCM images showed a focal area with atypical melanocytes and few small nests at the DEJ in one in situ melanoma, showing how careful one must be when assessing this feature. However, the second in situ melanoma did not show RCM features suggestive of melanoma when the available RCM images were reevaluated. Clinical, dermoscopic and RCM features of the invasive melanoma were most compatible with

the diagnosis of a nevus in this relatively young, 43-year-old female patient.

The diagnostic specificity for detection of malignant facial lesions was significantly better with ancillary RCM than with clinical/dermoscopic examination alone (58 % vs 28 %), as were positive (77 % vs 66 %) and negative (84 % vs 78 %) predictive values. However, the sensitivity was slightly lower for the RCM-based image evaluation (93 % vs 95 %) due to misclassification of one in situ SCC and one lymphoma (Table 3).

Excisions due to melanoma (in the primary or differential diagnosis) were recommended in 61 % (98/160) of skin lesions in the first step of image evaluation (clinical/dermoscopic images), comprising 70 % (67/96) of malignant lesions and 48 % (31/64) of benign lesions. Of the 69 melanomas included in the study, 87 % (60/69) were suspected melanomas; the remaining cases were either classified as other skin malignancies and therefore destined for biopsy (9 %; 6/69) or misclassified as benign (4 %; 3/69).

In the second step of image evaluation (clinical/dermoscopic and RCM images together), only 48 % (76/160) of skin lesions were suspected melanomas, including 69 % (66/96) of malignant lesions and 16 % (10/64) of benign lesions. With ancillary RCM, 89 % (61/69) of melanomas were correctly diagnosed. Again, the remaining melanomas were either suspected to be other types of skin malignancies with subsequent recommendation for biopsy (7 %; 5/69) or were regarded as benign (4 %; 3/69). Additional RCM reduced the

**Table 3** Comparison of diagnostic performance of clinical/dermoscopic and combined image evaluation.

n = 160	Excision due to suspicion of malignancy				Excision due to suspicion of melanoma					
	Number (percentage) of lesions	Sensitivity	Specificity	PPV	NPV	Number (percentage) of lesions	Sensitivity	Specificity	PPV	NPV
Clinical Exam/ Dermoscopy	n = 137/160 (86 %)	0.95	0.28	0.66	0.78	n = 98/160 (61 %)	0.87	0.58	0.61	0.85
Clinical Exam/ Dermoscopy and RCM	n = 116/160 (73 %)	0.93	0.58	0.77	0.84	n = 76/160 (48 %)	0.88	0.84	0.80	0.90

Abbr.: RCM, reflectance confocal microscopy; PPV, positive predictive value; NPV, negative predictive value.

number of benign skin lesions that were incorrectly diagnosed as melanoma by 33 % (21/64).

In terms of melanoma diagnosis, RCM-based image evaluation was generally superior to clinical/dermoscopic evaluation alone. Sensitivity and negative predictive value for melanoma diagnosis were only slightly better with ancillary RCM (88 % vs 87 % and 90 % vs 85 %, respectively), but melanoma specificity and positive predictive value were significantly higher (84 % vs 58 % and 80 % vs 61 %). In addition, the percentage of melanomas destined for biopsy because melanoma was the primary (but not the) differential diagnosis was increased by ancillary RCM (90 % vs 77 %), reflecting a higher level of confidence.

Subanalysis of flat facial lesions included in the study (120/160; 75 %) showed comparable results for detection of skin malignancies and diagnosis of melanomas.

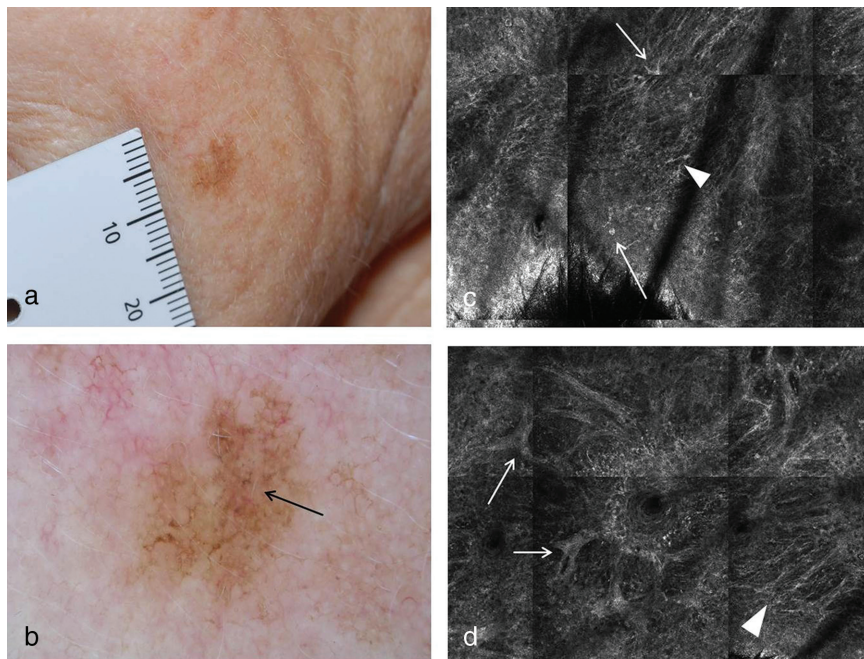
### Discussion

In our study, we evaluated the diagnostic impact of RCM as a second-level examination in a series of 160 consecutive facial skin lesions. Clinical and dermoscopic images of all lesions were assessed in a blinded manner in two separate steps, first without and then with the respective RCM images.

To better approximate real-life conditions, we assessed a series of unselected skin lesions comprising flat, elevated, pigmented and non-pigmented skin neoplasms. Of the skin lesions, 60 % (96/160) were malignant; 72 % (69/96) of these were melanomas, 15 % (14/96) BCCs, 8 % (8/96) in situ SCCs (Bowen's), and 5 % (5/96) lymphomas. Of the included skin lesions, 82 % (131/160) were biopsy-proven (98 % of malignant lesions and 58 % of benign lesions), while the remaining cases were clinically either clearly benign or clearly BCCs destined for non-invasive treatment (Table 1).

With clinical and dermoscopic evaluation alone, 95 % (91/96) of malignant skin lesions were correctly classified as malignant, whereas only 93 % (89/96) were considered malignant if RCM images were also assessed; one in situ SCC and one lymphoma were misclassified as benign. With RCM-based image evaluation, the number of incorrectly diagnosed benign skin lesions and therefore the number of unnecessary recommendations for biopsies in this cosmetically sensitive area was reduced by 30 % (27/64; 42 % vs 46/64; 72 %) (Figure 1). In summary, the diagnostic specificity for the detection of malignant facial lesions was significantly better with additional RCM than with clinical/dermoscopic examination alone (58 % vs 28 %), as were positive (77 % vs 66 %) and negative (84 % vs 78 %) predictive values. The sensitivity was slightly lower (93 % vs 95 %), but the detection rate of melanoma was unaltered (Table 3).

Concerning melanoma diagnosis, RCM-based image evaluation generally achieved better results than clinical



**Figure 2** Clinical, dermoscopic, and RCM images of a lentigo maligna. The primary diagnosis after clinical/dermoscopic examination was solar lentigo with regression; however, lentigo maligna was in the differential diagnosis. On clinical examination, an irregularly shaped tan macule is seen in the left mandibular area (a). With dermoscopy, a tan pseudonetwork with focal dark-brown angulated lines and streaks as well as an area with a few gray dots (arrow) can be seen (b). RCM of upper epidermal layers (approximately 1 mm x 1 mm field of view) shows loss of the regular epidermal architecture due to presence of large, bright, round and dendritic pagetoid cells (arrows) as well as sheets of

dendrites (c; arrowhead). At the DEJ (approximately 1 mm x 1 mm field of view), there are bright dendrites (arrowhead) and tubular cell nests of various reflectivities (arrows) in irregularly shaped rete ridges with abrupt endings, also referred to as “medusa head-like structures” or “irregular meshwork pattern” at the DEJ [28]; outlines of single cells are occasionally observed within the nests. These RCM findings are consistent with lentigo maligna (d).

and dermoscopic evaluation alone. In the first step of image evaluation, 87 % (60/69) of melanomas were considered suspicious for melanoma and with additional RCM, the amount increased to 89 % (61/69) of melanomas. In addition, diagnostic confidence was higher with RCM; the percentage of melanomas destined for biopsy because melanoma was the primary diagnosis was greater (90 % vs 77 %) (Figure 2; Figure 3 online only supplement). Of misclassified melanomas, 6/9 and 5/8 were suspected of being other skin malignancies with clinical/dermoscopic and combined image evaluation, respectively, and subsequently destined for biopsy, while 4 % (3/69) melanomas were considered benign in both steps of image evaluation. These melanomas were originally biopsied due to a relevant patient history indicative of malignancy, which highlights the importance of a holistic approach to non-invasive melanoma diagnosis that takes into consideration not only site-specific features, but also patient characteristics and lesion evolution.

As a result, sensitivity and negative predictive value for melanoma diagnosis were only slightly better for ancillary RCM (88 % vs 87 % and 90 % vs 85 %, respectively), but melanoma specificity and positive predictive value were significantly higher (84 % vs 58 % and 80 % vs 61 %) than for clinical/dermoscopic evaluation alone. With ancillary RCM, the number of benign skin lesions that were incorrectly

suspected of melanoma and destined for biopsy was reduced by 33 % (10/64; 16 % vs 31/64; 48 %).

A subanalysis for flat facial lesions (75 %; 120/160) showed results for the detection of skin malignancies and for melanoma diagnosis that were similar to the result for all facial lesions together.

Our results are consistent with those of previous studies on the diagnostic accuracy of RCM for skin neoplasms in general; a recent meta-analysis showed a considerably better diagnostic specificity for malignant skin tumors with RCM than for dermoscopy [25]. The pooled sensitivity of dermoscopy for malignant skin tumors was similar to that of RCM (88.1 % vs 93.5 %), but the specificity of dermoscopy was significantly lower than that of RCM (52.9 % vs 80.3 %). Pooled sensitivities and specificities for melanoma detection were 88.4 % and 49.1 % for dermoscopy and 93.5 % and 78.8 % for RCM. A longitudinal prospective study on the value of RCM as a second-level examination in a routine workflow at a pigmented lesion outpatient clinic showed that the systematic application of RCM for equivocal lesions saved over 50 % of benign lesions from unnecessary excision and significantly reduced the number needed to excise a melanoma [26], which was also confirmed by another study group [27].

Discrepancies between the results of our study and the two recent studies comparing the diagnostic value of RCM

vs dermoscopy in facial skin may be partially explained by the different study settings [15, 16], especially the separate assessment of clinical/dermoscopic and RCM characteristics of a given skin lesion by different observers.

Our study has limitations, most notably the retrospective study design, which only allows a theoretical approximation to real-life conditions and limits the validity of the results. In addition, not all skin lesions included in the study were biopsy-proven, which was justified by the characteristics of the anatomical site.

In conclusion, we found that RCM is a valuable diagnostic tool as an adjunct to clinical and dermoscopic examination of facial skin, especially due to the increased diagnostic specificity with malignant skin lesions in general and melanoma in particular. Approximately one third of skin biopsies in this cosmetically sensitive area could be prevented with ancillary RCM by increasing the rate of correct melanoma diagnoses. However, a prospective study including a consecutive series of facial skin lesions is needed to confirm our results in real life.

### Correspondence to

Verena Ahlgrimm-Siess, MD  
 Department of Dermatology  
 Paracelsus Medical University of Salzburg  
  
 Muellner Hauptstrasse 48  
 5020 Salzburg, Austria  
  
 E-mail: v.ahlgrimm-siess@salk.at

### References

- Schiffner R, Schiffner-Rohe J, Vogt T et al. Improvement of early recognition of lentigo maligna using dermatoscopy. *J Am Acad Dermatol* 2000; 42(1 Pt 1): 25–32.
- Akay BN, Kocyigit P, Heper AO et al. Dermatoscopy of flat pigmented facial lesions: diagnostic challenge between pigmented actinic keratosis and lentigo maligna. *Br J Dermatol* 2010; 163(6): 1212–7.
- Tanaka M, Sawada M, Kobayashi K. Key points in dermoscopic differentiation between lentigo maligna and solar lentigo. *J Dermatol* 2011; 38(1): 53–8.
- Lallas A, Argenziano G, Moscarella E et al. Diagnosis and management of facial pigmented macules. *Clin Dermatol* 2014; 32(1): 94–100.
- Rajadhyaksha M, González S, Zavislan JM et al. In vivo confocal scanning laser microscopy of human skin II: Advances in instrumentation and comparison with histology. *J Invest Dermatol* 1999; 113: 293–303.
- Langley RG, Burton E, Walsh N et al. In vivo confocal scanning laser microscopy of benign lentiginosities: comparison to conventional histology and in vivo characteristics of lentigo maligna. *J Am Acad Dermatol* 2006; 55(1): 88–97.
- Gómez-Martín I, Moreno S, Andrades-López E et al. Histopathologic and immunohistochemical correlates of confocal descriptors in pigmented facial macules on photodamaged skin. *JAMA Dermatol* 2017; 153(8): 771–80.
- De Carvalho N, Farnetani F, Ciardo S et al. Reflectance confocal microscopy correlates of dermoscopic patterns of facial lesions help to discriminate lentigo maligna from pigmented nonmelanocytic macules. *Br J Dermatol* 2015; 173(1): 128–33.
- Star P, Guitera P. Lentigo maligna, macules of the face, and lesions on sun-damaged skin: confocal makes the difference. *Dermatol Clin* 2016; 34(4): 421–9.
- Ferrari B, Pupelli G, Farnetani F et al. Dermoscopic difficult lesions: an objective evaluation of reflectance confocal microscopy impact for accurate diagnosis. *J Eur Acad Dermatol Venereol* 2015; 29(6): 1135–40.
- Ahlgrimm-Siess V, Massone C, Scope A et al. Reflectance confocal microscopy of facial lentigo maligna and lentigo maligna melanoma: a preliminary study. *Br J Dermatol* 2009; 161(6): 1307–16.
- Guitera P, Pellacani G, Crotty KA et al. The impact of in vivo reflectance confocal microscopy on the diagnostic accuracy of lentigo maligna and equivocal pigmented and nonpigmented macules of the face. *J Invest Dermatol* 2010; 130(8): 2080–91.
- Braga JC, Scope A, Klaz I et al. The significance of reflectance confocal microscopy in the assessment of solitary pink skin lesions. *J Am Acad Dermatol* 2009; 61(2): 230–41.
- Guitera P, Menzies SW, Argenziano G et al. Dermoscopy and in vivo confocal microscopy are complementary techniques for diagnosis of difficult amelanotic and light-coloured skin lesions. *Br J Dermatol* 2016; 175(6): 1311–9.
- Wurm F, Pellacani G, Longo C et al. The value of reflectance confocal microscopy in diagnosis of flat pigmented facial lesions: a prospective study. *J Eur Acad Dermatol Venereol* 2017; 31(8): 1349–54.
- Cinotti E, Labeille B, Debarbieux S et al. Dermoscopy vs. reflectance confocal microscopy for the diagnosis of lentigo maligna. *J Eur Acad Dermatol Venereol* 2018 Jan 17. [Epub ahead of print].
- Scope A, Benvenuto-Andrade C, Agero AL et al. In vivo reflectance confocal microscopy imaging of melanocytic skin lesions: consensus terminology glossary and illustrative images. *J Am Acad Dermatol* 2007; 57(4): 644–58.
- Rishpon A, Kim N, Scope A et al. Reflectance confocal microscopy criteria of squamous cell carcinoma and actinic keratoses. *Arch Dermatol* 2009; 145(7): 766–72.
- Moscarella E, Rabinovitz H, Zalaudek I et al. Dermoscopy and reflectance confocal microscopy of pigmented actinic keratoses: a morphological study. *J Eur Acad Dermatol Venereol* 2015; 29(2): 307–14.
- Guitera P, Menzies SW, Longo C et al. In vivo confocal microscopy for diagnosis of melanoma and basal cell carcinoma using a two-step method: analysis of 710 consecutive clinically equivocal cases. *J Invest Dermatol* 2012; 132(10): 2386–94.
- Ahlgrimm-Siess V, Cao T, Oliviero M et al. Seborrheic keratosis: reflectance confocal microscopy features and correlation with dermoscopy. *J Am Acad Dermatol* 2013; 69(1): 120–6.
- Bassoli S, Rabinovitz HS, Pellacani G et al. Reflectance confocal microscopy criteria of lichen planus-like keratosis. *J Eur Acad Dermatol Venereol* 2012; 26(5): 578–90.

- 23 Laimer M, Arzberger E, Kirchner CA et al. Noninvasive RCM for differentiation of melanotic macules from melanocytic lesions-blinded evaluation of a series of 42 pigmented macules. *Dermatol Surg* 2017; 43(7): 911–9.
- 24 Wurm EM, Curchin CE, Lambie D et al. Confocal features of equivocal facial lesions on severely sun-damaged skin: four case studies with dermatoscopic, confocal, and histopathologic correlation. *J Am Acad Dermatol* 2012; 3: 463–73.
- 25 Xiong YQ, Ma SJ, Mo Y et al. Comparison of dermoscopy and reflectance confocal microscopy for the diagnosis of malignant skin tumours: a meta-analysis. *J Cancer Res Clin Oncol* 2017; 143(9): 1627–35.
- 26 Pellacani G, Pepe P, Casari A, Longo C. Reflectance confocal microscopy as a second-level examination in skin oncology improves diagnostic accuracy and saves unnecessary excisions: a longitudinal prospective study. *Br J Dermatol* 2014; 171(5): 1044–51.
- 27 Alarcon I, Carrera C, Palou J et al. Impact of in vivo reflectance confocal microscopy on the number needed to treat melanoma in doubtful lesions. *Br J Dermatol* 2014; 170: 802–8.
- 28 Persechino F, De Carvalho N, Ciardo S et al. Folliculotropism in pigmented facial macules: Differential diagnosis with reflectance confocal microscopy. *Exp Dermatol* 2018; 27(3): 227–32.