

## ORIGINAL ARTICLE

# Flat scalp melanoma dermoscopic and reflectance confocal microscopy features correspond to histopathologic type and lesion location

F. Garbarino,<sup>1,†</sup>  R. Pampena,<sup>2,†</sup>  M. Lai,<sup>2</sup>  A.R. Pereira,<sup>3,4</sup> S. Piana,<sup>5</sup> A.M. Cesinaro,<sup>6</sup> E. Cinotti,<sup>7</sup> D. Fiorani,<sup>7</sup> S. Ciardo,<sup>1</sup> F. Farnetani,<sup>1</sup>  J. Chester,<sup>1</sup>  G. Pellacani,<sup>8</sup>  P. Guitera,<sup>3,4,9</sup> C. Longo<sup>1,2,\*</sup> 

<sup>1</sup>Department of Dermatology, University of Modena and Reggio Emilia, Modena, Italy

<sup>2</sup>Azienda Unità Sanitaria Locale – IRCCS di Reggio Emilia, Centro Oncologico ad Alta Tecnologia Diagnostica-Dermatologia, Reggio Emilia, Italy

<sup>3</sup>Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital, Sydney, NSW, Australia

<sup>4</sup>Faculty of Medicine & Health, University of Sydney, Sydney, NSW, Australia

<sup>5</sup>Pathology Unit, Azienda Unità Sanitaria Locale - IRCCS di Reggio Emilia, Reggio Emilia, Italy

<sup>6</sup>Department of Pathology, Azienda Ospedaliero-Universitaria, Policlinico di Modena, Modena, Italy

<sup>7</sup>Department of Medical, Surgical and Neurological Science, Dermatology Section, University of Siena, S. Maria Alle Scotte Hospital, Siena, Italy

<sup>8</sup>Department of Dermatology, University of La Sapienza, Roma, Italy

<sup>9</sup>Melanoma Institute Australia, Sydney, NSW, Australia

\*Correspondence: C. Longo. E-mail: longo.caterina@gmail.com

## Abstract

**Background** Dermoscopy and Reflectance Confocal Microscopy (RCM) features of scalp melanoma according to lesion location and histopathology have not been fully investigated.

**Objectives** To reveal dermoscopic and RCM features of scalp melanoma according to lesion location and histopathology.

**Methods** We retrospectively retrieved images of suspicious, atypical excised, flat melanocytic lesions of the scalp, assessed on dermoscopy and RCM at five centres, from June 2007 to April 2020. Lesions were classified according to histopathological diagnoses of nevi, lentigo maligna melanoma (LM/LMM) or superficial spreading melanoma (SSM). Clinical, dermoscopic and RCM images were evaluated; LM/LMM and SSM subtypes were compared through multivariate analysis.

**Results** Two hundred forty-seven lesions were included. *In situ* melanomas were mostly LM (81.3%), while invasive melanomas were mostly SSM (75.8%). Male sex, baldness and chronic sun-damaged skin were associated with all types of melanomas and in particular with LM/LMM. LMs were mostly located in the vertex area and SSM in the frontal (OR: 8.8;  $P < 0.05$ , CI 95%) and temporal (OR: 16.7;  $P < 0.005$ , CI 95%) areas. The dermoscopy presence of pseudo-network, pigmented rhomboidal structures, obliterated hair follicles and annular–granular pattern were associated with LM diagnoses, whereas bluish-white veil was more typical of SSM. Observations on RCM of atypical roundish and dendritic cells in the epidermis were associated with SSM (42.4%) and dendritic cells with LM (62.5%) diagnoses. Folliculotropism on RCM was confirmed as a typical sign of LM.

**Conclusions** Flat scalp melanomas reveal specific dermoscopic and RCM features according to histopathologic type and scalp location.

Received: 4 February 2021; Accepted: 13 April 2021

## Conflict of interest

None declare.

## Funding sources

None.

<sup>†</sup>These Authors share the first authorship.

## Introduction

Melanoma of the scalp is an uncommon condition, accounting for nearly 3–5% of all cutaneous melanomas,<sup>1,2</sup> falling under the umbrella of melanoma located on special sites.<sup>3,4</sup> Previous studies report poor associated prognosis,<sup>5–11</sup> which may be due to the abundance of vessels and lymphatics in this anatomical location.<sup>12–16</sup> However, delayed diagnosis may also play a role, as detailed clinical and dermoscopic examination is often hindered by the presence of hair.

Sun damage, male sex and baldness are clinical factors reported to increase melanoma risk and they may also be determinant in melanoma subtype.<sup>17,18</sup> In particular, lentigo maligna melanoma (LMM) is more often associated with chronic sun exposure and sun damage, while superficial spreading melanoma (SSM) mostly depends on intermittent sun exposure and history of sunburns.<sup>19–22</sup> Dermoscopy has already been confirmed as a useful tool for early diagnosis of melanoma of the scalp.<sup>23–28</sup> Interestingly, previous studies have described the scalp as a transition area, because specific dermoscopic criteria of both facial and body (trunk and limbs) melanocytic lesions frequently coexist in this body site.<sup>1,29–31</sup>

Reflectance confocal microscopy (RCM) is a non-invasive imaging technique<sup>32</sup> that enables *in vivo* horizontal scanning of skin lesions at nearly histological resolution and has been proven to assist in routine evaluation of melanocytic lesions.<sup>33–39</sup> To date, RCM features of scalp melanocytic lesions have only been reported for a small number of cases.<sup>4</sup>

The current study aims to reveal dermoscopic and RCM features of atypical melanocytic lesions of the scalp, according to distinct topographic areas and histopathology melanoma classification as LMM or SSM.

## Materials and methods

### Study population

This multicentric study retrospectively collected atypical, suspicious melanocytic lesions of the scalp, excised between June 2007 and April 2020, from five tertiary, referral centres (Division of Dermatology, University of Modena and Reggio Emilia, Italy; Centro Oncologico ad Alta Tecnologia Diagnostica, Arcispedale S. Maria Nuova, Reggio Emilia, Italy; Dermatology Section, S. Maria alle Scotte Hospital, University of Siena, Italy; Melanoma Institute Australia and Sydney Melanoma Diagnostic Centre, University of Sydney, Australia). Only melanoma or highly suspicious nevi with high quality clinical, dermoscopy and RCM images (VivaScope 1500 or VivaScope 3000, Mavig, Munich, Germany) and histological diagnoses or >12 months follow-up were included. Nodular lesions were excluded.<sup>40</sup>

### Histology assessment

In cases where a generic melanoma diagnosis was available, LMM or SSM type was retrospectively classified in accordance

with two Pathologists (AMC and SP), according to WHO classification of skin tumours.<sup>41</sup>

In detail, LMM diagnoses characterized lesions of invasive melanoma, associated with a prevalent lentiginous, *in situ* component (LM); the latter, LM, although widespread, tends to be cytologically inconspicuous and mostly located in the basal epidermis. Pagetoid spread is usually absent. SSM is associated with a prevalent invasive melanoma made up by large cells with an evident pagetoid spread. Nevi were lesions with either confirmed histopathological diagnosis or referred to clinical and instrumental follow-up (12 months minimum follow-up) without excision.

### Clinical, dermoscopic and RCM assessment

All clinical, dermoscopic and RCM images were retrospectively evaluated by a single author (FG) with the supervision of a dermoscopy and confocal microscopy expert dermatologist (RP), for the presence of a predefined set of criteria:

- Clinical criteria: sun damage of the scalp, presence of baldness and subsite scalp location according to Stanganelli *et al.*<sup>29</sup>
- Dermoscopic and RCM criteria: a list of criteria published in literature and associated with LM/LMM and SSM in other body areas was created by two expert dermatologists (CL, GP).<sup>20,23,24,28,33,35,36,42,43</sup> The global dermoscopic and RCM patterns were also evaluated.<sup>44</sup>

### Statistical analysis

Quantitative variables were assessed for normal distribution and then compared using Student's *t*-test or the Mann–Whitney *U*-test. For qualitative variables, the chi-square or Fisher's exact tests were applied. For statistical purposes, *in situ* non-LM melanoma was considered SSM, and LM and LMM were classified together. Pairwise comparisons were performed between clinical/demographics, dermoscopic and RCM variables according to final diagnosis (nevus, LM/LMM, SSM). Univariate logistic regression analysis identified variables significantly associated with LM/LMM or SSM diagnoses. Multivariable logistic regression model with backward stepwise variable selection defined independent demographics, clinical, dermoscopic and RCM features associated with LM/LMM and SSM diagnosis. Alpha level was set at 0.05, while 0.10 was used as the cut-off for variable inclusion in the multivariable model. Statistical analyses were performed using the IBM SPSS 26.0 package (Statistical Package for Social Sciences, IBM SPSS Inc., Chicago, IL, USA.)

## Results

### Study population

A total of 247 lesions (245 patients) were included; median age was 59 years [interquartile range (IQR): 45.5–76.9 years] and most (64.9%) patients were male. Among the lesions, 39.2%

( $n = 97$ ) were diagnosed at histopathology as melanoma (49 LMs, 15 LMMs, eight *in situ* melanomas and 25 SSMs) and 20.8% ( $n = 53$ ) with histological confirmation of nevi (15 blue nevi, 19 compound nevi, one congenital nevus, eight dermal nevi, nine junctional nevi, one Spitz nevus). The remaining lesions (39.6%;  $n = 97$ ) underwent clinical/dermoscopic or RCM follow-up ( $\geq 12$  month) without excision.

Most melanomas were diagnosed as *in situ* (58.8%), of which, most were LMs subtype (76.6% LMs vs. 24.2% SSM,  $P < 0.001$ ). The Median Breslow thickness of all invasive melanoma was 0.5 mm (IQR: 0.4–1.3 mm), with no significant differences between LMM and SSM groups (Table 1).

**Table 1** Melanoma histopathologic features

Variables	Final diagnosis		Total	P value	
	LM/LMM	SSM			
Stage	<i>In situ</i>	49 (76.6%)	8 (24.2%)	57 (58.8%)	<0.001
	Invasive	15 (23.4%)	25 (75.8%)	40 (41.2%)	
Median Breslow (IQR)	0.5 (0.3–0.6)	0.6 (0.4–1.8)	0.5 (0.4–1.3)	0.17	
Ulceration	0 (0.0%)	4 (12.1%)	4 (4.1%)	0.012*	
Mitosis	2 (13.3%)	10 (40.0%)	12 (30.0%)	0.152*	
<b>Total</b>	<b>64</b>	<b>33</b>	<b>97</b>		

The SSM groups also include *in situ* non-LM melanomas. IQR, interquartile range; LM/LMM, lentigo maligna and lentigo maligna melanoma; SSM, superficial spreading melanoma.

\*Fisher's exact test.

### Clinical assessment

Clinical baseline characteristics confirmed that melanoma diagnoses were significantly associated with male sex ( $<0.001$ ) and baldness ( $<0.001$ ) compared to nevi diagnoses (Table 2). Clinically evident sun damage of the scalp was recorded more frequently in association with LM/LMM diagnoses than SSM ( $P < 0.001$ ) and more frequently reported among melanomas than nevi ( $P < 0.001$ ). Nevi and SSM lesions were mostly located in the fronto-temporal area (56.7% and 51.5%, respectively), whereas LM/LMM were mainly detected on the vertex (50%).

### Dermoscopy assessment

Dermoscopy evaluation revealed that atypical criteria more frequently encountered among nevi were atypical pigment network (10.6%) and atypical vascular pattern (11.3%; Table 3). Atypical network was also observed in the majority of SSMs (63.6%) and in 34.4% of LM/LMM (Figs 1 and 2). Whereas concerning atypical vessels, they were found in 36.4% of SSM, but no significant differences were observed between nevi and LM/LMM (11.3% vs. 10.9%,  $P > 0.99$ , respectively). According to the global pattern, the majority of nevi displayed a regular and symmetric global pattern, with a prevalence of the homogenous pattern (42.7%), whereas for both melanomas subtypes the main pattern was multicomponent /asymmetrical (in almost all cases).

Among the melanoma lesions, SSM was mainly and more frequently characterized by regression features (75.8%) and

**Table 2** Clinical and demographics features

Variables	Final diagnosis			Total	P values		
	Nevi	LM/LMM	SSM		LM/LMM vs. SSM	Nevi vs. melanoma	
Median age, years (IQR)	50 (39–61)	77.5 (65.5–81)	71 (59.5–84.5)	59 (45.5–76.9)	0.529	<0.001	
Sex	Male	75 (51.0%)	56 (90.3%)	25 (75.8%)	158 (64.8%)	0.072	<0.001
	Female	72 (49.0%)	6 (9.7%)	8 (24.2%)	87 (35.2%)		
<b>Total patients</b>	<b>147</b>	<b>62</b>	<b>33</b>	<b>245</b>			
Scalp site	Frontal	36 (24.0%)	11 (17.2%)	8 (24.2%)	55 (22.3%)	0.01	0.001*
	Parietal	22 (14.7%)	15 (23.4%)	4 (12.1%)	41 (16.6%)		
	Temporal	49 (32.7%)	5 (7.8%)	9 (27.3%)	63 (25.5%)		
	Vertex	31 (20.7%)	32 (50.0%)	9 (27.3%)	72 (29.1%)		
	Occipital	11 (7.3%)	1 (1.6%)	3 (9.1%)	15 (6.1%)		
	Nucal	1 (0.7%)	0 (0.0%)	0 (0.0%)	1 (0.4%)		
Hair coverage	Bald	51 (34.0%)	47 (73.4%)	19 (57.6%)	117 (47.4%)	0.248	<0.001
	Thinning of hair	37 (24.7%)	10 (15.6%)	7 (21.2%)	54 (21.9%)		
	Abundant hair	62 (41.3%)	7 (10.9%)	7 (21.2%)	76 (30.8%)		
Sun damage	34 (22.7%)	57 (89.1%)	19 (57.6%)	110 (44.5%)	<0.001	<0.001	
<b>Total lesions</b>	<b>150</b>	<b>64</b>	<b>33</b>	<b>247</b>			

LM/LMM, lentigo maligna and lentigo maligna melanoma; SSM, superficial spreading melanoma.

The SSM groups also include *in situ* non-LM melanomas.

\*No more significant when comparing nevi with SSM ( $P = 0.941$ ).

**Table 3** Dermoscopic characteristics of nevi, SSM and LM/LMM

Variables	Final diagnosis			Total	P values	
	Nevi	LM/LMM	SSM		LM/LMM vs. SSM	Nevi vs. melanoma
Atypical pigment network	16 (10.7%)	22 (34.4%)	21 (63.6%)	59 (23.9%)	0.006	<0.001
Blue-white veil	2 (1.3%)	6 (9.4%)	14 (42.4%)	22 (8.9%)	<0.001	<0.001
Atypical vascular pattern	17 (11.3%)	7 (10.9%)	12 (36.4%)	36 (14.6%)	0.003	0.037‡
Irregular streaks	2 (1.3%)	1 (1.6%)	6 (18.2%)	9 (3.6%)	0.006*	0.032*,‡‡
Irregular pigmented blotches	6 (4.0%)	12 (18.8%)	14 (42.4%)	32 (12.9%)	0.013	<0.001
Irregular dots/globules	1 (0.7%)	3 (4.7%)	6 (18.2%)	10 (4.0%)	0.058*	0.001*,‡‡‡
Inverse network	3 (2.0%)	1 (1.6%)	4 (12.1%)	8 (3.2%)	0.044*	0.094*,‡‡
Regression	7 (4.7%)	27 (42.2%)	25 (75.8%)	59 (23.9%)	0.002	<0.001
Regression ≥50%	1 (0.7%)	5 (7.8%)	8 (24.2%)	14 (5.7%)	0.032*	<0.001
Atypical pseudo-network	5 (3.3%)	38 (59.4%)	7 (21.2%)	50 (20.2%)	<0.001	<0.001
Annular–granular pattern	2 (1.30%)	37 (57.8%)	4 (12.1%)	43 (17.4%)	<0.001	<0.001
Circle within a circle	1 (0.7%)	13 (20.3%)	2 (6.1%)	17 (6.9%)	0.066	<0.001†
Pigmented rhomboidal structures	2 (1.3%)	24 (37.5%)	5 (15.2%)	31 (12.5%)	0.023	<0.001
Obliterated hair follicle	1 (0.7%)	21 (32.8%)	2 (6.1%)	24 (9.7%)	0.003	<0.001†
<b>Global pattern</b>					<b>0.341</b>	<b>&lt;0.001</b>
Multicomponent asymmetric	3 (2.0%)	60 (93.8%)	33 (100%)	96 (38.9%)		
Globular	25 (16.7%)	3 (4.7%)	0 (0.0%)	28 (11.3%)		
Reticular	28 (18.7%)	1 (1.6%)	0 (0.0%)	29 (11.7%)		
Homogeneous	64 (42.7%)	0 (0.0%)	0 (0.0%)	64 (25.9%)		
Multicomponent symmetrical	30 (20.0%)	0 (0.0%)	0 (0.0%)	30 (12.1%)		
<b>Total</b>	<b>150</b>	<b>64</b>	<b>33</b>	<b>247</b>		

The SSM groups also include *in situ* non-LM melanomas.

LM/LMM, lentigo maligna and lentigo maligna melanoma; SSM, superficial spreading melanoma.

\*Fisher's exact test. †No more significant when comparing nevi with SSM ( $P = 0.084$ ). ††Significant when comparing nevi with SSM ( $P = 0.021$ ). ‡, ‡‡, ‡‡‡ no more significant when comparing nevi with LM/LMM ( $P = 0.933$ ;  $P > 0.99$ ;  $P = 0.081$ , respectively).

atypical pigmented network (63.6%), followed by blue-white veil, irregular pigmented blotches (both 42.4%) and atypical vascular pattern (36.4%). LM/LMM mainly displayed atypical pseudo-network (59.4%) and annular–granular pattern (57.8%), followed by pigmented rhomboidal structures (37.5%) and obliterated hair follicles (32.8%).

Interestingly, some LM/LMM specific criteria were also observed in SSM; in particular atypical pseudo-network (21.2% of cases) and more than one third of LM/LMM also displayed at least one 7-point check list criterion, in particular atypical pigmented network (34.4%) and regression features (42.2%).

### RCM assessment

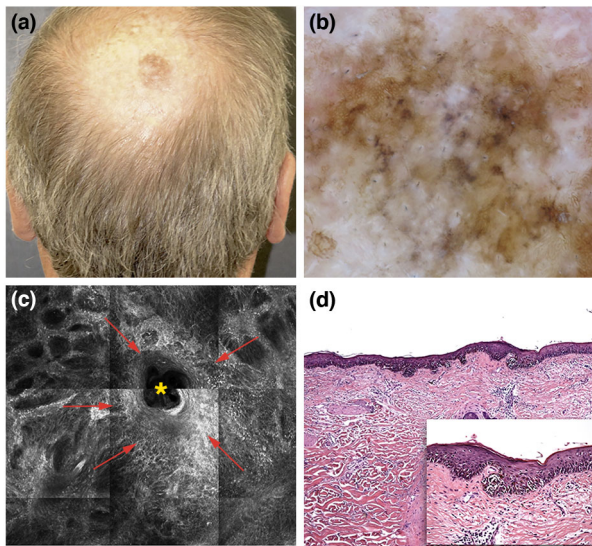
Only a minority of nevi displayed atypical features on RCM examination. More than 10% had atypical pagetoid (epidermal) or junctional atypical cells, which were almost exclusively dendritic in shape. Regarding the global confocal pattern of scalp nevi, they were almost equally characterized in our series by a ringed, meshwork, clod and aspecific pattern.

No significant differences were observed when comparing SSM and LM/LMM, with the exception of folliculotropism, which was more frequently reported in LM/LMM than SSM (68.6% vs. 42.4%, respectively,  $P = 0.012$ ). Pagetoid cells and

atypical junctional cells were observed in the great majority of melanoma cases, with a prevalence of the dendritic shape. The coexistence of dendritic and roundish pagetoid and junctional atypical cells was more frequently seen among SSMs than LM/LMMs (42.4% vs. 21.9% and 48.5% vs. 26.6%, respectively,  $P < 0.001$ ). Concerning the global pattern, most melanoma cases had a meshwork (37.5% of LM/LMM and 45.5% of SSM) or aspecific pattern (57.8% of LM/LMM and 39.4% of SSM; Table 4).

### Logistic regression analysis

Univariate logistic regression analysis was first performed to evaluate which clinical/demographics, dermoscopic, confocal and histopathological factors were significantly associated with LM/LMM or SSM diagnosis (Table S1). A multivariable model was then constructed including factors significantly associated with melanoma subtypes in univariate analysis (Table 5). We demonstrated that SSM subtype was independently associated with an invasive stage (OR: 10.1; 95% CI: 2.5–40.0,  $P = 0.001$ ), with the temporal and frontal locations (OR: 55.8; 95% CI: 6.1–506.9,  $P < 0.001$ ; OR: 10.5; 95% CI: 1.6–70.2,  $P = 0.015$ ) and with the presence of blue-white veil on dermoscopic examination (OR: 9.9; 95% CI: 1.7–56.5,  $P = 0.009$ ). Conversely, the LM/LMM



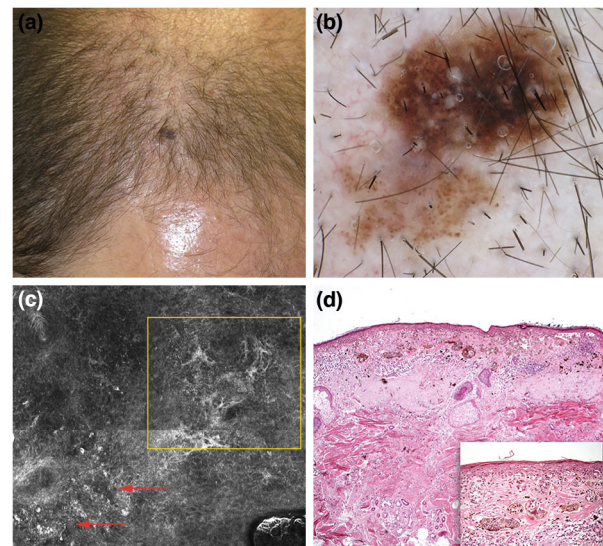
**Figure 1** Lentigo maligna of the vertex region in a bald man. (a) Dermoscopic features of lentigo maligna (b) including atypical pseudo-network, annular-granular pattern, grey colour and rhomboidal structures. (20 $\times$  magnification). Reflectance confocal microscopy reveals the presence of many dendritic cells (red arrows) at the dermoepidermal junction, with folliculotropism. (yellow asterisk within follicle) (c). Histological slide (H&E staining); melanoma *in situ* with lentigo maligna pattern of growth. At high power, melanoma cells grow mainly at the base of the epidermis and are singularly dispersed.

subtype was more frequently *in situ* (LM) and located on the vertex.

## Discussion

This study reveals that scalp LM/LMM subtype is associated with sun damaged and is predominantly located on the vertex, characterized on dermoscopy by classic facial LM features and on RCM by classic melanoma features plus folliculotropism. Scalp SSM is mostly located on the frontal and temporal areas and is characterized by typical dermoscopy and RCM features of SSM in other body areas. Nevi were also mainly located on the frontal and temporal areas; RCM features of nevi were reassuring although a subset of them revealed cytologic atypia (pagetoid cells or atypical melanocytes at dermal-epidermal junction) on RCM.

The study confirms the common risk factors of baldness, male sex and chronic sun damage for scalp melanoma,<sup>19,21,22,45</sup> in particular with LM/LMM diagnoses.<sup>17</sup> We observed that 50% of LM/LMMs were located on the vertex, whereas SSMs were more frequently seen on the temporal and frontal areas. These data can be explained by the different pattern of UV exposure of these areas; the vertex is more chronically exposed in bald individuals, while the frontal-temporal area is more at risk of intermittent sun exposure.<sup>17</sup> Interestingly, nevi share a similar distribution pattern as SSMs, which suggest a common pathogenetic



**Figure 2** Superficial spreading melanoma of the parietal region of the scalp in a man with thinning hair. (a) Dermoscopic features (b), asymmetric lesion with globular pattern in the lower part, white veil in the intermedium portion, atypical network, globules and multiple colours in the upper part. (20 $\times$  magnification) Reflectance confocal microscopy shows pagetoid spreading of roundish (red arrows) and dendritic cells (yellow square) in the superficial layer. (c) Histological slide (H&E staining); superficial spreading melanoma with some infiltrating neoplastic aggregates in the dermis. The pattern of growth in depth is nested, and it is associated with an evident epidermotropism.

background that is less susceptible to UV radiation compared to LM/LMM type.

In our study population, most of the melanomas were *in situ*, which may be due to earlier diagnosis performed at our tertiary referral centres, utilizing both dermoscopy and RCM in routine clinical practice. Benati *et al.*<sup>4</sup> published a small cohort of scalp melanoma only, with a higher number of invasive melanomas, which may partially be explained by the majority of melanomas included being SSMs.

In accordance with previous data, bluish-white veil, pigmented blotches, atypical pigmented network and regression were dermoscopic criteria associated with scalp melanoma diagnoses. Stanganelli *et al.*<sup>29</sup> observed that blue-white veil and pigmented blotches are more frequent observed in thick melanomas ( $\geq 1$  mm) while atypical pigmented network and regression occur more often in *in situ* and thin ( $\leq 1$  mm) melanomas. The current study focused on thin melanoma, with the exclusion of nodular lesions. However, we demonstrated that all of the aforementioned dermoscopic criteria had a higher frequency in SSMs. Moreover, we found that other three criteria were significantly more observed among SSMs: atypical vascular pattern, irregular streaks and inverse network.

**Table 4** Reflectance confocal microscopy criteria

Variables	Final diagnosis			Total	P values		
	Nevi	LM/LMM	SSM		LM/LMM vs. SSM	Nevi vs. melanoma	
<b>Pagetoid cells</b>		17 (11.3%)	58 (90.6%)	29 (87.9%)	<b>104 (42.1%)</b>	<b>0.731*</b>	<b>&lt;0.001</b>
Pagetoid cells	Absent	133 (88.7%)	6 (9.4%)	4 (12.1%)	<b>143 (57.9%)</b>	<b>0.147</b>	<b>&lt;0.001</b>
	Dendritic	14 (9.3%)	40 (62.5%)	14 (42.4%)	<b>68 (27.5%)</b>		
	Round	2 (1.3%)	4 (6.3%)	1 (3.0%)	<b>7 (2.8%)</b>		
	Both	1 (0.7%)	14 (21.9%)	14 (42.4%)	<b>29 (11.7%)</b>		
<b>Atypical junctional cells</b>		18 (12.0%)	56 (87.5%)	29 (87.9%)	<b>103 (41.7%)</b>	<b>&gt;0.99*</b>	<b>&lt;0.001</b>
Atypical junctional cells	Absent	132 (88.0%)	8 (12.5%)	4 (12.1%)	<b>144 (58.3%)</b>	<b>0.174</b>	<b>&lt;0.001</b>
	Dendritic	12 (8.0%)	36 (56.3%)	12 (36.4%)	<b>60 (24.3%)</b>		
	Round	4 (2.7%)	3 (4.7%)	1 (3.0%)	<b>8 (3.2%)</b>		
	Both	2 (1.3%)	17 (26.6%)	16 (48.5%)	<b>35 (14.2%)</b>		
<b>Folliculotropism</b>		6 (4.0%)	44 (68.8%)	14 (42.4%)	<b>64 (25.9%)</b>	<b>0.012</b>	<b>&lt;0.001</b>
<b>Medusa-like structures</b>		1 (0.7%)	9 (14.1%)	4 (12.1%)	<b>14 (5.7%)</b>	<b>&gt;0.99*</b>	<b>&lt;0.001</b>
<b>Dermal atypia</b>		0 (0.0%)	6 (9.4%)	4 (12.1%)	<b>10 (4.0%)</b>	<b>0.731*</b>	<b>&lt;0.001*</b>
<b>Main RCM architecture</b>						<b>0.096</b>	<b>&lt;0.001</b>
	Aspecific	39 (26.0%)	37 (57.8%)	13 (39.4%)	<b>89 (36.0%)</b>		
	Ringed	34 (22.7%)	3 (4.7%)	3 (9.1%)	<b>40 (16.2%)</b>		
	Meshwork	38 (25.3%)	24 (37.5%)	15 (45.5%)	<b>77 (31.2%)</b>		
	Clod	39 (26.0%)	0 (0.0%)	2 (6.1%)	<b>41 (16.6%)</b>		
<b>Total</b>		<b>150</b>	<b>64</b>	<b>33</b>	<b>247</b>		

The SSM groups also include *in situ* non-LM melanomas.

LM/LMM, lentigo maligna and lentigo maligna melanoma; SSM, superficial spreading melanoma.

\*Fisher's exact test.

**Table 5** Multivariable logistic regression analysis

Variables	OR	95% CI for OR		P value	
		Lower	Upper		
Dermoscopy	Blue-white veil	9.9	1.7	56.5	0.009
	Atypical vascular pattern	5.4	0.8	34.9	0.073
	Inverse network	13.3	0.7	234.4	0.077
Scalp site	Vertex	ref.			0.01
	Parietal	2.5	0.3	18.2	0.357
	Temporal	55.8	6.1	506.9	<0.001
	Occipital	5.1	0	1568.6	0.578
	Frontal	10.5	1.6	70.2	0.015
Stage ( <i>in situ</i> vs. invasive)	10.1	2.5	40.9	0.001	

Factors independently associated with the diagnosis of lentigo maligna / lentigo maligna melanoma: LM/LMM groups vs. *in situ* non-LM / superficial spreading melanoma: SSM group. Variables entered at step 1: Atypical pigment network, Bluish-white veil, Atypical vascular pattern, Irregular streaks, Irregular pigmented blotches, Inverse network, Regression, Atypical pseudo-network, Scalp site, Stage (*in situ* vs. invasive), Folliculotropism.

CI, confidence interval; OR, odds ratio.

Concerning LM/LMM subtype, we confirmed that classic dermoscopic features described for LM on the face<sup>28,38,46</sup> were also observed in LM of the scalp.

The dermoscopic homogeneous/structureless patterns predominantly observed in the nevi included in the current study were in accordance with those observed by Zalaudek *et al.*,<sup>44</sup> despite a different nevus cohort with a more prevalent representation of blue nevi included in the current study.

Many authors have already described the useful application of *in vivo* RCM in detecting melanoma.<sup>33,35–37</sup> In line with previously published papers, most melanoma in the current study had atypical melanocytes at the dermoepidermal junction or in the epidermis (pagetoid spread).

We observed a higher number of dendritic pagetoid cells in the epidermis of LM as compared to SSM. However, SSM lesions more frequently exhibited pagetoid cells (dendritic and roundish

shape), compared to mostly dendritic cells in LM/LMM. Moreover, the presence of atypical cells at the dermal-epidermal junction and the presence of atypia in the dermis were statistically associated with melanoma diagnosis.

In accordance with Borsari *et al.*,<sup>47</sup> pagetoid spreading in the epidermis and atypical cells at the dermal-epidermal junction are RCM-positive predictors for thin melanoma diagnosis. When considering the presence of dendritic cells in the epidermis only, a differential diagnosis between nevus and melanoma is more difficult than in the presence of atypia in the DEJ or in case of roundish or dendritic shaped cells, which are more reliable markers of malignancy.<sup>40</sup> Although different types of cell shape have been described for SSM and LM/LMM, establishing the specific melanoma subtype based only on cell morphology seems to not be possible.

Folliculotropism, already described as a specific feature of facial LM/LMM, was also found to be specific for LM/LMM scalp lesions.<sup>34,38,48,49</sup> Further, medusae-like structures, an RCM feature suggestive of folliculotropism,<sup>38</sup> were associated with malignancy and observed in 14% of LM/LMM and 12% of SSM.

In our series, the most frequently observed invasive melanoma subtype was invasive SSM. Although it is rather difficult to interpret these data, a possible explanation could be related to a more accurate/early diagnosis of LM before the lesion progressed into an invasive lesion, or it may reflect the intrinsic relationship to a biologic, slow-growing attitude of LM.

The main limitations of this study were the retrospective design of the study, and the inclusion of a selected group of highly suspicious melanocytic nevi, sent for second level, *in vivo* assessment with RCM. Moreover, this study included a relatively small number of evaluators.

This study highlights that sun-damaged skin, lesion location on the scalp are specifically correlated with melanoma subtype. Notably, dermoscopy and RCM features commonly associated with melanoma or nevi diagnoses in other body areas can be applied to highly suspicious lesions of the scalp. These revelations should assist clinicians in identifying thin melanomas on this special body site, which may assist in early diagnoses and improved prognoses.

## Acknowledgement

The patients in this manuscript have given written informed consent to the publication of their case details.

## References

- Hofmann-Wellenhof R. Special criteria for special locations 2: scalp, mucosal, and milk line. *Dermatol Clin* 2013; **31**: 625–636.ix.
- Pereira AR, Collgros H, Guitera P *et al.* Melanomas of the scalp: is hair coverage preventing early diagnosis? *Int J Dermatol* 2021; **60**: 340–346.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; **69**: 7–34.
- Benati E, Longo C, Piana S, Moscarella E. Preliminary evaluation of reflectance confocal microscopy features of scalp melanoma. *Australas J Dermatol* 2017; **58**: 312–316.
- Borsari S, Pampena R, Raucci M *et al.* Neck melanoma: clinical, dermoscopic and confocal features. *Dermatology* 2020; **236**: 241–247.
- Lachiewicz AM, Berwick M, Wiggins CL, Thomas NE. Survival differences between patients with scalp or neck melanoma and those with melanoma of other sites in the surveillance, epidemiology, and end results (SEER) program. *Arch Dermatol* 2008; **144**: 144. <https://doi.org/10.1001/archderm.144.4.515>.
- Claeson M, Baade P, Brown S *et al.* Clinicopathological factors associated with death from thin ( $\leq 1.00$  mm) melanoma. *Br J Dermatol* 2020; **182**: 927–931.
- Ozao-Choy J, Nelson DW, Hiles J *et al.* The prognostic importance of scalp location in primary head and neck melanoma. *J Surg Oncol* 2017; **116**: 337–343.
- Garbe C, Büttner P, Bertz J *et al.* Primary cutaneous melanoma. Prognostic classification of anatomic location. *Cancer* 1995; **75**: 2492–2498.
- Green AC, Baade P, Coory M *et al.* Population-based 20-year survival among people diagnosed with thin melanomas in Queensland, Australia. *J Clin Oncol* 2012; **30**: 1462–1467.
- Ringborg U, Afzelius LE, Lagerlöf B *et al.* Cutaneous malignant melanoma of the head and neck. Analysis of treatment results and prognostic factors in 581 patients: a report from the Swedish Melanoma Study Group. *Cancer* 1993; **71**: 751–758.
- Ettl T, Irga S, Müller S *et al.* Value of anatomic site, histology and clinicopathological parameters for prediction of lymph node metastasis and overall survival in head and neck melanomas. *J Craniomaxillofac Surg* 2014; **42**: e252–e258.
- Larson DL, Larson JD. Head and neck melanoma. *Clin Plast Surg* 2010; **37**: 73–77.
- de Giorgi V, Rossari S, Gori A *et al.* The prognostic impact of the anatomical sites in the ‘head and neck melanoma’: scalp versus face and neck. *Melanoma Res* 2012; **22**: 402–405.
- Schmalbach CE, Johnson TM, Bradford CR. The management of head and neck melanoma. *Curr Probl Surg* 2006; **43**: 781–835.
- Sparks DS, Read T, Lonnie M *et al.* Primary cutaneous melanoma of the scalp: patterns of recurrence. *J Surg Oncol* 2017; **115**: 449–454.
- Benati E, Longo C, Bombonato C *et al.* Baldness and scalp melanoma. *J Eur Acad Dermatol Venereol* 2017; **31**: e528–e530.
- Xie C, Pan Y, McLean C *et al.* Scalp melanoma: distinctive high risk clinical and histological features. *Australas J Dermatol* 2017; **58**: 181–188.
- Higgins HW, Cho E, Weinstock MA *et al.* Gender differences, UV exposure and risk of lentigo maligna in a nationwide healthcare population cohort study. *J Eur Acad Dermatol Venereol* 2019; **33**: 1268–1271.
- Todorovic-Zivkovic D, Argenziano G, Lallas A *et al.* Age, gender, and topography influence the clinical and dermoscopic appearance of lentigo maligna. *J Am Acad Dermatol* 2015; **72**: 801–808.
- Gaudy-Marqueste C, Madjlessi N, Guillot B *et al.* Risk factors in elderly people for lentigo maligna compared with other melanomas: a double case-control study. *Arch Dermatol* 2009; **145**: 418–423.
- Austin PF, Cruse CW, Lyman G *et al.* Age as a prognostic factor in the malignant melanoma population. *Ann Surg Oncol* 1994; **1**: 487–494.
- Haenssle HA, Korpas B, Hansen-Hagge C *et al.* Seven-point checklist for dermatoscopy: performance during 10 years of prospective surveillance of patients at increased melanoma risk. *J Am Acad Dermatol* 2010; **62**: 785–793.
- Unlu E, Akay BN, Erdem C. Comparison of dermatoscopic diagnostic algorithms based on calculation: the ABCD rule of dermatoscopy, the seven-point checklist, the three-point checklist and the CASH algorithm in dermatoscopic evaluation of melanocytic lesions. *J Dermatol* 2014; **41**: 598–603.
- Lallas A, Apalla Z, Chaidemenos G. New trends in dermatoscopy to minimize the risk of missing melanoma. *J Skin Cancer* 2012; **2012**: 820474.
- Argenziano G, Fabbrocini G, Carli P *et al.* Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions. Comparison of the ABCD rule of dermatoscopy and a new 7-point checklist based on pattern analysis. *Arch Dermatol* 1998; **134**: 1563–1570.

- 27 Lallas A, Argenziano G, Moscarella E *et al.* Diagnosis and management of facial pigmented macules. *Clin Dermatol* 2014; **32**: 94–100.
- 28 Schiffner R, Schiffner-Rohe J, Vogt T *et al.* Improvement of early recognition of lentigo maligna using dermoscopy. *J Am Acad Dermatol* 2000; **42**: 25–32.
- 29 Stanganelli I, Argenziano G, Sera F *et al.* Dermoscopy of scalp tumours: a multi-centre study conducted by the international dermoscopy society: dermoscopy of scalp tumours. *J Eur Acad Dermatol Venereol* 2012; **26**: 953–963.
- 30 Zalaudek I, Leinweber B, Soyer HP *et al.* Dermoscopic features of melanoma on the scalp. *J Am Acad Dermatol* 2004; **51**: 88–90.
- 31 Lallas A, Longo C, Manfredini M *et al.* Accuracy of dermoscopic criteria for the diagnosis of melanoma *in situ*. *JAMA Dermatol* 2018; **154**: 414.
- 32 Wurm EMT, Longo C, Curchin C *et al.* *In vivo* assessment of chronological ageing and photoageing in forearm skin using reflectance confocal microscopy: assessment of chronological ageing and photoageing using RCM. *Br J Dermatol* 2012; **167**: 270–279.
- 33 Pellacani G, De Pace B, Reggiani C *et al.* Distinct melanoma types based on reflectance confocal microscopy. *Exp Dermatol* 2014; **23**: 414–418.
- 34 Farnetani F, Manfredini M, Chester J *et al.* Reflectance confocal microscopy in the diagnosis of pigmented macules of the face: differential diagnosis and margin definition. *Photochem Photobiol Sci* 2019; **18**: 963–969.
- 35 Longo C, Pellacani G. Melanomas. *Dermatol Clin* 2016; **34**: 411–419.
- 36 Pellacani G, Guitera P, Longo C *et al.* The impact of *in vivo* reflectance confocal microscopy for the diagnostic accuracy of melanoma and equivocal melanocytic lesions. *J Invest Dermatol* 2007; **127**: 2759–2765.
- 37 Pellacani G, Cesinaro AM, Seidenari S. *In vivo* assessment of melanocytic nests in nevi and melanomas by reflectance confocal microscopy. *Modern Pathol* 2005; **18**: 469–474.
- 38 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**: 128–133.
- 39 Borsari S, Pampena R, Lallas A *et al.* Clinical indications for use of reflectance confocal microscopy for skin cancer diagnosis. *JAMA Dermatol* 2016; **152**: 1093–1098.
- 40 Longo C, Farnetani F, Ciardo S *et al.* Is confocal microscopy a valuable tool in diagnosing nodular lesions? A study of 140 cases. *Br J Dermatol* 2013; **169**: 58–67.
- 41 Elder DE, Bastian BC, Cree IA *et al.* The 2018 World Health Organization classification of cutaneous, mucosal, and uveal melanoma: detailed analysis of 9 distinct subtypes defined by their evolutionary pathway. *Arch Pathol Lab Med* 2020; **144**: 500–522.
- 42 Pampena R, Borsari S, Lai M *et al.* External validation and comparison of four confocal microscopic scores for melanoma diagnosis on a retrospective series of highly suspicious melanocytic lesions. *J Eur Acad Dermatol Venereol* 2019; **33**: 1541–1546.
- 43 Wurm E, 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**: 1349–1354.
- 44 Zalaudek I, Schmid K, Niederkorn A *et al.* Proposal for a clinical-dermoscopic classification of scalp naevi. *Br J Dermatol* 2014; **170**: 1065–1072.
- 45 Howard MD, Wee E, Wolfe R *et al.* Anatomic location of primary melanoma: survival differences and sun exposure. *J Am Acad Dermatol* 2019; **81**: 500–509.
- 46 Marghoob AA, Malvey J, Braun RP. Atlas of dermoscopy, 2012. URL <http://www.crcnetbase.com/isbn/9781841847627> (last accessed: 30 September 2020).
- 47 Borsari S, Pampena R, Benati E *et al.* *In vivo* dermoscopic and confocal microscopy multistep algorithm to detect *in situ* melanomas. *Br J Dermatol* 2018; **179**: 163–172.
- 48 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; **32**: 1284–1291.
- 49 Dika E, Lambertini M, Patrizi A *et al.* Folliculotropism in head and neck lentigo maligna and lentigo maligna melanoma. *J Dtsch Dermatol Ges* 2021; **19**: 223–229.

### Supporting information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Univariate logistic regression analysis.