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Reflectance confocal microscopy terminology glossary for non-melanocytic skin lesions: A systematic review

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Abstract

Background: There is lack of uniformity in reflectance confocal microscopy (RCM) terminology for non-melanocytic lesions (NMLs).

Objective: To review published RCM terms for NMLs and identify likely-synonymous terms.

Methods: Systematic review of original research articles adhering to PRISMA guidelines was conducted until August 19, 2017. Two investigators gathered all published RCM terms used to describe basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and seborrheic keratosis/solar lentigo/lichen planus-like keratosis (SK/SL/LPLK). Synonymous terms were grouped based on similarity in definition and histopathological correlates.

Results: Thirty-one studies met inclusion criteria. Average frequency of use per term was 1.6 (range 1–8). By grouping synonymous terms, the number of terms could be reduced from 139 to 66 terms (52.5%) in total, from 66 to 18 for BCC, 58 to 36 for SCC, and 23 to 12 for SK/SL/LPLK. The frequency of terms usage stratified by anatomic layer (suprabasal epidermis vs. basal layer/DEJ/Superficial dermis) was 27 (25.7%) vs. 78 (74.2%) for BCC; 60 (64.5%) vs. 33 (34.5%) for SCC, and 15 (45.4%) vs. 18 (54.5%) for SK/SL/LPLK, respectively.

Limitations: Non-peer reviewed articles were excluded.

Conclusions: Systematic review of published RCM terms provides the basis for future NMLs terminology consensus.

Capsule summary:

- Use of reflectance confocal microscopy terminology is inconsistent.
- We built a glossary of reflectance confocal microscopy terms for diagnosis non-melanocytic lesions. We identified terms with similar definition and histopathological correlates and reduced the total number of terms by 52.5%. This systematic review may form the basis for attaining terminology consensus.

Keywords

reflectance confocal microscopy; melanoma; non-melanoma skin cancer; basal cell carcinoma; squamous cell carcinoma; seborrheic keratosis; actinic keratosis; lichen planus-like keratosis; diagnosis

INTRODUCTION

Reflectance confocal microscopy (RCM) allows for non-invasive *in vivo* visualization of the skin at a “quasi-histological” resolution.¹ In the 1990s, the histological correlates of RCM attributes of skin were first described.^{2, 3} Since then, more than two hundred articles have been published showing the added value of RCM in the diagnosis of melanoma^{4–6} and non-melanoma skin cancer, including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).^{7–9} Also, RCM has been used for the diagnosis of nevi and benign non-melanocytic skin lesions (NMLs).^{10, 11} While the increase in the number of RCM publications suggests a gradual wider adaptation of this technique, there appears to be an inconsistent usage of RCM

terminology in the literature. Furthermore, descriptive terms used for diagnosing a particular neoplasm, such as “polarization of nuclei” and “epidermal shadow” for BCC have shown to be associated with low inter-observer agreement.¹²

The first expert consensus on RCM terminology, published in 2007 by Scope *et al.* focused solely on melanocytic neoplasms.¹³ To the best of our knowledge, consensus on terminology related to the diagnosis of malignant and benign NMLs is lacking. Recently, category I Current Procedural Terminology (CPT) reimbursement codes by the Centers for Medicare and Medicaid Services in the United States were allotted to RCM imaging.^{1, 14} As a result, there is anticipation for increasing assimilation of RCM into routine clinical work-flow and into the dermatology residency curriculum.¹⁵ This forthcoming clinical integration necessitates standardization of RCM terminology, so that the terms are clearly defined and reproducible, enable structured reporting of RCM-based diagnosis, and facilitate RCM teaching to novices. Herein, we performed a systematic review of terms used in original papers, from 1995 to 2017, to describe RCM features of common NMLs.

METHODS

The results of this systematic review were obtained according to the guidelines for reporting systematic reviews as published in the PRISMA Statement (available in www.prismastatement.org). All images used for illustrating the terms were acquired at the Dermatology Service of Memorial Sloan Kettering Cancer Center, NY, and Dermatology Associates, Plantation, FL, using commercial RCM systems (Vivascope 1500 or Vivascope 3000, Caliber ID, Rochester, MN) and collected under an approved IRB retrospective protocol (#17–083). The basic principles of RCM image acquisition have been previously described.¹

Eligibility criteria

We included all peer-reviewed original articles published to date that contained the diagnosis of common benign and malignant NMLs, including BCC, SCC, actinic keratosis (AK), seborrheic keratosis (SK), solar lentigo (SL), and lichen-planus like keratosis (LPLK). We excluded NMLs that, in our experience, are relatively infrequently subjected to RCM imaging in current practice, such as poroma, clear cell acanthoma, dermatofibroma, atypical fibroxanthoma, and Merkel cell carcinoma, among others. We also excluded articles describing RCM features of NMLs at special anatomic sites, such as genitalia, nails and eyelids.

We excluded literature reviews, single case-reports, conference abstracts, animal studies, and publications lacking full-text. Due to the lack of peer-review process, we also excluded book chapters.

Information sources, search and Study selection

Systematic literature searches were conducted (August 19, 2017) in four databases with no specified date, age, sex, or language restrictions. The databases searched were: (1) MEDLINE (via PubMed); (2) Embase; (3) The Cochrane Library (Cochrane); and (4) Web of Science (WoS). In an effort to be comprehensive and include grey literature publications

into the data set of citations, conference proceedings and abstracts were retrieved from Embase and WoS by utilizing broad and inclusive publication-type filters. Search results were combined in a bibliographic management tool (EndNote, Clarivate Analytics) and duplicates were eliminated both electronically and manually to ensure an efficient de-duplication process. The search strategy employed the Medical Subject Headings (MeSH) phrases: “Microscopy, Confocal” AND (“Skin Neoplasms” OR “Dermatology” OR “Carcinoma” OR “keratosis, actinic” AND “in vivo”) AND (“Terminology” OR “Current Procedural Terminology” OR “Terminology as Topic” OR “Dictionaries as Topic” OR “Data Accuracy” OR “Algorithms” OR “Reproducibility of Results” OR “Classification”. For a complete list of keywords and the final search strategy, see Appendix A. Bibliographies within retrieved articles were also reviewed to identify additional studies. For this specific systematic review, we only included RCM terms pertinent for NML and excluded terms related to melanocytic neoplasms (i.e. melanoma and nevus). Two authors (C.N-D. and M.J.) independently screened all relevant titles and abstracts for eligibility. If necessary, full-text articles were screened. Differences in judgment were resolved with a third reviewer (A.S.) until consensus was reached (Figure 1).

Data collection and extraction process

Two authors (C.N-D. and M.J.) extracted data from the included studies independently. Disagreements were resolved by consensus; if no agreement could be reached, a third author (A.S.) was consulted. The following information was extracted from each study: RCM terms, definition of the RCM term, diagnosis associated with the term, and when known, the histopathological correlate associated with that term. All extracted RCM terms were recorded as published in the literature, chronologically, in an Excel spreadsheet (Microsoft, Redmond, WA). In addition, to weight the use-frequency of RCM terms, we recorded the number of studies that utilized each term. Lastly, we identified all terms that were likely synonymous, based on being associated with a similar RCM definition and histopathological correlates, such as “cleft”, “clefing”, and “cleft-like space”. Furthermore, terms were grouped by their pertinent anatomic level of skin: (1) “suprabasal epidermis” – including the corneal, granular and spinous layers, and (2) the epidermal basal layer / dermo-epidermal junction (DEJ) / and superficial dermis.

Summary measures and statistical analysis

Descriptive statistics were used to detail the number of RCM terms by diagnosis and by anatomic layer. ‘Use frequency’ describes the number of papers describing each RCM term. ‘Weighted use frequency’ describes the relative use frequency for RCM terms per diagnosis – it is the proportion between ‘use frequency’ for RCM terms (as individual terms or as subgroups of synonymous terms) divided by the total ‘use frequency’ for all terms describing that diagnosis.

RESULTS

Thirty-one studies met the inclusion criteria (Figure 1). We identified a total of 139 RCM terms for NMLs described in the literature, including 58 terms for diagnosis of BCC,^{6-8, 16-27} 58 terms for SCC and AK,^{6, 9, 28-37} and 23 terms for SK/SL/LPLK.^{10, 31, 38-42}

The use-frequency of each RCM term and of subgroups of likely-synonymous RCM terms are shown by diagnosis (Tables 1–3). The overall average use frequency of RCM terms was 1.6 (range 1–8). When stratified by specific diagnosis, the average use frequency of RCM terms was 1.8 (range 1–8), 1.6 (range 1–7), and 1.4 (range 1–3) times for the diagnosis of BCC, SCC/AK, and SK/SL/LPLK, respectively. For example, commonly utilized RCM terms included ‘increased vascularity’ – used 8 times among BCC-related papers, and ‘atypical honeycomb pattern’ – used 7 times across SCC-related articles. In contrast, the terms ‘prominent nucleoli’ and ‘fibrillar polarized pattern around tumor’ were used only once among BCC-related papers, and the term ‘multinucleated keratinocytes’ was used only once across SCC-related articles.

By grouping of individual RCM terms based on likely-synonymous definition and histopathological correlates, the total number of RCM terms could be reduced to 66 (52.5% reduction), including 18 terms (68.9% reduction) for BCC (Table 1), 36 terms (37.9% reduction) for SCC/AK (Table 2), and 12 terms (47.8% reduction) for SK/SL/LPLK (Table 3).

To weighed use-frequency for each subgroup of likely-synonymous RCM terms was analyzed by diagnosis. The most commonly used term-subgroups for BCC (Table 1) were “streaming / polarization of nuclei” (n=15, 14.2%), “increased vascularity / prominent vascularity” (n=14, 13.3%), and “tumor nodules / bright tumor islands” (n=10, 9.5%). The most commonly used term-subgroups for SCC/AK (Table 2) were “atypical honeycomb pattern” (n=10, 10.7%), “architectural disarray” (n=9, 9.6%), and “dyskeratotic cells” and “buttonhole vessels” (n=7 for each term; 7.5% each). The most commonly used term-subgroups for SK/SL/LPLK (Table 2) were “bulbous projections” (n=7, 21.2%), “milia-like cysts” (n=4, 13.3%), “typical honeycomb pattern” (n=4; 12.1%), “presence of plump cells/ melanophages” (n=4; 12.1%), and “polycyclic dermal papillae” (n=4; 12.1%).

We also stratified RCM terms by their anatomical level in the skin described, stratified by suprabasal epidermis vs. basal layer/DEJ/superficial dermis.

For BCC, 13 (22.4%) individual RCM terms (in 6 synonymous-term subgroups, 33.3%) were categorized to suprabasal epidermal, while 45 (75%) individual RCM terms (in 12 synonymous-term subgroups, 66.6%) were categorized to basal layer/DEJ/superficial dermis. The weighted use frequency for basal layer/DEJ/superficial dermis terms was higher than suprabasal epidermis terms (n=78 [74.2%] vs. n=27 [25.7%], respectively).

For SCC/AK, 37 (63.7%) individual RCM terms (in 19 synonymous-term subgroups, 51.3%) were categorized to suprabasal epidermal, while 21 (36.2%) individual RCM terms (in 18 synonymous-term subgroups, 48.6%) were categorized to basal layer/DEJ/superficial dermis. The weighted use frequency for suprabasal epidermis terms was higher than basal layer/DEJ/superficial dermis terms (n=60 [64.5%] vs. n=33 [35.4%], respectively).

For SK/SL/LPLK, 9 (39.1%) individual RCM terms (in 6 synonymous-term subgroups, 50%) were categorized to suprabasal epidermal, while 14 (60.8%) individual RCM terms (in 6 synonymous-term subgroups, 50%) were categorized to basal layer/DEJ/superficial

dermis. The weighted use frequency for suprabasal epidermis terms was similar to that of basal layer/DEJ/superficial dermis terms (n=15 (45.4%) vs. n=18 (54.5%), respectively).

DISCUSSION

RCM is a non-invasive imaging technique that has demonstrated good clinical utility in the diagnosis, margin assessment, and treatment monitoring of skin neoplasms.^{1, 43} However, learning to read RCM images may be perceived, at present, as a daunting task that should be left in the hands of dedicated experts. The inconsistent use of RCM terminology in the literature and in scientific meetings, may pose a barrier to the adaptation of RCM by novices. As RCM terminology is still evolving, a systematic review of the terms is warranted at this juncture. Toward improving the consistency of RCM terminology use, we conducted a systematic review of terms for the diagnosis of common benign and malignant NMLs. The goal was to create a more concise and unified glossary of RCM terms for NMLs. First, we gathered all RCM terms described in pertinent original peer-reviewed papers, and then, identified likely-synonymy across terms with similar definition and histopathology correlates. We found a total of 139 RCM terms used to describe features of common NMLs in the literature—an overwhelming number for a novice to comprehend. By grouping based on ‘likely-synonymy’ in the associated definition or histopathological correlation, the list of terms could be reduced by at least half. Furthermore, we assigned a relative weighted score for each RCM term based on its frequency of usage in the literature. We found an average use of 1.6 times for a given term across the 31 studies, highlighting the inconsistent usage of the RCM terms.

Another observation is that the frequency of use of terms was highest at the anatomical level in which the neoplasms is expected to proliferate based on the histopathological correlation. For instance, most of the RCM terms (~75%) for BCC are described at the level of DEJ/superficial dermis level, where BCC aggregates proliferate. Likewise, roughly two-thirds (64.5%) of the RCM terms for SCC/AK were located at epidermal levels, corresponding to pertinent anatomic level of histopathological diagnostic criteria for this the neoplasms. This finding confirms at a larger scale (systematic review) the good correlation between histopathology and RCM. Interestingly, Farnetani *et al.* found a higher interobserver reproducibility for epidermal than dermal RCM terms;¹² they conjectured that the degrading RCM optical resolution and image quality with increasing imaging depth accounts for this observation.¹² Larger studies are needed to confirm this observation.

Towards generating a shortlist of most pertinent RCM terms, we propose several steps. First, “redundant terms” need to be unified, as suggested herein. Second, omission of most infrequently used terms (e.g., ‘prominent nucleoli’ and ‘onion-like’ for BCC^{7, 23}) should be considered. Third, unified terms that have been assigned diagnostic value in studies (e.g. tumor islands for BCC) should be ranked higher than descriptive/supportive terms (e.g., presence of ‘plump cells’ in the dermis and ‘button-hole sign’ for SCC) without clear diagnostic utility. Finally, for select RCM terms with clear-cut histopathological correlates and future new terms, the histopathological term could be preferred (e.g., “dyskeratotic cells” instead of “targetoid cells”), facilitating communication between clinicians and dermatopathologists.

Our study has limitations. First, while the initial tier of our search did not impose any language restrictions, we only included full-text articles in English. This was done to allow direct comparisons of terms without biases due to translation. However, distinct RCM terms in non-English language papers may have been missed. Second, for standardization, all non-peer reviewed articles such as book chapters, conference papers, and case reports were excluded; we may have missed some up-to-date terms, coined by the experts, especially in book chapters. Third, the weightage given to the RCM terms in this review may be influenced by frequency of publications by a specific researcher or a group.

Conclusion:

Through systematic review, we presented a glossary of RCM terms for the diagnosis of NMLs. By grouping the terms, based on likely-synonymy in the associated definition and histopathological correlation, the number of RCM terms published in the literature could be reduced by 50%. This systematic review may form the basis for an expert Delphi consensus process on NML terminology. A concise reproducible glossary of RCM terms can facilitate learning and clinical application of RCM by dermatologists.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Founding source:

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Figure 1:
PRISMA diagram.

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:[10.1371/journal.pmed1000097](https://doi.org/10.1371/journal.pmed1000097)

TABLE 1.

BASAL CELL CARCINOMA: RCM TERMS, FREQUENCY OF LITERATURE USE, SUGGESTED GROUPING BASED ON SIMILARITY IN DEFINITIONS AND HISTOPATHOLOGICAL CORRELATES

RCM terms	Frequency of use of an individual RCM term	Definition	Histopathological correlates
SUPRABASAL EPIDERMIS TERMS (N=13; 22.4%)			
Actinic changes in honeycomb ^{7,8,19 *}	3	Keratinocytic atypia with varying size of nuclei, pleomorphism, architectural disarray, parakeratotic nuclei	Keratinocytic atypia within the epidermis
Architectural disorder of overlying epidermis ¹⁸	1		
Mild keratinocyte atypia ²¹	1		
Atypical honeycomb pattern ⁶	0		
Subtotal (weight **)	5 (4.7%)		
Elongated nuclei in the epidermis ^{7,8,19}	3	Elongated monomorphic basaloid nuclei both in the epidermis aligned in the same axis and underlying tumor nests	No known histopathologic correlate. Probably the <i>en face</i> view of the uppermost part of a tumor nest or cord with palisading
Streaming of the epidermis ²¹⁻²⁶	6		
Polarization ^{19, 27}	2		
Polarized in the honeycomb ⁶	1		
Polarization of nuclei of the epidermis ^{7,8,19}	3	Visible nucleoli inside the nucleus of a BCC elongated cell	Prominent nucleoli in the nucleus of keratinocytes
Subtotal (weight)	15 (14.2%)		
Prominent nucleoli ⁷	1		
Subtotal (weight)	1 (0.9%)		
Epidermal shadow ^{6,27}	2	Large featureless area with blurred border disrupting the normal epidermis and corresponding to the horizontal clefting	Not known, probably an optical effect of the <i>en face</i> view of a tumor nest
Subtotal (weight)	2 (1.9%)		
Ulceration ^{23,26}	2	Disruption in the bright skin surface and in the underlying layers of the epidermis, seen as a dark area with or without bright amorphous or fibrillar debris ^{1,2}	Ulceration of the epidermis
Subtotal (weight)	2 (1.9%)		
Onion-like structure ^{23,26}	2	Round black spaces centered by brightly refractile material, corresponding to milia-like cysts	Epidermal cysts
Subtotal (weight)	2 (1.9%)		
Total for Suprabasal Epidermis (weight)	27 (25.7%)		

RCM terms	Frequency of use of an individual RCM term	Definition	Histopathological correlates
BASAL LAYER/DEJ/SUPERFICIAL DERMIS TERMS (N=45; 77.6%)			
Pigmented nests of basal cells ¹⁶	1	Highly packed cells corresponding to islands of basaloid tumor cells with high refractivity	Nests of basaloid cells in the DEJ or superficial dermis. Mostly associated to the nodular subtype
Tumor nodules ^{18,19}	2		
Nests of basaloid cells ²¹	1		
Tumor island ^{22,25,26}	3		
Bright tumor islands ²⁴	1		
◦ Small tumor islands ²³	1	Tumor islands <300 um diameter	Organization of the basaloid cells at the periphery of the tumor nests
◦ Big tumor islands ²³	1	Tumor islands >300 um diameter	
Subtotal (weight)	10 (9.5%)		
Basaloid cells ¹⁷	1	Cells with elongated nuclei and a palisading in the periphery of the tumor parenchyma	Clear spaces between the tumor parenchyma and the surrounding stroma. Most probably correspond to mucin.
Palisading ^{18,22}	2		
Peripheral palisading ^{21,23-26}	5		
Subtotal (weight)	8 (7.6%)		
Peritumoral dark space ¹⁸	1	Cleft-like hyporefractive spaces surrounding tumor nests	Nests of basaloid cells connected to the DEJ. Highly associated to the superficial subtype
Cleft-like spaces ²⁰	1		
Clefting ^{6,23,27}	3		
Clefts ⁴⁴	1		
Peripheral clefting ²⁶	1		
Dark peritumoral cleft ^{24,25}	2	Tightly packed tumor cells forming trabeculae	When within the tumor nest, mostly they correspond to melanocytes (Melan-A stain) and few are Langerhans cell (CD 1a)
Subtotal (weight)	9 (8.6%)		
Cord-like structures ^{18,26}	2		
Basaloid cords and nodules ^{6,27}	2		
Cord ²³	1		
Subtotal (weight)	5 (4.7%)		
Dendritic structures ¹⁹	1	Bright thin or coarse dendritic-like structures within tumor islands frequently associated to a clearly visible nucleated cell	
Dendritic-like features ⁶	1		

RCM terms	Frequency of use of an individual RCM term	Definition	Histopathological correlates
Nucleated cell within tumor island ⁶	1		
Bright dendritic structures ^{19,24}	1		
Dendritic cells ^{26 ***}	1		
Bright round cells ²⁴	1		
Subtotal (weight)	6 (5.7%)		
Dark silhouettes ²²⁻²⁶	5	Low reflectance tumor islands / Longo; ²³ Hyporefective areas outlined by bright collagen bundles in the surrounding dermis that correspond to basaloid islands	Nests of basaloid cells in the superficial dermis or deeper, not visible due to the lack of resolution after 150 – 200 µm. Associated to the infiltrative subtype
Dark nodules ^{26,27 ***}	1		
Subtotal (weight)	6 (5.7%)		
Solar elastosis ²¹	2	Peppelman et al. ²¹ bright irregular bundles and lacelike structures	Degeneration of the elastic fibers of the chronically sun-exposed skin
Subtotal (weight)	2 (1.9%)		
Melanophages ^{16,18}	2	Irregularly shaped bright cells with ill-defined borders and usually no visible nucleus distributed within and outside tumor islands	Melanin-laded macrophages in the superficial dermis
Plump bright cells ^{19,21,22}	3		
Subtotal (weight)	5 (4.7%)		
Collagen bundles ¹⁷	1	Increased number of fibers bundles orientated parallel, surrounding tumor	Collagen reaction to the tumor in the surrounding stroma
Fibrosis surrounding tumor nests ²¹	1		
Stromal reaction ^{26 ***}	1		
Thickened collagen bundles ^{24,25}	2		
Subtotal (weight)	5 (4.7%)		
Increased vascularity ^{7,8,18,19,21-23,26}	8	Increased number of dilated (10 – 105 µm) blood vessels with occasional rolling of leukocytes (starting at 35 – 50 µm below epidermal surface); these vessels are often horizontal (parallel)	Dilated blood vessels running parallel to the epidermal surface
Enlarged blood vessels ¹⁷	1		
Prominent vasculature ¹⁹	1		
Linear telangiectasia-like horizontal vessels ⁶	1		
Linear or convoluted dilated blood vessels ^{25,26}	2		
Linear blood vessels ²⁴	1		
Subtotal (weight)	14 (13.3%)		

RCM terms	Frequency of use of an individual RCM term	Definition	Histopathological correlates
Fibrillar polarized pattern around tumor ⁶	1	Fibrillary polarized features drawing a reticulation pattern around tumor island	N/A
Subtotal (weight)	1 (0.9%)		
Inflammatory infiltrate	1	Bright, highly refractile round or scattered cells representing leukocytes and neutrophils, respectively	Infiltrate of lymphocytes and leukocytes in the tumor parenchyma and stroma
Prominent inflammatory infiltrate ^{7, 8, 19}	3		
Inflammatory particles ^{2,6}	1		
Inflammation ²³	1		
Subtotal (weight)	6 (5.7%)		
Total for basal layer/DEJ/superficial dermis (weight)	78 (74.2%)		
TOTAL TERMS FOR BCC (N=58; 100%)	105 (100%)		

* Superscripted numbers denote reference numbers.

** Weight calculates the relative frequency of use for each subgroup of terms; the denominator is the total times BCC terms were used in the literature (n=78).

*** These terms had no definition in the cited articles and thus grouping under each likely-synonymous term was done by the authors of this paper.

TABLE 2.

SQUAMOUS CELL CARCINOMA: RCM TERMS, FREQUENCY OF LITERATURE USE, SUGGESTED GROUPING BASED ON SIMILARITY IN DEFINITIONS AND HISTOPATHOLOGICAL CORRELATES

RCM Term	Frequency of use of individual RCM terms	Definition	Histopathological correlates
SUPRABASAL EPIDERMIS TERMS (N=37; 63.7%)			
Hyperkeratosis ^{32,35,37}	3	Thickening of the stratum corneum >15um	Hyperkeratosis
Subtotal (weight ***)	3 (3.2%)		
Parakeratosis ^{32,34-37}	5	Nucleated cells appearing as dark nuclei surrounded by a bright outline centrally stratum corneum corneocytes	Parakeratosis
Subtotal (weight ***)	5 (5.3%)		
Detached corneocytes ³²	1	White, highly refractive polygonal structure of approximately 30–40 um in diameter in the stratum corneum	Detached corneocytes
Polygonal nucleated cells at the stratum corneum ⁹	1		
Disruption/individual cells ³⁶	1		
Individual corneocytes ³⁷	1		
Superficial epidermal disruption ³³	1		
Subtotal (weight ***)	5 (5.3%)		
Stratum corneum disruption	1	Alteration of the smooth contour of the stratum corneum observed in mosaic images	N/A
Subtotal (weight ***)	1 (1.1%)		
Orthokeratosis ³²	1	Hyperkeratosis without parakeratosis	Orthokeratosis
Subtotal (weight ***)	1 (1.1%)		
Scale ^{9,34,36}	3	Variably refractile, amorphous material in stratum corneum	Hyperkeratosis
Subtotal (weight ***)	3 (3.2%)		
Atypical honeycomb pattern ^{6,9,31-33,35,36 *}	7	Irregularly shaped cells deviating from the normal honeycomb pattern	Variation in cellular and nuclear shape and size of epidermal keratinocytes
Diamond shaped honeycomb ⁶	1		
Irregular honeycomb pattern ^{29,34}	2		
Subtotal (weight ***)	10 (10.7%)		

RCM Term	Frequency of use of individual RCM terms	Definition	Histopathological correlates
Architectural disarray ^{28,32}	2	Severe disarranged epidermal pattern in which the honeycomb pattern is no longer visible	Severe variation in cellular and nuclear shape and size of epidermal keratinocytes
Honeycomb atypical and disarrayed ⁶	1		
Loss of regular stratification of epidermal layers ²⁹	1		
Disarranged epidermal pattern ^{9,31,36}	3		
Architectural disarrangement ^{3,5,37}	2		
Subtotal (weight ***)	9 (9.6%)	Variation in cellular and nuclear shape and size	Variation in cellular and nuclear shape and size
Cellular and nuclear pleomorphism (of the epidermis) ³²	1		
Different size and shape of the nuclei of keratinocytes ²⁹	1		
Keratinocyte pleomorphism ³⁷	1		
Pleomorphic nuclei of keratinocytes ²⁸	1		
Subtotal (weight ***)	4 (4.3%)	Irregular borders of keratinocytes	N/A
Irregular borders of keratinocytes ²⁹	1		
Subtotal (weight ***)	1 (1.1%)		
Irregular intercellular keratinocyte connections ²⁹	1	Irregular intercellular keratinocyte connections	N/A
Subtotal (weight ***)	1 (1.1%)		
Targetoid cells ^{32,33,35,36,7}	4		
Dyskeratotic areas ²⁹	1	Two cell types have been described: Large cell with a bright center and a dark peripheral halo (denoted as 'Targetoid cells 1'), ^{32,33} Large cell with a dark center and a bright rim surrounded by a dark halo (denoted as 'Targetoid cells 2') ^{32,33}	Dyskeratotic keratinocytes within the epidermis
Round nucleated cells at spinous-granular layer ⁹	1		
Dyskeratotic cell ²⁸	1		
Subtotal (weight ***)	7 (7.5%)		
Multinucleated keratinocytes ³²	1		
Large cells with aggregated nuclei in the epidermis ³³	1	Large cells with tight aggregates of bright nuclei	Multinucleated keratinocytes
Subtotal (weight ***)	2 (2.1%)		

RCM Term	Frequency of use of individual RCM terms	Definition	Histopathological correlates
Spongiosis ^{3,2,35}	2	Enlargement of the bright intercellular spaces due to fluid accumulation between keratinocytes	Spongiosis
Subtotal (weight ***)	2 (2.1%)		
Exocytosis ³²	1	Inflammatory cells appearing as highly refractive structures in the epidermis	Exocytosis
Subtotal (weight ***)	1 (1.1%)		
Spindle-shaped cells with dendritic branches infiltrating the epidermis ³⁴	1	Bright cells with elongated branching structures extending from fusiform cell body; seen at the spinous and granular layers of the epidermis (corresponding to Langerhans cells of pigmented SCC or pigmented AK)	Langerhans cells infiltrating the epidermis
Dendritic cells in the epidermis ^{35,36 ¶}	2		
Subtotal (weight ***)	2 (2.1%)		
Erosion/ulceration ³⁵	1	Dark areas, with sharp borders and irregular contours, filled with amorphous material, cellular debris and small particles	Ulceration of the epidermis
Subtotal (weight ***)	1 (1.1%)		
Corneal pseudocysts ³⁶	1	Well circumscribed large, round, highly refractile intraepidermal structures	Intraepidermal cysts
Subtotal (weight ***)	1 (1.1%)		
Speckled nucleated cells in the epidermis	1	Roundish-to-polygonal cells with speckled appearance and dark nucleus in the epidermis. Size is slightly larger than surrounding keratinocytes. They are larger than lymphocytes and have polygonal shape that differentiate them from dendritic cells	N/A
Subtotal (weight ***)	1 (1.1%)		
Total for Suprabasal Epidermis (weight)	60 (64.5%)		
BASAL LAYER/DEJ/SUPERFICIAL DERMIS TERMS (N=21; 36.2%)			
Elongated dermal papillae ²⁸	1	Elongated dermal papillae	N/A
Subtotal (weight ***)	1 (1.1%)		
Edged papillae ³⁴	1	Multiple scattered dermal papillae demarcated by a rim of bright cells. In pigmented SCC, the edged papillae are mostly peripheral in location with widened interpapillary spaces	Atypical pigmented keratinocytes
Subtotal (weight ***)	1 (1.1%)		
Mottled pigmentation ^{36 ¶}	1	Corresponds to presence of clustered bright keratinocytes detectable in context of honeycombed pattern	Basilar pigmented keratinocytes
Subtotal (weight ***)	1 (1.1%)		
Keratin pearl ^{32,35}	2	Whorl-shaped accumulation of keratin appearing as highly refractive, speckled structure in the dermis ⁷⁷	Keratinization
Subtotal (weight ***)	2 (2.1%)		
Convolutated glomerular vessel ⁶	1	Coiled canalicular vessels	Aberrant vessels

RCM Term	Frequency of use of individual RCM terms	Definition	Histopathological correlates
Subtotal (weight^{***})	1 (1.1%)		
Linear vessels ³⁶	1	Vessels oriented parallel to the imaging plane	Aberrant vessels
Subtotal (weight^{***})	1 (1.1%)		
Round blood vessels traversing the dermal papillae ^{9,36}	2	Dilated blood vessels within the dermal papillae that run perpendicular to the horizontal RCM plane of imaging / Dilated blood vessels within the dermal papillae looping perpendicular to the horizontal plane of RCM imaging. The presence of multiple looping vessels renders the dermal papillae a Button-hole like appearance	Aberrant and neo formed vessels
Round-to-oval vessels ³³	1		
Buttonhole vessels ^{35,36}	2		
Dilated looping blood vessels within papillae ^{34,35}	2		
Subtotal (weight^{***})	7 (7.5%)		
Increased number of blood vessels ^{32,37}	2	> 5 blood vessels per 0.5 × 0.5 mm	Neovascularization
Subtotal (weight^{***})	2 (%)		
Increased blood vessel dilatation ^{32,37}	2	Blood vessels of diameter >5 um	Aberrant vessels
Subtotal (weight^{***})	2 (2.1%)		
S-shaped vessels ³³	1	Round-to-oval vessels with increased tortuosity at the center of the dermal papillae, S-shaped at lower papillary dermis	N/A
Subtotal (weight^{***})	1 (1.1%)		
Solar elastosis ^{32,37}	2	Network of thick, highly refractile collagen bundles intermixed with moderately refractive, lace-like elastic fibers	Solar elastosis
Curled fibers ³⁶	1		
Subtotal (weight^{***})	3 (3.2%)		
Huddled collagen bundles ³⁶	1	Large hyporefractive blotches of amorphous and hyporefractive material; individual collagen fibers are no longer visible	N/A
Subtotal (weight^{***})	1 (1.1%)		
Coarse collagen bundles ³⁶	1	Bright fibrillar structures that appear finely reticulated, forming a web-like	N/A
Subtotal (weight^{***})	1 (1.1%)		
Nest-like structures ^{32,35}	2	Round, demarcated structures in the dermis that are often surrounded by fibrosis	N/A
Subtotal (weight^{***})	2 (2.1%)		
Plump cells ^{34–36}	3	Melanophages	Melanin-laden macrophages in dermis

RCM Term	Frequency of use of individual RCM terms	Definition	Histopathological correlates
<i>Subtotal (weight ***)</i>	3 (3.2%)		
Speckled nucleated cells in the dermis ³⁵	1	Roundish to polygonal cells with speckled appearance and dark nucleus within the dermis. They are larger than the usual size of lymphocytes and have a polygonal shape that differentiate them from plump bright cells	N/A
<i>Subtotal (weight ***)</i>	1 (1.1%)		
Inflammatory cells ^{2,3,33,37}	3	Highly refractile structures of 8–10 µm in diameter located in the epidermis or dermis	Inflammatory cells: lymphocytes and neutrophils
<i>Subtotal (weight ***)</i>	3 (3.2%)		
Total for basal layer/DEJ/superficial dermis	33 (35.4%)		
TOTAL TERMS FOR SCC (N=58)	93 (100%)		

* Most studies recommend stating partial thickness or full thickness atypia to differentiate between actinic keratosis and squamous cell carcinoma.

** Superscripted numbers denote reference numbers.

*** Weight calculates the relative frequency of use for each subgroup of terms; the denominator is the total times SCC terms were used in the literature (n=71).

[‡] This term has been mainly described in association with Bowen's disease.

[¶] Features of pigmented actinic keratosis

^{‡‡} This feature can be also seen at the level of the epidermis.

TABLE 3.

SEBORRHEIC KERATOSIS, SOLAR LENTIGO AND LICHEN PLANUS-LIKE KERATOSIS: RCM TERMS, FREQUENCY OF LITERATURE USE, SUGGESTED GROUPING BASED ON SIMILARITY IN DEFINITIONS AND HISTOPATHOLOGICAL CORRELATES

RCM Terms	Frequency of use of an individual RCM term	Definition	Histopathological correlates
SUPRABASAL EPIDERMIS TERMS (N=9; 39.1%)			
Milia-like cysts ³¹	1	Homogeneous and bright areas without sharply demarcated borders surrounded by a dark halo within the epidermis	Intraepidermal keratin cysts
Corneal pseudo cysts ^{10,39,41}	3		
Subtotal (weight [*])	4 (12.1%)		
Keratin-filled invaginations ^{10,41}	2	Round to longitudinal invaginations of the lesion surface, harboring structureless amorphous material of variable brightness on RCM	Keratin-filled papillomatous epidermis
Surface holes and fissures ³⁹	1		
Subtotal (weight [*])	3 (9.1%)		
Cerebriform appearance ³⁸	1	Round to linear structures, darker than the surrounding epidermis, resembling the surface of a brain (<i>gyri and sulci</i>)	Papillomatous epidermis
Subtotal (weight [*])	1 (3.03%)		
Typical honeycomb pattern ³⁹	1	Honeycomb pattern with regular thickness of lines and sizes of holes	Regular epidermis
Regular honeycomb pattern ^{10,41,42}	3		
Subtotal (weight [*])	4 (12.1%)		
Epidermal projections ^{10,41}	2	Projections of the epidermal surface of the lesion	Projections of rete ridges
Subtotal (weight [*])	2 (6.1%)		
Small bright homogeneous cells ³¹ **	1	Small bright homogeneous cells present on basal layers, corresponding to pigmented keratinocytes	Pigmented keratinocytes in the basal layer
Subtotal (weight [*])	1 (3.03%)		
Total for Suprabasal Epidermis (weight)	15 (45.4%)		
BASAL LAYER/DEJ/SUPERFICIAL DERMIS TERMS (N=14; 60.8%)			
Polycyclic shapes of dermal papillae ³⁸	1	At the DEJ level, densely packed round to polymorphous dermal papillae, usually with pigmented keratinocytes.	Elongated and bridging rete ridges with pigmented keratinocytes
Densely packed round to polymorphous dermal papillae ¹⁰	1		
Packed dermal papillae ⁴¹	1		

RCM Terms	Frequency of use of an individual RCM term	Definition	Histopathological correlates
Polycyclic papillary contours ⁴⁰	1		
Subtotal (weight %)	4 (12.1%)		
Edged papillae ⁴²	1	Dark round to oval structures surrounded by a rim of bright monomorphic cells	Pigmented keratinocytes at the DEJ
Subtotal (weight %)	1 (3.03%)		
Cords ^{***} and bulbous projections ^{10,41}	2	Elongated bright tubular structures (cords ^{***}) with bulbous projections at the DEJ	Elongated and bridging rete ridges with pigmented keratinocytes
Cord-like ^{***} rete ridges ⁴²	1		
Elongated cords ^{39 ***}	1		
Anastomosing epithelial cords ^{31 ***}	1		
Bulbous projections ³⁹	1		
Subtotal (weight %)	7 (21.2%)		
Mixed vascular pattern ^{10,41}	2	A prominent vascular pattern with dilated round and linear blood vessels (running perpendicular and parallel, respectively)	Neovascularization
Subtotal (weight %)	2 (6.1%)		
Plump bright cells ^{10,31,39 †}	3	Irregularly shaped bright cells with ill-defined borders and no visible nucleus, corresponding to melanophages	Melanophages in the dermis
Melanophages ^{10 †}	1		
Subtotal (weight %)	4 (12.1%)		
Bright stellate spots ^{39 ††}	1	Small bright round structures (<20 um) without visible nucleus corresponding to leukocytes	Inflammatory cells: lymphocytes and neutrophils
Subtotal (weight %)	1 (3.03%)		
Total for basal layer/DEJ/superficial dermis	18 (54.5%)		
TOTAL TERMS FOR SL/SK/LPLK (N=23; 100%)	33 (100%)		

Superscripted numbers refer to the publication.

* Weight calculates the relative frequency of use for each subgroup of terms; the denominator is the total times SL/SK/LPLK terms were used in the literature (n=30).

** Despite not defined for this group of lesions, we recommend using the standard term "cobblestone pattern" to avoid confusion.

*** We do not recommend using the term 'cords' to avoid confusion with 'cord-like' structures of Basal cell carcinoma.

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⁷ These criteria have been associated mostly to lichen planus-like keratosis.

⁷⁷ The term “Inflammatory infiltrate”, was not used in the literature in reference to SL/SK/LPLK; for consistency with the literature, we recommend using “bright stellate spots”.