Pigmented Lesions and Melanoma - Confocal and Pathology Correlation

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Conflict of Interest: Consulting Investigator, DBV Technologies

Prior Relationships

- Avon
- Castle Biosciences
- Cynosure
- Discovery Research Group
- Edimer Pharmaceuticals
- Energizer (Schick)
- Gerson Lehrman Group
- Gojo
- Johnson & Johnson
- Lancelotta Consulting
- Leerink Partners (Leerink Swann)
- Lucid
- MEDACorp
- Myriad Genetics Laboratories
- Palomar Medical Technologies
Goals

• Learn how in vivo Reflectance Confocal Microscopy (RCM) fits into the spectrum of diagnostic tools for melanocytic neoplasms

• Understand the advantages and disadvantages of RCM as compared to histopathology

• Review how RCM is being used in the melanoma clinic
Of the non-invasive toolset, RCM is the only tool that enables in vivo cellular level resolution- Closest to histopathology!

Pagetoid Cells = Pagetoid Melanocytes
(Hyperreflective, Roundish)
RCM features correlate with histological features enabling specific in vivo diagnoses or **NON-INVASIVE DERMATOPATHOLOGY!**
CONSIDER REFLECTANCE CONFOCAL MICROSCOPY A SHAVE BIOPSY!
(viewed horizontally in black & white with more representative sampling!)
Advantages and Limitations of RCM

**ADVANTAGES:**

- **Non-invasive:** No adverse events or pain
- **Allows for direct correlation with dermoscopy:** SAME ORIENTATION!
  - Areas of concern can be more thoroughly sampled
- **More representative sampling:** Entire surface area of lesion sampled at multiple levels
- **Lesion can be followed over time at the cellular level**

**LIMITATIONS:**

- **Depth of imaging:** *Akin to shave biopsy*, a deeper dermal lesion may not be sampled and dermal-based features of importance, such as vertical maturation and vertical contour are difficult to evaluate.
- **Resolution:** Distinction between cell types can be challenging on RCM, and ancillary studies (IHC) are not available. Certain cytologic features, such as chromatin quality, nucleolar detail and mitotic figures, cannot be visualized on RCM.
- **Cellular Resolution Decreases with Increasing Imaging Depth**
Limitation of RCM- Depth of Imaging

Absence of lesional features on reflectance confocal microscopy: Quality control steps to avoid false-negative results

Melissa Gill, MD,1,2 Jane M. Grant-Kels, MD,3 and Christi Alessi Fox, MS4

JAAD 2019
Limitation of RCM- Resolution Pagetoid Cells

**Lentigo Maligna**

Langerhans cells and melanocytes share similar morphologic features under in vivo reflectance confocal microscopy: a challenge for melanoma diagnosis

Pantea Hashemi, MD, Melissa P. Pulitzer, MD, Alon Scope, MD, Ivanka Kovalyshyn, DO, Allan C. Halpern, MD, and Ashfaq A. Marghoob, MD


**SK-Langerhans cells**

**EMPD**

**Amelanotic MM**
Limitations of Histopathology

• **SAMPLING! SAMPLING! SAMPLING!**

• **Vertical sectioning** does not allow for evaluation of the entire lesional area resulting in the following types of **sampling errors**:  
  • under-calling asymmetry (concerning feature)  
  • over-calling peripheral rim of nests (reassuring feature)  
  • missed areas of concern or melanoma arising in a nevus

• **Shave biopsy, akin to in vivo RCM**, may not sample a deeper dermal lesion and/or dermal-based features of importance, such as vertical maturation, vertical contour and location/number of mitotic figures may be difficult to evaluate.

TCRCM Minimum Sampling:  
Dermoscopy & at least 4 registered up to 8x8mm mosaics including: upper epidermis, deep epidermis, Dej, and dermis

Histopath Minimum Sampling:  
one vertical slide

3D images courtesy of Kivanc Kose
Histopathology Sampling Errors - Beware of Dermoscopic Islands!

RCM Allows for In Vivo Diagnosis of Dermoscopic Islands

Reflectance Confocal Microscopy: A Promising Tool to Identify Malignancy in Melanocytic Lesions Exhibiting a Dermoscopic Island.

Diagnostic accuracy of reflectance confocal microscopy for lesions typified by dermoscopic island.

Reflectance confocal microscopy accurately discriminates between benign and malignant melanocytic lesions exhibiting a 'dermoscopic island'.

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Summary: RCM Versus Histopathology

- Unlike histopathology, RCM allows for direct correlation of concerning dermoscopic structures.
- RCM provides more complete sampling of epidermal structures via horizontal imaging.
- Histopathology provides superior sampling of dermal structures via vertical sectioning.
- RCM is superior to histopathology at detecting asymmetry, peripheral rim of nests and zonal areas of concern, such as melanoma in situ arising in a nevus.
- Histopathology with IHC can distinguish cell types that represent diagnostic pitfalls on RCM, such as hyporeflective round or bright dendritic Pagetoid cells.
- Histopathology (but not shave biopsy!) is needed to diagnose certain tumors, in which diagnosis relies on vertical or deeper dermal features that may not be visualized with RCM.
RCM- Applications in the Melanoma Clinic

• Diagnostic aid for primary diagnosis (TCRCM)

• Serial RCM (combined with dermoscopy) to allow for more detailed longitudinal follow-up of suspicious lesions (TCRCM)

• Choosing best biopsy site in a large lesion (TCRCM or HHRCM)

• Following non-invasive therapy (TCRCM or HHRCM)

• Lentigo Maligna Margin Mapping (TCRCM or HHRCM)
Avoiding Unnecessary Biopsies by Utilizing RCM Can Be cost Effective

Impact of *in vivo* reflectance confocal microscopy on the number needed to treat melanoma in doubtful lesions
I. Alarcon,1 C. Carrera,1,2 J. Palou,3 L. Alos,3 J. Malvehy1,2 and S. Puig1,2,4
British Journal of Dermatology (2014) 170, pp802–808

NNT: 3.73 → 2.87

Reflectance confocal microscopy as a second-level examination in skin oncology improves diagnostic accuracy and saves unnecessary excisions: a longitudinal prospective study*
G. Pellacani,1 P. Pepe,1 A. Casari1 and C. Longo2
British Journal of Dermatology (2014) 171, pp1044–1051

NNT: 7.96 → 4.78

Combined in vivo reflectance confocal microscopy and digital dermoscopy for follow up of patients at high risk of malignant melanoma: A prospective case series study.
Floristán Muruzábal U1, Gamo Villegas R1, Pampín Franco A1, Pinedo Moraleda F2, Pérez Fernández E3, Lópeez-Estebaranz JL1

NNT: 8.00 → 3.73

Cost–benefit of reflectance confocal microscopy in the diagnostic performance of melanoma
G. Pellacani,1,* A. Witkowski,1 A.M. Cesinaro,2 A. Losi,1 G.L. Colombo,3 A. Campagna,4 C. Longo,5 S. Piana,6 N. De Carvalho,1 F. Giusti,1 F. Farnetani1

27% decrease in cost projected by incorporating RCM in algorithm for evaluating melanocytic neoplasms in Province of Modena, Italy

JEADV. 2015 Oct 7, Epub
VivaScope® 1500 and 3000 systems for detecting and monitoring skin lesions: a systematic review and economic evaluation

Steven J Edwards, Ifigeneia Mavranezouli, George Osei-Assibey, Gemma Marceniuk, Victoria Wakefield and Charlotte Karner

Conclusions: The use of VivaScope appears to be a cost-effective strategy in the diagnostic assessment of equivocal melanomas and BCCs, and in margin delineation of LM prior to surgical treatment.
Dermatopathologist’s Stepwise Approach to RCM Interpretation

**PRE-EXAMINATION PHASE:** Can I evaluate this?
- Is this lesion appropriate for RCM imaging?
- Is the image set adequate (dermoscopy + 4 mosaics representing all anatomic levels)?
- Are the images free of significant obscuring artifact?

**EXAMINATION PHASE:** What can I see?
- What diagnostic features are present?

**POST-EXAMINATION PHASE:** What may I be missing?
- Circle back to the clinical and dermoscopic information: Have all concerning features been accounted for?
- If questions/concerns persist, second opinion, re-imaging or biopsy may be needed.


Features of Melanocytic Neoplasms

- Perifollicular Dendritic Cells (Medusa Sign)
- Pleomorphic Pagetoid & Atypical Cells a DEJ
  - SG/SS

Dense Junctional & Dermal Nests

Irregular JN & Junctional Thickenings w/ Short Interconnections (Bridging)

Banal Nevi  Dysplastic Nevi  Melanomas (SS)  Melanoma (LM)

Clod/Nested Pattern = Globular/Nested Pattern

Ringed Pattern = Lentiginous Pattern

Meshwork Pattern

Non-Edged Papillae and Nonspecific Pattern

DEJ
RCM Algorithm for Categorizing Clinically and/or Dermoscopically Atypical Melanocytic Lesions

1st STEP
Presence of at least 1 of the following parameters:
- Round Pagetoid cells
- Atypical cells at DEJ
- Irregular junctional nests
- Short interconnections between junctional nests
- Non homogeneous cellularity within junctional nests

NO

YES

NON-DYSPLASTIC NEVUS

Classification:
13/19 Non-dysplastic nevi (True positive)
4/27 Dysplastic nevi
0/14 MMs

Sensitivity 68%
Specificity 90%

Sensitivity 100%
Specificity 74%

2nd STEP
Presence of at least 1 of the following parameters:
- Round Pagetoid cells, widespread (extending over at least 50% of lesional area)
- Atypical cells at DEJ, widespread (extending over at least 50% of lesional area)
- Non-edged papillae (extending over at least 10% of the lesion area)

NO

YES

DYSPASTIC NEVUS

Classification:
3/19 Non-dysplastic nevi
14/27 Dysplastic nevi (True positive)
0/14 MMs

Sensitivity 52%
Specificity 91%

Sensitivity 100%
Specificity 74%

MELANOMA

Classification:
3/19 Non-dysplastic nevi
9/27 Dysplastic nevi
14/14 MMs (True positive)
### Compound Nevus, Congenital Pattern

**Epidermis:**
- Typical honeycomb pattern

**DEJ/Dermis:**
- Symmetry
- “Clods” composed of individual round cells with variably bright cytoplasm filling papillary dermis
- Maturation: with increasing depth, dermal melanocytes smaller and less bright
- Periadnexal melanocytes

### Compound Nevus (Amelanotic, Globular)

**Epidermis:**
- Typical honeycomb pattern
- No Pagetoid cells

**DEJ/Dermis:**
- Symmetry
- Typical nested pattern
- No atypical cells
- Homogenous, dense JN
- Dense dermal nests

### Lentiginous Compound Nevus

**Epidermis:**
- Typical cobblestone/honeycomb pattern
- No Pagetoid cells

**DEJ/Dermis:**
- Symmetry
- Typical ringed pattern
- No atypical cells
- Homogenous, dense JN
- Dermal nests

**Dysplastic Nevus**

- Usually shows a mixed global DEJ pattern (ringed meshwork)
- Atypia or rare Pagetoid cells are limited to center of lesion

**Cytologic Atypia**

- Atypical cells at DEJ
- Dishomogenous nests

**Mild**: melanocytes similar in size to surrounding keratinocytes

**Moderate**: melanocytes (especially nuclei) are somewhat larger than adjacent keratinocytes

**Severe**: melanocytes are much larger than surrounding keratinocytes (can usually see on low power)

**Architectural Disorder**

- Asymmetry
- Lack of peripheral rim of nests/ill-defined border
- Irregular size and shape of junctional nests
- Short interconnections between junctional nests/thickenings

DYSPLASTIC NEVUS

• Ill-defined borders
• Fairly Symmetric
• Ringed Meshwork Pattern
• Plump Bright Cells
• Minimal central atypia

• Mildly atypical melanocytes singly/small nests
• Brisk infiltrate with several melanophages
DYSPLASTIC NEVUS

37 yo male with H/O MM

RCM:
- Asymmetry
- Zonal absence of peripheral rim of nests
- Mixed ringed, clod and meshwork pattern

Lentiginous=Ringed

Nested=Nested

Histopathology:
Symmetry and peripheral rim of nests
NOT REPRESENTATIVE OF ENTIRE LESION!
Superficial Spreading Melanoma

**Superficial Epidermis:**
- Pleomorphic or roundish Pagetoid cells
- Irregular honeycomb/cobblestone pattern

**DEJ:**
- Asymmetry
- Ill-defined border
- Usually Mixed Atypical Meshwork/Aspecific Patterns
- Widespread atypical cells
- Dishomogenous junctional thickenings
- Non-edged papillae
Nodular Component of SSMM

**Epidermis:**
- Disarranged pattern
- Pleomorphic or roundish Pagetoid cells

**Dermis:**
- Cerebriform nests
- Vascular pattern mimics dermoscopy

**In Vivo Microscopic Features of Nodular Melanomas**
*Dermoscopy, Confocal Microscopy, and Histopathologic Correlates*

*Juma Seghezzi, MD, Giovanni Filippucci, MD, Joanne Pag, FPHC, Caterina Longo, MD, Sara Bentol, MD, Dominique Coutte, MD, Jose Vivas, MD, Scan Menkes, MD, PM, Stefano Scalfari, MD, Jose Melnik, MD*

*Arch Dermatol. 2008;144(10):1311-1320*
Lentigo Maligna Melanoma

**Epidermis:**
- Irregular or disarranged cobblestone or honeycomb pattern
- Pagetoid cells (usually pleomorphic)

**DEJ:**
- Atypical ringed, meshwork or aspecific patterns
- Lentigo-like areas
- Atypical cells - usually dendritic- often in sheets
- Clusters/tangles of atypical cells
- Medusa sign: radially arranged perifollicular dendritic or spindled cells
LM: Re-imaging for Biopsy Site Selection post topical steroid

- Lentigo maligna Confirmed on histopathology
- Patient refused surgical treatment
- Undergoing imiquimod therapy
- Will monitor response to therapy with RCM

RCM for Monitoring Non-Invasive Therapy of Lentigo Maligna
Lentigo Maligna Margin Mapping

RCM margin mapping changed management in 73% (27/37) patients
Sensitivity 91.7%, Specificity 96.8% (compared to histopathology)

Concordance of handheld reflectance confocal microscopy (RCM) with histopathology in the diagnosis of lentigo maligna (LM): A prospective study

89% RCM/histo concordance
RCM Sens 100%, Spec 71%, 17 patients, 63 sites
LM margin mapping via videomosaic with HHRCM

- Presurgical in vivo quasi histologic mapping of entire margin (even in tight spots)
- Eliminates need for mapping biopsies
- Reduced defect size
- 1 visit

Images courtesy of Kivanc Kose
Take Home Points

• RCM allows for non-invasive diagnosis and management of melanocytic lesions, in which diagnostic information is present within the epidermis, DEJ or superficial dermis.

• RCM and histopathology provide overlapping, complimentary information, which, if representative, should explain concerning features.

• Never forget to close the Clinical-Dermoscopy-RCM-Histopathology loop!
  - If questions remain after visual inspection, proceed to dermoscopy
  - If questions remain after dermoscopy, proceed to RCM
  - If RCM does not explain concerning features on dermoscopy, DO A BIOPSY!
  - If histopathology does not explain area of concern on dermoscopy/RCM, GET LEVELS!
Additional resource:
International Confocal Working Group
https://www.confocal-icwg.com

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