Actas Dermosifiliogr. 2014;105(5):446–458

ACTAS Dermo-Sifiliográficas

Full English text available at
www.actasdermo.org

REVIEW

# Confocal Microscopy Patterns in Nonmelanoma Skin Cancer and Clinical Applications☆

**S. González,[a,b,*] V. Sánchez,[c] A. González-Rodríguez,[d] C. Parrado,[e] M. Ullrich[f]**

[a] *Dermatology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA*
[b] *Servicio de Dermatología, Hospital Ramón y Cajal, Madrid, Spain*
[c] *Servicio de Dermatología, Hospital Universitario Madrid Sanchinarro, Universidad CEU San Pablo, Madrid, Spain*
[d] *Servicio de Atención Primaria, SAS, Málaga, Spain*
[e] *Departamento de Histología y Anatomía Patológica, Universidad de Málaga, Málaga, Spain*
[f] *Skin Cancer Center Charité, Department of Dermatology, Charité University Medicine, Berlín, Alemania*

Received 19 December 2012; accepted 18 March 2013
Available online 14 May 2014

**KEYWORDS**
Reflectance confocal microscopy;
Basal cell carcinoma;
Squamous cell carcinoma;
Actinic keratosis;
Optical diagnosis

**Abstract** Reflectance confocal microscopy is currently the most promising noninvasive diagnostic tool for studying cutaneous structures between the stratum corneum and the superficial reticular dermis. This tool gives real-time images parallel to the skin surface; the microscopic resolution is similar to that of conventional histology. Numerous studies have identified the main confocal features of various inflammatory skin diseases and tumors, demonstrating the good correlation of these features with certain dermatoscopic patterns and histologic findings. Confocal patterns and diagnostic algorithms have been shown to have high sensitivity and specificity in melanoma and nonmelanoma skin cancer. Possible present and future applications of this noninvasive technology are wide ranging and reach beyond its use in noninvasive diagnosis. This tool can also be used, for example, to evaluate dynamic skin processes that occur after UV exposure or to assess tumor response to noninvasive treatments such as photodynamic therapy. We explain the characteristic confocal features found in the main nonmelanoma skin tumors and discuss possible applications for this novel diagnostic technique in routine dermatology practice.


**PALABRAS CLAVE**
Microscopio confocal reflectante;

## Patrones de microscopia confocal para el cáncer cutáneo no melanoma y aplicaciones clínicas

**Resumen** Actualmente la microscopia confocal reflectante es la técnica diagnóstica no invasiva más prometedora para el estudio de estructuras cutáneas situadas entre la capa córnea y la

☆ Please cite this article as: González S, Sánchez V, González-Rodríguez A, Parrado C, Ullrich M. Patrones de microscopia confocal para el cáncer cutáneo no melanoma y aplicaciones clínicas. Actas Dermosifiliogr. 2014;105:446–458.

* Corresponding author.
*E-mail address:* gonzals6@mskcc.org (S. González).

Carcinoma basocelular;
Carcinoma espinocelular;
Queratosis actínica;
Diagnóstico óptico

dermis reticular superficial, obteniendo imágenes paralelas a la superficie cutánea en tiempo real y con una resolución microscópica similar a la observada en la histología convencional. Numerosos estudios han señalado las principales características confocales que se observan en distintas enfermedades cutáneas, tanto tumorales como inflamatorias, demostrando una buena correlación con ciertos patrones dermatoscópicos, así como con el examen histológico. Además, se han descrito algoritmos diagnósticos y patrones confocales que han demostrado unas altas tasas de sensibilidad y especificidad para el diagnóstico de tumores cutáneos de tipo melanoma y no melanoma. Las posibles aplicaciones presentes y futuras de esta tecnología son muy amplias, no solo como herramienta diagnóstica no invasiva, sino también para la evaluación de distintos procesos dinámicos como aquellos que ocurren tras la exposición de la piel a la radiación ultravioleta, o la respuesta de los tumores a terapias no invasivas como la terapia fotodinámica. Explicamos con detalle los hallazgos confocales característicos de los principales tumores cutáneos de tipo no melanoma y discutimos las posibles aplicaciones de esta novedosa técnica diagnóstica en la práctica diaria de la consulta dermatológica.


## Introduction

In recent years, we have witnessed a true technological revolution in the field of dermatology, with implications for both clinical diagnosis and treatment. The growing preference for less invasive procedures has driven the development of new imaging technologies[1–7] and even drugs that in many cases eliminate the need for skin tumor surgery.[8–10]

Nonmelanoma skin cancer is the most common cancer in white individuals and its incidence continues to rise.[11] Histologic examination is the gold standard for the diagnosis of skin cancer, but it has limitations, such as the need to remove small amounts of tissue for ex-vivo analysis, which is usually performed at a later stage. These limitations have led to the development of new noninvasive diagnostic methods that offer real-time, in vivo, and in situ results without scarring. One of the main advantages of these new methods is that they provide dynamic information that can be used in the longitudinal monitoring of different skin conditions. Examples of these noninvasive technologies are magnetic resonance imaging, high-frequency ultrasound imaging, optical coherence tomography, and, more recently, reflectance confocal microscopy (RCM).[12,13]

Of the above techniques, RCM provides the best imaging-histologic correlation and has both high sensitivity and specificity for the diagnosis of nonmelanoma skin cancer.[14–16]

Researchers have described a range of RCM features and patterns that can be used to identify a range of skin tumors and differentiate these from normal skin.

## RCM and Confocal Patterns of Normal Skin

Of the numerous diagnostic imaging technologies to emerge in recent years, RCM has been studied most in clinical trials. It has also resulted in real clinical applications, particularly in the field of skin cancer. Among its strengths are its noninvasive nature and the fact that it provides real-time, in vivo images with a microscopic resolution similar to that of conventional histology (lateral and axial resolution of up to 1 μm and 3 μm, respectively).[13]

Like any optical system, the confocal microscope consists of a light source (generally a low-power diode laser), a condenser lens, an objective lens, a pinhole, and a detector. It is called *confocal* because the tissue plane studied is conjugate to the light source plane and the pinhole in front of the detector.[4] RCM provides en face (horizontal) real-time images formed by light reflected from a focal plane. In other words, all light reflected by structures located outside this plane is rejected by the pinhole. Image contrast is produced by differences in the refractive indices of the varying tissue and cell structures. Melanin-containing structures (melanosomes, melanocytes, melanophages, and pigmented keratinocytes, among others) have the highest refractivity, followed by keratin-containing structures, such as the stratum corneum, the infundibulum, and the hair follicle. Nuclei, air, and serum exhibit minimum reflectivity.[17] Microscopic structures, which are of a similar size to the wavelength of the incident light, have the highest refractive indices (Table 1). The maximum imaging depth that has been achieved to date with RCM is approximately 300 μm,[13] although this may increase in the near future.

**Table 1** Reflection of Skin Structures Seen by Reflectance Confocal Microscopy (From Highest to Lowest Refractivity).

| |
|---|
| Melanin (maximum refractivity): melanocytes, melanophages, pigmented keratinocytes |
| Keratin-containing structures: stratum corneum, infundibulum, hair follicle |
| Activated Langerhans cells |
| Keratinocytes in the stratum granulosum and stratum spinosum |
| Adipocytes |
| Collagen |
| Blood cells |
| Nuclei (minimum refraction) |
| Air and serum (no refraction) |