

Shining into the White

The Spectrum of Epithelial Tumors from Actinic Keratosis to Squamous Cell Carcinoma

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KEYWORDS

- Actinic keratosis • Bowen disease • Squamous cell carcinoma • Reflectance confocal microscopy
- Dermoscopy • Skin imaging

KEY POINTS

- Reflectance confocal microscopy (RCM) allows the evaluation of the superficial parts of the skin at high resolution.
- In the past 15 years, the research of RCM has continuously been growing, and several independent groups have shown its applicability for non-hyperkeratotic actinic keratosis.
- Although the applicability of RCM has clearly been proven, RCM also has limitations in this field.
- RCM may be very useful in the diagnosis and monitoring of squamous neoplasia, but future studies are required to show its additional use in clinical practice.

INTRODUCTION

Invasive squamous cell carcinoma (SCC) represents the second most common skin cancer in humans, but their earliest form, namely actinic keratoses (AK), affects up to 60% of the elderly population.¹ AKs typically arise in the context of field cancerization, representing one step in the continuum from chronic photo damage with subclinical dysplasia to invasive SCC.^{2,3} In this regard, AKs have been referred to as early in situ SCC with different grades describing the level of epidermal involvement⁴ (**Table 1**).

Despite this classic pathway that describes the stepwise progression from AK to invasive SCC, recent data suggest an alternative pathway of AK grade 1 directly progressing to invasive SCC.⁵

The clinical grading of AKs is mainly based on the grade of hyperkeratosis,⁶ which has not yet

been shown to correlate with histologic grading of AK. In fact, although the clinical grade III refers to hyperkeratotic AKs, grade III in histopathology refers to fully developed intraepithelial carcinoma affecting the whole epidermis.

In most cases, the diagnosis of AK has been made clinically. However, the distinction between AK and other forms of nonmelanoma skin cancer, such as superficial basal cell carcinoma or benign lesions, may pose a diagnostic challenge. Furthermore, the distinction from different grades of AK, in situ SCC/Bowen disease, or even invasive SCC may be difficult, but is of major importance for treatment selection. Dermoscopy seems to aid the differentiation between the different stages in the continuum of keratinocyte skin cancer, because AK, in situ SCC/Bowen disease, and invasive SCC have been related to different patterns.^{7,8}

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Table 1
Histologic grading of actinic keratosis, modified according to Roewert-Huber and colleagues

AK grade 1	Intraepidermal dysplasia of keratinocytes involving the lower third of the epidermis
AK grade 2	Intraepidermal dysplasia of keratinocytes involving the lower two-thirds of the epidermis
AK grade 3	Intraepidermal dysplasia of keratinocytes involving the complete epidermis. By some investigators, AK grade 3 are defined as SCC in situ, whereas others define AK in general as SCC in situ

The criteria of AK have already been described in the beginning of the era of reflectance confocal microscopy (RCM) by Aghassi and colleagues,⁹ and further studies have analyzed the sensitivity and specificity of the AK criteria as well as the differentiation of AK from Bowen disease/SCC in situ and invasive SCC.^{10–13}

Herein, the morphologic criteria of the complete spectrum of squamous neoplasia on RCM evaluation are described. Furthermore, the use of RCM for the monitoring of AK is discussed.

REFLECTANCE CONFOCAL MICROSCOPY CRITERIA OF SQUAMOUS NEOPLASIA

Actinic Keratosis and Actinic Cheilitis

On RCM, mosaics AK are characterized by central or multilocal disruption of the stratum corneum by overlying hyperkeratotic or parakeratotic scale (Fig. 1A). On higher magnification, RCM single images (0.5 mm × 0.5 mm) allow the identification of single detached keratinocytes and small bright round structures corresponding to parakeratosis. In hyperkeratotic lesions, the scale may be compact, and if covering the complete or majority of a lesion, it may significantly impair the evaluation. Rarely, inflammatory cells may be observed within the stratum corneum as a sign of impetiginization. At the level of the stratum granulosum and spinosum, an atypical honeycomb pattern may be observed. Atypical keratinocytes show pleomorphism by variations in their size and shape, thus resulting in an architectural disarray of the epidermis. In the papillary dermis, discrete increase in vasculature may be observed showing small, elongated vessels. Curled fibers may commonly be

observed in the upper dermis, corresponding to solar elastosis. Furthermore, other changes of the collagen such as huddles may often be seen as a sign of photoaging.¹⁴ Recently, it has been shown that according to the grading, a histopathology of different grades of AK may also be differentiated by RCM, thus allowing an improved severity assessment and better selection of treatment.¹⁵ Actinic cheilitis shows similar criteria with atypical keratinocytes at the epidermal layers¹⁶ (see Fig. 1).

REFLECTANCE CONFOCAL MICROSCOPY FEATURES OF ACTINIC KERATOSES

- Bright cells in the stratum corneum (parakeratosis)
- Atypical honeycombed pattern
- Upper dermis with curled fibers and slightly elongated vessels

SQUAMOUS CELL CARCINOMA IN SITU/BOWEN DISEASE

AK and SCC in situ/Bowen disease share some findings on RCM evaluation because both represent different stages of the same disease continuum and also molecular and histopathological characteristics. Although SCC in situ arising in AK and typical Bowen disease arising as single lesions on trunk and/or extremities may show slight differences on histology, they are summarized in this paragraph and are synonymously used. Parakeratosis, hyperkeratosis, and atypical honeycomb pattern may similarly be seen in AK and SCC in situ. However, marked atypia in the stratum granulosum is highly suggestive of SCC in situ as a sign for atypical proliferation of keratinocytes involving the complete epidermis. When applying RCM in clinical practice, the correct identification of the stratum granulosum may pose a significant challenge, especially for less-experienced observers. In that regard, atypical honeycomb pattern that appears directly underneath the stratum corneum is a good indicator for SCC in situ. Furthermore, SCC in situ is characterized by the presence of targetoid cells in the epidermis. Targetoid cells represent apoptotic epidermal keratinocytes, and corresponding to different stages of apoptosis, they may occur either as bright round cells with a dark rim or as a round structure with a dark center, a bright rim, and another dark rim in the periphery. The first type of targetoid cells is more common and represents apoptotic cells without nuclei, whereas the latter corresponds to apoptotic cells still containing a central nucleus.¹³ Marked pleomorphism of

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