Objective: To identify criteria for the diagnosis of squamous cell carcinoma (SCC) and actinic keratosis (AK) by in vivo reflectance confocal microscopy (RCM).

Design: Prospective RCM imaging of lesions suspected clinically and/or dermoscopically to be SCC or AK, followed by RCM assessment of the biopsy-proven SCCs and AKs.

Setting: Private skin cancer clinic, Plantation, Florida. Patients A total of 38 lesions in 24 patients were assessed, including 7 AKs, 25 SCCs in situ, 3 invasive SCCs, and 3 keratoacanthomas. Interventions Prior to undergoing biopsy, all lesions were assessed by RCM.

Results: Mosaic RCM images at the stratum corneum level revealed scale in 29 SCCs (95%) and in all 7 AKs. Polygonal nucleated cells at the stratum corneum were seen in 3 SCCs (10%) and 1 AK (14%). All 38 cases displayed an atypical honeycomb and/or a disarranged pattern of the spinous-granular layer of the epidermis; round nucleated cells were seen in the spinous-granular layer in 20 SCCs (65%) and 1 AK (14%). Round blood vessels in the superficial dermis were seen in 28 SCCs (90%) and 5 AKs (72%).

Conclusions: An increasing frequency of abnormal RCM features can be observed across the spectrum of keratinocytic neoplasias. The presence of an atypical honeycomb or a disarranged pattern of the spinous-granular layer, round nucleated cells at the spinous-granular layer, and round blood vessels traversing through the dermal papilla are the key RCM features of SCC.