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CME ARTICLE

Diagnosis and therapy of actinic keratosis

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Summary

Actinic keratosis (AK) is considered a chronic and recurring in situ skin neoplasia, with a possible transformation into invasive squamous cell carcinoma (SCC). Among others, predominant risk factors for development of AK are UV-light exposure and immunosuppression. Basal epidermal keratinocyte atypia (AK I) and proliferation (PRO score) seem to drive malignant transformation, rather than clinical appearance of AK (Olsen I–III). Due to the invasiveness of punch biopsy, those histological criteria are not regularly assessed. Non-invasive imaging techniques, such as optical coherence tomography (OCT), reflectance confocal microscopy (RCM) and line-field confocal OCT (LC-OCT) are helpful to distinguish complex cases of AK, Bowen's disease, and SCC. Moreover, LC-OCT can visualize the epidermis and the papillary dermis at cellular resolution, allowing real-time PRO score assessment. The decision-making for implementation of therapy is still based on clinical risk factors, ranging from lesion- to field-targeted and ablative to non-ablative regimens, but in approximately 85% of the cases a recurrence of AK can be observed after a 1-year follow-up. The possible beneficial use of imaging techniques for a non-invasive follow-up of AK to detect recurrence or invasive progression early on should be subject to critical evaluation in further studies.

KEYWORDS
Actinic keratosis, line-field confocal optical coherence tomography, confocal laser microscopy, non-invasive imaging, PRO score, topical therapy, photodynamic therapy

EPIDEMIOLOGY AND ETIOLOGY OF ACTINIC KERATOSIS

Actinic keratoses (AKs) are precancerous epidermal skin lesions considered to be precursors of invasive squamous cell carcinomas (SCCs) developing from atypical keratinocytes. Accordingly, actinic keratosis is also referred to as in situ neoplasia. It has been suggested that approximately 60% of SCCs arise from AKs.[1] SCC accounts for approximately 20% of nonmelanoma skin cancer (NMSC) or *keratinocyte cancer* (KC) and is, therefore, the second most common form or nonmelanoma skin cancer in immunocompetent patients after basal cell carcinoma (BCC).[2] Usually, AKs manifest on sun-exposed sites, such as scalp, dorsal aspect of the hands, or forearms. Accordingly, the cumulative amount of UV-light exposure during life is considered the most important cause for AK manifestation. In addition, other factors like age, gender, skin type (Fitzpatrick I and II), and immunosuppression contribute to the risk of developing AK.[3] It has been estimated that the prevalence of AK in the age group of 60–69 years is 4.6%, while the prevalence has almost tripled to 14.57% in the group older than 80 years.[4] In the German population, the examination of 90,800 individuals resulted in an estimated AK prevalence of 2.7% in all age groups, while in the older population, 11.5% of patients aged 60 to 70 years suffer from AK.[5] In addition, it was found that the male population is affected to a greater extent (3.5%) by AK than the female population (1.5%).[3]

While the life-time risk of malignant transformation to SCC is 6%–10% for patients with multiple AKs, the annual risk of malignant degeneration of individual actinic ker-

atoses ranges from 0.03%–20%.[1,5,6] Moreover, AK is considered a chronic recurrent disease, given that recurrence is observed in more than 85% of the treated AK cases after one year of follow-up.[7] The aging society and the high recurrence rate may partly explain why treatment of AK is a complex and expensive task presenting an estimated annual financial burden of nearly 1 to 1.68 billion US dollars for the American healthcare system.[8,9] These expenses include the examination of almost ten million patients with actinic skin damage per year.[8] The burden may further increase in an aging society and is supported by the fact that the incidence of SCC has even quadrupled in parts of the German population in the last 30 years.[3] Moreover, Leiter et al. predict for the year 2030 that the incidence of nonmelanoma skin cancer will double again, with a continuously increasing incidence in the long term.[2] The development of AK and the progression to invasive SCC is a multifactorial process driven by numerous endogenous and exogenous factors. On the genetic level, *TP53* acts as tumor suppressor gene in the human genome controlling numerous cell cycle mechanisms and playing a central role in the regulation of cell proliferation and induction of apoptosis in mutated cells. Mutations of *TP53* are predominantly found in human tumor tissue including SCC, where mutations of *TP53* are found in approximately 50% of the cases.[10–12] Sunlight, and UVB radiation in particular, has been identified as carcinogen with the ability of changing *TP53*.[13] *TP53* mutations identified in UVB-induced skin areas of mice resemble mutations in SCC, suggesting that these lesions are SCC precursors.[14] A characteristic UVB-induced mutation in the *TP53* gene is the conversion of cytidine to thymidine resulting in a loss of function of the *TP53* gene product.[15] Apart from *TP53*, other additional mutations in the genome may increase the risk of keratinocyte atypia or stimulate uncontrolled cell proliferation. Furthermore, it is known from mutations in the *KNSTRN* oncogene that they promote this cell atypia.[16] These mutations have been observed in 19% of SCCs and 13% of AKs, while they have never been identified in healthy skin.[15] Apart from genomic mutations in AK, other co-factors seem to stimulate the malignant transformation of AK. It has been suggested that viral infections like human papilloma virus (HPV) play a co-stimulating role in carcinogenesis in up to 30% of the cases of tumor manifestation. While the role of HPV in the development of nonmelanoma skin cancer is still subject of controversial discussion in the literature, a significant risk of developing nonmelanoma skin cancer is observed in patients with iatrogenic immunosuppression, in particular.[17] Although pharmacologic immunosuppression increases the probability that nonmelanoma skin cancer is colonized by HPV, the immunosuppression, which correlates significantly with the development of nonmelanoma skin cancer, is solely dependent on the duration of drug administration. The incidence of nonmelanoma skin cancer is 5% after immunosuppression for 2 years; this value increases significantly with time and reaches 60% in patients on immunosuppression for at least 20 years.[15] Recently published follow-up data from 2022 for a Finnish cohort of patients with organ transplants evaluated retrospectively for the last 30 years showed that nonmelanoma skin cancer accounts for 53% of all cancer manifestations.[18] Analogous to this situation, nonmelanoma skin cancer was observed as the main cause for tumor-associated mortality in patients with kidney transplants in the population of Australia and New Zealand.[19] Furthermore, non-iatrogenic immunosuppression, especially in case of non-Hodgkin lymphoma or chronic lymphocytic leukemia as underlying disease, seems to considerably increase the risk of nonmelanoma skin cancer including recurrence and a more aggressive course with metastasis.[20] In immunosuppressed patients, the probability to develop SCC and BCC is 4:1 and thus inversely proportional to the ratio in immunocompetent patients.[15] According to Schmitz et al., this can be explained in part by the higher progression rate of up to 30% of AKs to SCCs in immunosuppressed patients.[15] Given that AK is considered a squamous cell carcinoma in situ, the proliferation of atypical keratinocytes is restricted to the epidermis while the dermal-epidermal junction (DEJ) remains intact. Based on the histological assessment of specimens with SCC and adjacent AK tissue, Fernandez-Figueras et al. suggested two main pathways for malignant degeneration of AK to SCC.[21] The classical pathway describes the gradual development of keratinocyte atypia originating from the lower third of the epidermis (AK I) to atypia in the middle third (AK II), and eventually the upper third of the epidermis (AK III) according to the staging of atypia previously suggested by Roewert-Huber.[21,22] In the last stage of the disease, the invasive proliferation is defined based on the loss of integrity of the DEJ and the invasive infiltration of atypical keratinocytes into the dermis. Apart from the classical pathway, it was found that AK I can also progress directly to an invasive SCC without gradual development of atypia in higher epidermal layers, especially if an AK I is growing in close contact to adnexal tissue.[21] The progression from AK to SCC seems to be a complex process triggered by interactions between co-carcinogenic factors. The underlying mechanism is still poorly understood and therefore subject to controversial discussions in the current literature. Based on these assumptions, Schmitz et al. suggested the use of clinical and histological features found in AK lesions to estimate the risk of malignant transformation of AK.[15] The clinical classification according to Olsen and the two histological classifications (PRO score and Roewert-Huber) have the common objective to provide a grading system of the malignant potential of AK. The clinical benefit of these classifications is, however, critically discussed in the literature. Recent studies indicate that the clinical Olsen score alone is insufficient to predict the risk of malignant degeneration.[3,21,23]

The clinical manifestation of actinic keratosis does not correlate with the degree of underlying keratinocyte atypia and the histological PRO score.

In a study performed by Schmitz et al. in 2016, it was shown that the clinical manifestation of AK according to

the Olsen classification does not correlate with the degree of underlying keratinocyte atypia measured by Roewert-Huber classification.[23] Only in 53.8% of lesions were clinical and histological classifications equivalent, with the majority (83.1%) consisting of Olsen II and AK II.[23] Another study demonstrated that the expression of the mutated *TP53* gene in AK increases with a higher rate of keratinocyte dysplasia, but no significant level could be defined.[12] Moreover, no significant correlation was found in AK between *TP53* expression, degree of epidermal dysplasia and clinical thickness or thickness of the stratum corneum.[12]

Based on these findings, Heerfordt et al.[12] supported the hypothesis of Schmitz et al.[23] that the clinical manifestation of AK is not a sufficient and reliable predictor for the malignant transformation to SCC. In contrast, Bakshi et al. showed that the mutated state of *TP53* and its increased protein expression could be found in clinically apparent AK, while significantly lower levels were found in regressed AK.[24] In 2019, Schmitz et al.[25] assessed, analogous to the study of Fernandez-Figueras et al.[21], the epidermis overlying and adjacent to invasive SCC in histological specimens. The epidermal layers were examined with respect to keratinocyte atypia (Roewert-Huber, AK I–III) and basal growth pattern (PRO score I–III). The majority (39.4%) of SCCs showed PRO III in the adjacent epidermis, followed by PRO II (31.9%) and PRO I (25.7%).[25] Furthermore, basal proliferations of atypical keratinocytes (Roewert-Huber AK I) were found in more than 50% of the assessed adjacent AK lesions.[25] The finding that AK I is predominantly associated with invasive SCC was consistent with the study of Fernandez-Figueras et al. who reported that keratinocyte atypia often arises from the lower third of the epidermis (AK I).[21,25] If an AK I advances along adnexal structures, this may also facilitate further development of SCC from AK I lesions.[21] In spite of these controversies, the most recent S3 guidelines for AK and SCC provide no recommendation with respect to risk factors for the development of malignancy in AK.[3] Furthermore, there is no evidence that the risk of malignant degeneration can be predicted based on clinical manifestation.[3] The new insights indicate that downward-directed proliferation and basal atypia in AK represent two major factors for distinguishing high-risk AK. Unfortunately, it is not possible to determine these factors by clinical manifestation and to consistently examine them during follow-up due to the invasiveness and lack of reproducibility of skin biopsy.[21,23] Accordingly, there are no long-term follow-up data of AK documenting the various changes in cellular morphology and epidermal architecture on the pathway to malignant degeneration.

CLINICAL MANIFESTATION AND DIAGNOSIS OF ACTINIC KERATOSIS

Clinical manifestation and dermoscopy

While the clinical manifestation of AKs may vary, they generally present as circumscribed reddish, sometimes discrete brownish macules accompanied by hyperkeratosis of varying thickness and scaling (Figure 1a). Usually, the lesions arise individually to disseminated, but may, however, coalesce to larger plaque-like formations, also known as field cancerization, in later stages. Apart from the clinical features, AKs may be accompanied by pruritus, erosions, or bleeding.

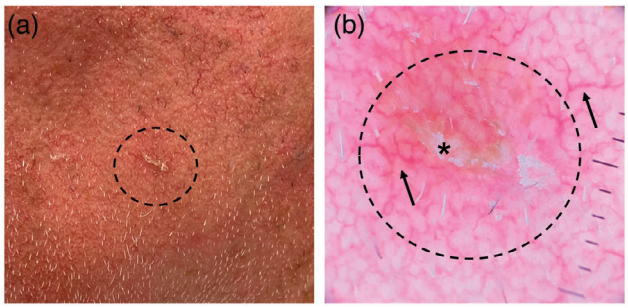

FIGURE 1 (a) Clinical manifestation of AK. Slightly reddish macule, accompanied by keratosis on the left cheek of a patient (circle). (b) Using dermoscopy (DermLite® DL4 dermatoscope, 3Gen Inc., San Juan Capistrano, California, USA), keratosis (asterisk) and a strawberry pattern (circle) with linear waved vessels (arrow) can be appreciated.

Generally, the diagnosis of AK is based on clinical and dermoscopic examination of the skin and observation of the clinical features already mentioned. Dermoscopy reveals the so-called "strawberry pattern" characterized by linear reticular vessels surrounding the follicular openings resulting in the appearance of an erythematous pseudonetwork (Figure 1b).[15,26] Compared to histology, dermoscopy has a sensitivity of 98.7% and a specificity of 95% in diagnosis of AK.[26] According to Valdés-Morales, the most common dermoscopic features of AK are scaling (86.7%), followed by follicular openings (83.1%), erythematous pseudonetwork (79.9%), and linear wavy vessels (71.2%).[26]

Clinical classification according to Olsen

According to Olsen, the manifestation of AK can be classified based on three clinical characteristics (Olsen I–III): erythema, hyperkeratosis, and scaling.[27] In Olsen I, AK presents as a reddish or brownish pigmented macule. In this stage, it is difficult to detect and is easier felt than seen, given that erythema and hyperkeratosis are more or less absent according to the definition (Figure 2a).[27] Actinic keratoses according to Olsen II and III are usually easier to diagnose, given that erythema and the moderate (II) to thick (III) hyperkeratosis provide visible and palpable evidence for the diagnosis (Figure 2b, c).[27] Although the diagnosis of AK is in many cases based on the different degree of the three clinical characteristics (erythema, hyperkeratosis, and scaling), the diagnosis may be challenging in some cases, especially if the lesion is pigmented. In these difficult cases, histology may assist in the differentiation of AK from other

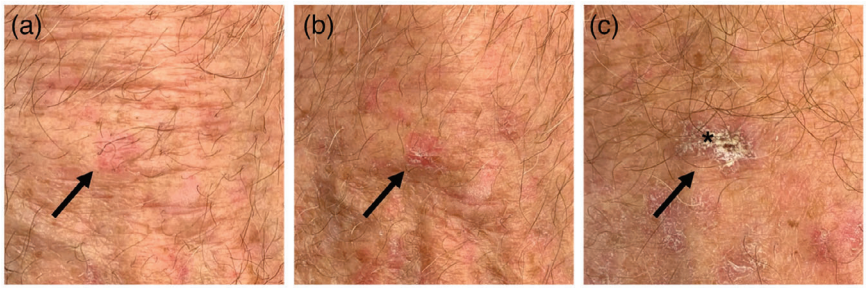

FIGURE 2 (a) Clinical AK classification according to Olsen. Olsen I manifests as a mild erythematous macule (arrow) on the right hand's dorsum. (b) For Olsen II, increasing erythema and keratosis (arrow) can be appreciated. (c) Olsen III is characterized by thick hyperkeratosis (asterisk).

diagnoses, such as Bowen's disease, seborrheic keratosis, or invasive SCC, due to clear histological characteristics.

Histology and histological grading system

Histology represents the gold standard for the diagnosis of AK. Histologically, AK is defined by the mandatory keratinocyte atypia in the epidermis.[3] Keratinocyte atypia itself can be detected based on the morphological changes of keratinocyte nuclei, such as pleomorphism, hyperchromasia, and increased nuclear-to-cytoplasmic ratio.[3] Apart from the hyperplasia of atypical keratinocytes and the loss of cell polarity, crowding of basal keratinocytes in the epidermal layers can be identified.[3] Typically, the stratum corneum of the epidermis presents with vertically alternating layers of parahyperkeratosis and orthohyperkeratosis, while the epidermis may be atrophic or acanthotic. The subjacent papillary dermis may present with perivascular inflammation consisting of lymphocytes and plasma cells, while the dermal actinic elastosis is a key feature indicating the underlying UV exposure. AK may also be acantholytic or pigmented. Given that AK is *per definition* a precursor of invasive skin cancer in the form of carcinoma in situ, the integrity of the DEJ presents an important differentiating feature between AK and invasive SCC. Keratinocyte atypia is present in the whole lesion and usually arises from the basal epidermal layers spreading to the uppermost layers.[21,22] While the DEJ remains intact in AK lesions, the basal growth pattern may change during the transformation process to an invasive SCC resulting in epidermal undulation.[28] This undulation may be classified histologically based on the PRO score I–III introduced by Schmitz et al.[28] In summary, the horizontal upward-directed spreading of keratinocyte atypia can be classified by the Roewert-Huber classification, while the PRO score was established to categorize the degree of downward-directed proliferation.[22,28]

Roewert-Huber classification

The histological grading system of Roewert-Huber evaluates the distribution of keratinocyte atypia originating from the basal cell layer and spreading upwards to the uppermost epidermal layers.[22] For classification of the degree of atypia, the epidermis is divided into three parts. This implies that atypia dominating in the upper third is typical for the most advanced AK (AK I–III). While grade I atypia is limited to the basal third of the epidermis, grade II atypia is reaching the middle part of the epidermis, and grade III atypia can be observed also in the upper third beneath the stratum corneum of the epidermis. Accordingly, in AK III the whole epidermis presents with atypia.[22]

PRO score classification

Histologically, the downward-directed proliferation of AK can be classified by PRO score I–III established by Schmitz et al.[28] The early stage of PRO I is characterized by *crowding* of atypical keratinocytes in the basal cell layer (Figure 3a). In PRO II, round nests have formed in the upper papillary dermis (*budding*) resulting in undulation of the basal epidermal layer (Figure 3b).[28] PRO III is characterized by proliferation of atypical keratinocytes forming epidermal buds that protrude into the dermis and exceed the thickness of the epidermis (*papillary sprouting*) (Figure 3c).[28]

Histologically, the downward-directed proliferation of AK can be classified by PRO score I–III.

Non-invasive imaging techniques

Optical coherence tomography

Optical coherence tomography (OCT) was originally developed in ophthalmology and is used as non-invasive diagnostic tool in dermatology since the late 1990s.[29,30] The only commercial OCT device currently available is the VivoSight® Dx (Michelson Diagnostics, Kent, United Kingdom) with a lateral resolution of < 7.5 µm and an axial resolution of 10 µm. The penetration depth into the skin is 1.5 to 2 mm. The 3D image has a size of 6 mm x 6 mm x 2 mm. Apart from the diagnosis of BCC, OCT is often used also for AK and facilitates, among others, the differentiation from SCC.[3] Friis et al. analyzed 16 studies on the diagnosis of AK by OCT.[31] Especially morphological criteria, such as disruption of epidermal cell layers (16/16), thickened epidermis (14/16), and evidence for hyperreflective epidermal morphology of streaks and dots (11/16), may facilitate the diagnosis of AK.[31] Additional diagnostic criteria include an

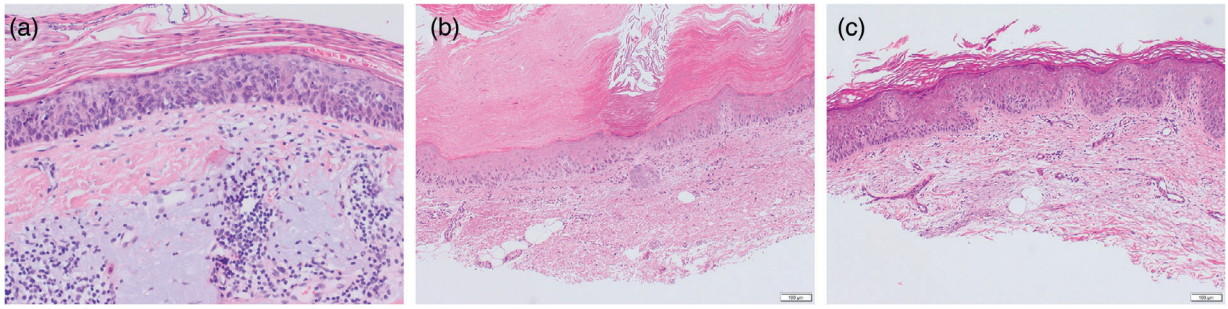

FIGURE 3 Histological PRO score. PRO I is characterized by crowding of atypical keratinocytes, in the epidermal layer, but no epidermal undulation can be detected (a). For PRO II, the vertical extension of the DEJ protrusion into the papillary dermis does not exceed the thickness of the epidermal layer. For PRO III, the vertical extension of cone-like protrusions exceeds the thickness of the epidermal layer.

atypical honeycomb pattern and the preservation of the DEJ in the vertical OCT view.[31] Moreover, Schuh et al. could show that OCT enables the diagnosis of actinic keratosis, as well as its significant differentiation from BCC based on signal intensity and the respective differences in layer thickness of stratum corneum and epidermis.[32] Marneffe et al. suggested a suitable algorithm for the differentiation of healthy skin, AK, and SCC with high-definition OCT (HD-OCT), still available at the time, as follows: first, the integrity of the DEJ should be assessed. If the DEJ is intact, an invasive SCC can be largely excluded. The presence of AK can be verified based on the patterns mentioned above. The diagnosis of AK should be considered, in particular, if an atypical honeycomb pattern and an alternating sequence of hyperkeratosis and parakeratosis are observed.[33] Assessment of the adnexal structures in *en face* view with evidence of a cockade pattern allows for the exclusion of epithelial involvement of adnexal structures. When the cockade pattern is lost, however, involvement of the adnexal epithelium has to be assumed.[33] This is relevant, since AKs showing only basal atypia (Roewert-Huber AK I) but adnexal involvement often progress directly to an invasive SCC, without passing though the atypia stages AK II and III.[21] One study with OCT reported a diagnostic sensitivity of 100% for clinically apparent AKs and of 73% for subclinical AKs.[34] In dynamic OCT (D-OCT) that also allows for the visualization of blood flow by means of repetitive measurements of moving particles, *curved vessels* were found in AK at a penetration depth of 300 µm in approximately 44% of the cases (versus 8.3% in Bowen's disease and 12.3% in SCC). This criterion seems to be particularly relevant for the differentiation from Bowen's disease, given that in Bowen's disease this vascular pattern is undetectable in 58% of the cases. At a depth of 500 µm, the vascular pattern appears homogeneous and arranged in a reticular pattern (Table 1).[35]

Line-field confocal optical coherence tomography

Line-field confocal optical coherence tomography (LC-OCT) is a non-invasive imaging tool developed from OCT. It was developed by Arnaud Dubois in 2018 to detect early forms of skin cancer at cellular resolution.[36] The deepLive™ (DAMAE Medical, Paris, France) is the only LC-OCT device currently available. LC-OCT combines the benefits of OCT and confocal laser microscopy (CLM) with a high resolution of 1 µm and a sufficient penetration depth of 500 µm. It enables vertical, horizontal and 3D image visualization showing the morphological characteristics similar to histological tissue sections. The individual image section has a size of 1.2 mm x 0.5 mm in the horizontal and vertical view.

With LC-OCT, the PRO score in actinic keratosis can be determined in a non-invasive manner.

Since introduction of LC-OCT, numerous studies have assessed its use in clinical dermatology to visualize benign and malignant skin lesions like AK, BCC, Bowen's disease, and SCC. Furthermore, Ruini et al. discovered that LC-OCT succeeds in non-invasive assessment of DEJ in real time and thus in quantification of the PRO score (Figure 4a–c).[37,38] Due to their cellular resolution, LC-OCT images also correlate strongly with conventional histopathological sections.[39]

Confocal laser microscopy

Similar to dermoscopy and OCT, confocal laser microscopy (CLM) can also be used for the diagnosis of AK and SCC in clinically ambiguous lesions.[40] The only device currently commercially available is the VivaScope® 1500 from the company Mavig (Munich, Germany). Individual images are only acquired horizontally and with a size of 750 µm x 750 µm up to a depth of approximately 200 µm. They can be merged to mosaic pictures of 8 mm x 8 mm. Furthermore, there is the VivaScope® 3000 as manual device for more flexible, rapid acquisition. CLM can be used for the detection of subclinical AK lesions and field cancerization.[40] Typically, identification of AK in CLM is based on an atypical honeycomb pattern. A similar pattern can be observed in Bowen's disease. In squamous cell carcinomas, bright reflective horny structures are found in the papillary dermis. After application of topical or other therapies, regular polygonal

TABLE 1 Overview on the morphological criteria, which allow to distinguish between the three entities: Bowen's disease, AK, SCC using (D-)OCT.[31,33,35,93]

	Bowen's disease	Actinic keratosis	Squamous cell carcinoma
Epidermis	Acanthosis	Acanthosis or atrophy, disrupted epidermal cell layers, hyperreflective pattern of dots and streaks	Hyperreflective tumor infiltrates, periadnexal epithelial infiltration
Dermal-epidermal junction zone	Intact	Intact	Not intact
Vessels	Normal vessel diameter	Normal vessel diameter	Increased vessel diameter
Vascular pattern	Oval or drop-like red structures (blobs)	Curved vessels, homogeneous reticular vascular structure	Disorganized and inhomogeneous vascular pattern without reticular pattern

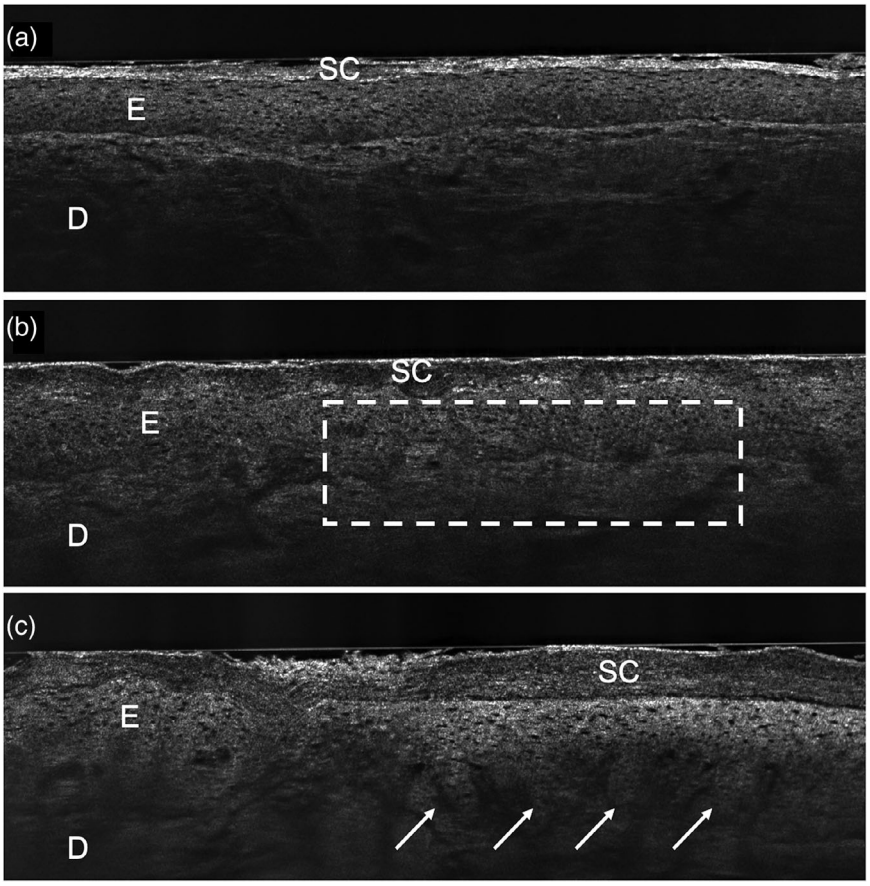

FIGURE 4 Visualization of the PRO score using LC-OCT. For (a) PRO I, no protrusion or DEJ undulation can be detected. For (b) PRO II, a slight DEJ undulation (square), and for (c) PRO III, cone-like protrusions (arrows) can be appreciated (LC-OCT, deepLive™, DAMAE Medical, Paris, France; image size: 1.2 × 0.5 mm^2, lateral and axial resolution: 1.1 µm x 1.3 µm). *Abbr.*: SC, stratum corneum; E, epidermis; D, dermis

keratinocytes and a normalization of the honeycomb pattern are once again recognized.[41–44] A review on CLM found a sensitivity of 91%–100% for AK and of 100% for SCC.[45] For the diagnosis of AK, the epidermal pleomorphism of stratum spinosum and stratum granulosum was used as criterion for the highest sensitivity and specificity.[46]

Therapy of actinic keratosis

Given that no clinically definite and lesion-specific risk factors for the malignant degeneration of AK have been identified yet, no consensus exists concerning the question which AKs require therapy. The decision to start a therapy is made even more difficult by the fact that the estimated annual risk of malignant degeneration for each individual AK ranges from 0.03% to 20% and that 60% of SCCs are associated with a precursor AK.[1,6,47] On the other hand, spontaneous remission of AK can be observed in up to 60% of the cases.[47] Based on the results of Schmitz et al.[23,25] and Fernandez-Figueras et al.,[21] the watch-and-wait approach has been increasingly abandoned.[3] Schmitz et al. even state that each individual AK should be treated after diagnosis, given the inadequate predictability of the potential for malignant degeneration.[22] Numerous therapeutic options for the treatment of AK are available ranging from

topical therapies via physical treatment options, such as cryotherapy and light therapy, to ablative regimens. For the decision process of selecting the adequate treatment method for the respective AK, the German S3 guideline recommends the consideration of several secondary aspects, such as age, comorbidity, immunosuppression, number of AK lesions, *compliance* of the patient, and adherence to therapy.[3] With respect to available therapeutic options, lesion-directed treatment options and field-directed therapies targeting not only individual lesions but treating a larger affected anatomical area are distinguished. Accordingly, the latter option also allows for the treatment of subclinical lesions. Lesion-directed therapies include mechanically destructive procedures, such as deep *shave* excisions, curettage or surgical excisions, cryotherapy, and laser therapy, but also photodynamic therapy (PDT) and topical therapies like 5-fluorouracil 0.5% (5-FU) with salicylic acid 10% (Table 2).[15] Cryotherapy is an easy option to induce irreversible damage to cellular organelles or atypic keratinocytes in AK lesions by formation of ice crystals. For this purpose, liquid nitrogen (–196°C) is applied for at least two freeze-thaw cycles for 15–60 seconds to the lesions until whitish markings develop. While the therapy is effective due to the induced physical cell damage, it is not specific and, accordingly, will not protect the adjacent healthy skin from harm. A meta-analysis reported a successful treatment outcome free of recurrence in 68% of the cases.[48,49]

Refractory actinic keratoses must be classified as high-risk for malignant degeneration to SCC, given that they frequently exhibit aggressive basal proliferation patterns (PRO III) and a high degree of atypia (AK III).

PDT using 5-aminolevulinic acid (ALA) or the methyl ester methyl aminolevulinate (MAL) is similarly effective in treating individual AK lesions (Olsen I–II) or field cancerization. 5-aminolevulinic acid and MAL act as photosensitizers accumulating specifically in AK. As precursor of the endogenous heme biosynthesis pathway, ALA is converted into the photoactive protoporphyrin IX. During light exposure, reactive oxygen species are formed by photochemical and physical processes within precancerous keratinocytes resulting in DNA strand breaks and thus in induction of apoptosis. A red-light source or daylight can be used for light exposure. Recently published studies indicate that red-light PDT (RL-PDT) is significantly accompanied by hemodynamically relevant side effects like hypertension due to the more severe pain compared to the well-tolerated daylight PDT (DL-PDT).[50] Moreover, DL-PDT appears to be equivalent to RL-PDT in clinical effectiveness while causing less pain. Lacour et al. report a complete clearance rate of treated lesions of 74% for RL-PDT compared to 70% for DL-PDT.[51] With respect to the long-term effect over 24 weeks, Rubel et al. could also show an almost similarly high clearance rate of 96% for DL-PDT compared to 96.6% for RL-PDT.[52] A study performed by Garcia-Gil could demonstrate that DL-MAL-PDT performed at home can be implemented successfully, if AK lesions are pretreated with 30% urea 7 days prior to therapy. After 3 and 12 months, complete clearance was observed in 47.7% ($p < 0.001$) and 65.9% ($p < 0.001$) of AK lesions, respectively, with the best response rate achieved for AK according to Olsen II and a significant reduction in AKASI score after 12 months.[53] Furthermore, the effectiveness of PDT can be increased by additional pretreatment of AK. Pretreatment can, for example, be performed by topical, systemic, or ablative procedures.[54–56] A study by Maytin et al. could show that the doses of accumulated photoactive protoporphyrins measured in skin biopsies were increased 2 to 3-fold compared to non-pretreated AKs after pretreatment of AKs with 5-FU for 6 days and subsequent exposure to MAL for three additional hours.[55] The subsequently performed RL-PDT achieved a significantly higher clearance rate after 3 and 6 months in pretreated AKs.[55] These results were also observed in other studies.[57–61] Imiquimod 5%/3.75% can also be combined successfully with ALA-PDT.[56] Application of topical retinoids (tazarotene gel 0.1%) twice daily for one week on the upper extremity with subsequent ALA-PDT resulted in significant reduction of more than 50% of treated AK lesions.[62] After pretreatment with adapalene gel 0.1%, ALA-PDT 10% could also achieve a significant reduction of AK lesions on dorsal hands and forearms.[63] Concerning the use of ALA-PDT it should be borne in mind that the treatment of AK on trunk, neck, and extremities is only approved as RL-PDT and that DL-ALA-PDT in these locations is performed in off-label use.

The topical application of vitamin D products (calcitriol/calcipotriol) was also shown to result in enrichment of photoactive protoporphyrins and to induce apoptosis in pretreated AKs, thus achieving a better therapeutic response.[64] Galimberti et al.[65] and Torezan et al.[66] achieved a significantly better therapeutic response for pretreated AKs treated subsequently with MAL-PDT. The combination of systemic therapeutics and combined PDT is an element of preclinical research. Preclinical studies with SCC cell cultures or mouse models have demonstrated a higher apoptosis rate in SCC cell lines or an increased cellular accumulation of protoporphyrins for administration of systemic therapeutics including vitamin D, methotrexate, and acitretin in combination with PDT.[67–69] Interestingly, it was shown that a therapeutic response, based on histological criteria, in AK after MAL-PDT is significantly correlated with increased serum vitamin D levels.[69] Apart from local and systemic combination therapies, PDT can also be combined with mechanical therapeutic procedures, especially to increase the ability of ALA/MAL to penetrate into the lesioned skin.[70] Suitable methods are, for example, ablative laser techniques that remove the uppermost physical skin barrier, the stratum corneum, and create microscopic vertical penetration channels in the epidermis.[70] In this context, the use of Er:YAG and CO_2 lasers in combination with ALA/MAL-PDT is particularly notable, given that this approach achieved a significant reduction of AK lesions and a lower recurrence rate in many application studies even

TABLE 2 Overview of the different therapy regimens for actinic keratoses.

Therapy and mode of action	Grade (Olsen I–III)	Approach	Location/ max. treatment area (cm^2)	Application	Field cancerization	Effectiveness (complete remission)
Imiquimod 5% (toll-like receptor 7 agonist)	I–II	F, L	Face, scalp (≤ 25 cm^2)	3 x/week for 4 weeks	x, approval for immunosuppressed patients restricted	53.7–55%[94,95]
Imiquimod 3.75% (toll-like receptor 7 agonist)	I–II	F	Face, scalp (≥ 25 cm^2)	1 x/day for 2 weeks, break of 2 weeks, 1 x/day for 2 weeks	x	34–35.6%[96,97]
Diclofenac sodium 3% in hyaluronic acid 2.5% gel (cyclooxygenase 2 inhibitor)	I–II	F	Face, scalp (≤ 25 cm^2)	2 x/day for 60–90 days	x	41%[98]
5-fluorouracil 5% cream (cytostatic)	I–II	F	Face, scalp	2 x/day for a maximum of 4 weeks	x	42.9–76.6%[99]
5-fluorouracil 0.5% with salicylic acid 10% in solution (cytostatic and keratolytic)	I–II	L, F	Face, scalp (≤ 25 cm^2)	1 x/day until clearance (maximum of 12 weeks)	x	47.5–57.8%[100]
5-fluorouracil 4% cream (cytostatic)	I–II	L	Face, scalp	1 x/day for a maximum of 4 weeks	x	80%[101]
1% tirbanibulin (spindle inhibitor)	I	L	Face, scalp (≤ 25 cm^2)	1 x/day for 5 days	x	49%[102]
8% ALA-PDT; 16% MAL-PDT (precursor of protoporphyrin (photosensitizer))	I–II	F, L	Face, scalp, extremities	Incubation for 3 h under light-protection bandage, then exposure to red light for 10–20 min; repetition in 4–12 weeks	x	69–93% (face, scalp) 44–80% (extremities)[3]

(Continues)

TABLE 2 (Continued)

Therapy and mode of action	Grade (Olsen I–III)	Approach	Location/ max. treatment area (cm^2)	Application	Field cancerization	Effectiveness (complete remission)
DL-ALA/MAL-PDT (precursor of protoporphyrin (photosensitizer))		F, L	Face, scalp	Incubation for approx. 30 min, exposure to sun light for 2 h, repetition in 4–12 weeks	x	70–89%[52,103]
Surgical procedures	I–III	L	Face, scalp, trunk, extremities	Curettage, deep shave excision, or surgical excision		No data from RCTs
Cryosurgery	I–III	L	Face, scalp, trunk, extremities	1–2 freeze-thaw cycles with liquid nitrogen (–196°C) for 15–60 s (blanching)		39–76%[3]
Ablative laser methods (CO_2 laser, Erbium:YAG laser)	I–III	L	Face	Several settings, if necessary; depending on clinical response rate	x	72.4–91.91%[3]
Non-ablative laser methods (Nd:YAG laser, 1540 nm fractional laser)	I–III	L	Face	Several settings, if necessary; depending on clinical response rate		No data from RCTs
Chemical peelings (e. g., trichloroacetic acid)	I–III	F, L	Face, scalp		x	31.9%[3]

Abbr.: F, field-directed; L, lesion-directed; RCT, randomized controlled trial

in difficult-to-treat patients on immunosuppression.[72–76] In a meta-analysis by Pei et al.[61], a significantly higher rate of completely cleared AKs was reported after application of ablative laser therapy in combination with PDT compared to PDT alone. However, this meta-analysis was given only a low evidence level. Similar therapeutic approaches for improving the penetration of ALA/MAL into lesioned skin are pretreatment of AK by microneedling or microdermabrasion to the dermis. Accumulation of protoporphyrins in lesioned skin and a significantly higher rate of completely cleared AK have been demonstrated for both procedures, while microdermabrasion resulted also in improvement of dyspigmentation and skin texture.[77–82] No superior effect was shown for microneedling using needles penetrating the epidermis only.[83]

The treatment of AK may also be performed with ablative laser techniques alone. This is particularly useful for treatment of individual AK Olsen I–III, but is also possible for treatment of field cancerization in immunocompetent individuals.[3] For this purpose, ablative lasers, such as 2940 nm Er:YAG laser or 10,600 nm CO_2 laser (scanned continuous wave), should be used.[84] As already mentioned, treatment of field cancerization with the fractional laser should be performed in combination with RL-PDT or DL-PDT. A fractional 10,600 nm CO_2 laser may also be implemented in off-label use for *laser-assisted drug delivery* (LAAD) to facilitate better penetration of a subsequent topical therapy, such as fluorouracil 5%.[84]

Surgical procedures for individual lesions include curettage, superficial shave excision, and simple surgical excision (Table 2). These procedures are usually restricted to individual AK lesions (Olsen I–III) and should be considered if SCC cannot be excluded with complete certainty by the clinical features.[3]

Field-directed therapeutic options include ALA-PDT and MAL-PDT, but also numerous topical therapies such as 5-fluorouracil (FU) 5%, diclofenac sodium 3%, and imiquimod 3.75% and 5%. Apart from 5-FU 5%, two new 5-FU formulations are currently available for the topical therapy of AK according to Olsen I–II (Table 2). 5-Fluorouracil cream 4% is applied once daily for 2 to 4 weeks and is superior to 5-FU cream 5% applied twice daily.[85] Another topical therapy is the 0.5% solution of 5-FU with 10% salicylic acid (5-FU-SA) that has also shown high effectiveness in field cancerization compared to placebo when applied for treatment of AK on face and scalp once daily for 12 weeks on a maximum treatment area of 25 cm^2.[86] In a monocentric randomized phase III trial, low-dose 5-FU-SA was superior to 3% diclofenac gel in hyaluronic acid in terms of histological response rate (72% vs. 59.1%) and complete clinical clearance (55.4% vs. 32.0%).[87] Tirbanibulin 1%, a reversible tubulin polymerase inhibitor approved in 2021, is another topical therapy for the early stages of AK. Tirbanibulin inhibits Src tyrosine kinase signaling resulting in cell cycle inhibition during mitosis and thus apoptosis and triggering antiproliferative and antitumoral effects in AK lesions.[88] Tirbanibulin has been approved by the European Medicines Agency (EMA) for the treatment of non-hyperkeratotic and non-hypertrophic AK (Olsen I) on the face and scalp. Tirbanibulin should be applied on intact skin of an AK lesion once daily for five consecutive days treating a maximum skin area of 25 cm^2. The therapeutic effect can be assessed clinically 8 weeks after therapy start. If residuals remain, other therapeutic options should be considered, given that there is so far no evidence for the clinical efficacy of tirbanibulin for more than one cycle. The clinical effectiveness of tirbanibulin has been demonstrated in two identical double-blind phase III trials comprising 702 adults with 4–8 AK lesions on the face or scalp.[89] Adults using tirbanibulin as described had significantly higher complete (100%) response rates than those on placebo ($p < 0.0001$) at day 57: 44% vs. 5% and 54% vs. 13%. Significantly higher treatment outcome rates for tirbanibulin compared to placebo were also identified for a partial response (≥ 75%) at day 57: 68% vs. 16% and 76% vs. 20%. Effectiveness was found consistently in all examined subgroups including age, gender, AK number at treatment start, and skin type according to Fitzpatrick. After 1 year, recurrence was observed in 47% of the patients with complete (100%) clearance.

A meta-analysis conducted by Heppt et al. showed that tirbanibulin was superior to 3% diclofenac with respect to clearance of lesions and achieved outcomes similar to 5-FU 5%, 4% and 0.5% in combination with salicylic acid, imiquimod 3.75% and 5%, ALA-PDT and MAL-PDT, and cryotherapy.[90] Another new therapy currently in phase I/II is AVX001, a cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$) enzyme inhibitor, presenting a novel anti-inflammatory field-directed topical therapy.[91]

Although the mentioned therapeutic options show a good clinical effect, recurrence can be observed in up to 85% of the treated AK cases after 1 year of follow-up. Here the definition of recurrence probably also includes newly developed AKs.[7]

Thus, refractory AKs must also be considered high-risk for malignant degeneration to SCC, given that they frequently show aggressive basal proliferation patterns (PRO III) and a high degree of atypia (AK III).[92] Apart from the mentioned histological criteria, Schmitz et al. could retrospectively identify painfulness of AK as clinically independent predictor for refractory behavior of AK.[92] This clinical indicator may, therefore, be useful when selecting a suitable therapy and should also be considered during the follow-up of AK.

Currently, no topical therapeutics are approved for the treatment of actinic keratosis Olsen III.

The therapy of AK Olsen III presents another challenge, given that the topical therapeutics (Table 2) are only approved for AK Olsen I and II. In a cohort of 892 AKs histologically assessed by Schmitz et al.[23], the proportion of AK Olsen III was only 11.3%. However, in this representative sample and with respect to the overall high prevalence of AK, this percentage of AK Olsen III seems to represent a quite significant subgroup with only limited treatment

options available. In general, AK Olsen III should, therefore, be treated by invasive surgical or ablative procedures such as cryotherapy or laser therapy in everyday clinical routine. Given the histological fact that AK Olsen III does not correlate with an enhanced risk of malignancy, these more invasive treatment regimens seem, therefore, not necessarily indicated. If an SCC cannot be excluded with complete certainty, surgical therapy with histological diagnostic workup should be chosen. Pretreatment of hyperkeratosis in AK Olsen III with keratolytic agents or by physical ablation may be helpful to achieve the desired treatment success. In addition, chemical peelings are available for treatment of AK Olsen III, although a satisfactory treatment effect is only achieved in approximately one third of the cases (Table 2).

Outlook

The frequently chronic recurrent course of AK suggests that subclinical, histological criteria, such as basal atypia or high PRO score, play a role in malignant transformation or development of recurrence in AK. Since the invasiveness of punch biopsy largely prevents a follow-up of AK, non-invasive imaging methods like LC-OCT may avoid this dilemma and present a suitable instrument for early detection, risk stratification, monitoring during therapy, as well as follow-up and diagnosis of recurrence in the future.

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CONFLICT OF INTEREST STATEMENT

The authors are conducting a sponsored clinical phase IV trial with the title: "Line-field confocal optical coherence tomography (LC-OCT) for non-invasive imaging of epidermal changes, quantification (PRO score), monitoring of changes during treatment and recovery of actinic keratosis lesions under the treatment with Tirbanibulin (Klisyri®)" for the company Almirall S.A. J.T. has no other conflict of interest to declare. J.W. received consulting fees from Almirall and Janssen, lecture fees from Almirall, Novartis, Janssen, LEO Pharma, Boehringer-Ingelheim, BMS and a travel grant from Janssen. J.W. also holds the position of President of the German Dermatological Society. S.S. has no other conflict of interest to declare. The manuscript was created without any support of the pharma industry. The reported coflict of interest does not have any influece on the article's content.

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CME QUESTIONS / LERNERFOLGSKONTROLLE

1. Welche Aussage zu aktinischen Keratosen (AK) trifft zu?
   a. AK sind frühe dermale in-situ Plattenepithelkarzinome.
   b. Sie werden als Vorstufen des Basalzellkarzinoms betrachtet.
   c. 60% der Plattenepithelkarzinome gehen aus AK hervor.
   d. AK Olsen III weisen ein hohes Risiko auf in ein invasives Plattenepithelkarzinom überzugehen.
   e. AK manifestieren sich üblicherweise an Fußrücken und Fußsohlen sowie am Stamm.

2. Welcher Risikofaktor trägt **nicht** dazu bei, aktinische Keratosen zu entwickeln?
   a. UV-Licht
   b. Alter
   c. Hauttyp (Fitzpatrick I und II)
   d. Immunsuppression
   e. Autoimmunerkrankung

3. Welche Aussage zu *TP53*-Mutationen bei aktinischen Keratosen trifft zu?
   a. *TP53* ist ein Spindelgift.
   b. Mutationen von *TP53* finden sich zu 70% bei Plattenepithelkarzinomen.
   c. UVA-Strahlung führt zu *TP53*-Mutationen.
   d. Die *TP53*-Mutation führt zur Umwandlung von Adenosin in Guanin.
   e. *TP53*-Mutationen stimulieren die unkontrollierte Zellproliferation.

4. Immunsuppression spielt eine wesentliche Rolle bei der Entwicklung von Plattenepithelkarzinomen aus aktinischen Keratosen. Welche Aussage trifft hierzu **nicht** zu?
   a. Mit der Dauer der Immunsuppression steigt die Inzidenz von nichtmelanozytärem Hautkrebs an.
   b. Bei Organtransplantierten macht nichtmelanozytärer Hautkrebs circa die Hälfte aller Manifestationen von Krebs aus.
   c. Nichtmelanozytärer Hautkrebs ist die Hauptursache für die Tumor-assoziierte Mortalität bei nierentransplantierten Patienten.
   d. Bei immunsupprimierten Patienten liegt die Wahrscheinlichkeit des Auftretens von nichtmelanozytärem Hautkrebs bei 2 : 1.
   e. Immunsupprimierte Patienten weisen eine höhere Progressionsrate von 30% der aktinischen Keratosen hin zu Plattenepithelkarzinomen auf.

5. Welche Aussage zur malignen Entartung von aktinischen Keratosen trifft zu?
   a. Aktinische Keratosen Grad I (nach Röwert-Huber) können auch direkt in ein Plattenepithelkarzinom fortschreiten.
   b. Eine HPV-Kolonisation stellt einen wesentlichen Trigger zur Entartung von aktinischen Keratosen dar.
   c. Aktinische Keratosen entwickeln sich mit zunehmender Atypie der Keratinozyten vom Stratum granulosum ausgehend bis zur dermoepidermalen Junktionszone in ein Plattenepithelkarzinom.
   d. UV-Licht stellt das einzige Karzinogen für die Entwicklung von AK dar.
   e. Das Risiko für die maligne Entartung einer aktinischen Keratose liegt bei 60%.

6. Aktinische Keratosen können verschieden klassifiziert werden. Welche Aussage zur PRO-Klassifikation trifft zu?
   a. Dabei wird die Epidermis in drei Drittel geteilt.
   b. Die PRO-Klassifikation beurteilt das Ausmaß der Abwärtsproliferation anhand der PRO-Scores I–III.
   c. Sie wurde von Röwert-Huber entwickelt.
   d. PRO III beurteilt die Keratinozytenatypien im oberen Drittel unter der Hornschicht der Epidermis.
   e. PRO I ist charakterisiert durch das Zusammendrängen von atypischen Keratinozyten im Stratum spinosum.

7. Welche der genannten bildgebenden Techniken ermöglicht die Quantifizierung des PRO-Scores von aktinischen Keratosen in vivo in Echtzeit?
   a. Dermatoskopie
   b. Optische Kohärenztomographie (OCT)
   c. Konfokale Lasermikroskopie (KLM)
   d. Line-Field konfokale Lasermikroskopie (LC-OCT)
   e. Hochfrequenz-Ultraschall

8. Welche der Kombinationen aus diagnostischem Merkmal und nichtinvasivem bildgebenden Gerät trifft zu?
   a. Erythematöses Pseudonetzwerk – konfokale Lasermikroskopie
   b. Nachweis von hyperreflektiven Streifen und Punkten – Hochfrequenz-Ultraschall

c. Atypisches Honigwabenmuster – konventionelle optische Kohärenztomographie
d. Kurven-förmige Gefäße in 300 µm Tiefe – dynamische optische Kohärenztomographie
e. Verdickung der Epidermis – Dermatoskopie

9. Welche Therapieoptionen kommen für die Feldkanzerisierung von aktinischen Keratosen **nicht** in Frage?
   a. Imiquimod
   b. 5-Fluorouracil
   c. PDT
   d. Großflächige chirurgische Verfahren
   e. Chemische Peelings

10. Welche Kombination aus Wirkmechanismus und Therapie trifft zu?
    a. Imiquimod – Cyclooxygenase-2-Hemmer
    b. 5-Fluorouracil – Vorstufe von Protoporphyrin
    c. Diclofenac-Natrium – Toll-like-Rezeptor-7-Agonist
    d. Tirbanibulin – Spindelgift
    e. ALA-PDT – Zytostatikum

Liebe Leserinnen und Leser, der Einsendeschluss an die DDA für diese Ausgabe ist der 31. Juni 2024.

Die richtige Lösung zum Thema "Mikrozirkulationsstörungen der Haut" von Heft 2 2024 ist:
1b, 2c, 3e, 4d, 5a, 6c, 7a, 8c, 9a, 10b

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