JDDG
Journal of the German Society of Dermatology

Guideline

DOI: 10.1111/ddg.14048

S3 guideline for actinic keratosis and cutaneous squamous cell carcinoma – short version, part 1: diagnosis, interventions for actinic keratoses, care structures and quality-of-care indicators

Supporting information for this article is available on the WWW under https://doi.org/10.1111/ddg.14048

AWMF registration number:
032/022OL
Valid until 06/2024 or until next guideline update
Guidelines commissioned by:
Dermatological Cooperative Oncology Group (DeCOG) (Arbeitsgemeinschaft Dermatologische Onkologie; ADO) of the German Cancer Society and the German Society of Dermatology (Deutsche Dermatologische Gesellschaft; DDG)

Markus V. Heppt[2,25]*, Ulrike Leiter[1]*, Theresa Steeb[2,25], Teresa Amaral[1], Andrea Bauer[3], Jürgen C. Becker[4], Eckhard Breitbart[5], Helmut Breuninger[1], Thomas Diepgen[6], Thomas Dirschka[7], Thomas Eigentler[1], Michael Flaig[2], Markus Follmann[8], Klaus Fritz[9], Rüdiger Greinert[5], Ralf Gutzmer[10], Uwe Hillen[11], Stephan Ihrler[22], Swen Malte John[12], Oliver Kölbl[13], Klaus Kraywinkel[14], Christoph Löser[15], Dorothée Nashan[23], Seema Noor[1], Monika Nothacker[24], Christina Pfannenberg[16], Carmen Salavastru[9], Lutz Schmitz[17], Eggert Stockfleth[17], Rolf-Markus Szeimies[18], Claas Ulrich[19], Julia Welzel[20], Kai Wermker[21], Carola Berking[2,25#], Claus Garbe[1#]

(1) Department of Dermatology, Eberhard Karls University of Tübingen, Tübingen, Germany
(2) Department of Dermatology and Allergy, University Hospital, Ludwig-Maximilian University Munich, Munich, Germany
(3) Department of Dermatology, Carl Gustav Carus University Medical Center, Dresden, Germany
(4) Department of Dermatology, German Cancer Consortium (DKTK), Essen University Medical Center, Essen and German Cancer Research Center, Heidelberg, Germany
(5) Association of Dermatological Prevention, Buxtehude, Germany
(6) Department of Clinical Social Medicine, Occupational and Environmental Dermatology, University Hospital, Germany
(7) CentroDerm Clinic and Medical Faculty of Witten Herdecke University, Wuppertal, Germany
(8) German Cancer Society, Berlin, Germany
(9) Dermatology and Laser Center, Landau, Germany
(10) Skin Cancer Center Hannover, Department of Dermatology and Allergy, Hanover Medical School, Hanover, Germany
(11) Department of Dermatology and Venereology, Vivantes Medical Center, Berlin-Neukölln, Germany
(12) Institute for Interdisciplinary Dermatological Prevention and Rehabilitation (iDerm) at the University of Osnabrück, Osnabrück, Germany
(13) Department of Radiation Oncology, Regensburg University Medical Center, Regensburg, Germany
(14) Robert Koch Institute, Berlin, Germany
(15) Skin Hospital, Skin Cancer Center, Ludwigshafen Hospital, Ludwigshafen, Germany

(16) Department of Diagnostic and Interventional Radiology, University Medical Center, Tübingen, Germany
(17) Department of Dermatology, Ruhr University of Bochum, Bochum, Germany
(18) Department of Dermatology, Knappschaftskrankenhaus Recklinghausen, Recklinghausen, Germany
(19) Department of Dermatology, Charité University Medical Center, Berlin, Germany
(20) Department of Dermatology and Allergology, University of Augsburg, Augsburg, Germany
(21) Department of Oral and Maxillofacial Surgery, Klinikum Osnabrück, Osnabrück, Germany
(22) Dermpath, Munich, Germany
(23) Department of Dermatology, Klinikum Dortmund gGmbH, Dortmund, Germany
(24) Association of Scientific Medical Societies in Germany (AWMF), Berlin, Germany
(25) Department of Dermatology, Universitätsklinikum Erlangen, Friedrich Alexander University of Erlangen-Nürnberg, Erlangen, Germany

*The first two authors contributed equally to this manuscript.
#The last two authors contributed equally to this manuscript.

Participating societies:
- Deutsche Gesellschaft für Radioonkologie e.V. (DEGRO)
- Arbeitsgemeinschaft physikalische Diagnostik in der Dermatologie (ApDD)
- Arbeitsgemeinschaft Gesundheitsökonomie und Evidenz-basierte Medizin (AGED)
- Deutsche Dermatologische Gesellschaft (DDG)
- Deutsche Gesellschaft für Pathologie (DGP)
- Deutsche Gesellschaft der Plastischen, Rekonstruktiven und Ästhetischen Chirurgen (DGPRÄC)
- Deutsche Gesellschaft für Chirurgie (DGCH)
- Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie (DGHNO)
- Deutsche Gesellschaft für Mund-, Kiefer- und Gesichtschirurgie (DGMKG)
- Deutsche Röntgengesellschaft (DRG)
- Berufsverband der Deutschen Dermatologen e.V. (BVDD)
- Deutsche Gesellschaft für Dermatochirurgie e.V. (DGDC)
- Arbeitsgemeinschaft Dermatologische Histologie (ADH)
- Arbeitsgemeinschaft Dermatologische Prävention e.V. (ADP)
- Arbeitsgemeinschaft Dermatologische Onkologie (ADO)
- Arbeitsgemeinschaft Radiologische Onkologie (ARO)
- Arbeitsgemeinschaft Berufs- und Umweltdermatologie (ABD)
- Deutsche Gesellschaft für Arbeitsmedizin und Umweltmedizin e.V. (DGAUM)
- Arbeitsgemeinschaft Tumorklassifikation in der Onkologie (ATO)
- Hautkrebsnetzwerk (Patientenvertretung)
- Deutsche Gesellschaft für Palliativmedizin (DGP)
- Arbeitsgemeinschaft Palliativmedizin (APM)
- Bundesverband Deutscher Pathologen e.V. (BDPath)
- Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V. (DGGG)
- Arbeitsgemeinschaft Prävention und integrative Onkologie (PRIO)
- Arbeitsgemeinschaft Psychoonkologie (PSO)
- Deutsche Gesellschaft für HNO-Heilkunde, Kopf- und Hals-Chirurgie (DGHNOKHC)
- Deutsche Gesellschaft für Ultraschall in der Medizin (DEGUM)

The long version and the method report of the guideline can be found at www.awmf.org. This guideline was funded by the German Cancer Aid (DKH) and

issued by the German Guideline Program in Oncology of the German Cancer Society (DKG), DKH and the Association of the Scientific Medical Societies in Germany (AWMF).

Summary

Actinic keratoses (AK) are common lesions in light-skinned individuals that can potentially progress to cutaneous squamous cell carcinoma (cSCC). Both conditions may be associated with significant morbidity and constitute a major disease burden, especially among the elderly. To establish an evidence-based framework for clinical decision making, the guideline "actinic keratosis and cutaneous squamous cell carcinoma" was developed using the highest level of methodology (S3) according to regulations issued by the Association of Scientific Medical Societies in Germany (AWMF). The guideline is aimed at dermatologists, general practitioners, ENT specialists, surgeons, oncologists, radiologists and radiation oncologists in hospitals and office-based settings as well as other medical specialties involved in the diagnosis and treatment of patients with AK and cSCC. The guideline is also aimed at affected patients, their relatives, policy makers and insurance funds. In the first part, we will address aspects relating to diagnosis, interventions for AK, care structures and quality-of-care indicators.

1. Introduction

The guideline represents a short version of the complete guideline available as online supplement and at www.awmf.org. Information on "Epidemiology and etiology", "Surgical and systemic treatment of cutaneous squamous cell carcinoma", "Surveillance", "Prevention" and "Occupational disease" can be found in part 2 of the short version of the guideline or in the long version. A full list of references and the analysis of evidence underlying the recommendations and statements, along with the conflicts of interest of the authors involved in the present guideline, are available in the long version and in the guideline report.

2. Methodology

At the launch event, the guideline group initially defined key questions. Following research required to address these questions, recommendations and statements were developed at the S3 level according to AWMF regulations. To classify the risk of bias pertaining to the relevant studies that were identified, the authors used the 2011 version of the Oxford Centre for Evidence-based Medicine system. Pursuant to AWMF regulations, the methodology of the German Guideline Program in Oncology of the DKG, DKH and AWMF requires guideline authors to grade the recommendations as part of a formal consensus procedure. This included nominal group processes and structured consensus conferences moderated by AWMF representatives during which the recommendations were formally voted on by the mandate holders eligible to vote. Based on how many of them agreed with a given recommendation/statement, the strength of consensus was graded as shown in Table 1.

For each evidence-based statement and recommendation, the level of evidence of the underlying studies is indicated in the guideline; recommendations also include an indication as to their strength (grade). Three grades of recommendations are distinguished herein, which is reflected by how the recommendations are worded (Table 2).

The criteria used for determining the grades of the recommendations are explained in the guideline report (see long version). Statements include presentations or explanations of specific aspects or questions that do not immediately require any action. They are adopted in a formal consensus procedure, much in the same way as the recommendations; statements may be based either on study data or on expert opinions. Statements or recommendations that were considered to require modifications based on consensus of the experts

Table 1 Strength of consensus based on the percentage of agreement in the consensus process.

Strength of consensus	Percentage of agreement
Strong consensus	> 95 % of voters
Consensus	> 75–95 % of voters
Majority approval	> 50–75 % of voters
Dissent	< 50 % of voters

Table 2 Gradation of the strengths of recommendations.

Grade of recommendations	Description	Wording
A	Strong recommendation	Shall
B	Recommendation	Should
0	Open recommendation	May

involved are designated as "expert consensus". No symbols or letters were used for the gradation of "expert consensus" items; the strength of the various consensus points is reflected by the wording used (shall/should/may) (Table 2).

3. Diagnosis

3.1. Classification, definition and nomenclature of AK

	Consensus-based recommendation
Expert consensus	The term "actinic keratosis" shall be used.
	Strong consensus (100 %)

Actinic keratoses (AK) are clinically and histomorphologically identifiable skin lesions characterized by proliferation (hyperplasia) of atypical epidermal keratinocytes that have no basaloid phenotype. The cytomorphological and genetic changes in these atypical keratinocytes are similar to those seen in the neoplastic cells of invasive cutaneous squamous cell carcinoma (cSCC) developing in chronically UV-exposed skin. To date, there is insufficient evidence that histomorphological parameters have any clinical and/or therapeutic relevance. Thus, any detailed and comprehensive documentation of certain criteria beyond stating the diagnosis and subtype appears to be unnecessary and not very useful.

	Consensus-based recommendation
Expert consensus	The following histomorphological variants should be specified if detected: atrophic, hypertrophic, acantholytic, pigmented, lichenoid and bowenoid AK.
	Strong consensus (100 %)

The histomorphological presentation of AK ranges from merely actinically damaged skin with initial atypia of single keratinocytes to complete replacement of the epidermis by atypical keratinocytes. The latter corresponds to epidermal carcinoma in situ; if the keratinocytes are highly atypical and pleomorphic, the lesion is referred to as Bowen's disease. For further classification of this morphological spectrum, a three-stage classification scheme (keratinocytic intraepithelial neoplasia, KIN I–III) has been proposed that is based on the classification used for cervical intraepithelial neoplasia, whose lesions are predominantly HPV-induced. This suggests an analogy to cervical, vulvar, penile, anal or perianal intraepithelial neoplasia (the numbers correspond to the epithelial layers involved). However, this concept has been subject to widespread and controversial debate, given that invasive processes may occur at any stage and given that a three-stage classification system is naturally associated with a very high level of interobserver disagreement. Moreover, this concept has not resulted in any tangible clinical consequences for everyday clinical practice.

3.2. Classification, definition and nomenclature of cSCC

	Consensus-based statement
Expert consensus	cSCC is a malignant neoplasm of epidermal keratinocytes. Lesions may show various degrees of differentiation (see also WHO/UICC classification).
	Strong consensus (100 %)

	Consensus-based statement
Expert consensus	In most cases, yet not necessarily, cSCC arises from intraepidermal proliferation of atypical keratinocytes.
	Strong consensus (100 %)

	Consensus-based statement
Expert consensus	A cSCC is considered to be invasive if there is histomorphological evidence of disruption of the basement membrane below an intraepidermal proliferation of keratinocytes in non-traumatized skin.
	Consensus (87.5 %)

	Consensus-based statement
Expert consensus	Bowen's disease is defined as intraepidermal proliferation of highly atypical, pleomorphic keratinocytes that involves the entire width of the epidermis. Bowen's disease is thus a special variant that may evolve into invasive cSCC; the lesion then usually exhibits bowenoid differentiation (pleomorphic, poorly differentiated) and is referred to as Bowen's carcinoma.
	Strong consensus (100 %)

	Consensus-based statement
Expert consensus	The following variants of cSCC can be distinguished based on histomorphological criteria (some of these variants are also included in the WHO/UICC classification): – Adenosquamous cSCC – Acantholytic cSCC (synonym: adenoid or pseudoglandular cSCC) – Bowen's carcinoma/ cSCC with bowenoid differentiation – Desmoplastic cSCC – Keratoacanthoma-like cSCC/ keratoacanthoma – Lymphoepithelioma-like cSCC – Pseudovascular cSCC (synonym: pseudoangiosarcomatous or pseudoangiomatous cSCC) – Spindle cell cSCC (synonym: sarcomatoid cSCC) – Verrucous cSCC (synonym: epithelioma cuniculatum)
	Strong consensus (100 %)

	Consensus-based recommendation
Expert consensus	The classification of cSCC should be based on histological and clinical parameters according to the current TNM systems of UICC or AJCC.
	Strong consensus (100 %)

As special variant of cSCC, keratoacanthoma usually runs a benign course. There is no definitive clinical differentiation from cSCC. Although keratoacanthoma is readily characterized by its rapid growth and dome-shaped appearance, unequivocal clinical and/or histological differentiation is challenging and at times even arbitrary. Characteristic features include a central keratotic plug, high degree of differentiation, distinct symmetry and a broad-based infiltration pattern. The tumor has the ability to spontaneously regress. Primary treatment and histological processing should be the same as for cSCC. In particular, this applies to patients at increased risk of metastasis. Verrucous cSCC is a particularly well-differentiated variant that is known to be associated with invasive growth but only rarely gives rise to distant metastasis. Other entities subsumed under this histological diagnosis (according to WHO/UICC classification) include epithelioma cuniculatum, oral florid papillomatosis and so-called giant condyloma (Buschke-Löwenstein). Not yet included in the international classification is desmoplastic cSCC, which features abundant stroma and narrow cell strands and is characterized by distinctly infiltrative – occasionally perineural or perivascular – growth. Unlike other cSCC variants, this type is associated with high recurrence (about 25 %) and metastatic (about 10 %) rates.

Other than that, the WHO/UICC/AJCC classification can be used, which is particularly useful for very large cSCC tumors. Nevertheless, the classification of cSCC currently available does not appear to meet all necessary requirements, as it provides differentiating information for only a very small percentage of tumors. Traditionally, lesions have been clinically categorized as low-risk (diameter ≤ 20 mm) and high-risk tumors (diameter > 20 mm) (clinical parameter). However, there seems to be more evidence for using the vertical tumor thickness (measured histologically) as a parameter for classification as it allows for more accurate assessment of the metastatic risk. Depending on the patient population, the metastatic rate of cSCC is 3–6 %. A less favorable prognosis is observed in immunosuppressed patients following organ transplantation or high-dose chemotherapy. Desmoplastic cSCC is roughly 20 times more likely to locally recur than other cSCC variants. Local recurrences are considered to be prognostically unfavorable. In this context, it is unclear whether they themselves contribute to the worsening of the prognosis or whether they merely reflect the aggressive biological behavior of that particular cSCC variant [1].

3.3. Field cancerization

	Consensus-based statement
Expert consensus	There is no generally accepted definition of field cancerization. Field cancerization refers to an area with multiple AK surrounded by evident UV-induced skin damage.
	Strong consensus (100 %)

Field cancerization is clinically defined as an anatomical site with AK (or adjacent to them) and visible solar damage characterized by at least two of the following findings: telangiectasia, atrophy, dyspigmentation and a sandpaper-like texture. It is unclear whether a clinically visible AK is a prerequisite for field cancerization to be diagnosed [2]. Patients with these features and AK are recommended to undergo either field-directed treatment or field-directed treatment in combination with lesion-directed treatment. In case of clinical signs of field cancerization but no actual AK, it is recommended to take educational or preventive measures and to have patients monitor "the field" themselves [2].

3.4. Value of non-invasive diagnostic methods in the diagnosis of AK and cSCC

	Consensus-based statement
Expert consensus	The diagnosis is made by clinical examination and inspection.
	Strong consensus (100 %)

	Consensus-based recommendation
Expert consensus	Dermoscopy, confocal laser scanning microscopy and optical coherence tomography may be used for the diagnosis of AK and cSCC if clinical findings are ambiguous.
	Strong consensus (100 %)

3.5. Biopsy

	Consensus-based statement
Expert consensus	AK do not require histological confirmation if clinical findings are characteristic.
	Strong consensus (100 %)

	Consensus-based recommendation
Expert consensus	In recalcitrant and clinically ambiguous cases, a biopsy shall be obtained.
	Strong consensus (100 %)

AK do not require histological confirmation if the clinical findings are characteristic. Lesions that are clinically ambiguous, show signs of progression to cSCC, or whose biological behavior cannot be assessed should be biopsied. Histology shall also be obtained for AK that do not respond to adequate treatment.

	Consensus-based recommendation
Expert consensus	In case of clinical suspicion of cSCC or Bowen's disease, histology shall also be obtained to distinguish the lesion from other benign or malignant neoplasms. The maximum diameter of the tumor should be documented preoperatively.
	Consensus (94.7 %)

	Consensus-based statement
Expert consensus	Depending on the clinical situation, punch biopsies, shave biopsies or excisional biopsies are appropriate.
	Consensus (94.7 %)

	Consensus-based recommendation
Expert consensus	If the clinical presentation is unambiguously consistent with cSCC, complete excision may be performed without prior biopsy.
	Consensus (89.5 %)

In case of clinical suspicion of cSCC, obtaining a biopsy for histological evaluation is required. Depending on tumor size and therapeutic approach, appropriate options include punch, incisional or shave biopsies or the tumor may be excised [3]. The clinical features of cSCC may vary, and lesions usually present as hyperkeratotic plaques, flat ulcerations with a peripheral rim or keratotic nodules with or without ulceration. cSCCs can develop *de novo* or from AK precursor lesions (erythematous or hyperkeratotic patches and plaques) as well as from AK or leukoplakic lesions. Given the variable clinical picture and the clinical and morphological overlap with various other tumor entities, and given that it is impossible to distinguish early invasive cSCC with disruption of the basement membrane from a hyperkeratotic AK solely on clinical grounds, histological examination should be performed prior to treatment initiation; this approach is particularly important, as it helps rule out other benign or malignant cutaneous neoplasms. If the overall clinical context is unambiguous, it is justified to treat the lesion as if it were a confirmed case of cSCC.

3.6. Parameters of the pathology report in patients with AK and cSCC

	Consensus-based recommendation
Expert consensus	In addition to the diagnosis of cSCC, the pathology report shall also include the following information: – Histological tumor type (in case of special cSCC variants) – Description of the histological depth of invasion in relation to the anatomic skin level involved (especially from Clark level V, corresponding to infiltration of the subcutis)

	Consensus-based recommendation
	– Measurement of the depth of invasion if greater than 2 mm (roughly corresponds to the diameter of the field of view [magnification x10]) – If present, information on perineural spread, vascular invasion or poor differentiation – Information on whether the invasive tumor component has been completely resected
	Strong consensus (100 %)

3.7. Initial diagnostic workup

	Consensus-based recommendation
Expert consensus	If cSCC is suspected, the initial examination shall include inspection of the entire skin.
	Strong consensus (100 %)

3.7.1. Lymph node ultrasound

	Consensus-based recommendation
Expert consensus	Locoregional lymph node ultrasound shall be performed if locoregional metastases are suspected. Locoregional lymph node ultrasound should be performed if there are risk factors.
	Consensus (94.7 %)

3.7.2. Chest X-ray

	Consensus-based recommendation
Expert consensus	Routine chest X-ray shall not be performed if there is suspicion or evidence of locoregional or distant metastasis of cSCC.
	Consensus (94.7 %)

3.7.3. Abdominal ultrasound

	Consensus-based recommendation
Expert consensus	Routine abdominal ultrasound shall not be performed if there is suspicion or evidence of locoregional or distant metastasis of cSCC.
	Strong consensus (100 %)

3.7.4. Cross-sectional imaging

	Consensus-based recommendation
Expert consensus	If metastasis is suspected, cross-sectional imaging shall be performed.
	Strong consensus (100 %)

There are no studies investigating the routine use of cross-sectional imaging in the diagnostic workup of cSCC. Cross-sectional imaging studies should therefore be performed only in those cases in which clinical examination or other tests (e.g., lymph node ultrasound) have raised the suspicion of metastases. A discussion of the available imaging modalities is available in the long version.

4. Interventions for AK

4.1. Literature search and study selection

The evidence-based recommendations and statements presented herein were entirely based on prospective randomized controlled trials (RCTs) or systematic reviews and meta-analyses of RCTs that reported at least one of the previously defined critical efficacy outcomes. These included *(1)* complete response, *(2)* partial response, *(3)* mean reduction in lesions per patient or randomized field of treatment, *(4)* improvement in the Investigator's Global Improvement Index (IGII), and *(5)* improvement in the Participant's Global Improvement Index (PGII). Detailed information on the critical efficacy endpoints including the definition of relevant subgroups is available in the long version.

4.2. Indication for treatment and natural disease course

	Consensus-based recommendation
Expert consensus	The indication for treatment of AK should be based on clinical presentation, risk factors (e.g., immunosuppression, cumulative UV exposure, number of lesions), comorbidities, life expectancy and the patient's preferences.
	Consensus (93.8 %)

The likelihood with which AK may progress or spontaneously resolve without treatment has been the subject of intensive debate for years. Factors that potentially impede any accurate analysis of relevant data include, among other factors, the necessity for long-term follow-up (at least 6–12 months), limited generalizability of results, significant heterogeneity among study populations or the

fact that treatments may have been carried out in the meantime that affect the natural disease course. There are therefore only few cohorts in which the natural disease course was investigated without being influenced by interventions. Accordingly, data on the progression of AK to invasive cSCC vary widely, ranging from 0.03 % to 20 % per lesion and year [4–7]. On the other hand, there have also been reports of very high spontaneous remission rates between 15 % and 63 %. This begs the question as to whether every AK should be treated or whether watchful waiting is justifiable in a low-risk setting [8]. By contrast, it has been reported that roughly 60 % of invasive cSCC originate from AK lesions [5]. It has been shown that spontaneous regression rates are lower in cases in which a given field features multiple AK and signs of field cancerization [7]. What is more, recent studies on the pathogenesis of AK suggest that even early (i.e. clinically and histologically discreet) lesions may evolve into cSCC and that this does not require a gradual evolution through the various disease stages (moderate and eventually hyperkeratotic AK) [9]. These findings render it difficult to assess which lesions are at high risk of transformation to invasive cSCC and which are not. Even though the various studies differ – as described above – in terms of patient and tumor characteristics, there are risk factors and risk populations whose rates of disease progression are likely to be significantly higher. Such factors include immunosuppression, history of non-melanoma skin cancer, and cumulative UV exposure. The number of existing lesions is likewise an important indicator of the individual risk of developing invasive cSCC. Against this background, a watch-and-wait approach should be viewed critically. Ultimately, the general indication for treatment is also guided by the patient's life expectancy, comorbidities and preferences.

4.3. Principles of treatment

Given the multitude of options available for the treatment of AK, the choice of treatment may be difficult in everyday clinical practice. Direct comparison of the various interventions is frequently possible only to a limited extent, as many treatment modalities have not been studied in a head-to-head setting. While network meta-analyses do allow for estimating therapeutic effects despite the lack of direct comparative studies, they frequently focus on merely one endpoint (e.g., complete patient clearance), so that important information may be lost. The data obtained through network meta-analyses is therefore insufficient for definitive treatment decisions in everyday clinical practice, given that they may not provide information on tolerability or cosmetic outcomes [10, 11].

Table 3 Lesion-directed and field-directed treatments for AK.

Primarily lesion-directed treatments	Primarily field-directed treatments
Cryosurgery	Peels
Surgical procedures	Dermabrasion
Photodynamic therapy (patch PDT)	Photodynamic therapy
Topical agents (5-fluorouracil in salicylic acid 10 % solution)	Topical agents (diclofenac sodium 3 % in hyaluronic acid 2.5 % gel) (5-fluorouracil 5 % cream) (5-fluorouracil in salicylic acid 10 % solution) (ingenol mebutate gel) (imiquimod 5 % cream) (imiquimod 3.75 % cream)
Laser devices	Ablative laser devices

The choice of appropriate treatment is guided by patient-, lesion- and treatment-specific factors [12]. Patient-related factors include age, comorbidities, immunosuppression, comedication, patient's wishes and preferences, and adherence to treatment. Lesional aspects comprise the number of AK, site (scalp, face, extremities, trunk), clinical presentation (Olsen classification, hyperkeratotic lesions) as well as the size of the field affected. In clinical practice, it is not always possible to make a clear and unambiguous distinction between multiple AK and field cancerization, and this is rendered even more difficult due to the lack of a generally accepted definition of field cancerization.

The long version of these guidelines contains detailed information on the factors on which treatment decisions are based and on the various therapeutic approaches to AK. Lesion- and field-directed treatments for AK are shown in Table 3. Factors to be considered in the choice of treatment for AK are provided in Table 4 [12].

4.4. Combination treatment

	Consensus-based recommendation
Expert consensus	A combination of field-directed and lesion-directed treatments may be offered.
	Strong consensus (100 %)

Table 4 Factors to be considered in the choice of treatment for AK (modified after [12]).

Patient-related factors	Lesional factors	Treatment-related factors
Age	Number of lesions	Lesion-directed or field-directed
Preference in terms of treatment	Size of the affected area	Treatment modality (interventional, surgical, topical agents)
Comorbidities	Site (scalp, face, trunk, extremities)	Treatment duration
Individual risk (immunosuppression, organ transplantation)	Clinical presentation and demarcation	Effectiveness
Adherence/ compliance	Field cancerization	Side effects and tolerability
Social environment and resources		Self or third-party application
Ability to self-apply		Treatment costs

There is a large number of interventions available for the treatment of AK, which are frequently combined in clinical practice. Given the great heterogeneity among studies in terms of dosage, combination protocols used and outcomes investigated, sequential treatment combinations were not systematically evaluated or analyzed. Nevertheless, as various interventions are commonly combined in clinical practice, a consensus-based recommendation is presented herein. This recommendation is based on the rationale that the combination of different interventions is able to utilize the individual benefits of the various procedures and thus create potential synergistic effects through different mechanisms of action. Clinical experience has shown that combinations consisting of a field-directed and an ablative procedure are well tolerated. In particular, lesion-directed pretreatment of a thick hyperkeratotic AK using an ablative procedure may be combined with subsequent field treatment, as this allows for fast and effective treatment of both clinically manifest and subclinical lesions. Conversely, even after primary field-directed treatment, any remaining AK may be effectively treated with a lesion-directed approach.

4.5. Ablative modalities

4.5.1. Cryosurgery

	Evidence-based recommendation
Grade of recommendation B	Cryosurgery should be offered for single or multiple grade I–III AK (Olsen classification) in immunocompetent individuals.
Level of evidence 2	De novo research
	Strong consensus (100 %)

4.5.2. Surgical procedures

	Consensus-based recommendation
Expert consensus	Surgical removal of grade I–III AK (Olsen classification) (e.g,. by curettage, shave excision or complete excision) should be offered for single lesions in immunocompetent and immunosuppressed patients.
	Strong consensus (100 %)

While surgical removal of AK is a commonly employed treatment option in clinical practice, there is no evidence from RCTs. Our literature search – including systematic reviews and meta-analyses from various databases – failed to identify any RCTs on surgical procedures [13, 14]. On the other hand, however, there is long-standing experience in the use of surgery for individual, clinically well-circumscribed lesions. Depending on the clinical context, suitable procedures include curettage, shave biopsy and complete excision, and these techniques may be considered equivalent. The great advantage of surgical methods is that they allow for subsequent histological examination, especially to rule out invasive cSCC in clinically ambiguous cases.

4.5.3. Chemical peels

	Evidence-based statement
Level of evidence 2	Current data do not allow any recommendations for the treatment of AK with chemical peels.
	De novo research
	Strong consensus (100 %)

4.5.4. Dermabrasion

The effect of dermabrasion is based on mechanical removal of the superficial skin layers down to the dermoepidermal junction using a motorized handheld device (fraise). Used

for field-directed treatment of AK, dermabrasion is a relatively old procedure. No RCTs on mechanical dermabrasion were identified. Further information on dermabrasion in the treatment of AK can be found in the long version of the guideline.

4.5.5. Laser treatment

4.5.5.1. Ablative laser treatment

	Evidence-based recommendation
Grade of recommendation 0	Ablative laser treatment may be offered for single or multiple grade I–III AK (Olsen classification) as well as for field cancerization in immunocompetent patients.
Level of evidence 2–3	De novo research
	Consensus (92.3 %)

4.5.5.2. Non-ablative laser treatment

	Consensus-based recommendation
Expert consensus	Non-ablative laser treatment may be offered for single or multiple grade I–II AK (Olsen classification).
	Strong consensus (100 %)

4.6. Topical drugs

4.6.1. Diclofenac

	Evidence-based recommendation
Grade of recommendation B	Treatment with diclofenac sodium 3 % in hyaluronic acid 2.5 % gel should be offered for single or multiple grade I–II AK (Olsen classification) in immunocompetent individuals.
Level of evidence 1	De novo research
	Strong consensus (100 %)

	Evidence-based recommendation
Grade of recommendation B	Field-directed treatment with diclofenac sodium 3 % in hyaluronic acid 2.5 % gel should be offered for field cancerization.
Level of evidence 1	De novo research
	Strong consensus (100 %)

4.6.2. 5-fluorouracil (5-FU)

	Evidence-based recommendation
Grade of recommendation B	5-fluorouracil 5 % cream should be offered for the treatment of single and multiple grade I–II AK (Olsen classification).
Level of evidence 1	De novo research
	Consensus (88.2 %)

	Evidence-based recommendation
Grade of recommendation B	Field-directed treatment with 5-fluorouracil 5 % cream should be offered for field cancerization.
Level of evidence 2–3	De novo research
	Consensus (93.3 %)

	Evidence-based statement
Level of evidence 2	There is evidence for the efficacy of 5-fluorouracil 0.5 % cream in single and multiple grade I–II AK (Olsen classification). However, there is currently no approval for this concentration in Germany.
	De novo research
	Strong consensus (100 %)

	Evidence-based recommendation
Grade of recommendation B	5-fluorouracil 0.5 % in salicylic acid 10 % solution should be offered for single or multiple grade I–II AK (Olsen classification) as well as for field cancerization in immunocompetent individuals.
Level of evidence 2	De novo research
	Strong consensus (100 %)

4.6.3. Ingenol mebutate

	Evidence-based recommendation
Grade of recommendation B	Field-directed treatment using ingenol mebutate should be offered for single or multiple grade I–II AK (Olsen classification) as well as for field cancerization.*
Level of evidence 1–2	De novo research
	Strong consensus (100 %)

*In coordination with the European Medicines Agency (EMA), the pharmaceutical company LEO Pharma decided to suspend market authorization for Picato® (ingenol mebutate) in January 2020, and to no longer supply Picato® to German pharmacies. Given the potential increased risk of skin cancer in areas previously treated with Picato®, the agent should no longer be prescribed or used. The authors of the guideline therefore no longer recommend the use of ingenol mebutate for the treatment of AK.

4.6.4. Imiquimod

	Evidence-based recommendation
Grade of recommendation B	Field-directed treatment using imiquimod 5 % cream should be offered for single or multiple grade I–II AK (Olsen classification) as well as for field cancerization in immunocompetent individuals.
Level of evidence 1	De novo research
	Strong consensus (100 %)

	Evidence-based recommendation
Grade of recommendation B	Lesion-directed treatment with imiquimod 5 % cream should be offered for single grade I–II lesions (Olsen classification).
Level of evidence 2	De novo research
	Strong consensus (100 %)

	Evidence-based recommendation
Grade of recommendation B	Field-directed treatment using imiquimod 3.75 % cream should be offered for multiple grade I–II AK (Olsen classification) as well as for field cancerization of the face or scalp in immunocompetent individuals.
Level of evidence 2	De novo research
	Strong consensus (100 %)

4.6.5. Conventional photodynamic therapy

	Evidence-based recommendation
Grade of recommendation B	Conventional photodynamic therapy with 5-aminolevulinic acid or its methyl ester (5-ALA or MAL) should be offered for single or multiple grade I–II AK (Olsen classification) and for field cancerization.
Level of evidence 1	De novo research
	Strong consensus (100 %)

The principle of photodynamic therapy (PDT) is based on the application of photosensitizing substances. These photosensitizers selectively accumulate in atypical epidermal keratinocytes and are subsequently activated by exposure to light of a suitable wavelength. Photochemical and photophysical processes give rise to the formation of reactive oxygen species (ROS), which lead to cell damage and subsequently cell death in precancerous skin lesions. Photosensitizers commonly used for the treatment of AK are 5-aminolevulinate (ALA) and its methyl ester, methyl aminolevulinate (MAL). A precursor (prodrug) of endogenous heme synthesis, ALA is converted to photoactive porphyrins in the skin, such as protoporphyrin IX.

4.6.6. Daylight photodynamic therapy

	Evidence-based recommendation
Grade of recommendation B	Field-directed treatment using MAL in combination with daylight (daylight MAL-PDT) should be offered for non-pigmented single or multiple grade I–II AK (Olsen classification) as well as for field cancerization of the face and scalp in immunocompetent individuals.
Level of evidence 2–3	De novo research
	Strong consensus (100 %)

A new approach and approved for treatment since 2015, daylight PDT (same indication as conventional PDT) involves widespread application of the photosensitizer (MAL) to the face and scalp after prior application of a chemical UV filter

and removal of keratotic debris. Subsequently, the patient is exposed to daylight for two hours in suitable weather conditions (April–September, outside temperature > 10°C, sky may be cloudless or overcast, no rain). One advantage of daylight PDT is that it is associated with significantly less pain ful sensation than conventional PDT.

4.6.7. Other topical agents

	Evidence-based statement
Level of evidence 2	Current data does not conclusively allow for colchicine, difluoromethylornithine, canola phenolic acid, topical nicotinamide or UV filters to be recommended as treatment for AK.
	De novo research
	Consensus (87.5 %)

	Evidence-based recommendation
Grade of recommendation B	Given the lack of evidence for their benefit, birch bark extracts and glucans shall not be used for the treatment of grade I–III AK.
Level of evidence 2–3	De novo research
	Strong consensus (100 %)

4.7. Retinoids

	Evidence-based statement
Level of evidence 2–3	Current data does not allow for topical or systemic retinoids to be recommended as treatment for AK.
	De novo research
	Strong consensus (100 %)

4.8. Treatment in immunosuppressed patients and organ transplant recipients

	Evidence-based recommendation
Grade of recommendation B	Treatment with photodynamic therapy with MAL in combination with illumination by an artificial red-light source (630 nm) should be offered for single or multiple grade I–II AK (Olsen classification) as well as for field cancerization in immunosuppressed patients.
Level of evidence 3	De novo research
	Strong consensus (100 %)

	Evidence-based recommendation
Grade of recommendation 0	Field-directed treatment with imiquimod 5 % cream may be offered to immunosuppressed patients with multiple grade I–II AK (Olsen classification) as well as with field cancerization. The missing approval has to be considered here.
Level of evidence 2	De novo research
	Strong consensus (100 %)

	Evidence-based recommendation
Grade of recommendation B	Treatment with diclofenac sodium 3 % in hyaluronic acid 2.5 % gel should be offered to immunosuppressed patients with single or multiple grade I–II AK (Olsen classification) as well as with field cancerization.
Level of evidence 3	De novo research
	Strong consensus (100 %)

Patients on long-term immunosuppressive medication exhibit significantly increased cSCC-related morbidity and mortality than immunocompetent control groups [15]. Key interventions in these patients include early modification of immunosuppressive therapy by eliminating azathioprine from the regimen and switching to an mTOR inhibitor, and using the preventive effects of UV protection and vitamin B6 on AK progression, which also apply to immunosuppressed patients. In this context, early treatment of AK – as secondary prevention – has also been shown to play an increasingly pivotal role. Such treatment not only has to be effective, it is also essential to consider potential interactions the chosen field-directed approach might be associated with in terms of immunosuppression and transplant safety (i.e., signs of graft rejection).

4.9. Summary and balanced presentation of approved treatment options for AK

Treatment method	Approach	Type and application of the intervention Instructions for use and dosage#	Effectiveness[1]	Side effects and tolerability[2]	Cosmetic outcome (investigator and patient assessment)[3]	Treatment duration[4]	Direct treatment costs per cycle[5]	Practicability[6]		Strength of recommendation and evidence base within subgroups[7]			
								Physician	Patient	Single AK	Multiple AK	Field cancerization	Immunosuppression
Ablative methods													
Cryosurgery	L	One to two freeze-thaw cycles with liquid nitrogen (–196°C) Cold exposure of target lesions for 15–60 seconds (blanching) Open spray technique Contact method (cryostamp, cryoprobe)	++/+++ Lesion clearance rates: 41.9 %–88 % Patient clearance rates: 25 %–90.3 %	+++	+/++	⌛	€	++++	+++	↑ 2	↑ 2		
Surgical procedures[6]	L	Curettage ± electrocautery, shave biopsy or complete excision	+++ (no data available from RCTs)[8]	++ (no data available from RCTs)[8]	+/++ (no data available from RCTs)[8]	⌛	€–€€	+++	++	↑ EC			↑ EC
Chemical peels	F	Ablation of upper skin layers using chemical agents (e.g., trichloroacetic acid)	+ Lesion clearance rates: 31.9 % Patient clearance rates: 11.8 %	++/+++	++	⌛	€–€€	++	++	~ 2	~ 2	~ 2	~ 2
Dermabrasion[6]	F	Mechanical removal of superficial skin layers down to the dermoepidermal junction	+ (no data available from RCTs)[8]	+ (no data available from RCTs)[8]	++ (no data available from RCTs)[8]	⌛	€€	+/++	+	~	~	~	~

Laser[6]	L(+F)	Ablative laser devices (e.g., CO_2, erbium-YAG lasers)	++ Lesion clearance rates: 72.4 %–91.1 % Patient clearance rates: 8 %–65.3 %	++	++/+++	⌛	€–€€	+++	++	⇔ 2–3	⇔ 2–3	⇔ 2–3		
		Non-ablative laser devices (e.g., Nd:YAG laser, fractional lasers [1,540 nm])	++ (no data available from RCTs)[8]	+++ (no data available from RCTs)[8]	++ (no data available from RCTs)[8]	⌛	€–€€	+++	+++	⇔ EC	⇔ EC			
Topical drugs														
Diclofenac sodium 3 % in hyaluronic acid 2.5 % gel (Solaraze®) (Solacutan®)	F	Cyclooxygenase-2 inhibitor Twice daily for 60–90 days Maximum of 8 g/day for up to 200 sq cm	++ Lesion clearance rates: 51.8 %–81.0 % Patient clearance rates: 27 %–50 %	+++/++++	+/+++	⌛⌛⌛	€–€€	++++	++	↑ 1	↑ 1	↑ 2	↑ 3	
5-fluorouracil 5 % cream (Efudix®)	F	Cytostatic agent Twice daily for a maximum of 4 weeks Maximum area: 500 sq cm (approx. 23 × 23 cm)	+++/++++ Lesion clearance rates: 47 %–94 % Patient clearance rates: 38 %–96 %	+++	++/++++	⌛⌛	€–€€	+++	+++	↑ 1	↑ 1	↑ 2–3		
5-fluorouracil 0.5 % in salicylic acid 10 % solution (Actikerall®)	L(+F)	Cytostatic and keratolytic agents Once daily until the lesions have completely healed or up to a maximum of 12 weeks. Maximum area: 25 sq cm	+++ Lesion clearance rates: 39.4 %–98.7 % Patient clearance rates: 55.4 %	+++	+++	⌛⌛⌛	€	+++	++	↑ 2	↑ 2	↑ 2		

Ingenol mebutate gel (Picato®)*	F	Milkweed extract (cytotoxic) 0.015 % (face and scalp): once daily on 3 consecutive days 0.050 % (trunk, extremities): once daily on 2 consecutive days	+++ *Face/scalp:* Lesion clearance rates: 62.9 %–87.2 % Patient clearance rates: 36.4 %–61.6 % *Extremities/trunk:* Lesion clearance rates: 73 %–100 % Patient clearance rates: 22 %–54.4 %	++/+++	++	⌛	€	+++	+++	↑ 1–2	↑ 1–2	↑ 1–2	
Imiquimod 3,75 % cream (Zyclara®)	F	Toll-like receptor 7 agonist Once daily for 2 weeks, 2 weeks off treatment, once daily for 2 weeks (intermittent therapy) Per application up to 2 sachets (each contains imiquimod 250 mg cream)	+++ Lesion clearance rates: 34.0 %–81.8 %	+++	+++	⌛⌛	€€	+++	+++		↑ 2	↑ 2	
Imiquimod 5 % cream (Aldara®)	F (+L)	Toll-like receptor 7 agonist 3 times weekly for 4 weeks Recommended maximum dose is the content of one sachet	+++ Lesion clearance rates: 45.1 %–93.6 % Patient clearance rates: 24 %–85 %	+++	+++	⌛⌛	€€	+++	+++	↑ 1–2	↑ 1	↑ 1	⇔ 2

ALA-PDT (Ameluz®) (Alacare®)	F, L	Protoporphyrin precursor (photosensitizer) Application of ALA, UV protection bandage for 3 h or patch for 4 h, exposure to red light for approx. 10–20 min, if necessary repeat after 4–12 weeks Ameluz® Alacare® 4 sq cm (maximum of 6 patches)	+++/++++ Lesion clearance rates: 58.0 %–94.3 % Patient clearance rates: 50 %–91 %	++	+++/++++	⌛	€€–€€€	++/+++	++	↑ 1	↑ 1	↑ 1	
MAL-PDT (Metvix®)	F, L	Protoporphyrin precursor (photosensitizer) Application of MAL, occlusive UV protection bandage for 3 h, exposure to red light for approx. 10–20 min, if necessary repeat after 4–12 weeks	+++/++++ Lesion clearance rates: 67.1 %–90.3 % Patient clearance rates: 31.4 %–78 %	++	+++/++++	⌛	€€–€€€	++/+++	++	↑ 1	↑ 1	↑ 1	↑ 3

DL-MAL-PDT (Luxerm®) (Metvix®)	F, L	Protoporphyrin precursor (photosensitizer) Application of MAL and chemical UV filter, exposure to sunlight for 2 h Weather conditions: outside temperature > 10°C, sky may be cloudless or overcast, no rain	+++ Lesion clearance rates: 77.2 %–89.2 % Patient clearance rates: 31.8 %–42.9 %	+++/ ++++	+++	⌛	€€	++	++++	↑ 2–3	↑ 2–3	↑ 2–3

[1]Semiquantitative presentation taking into account lesion and patient clearance rates (+ = slightly effective, ++ = moderately effective, +++ = effective, ++++ = very effective).

[2]Semiquantitative presentation taking into account frequency and severity of treatment-related side effects (+ = poorly tolerated / many side effects, ++ = moderately tolerated, +++ = well tolerated, ++++ = very well tolerated).

[3]Semiquantitative presentation taking into account investigator- and patient-reported outcomes such as dyspigmentation, improvement of hyperkeratosis, global assessment (+ = predominantly poor, ++ = predominantly moderate, +++ = predominantly good, ++++ = predominantly excellent).

[4]⌛ = short (< 1 week), = ⌛⌛ medium (1–6 weeks), = ⌛⌛⌛ long (> 6 weeks).

[5]€ = < 100 euros, €€ = 100–500 euros, €€€ = > 500 euros; only immediate costs per treatment cycle were taken into account; topical drug prices were based on official pharmacy prices in Germany (as of February 2018); the prices for procedures were based on the German medical fee schedule (GOÄ; as of February 2018).

[6]Taking into account expert assessments.

[7]Strengths of recommendation: may = ⇔, should = ↑, shall = ↑↑; ~ no recommendation in case of inconclusive data; evidence levels are stated according to Oxford 2011.

[8]When using the aforementioned search strategy and inclusion and exclusion criteria.

[#]According to respective prescribing information (as of 02/2019).

*In January 2020, the company LEO Pharma, in agreement with the European Medicines Agency (EMA), decided to suspend the approval of Picato® (ingenol mebutate) and no longer to supply the preparation Picato® in Germany. As there is a potential risk of increased skin cancer development in the areas treated with Picato®, the preparation should no longer be prescribed and used. The authors of this guideline therefore no longer recommend the use of ingenol mebutate for the treatment of AK.

Abbr.: L, lesion directed; F, field directed; AK, actinic keratosis; EC, expert consensus; FC, field cancerization; RCT, randomized controlled trial.

Table 5 Quality-of-care indicators.

Quality-of-care indicator	Reference recommendation	Evidence base/further information
QI 1: Pathology report		
Numerator: Number of patients with the following information in the pathology report: – Histological tumor type – Histological depth of invasion (description and measurement) – Perineural spread – Vascular invasion – Degree of differentiation – R-classification of invasive tumor component *Denominator:* All patients with cSCC undergoing excision	*Recommendation:* In addition to the diagnosis of cSCC, the pathology report shall also include the following information: – Histological tumor type (in case of special cSCC variants) – Description of the histological depth of invasion in relation to the anatomic skin level involved (especially from Clark level V, corresponding to infiltration of the subcutis) – Measurement of the depth of invasion if greater than 2 mm (roughly corresponds to the diameter of the field of view [magnification x10]) – If present, information on perineural spread, vascular invasion or poor differentiation – Information on whether the invasive tumor component has been completely resected	Expert consensus *Quality objective:* The goal is to have as many pathology reports as possible contain complete information following cSCC excision.
The numerator is always a subset of the denominator. The quality-of-care indicators should not be documented with the basic oncological data set of the cancer registries (as of 10/2018).		

4.10. Preventive measures for AK

See chapter 3 (primary prevention) and chapter 4 (secondary prevention) of the S3 guideline for the 'Prevention of Skin Cancer' [16].

5. Care structures

The first German skin cancer center was established in Heidelberg in 2009. Until the end of 2018, a total of 63 centers had been certified. Certification occurs in two phases:

- Review of the data collection form for skin cancer centers (download www.onkozert.de) by two specialized auditors. The form is then returned to the respective center noting deviations or suggestions for improvement (evaluation of the data collection form).
- Audit performed by the same two auditors who evaluated the data collection form. Not only is the respective center visited but also cooperating departments.

Further information on the provision of care at skin cancer centers is available in the long version of the guideline.

6. Quality-of-care indicators

Further information on quality-of-care indicators (Table 5) at skin cancer centers is available in the long version of the guideline.

Conflicts of interest

See long version of the guideline at www.awmf.org .

Correspondence to

Markus V. Heppt, MD, MSc, MHBA
Department of Dermatology
Universitätsklinikum Erlangen
Friedrich Alexander University Erlangen-Nürnberg

Ulmenweg 18
91054 Erlangen, Germany

E-mail: markus.heppt@uk-erlangen.de

References

1 Brantsch KD, Meisner C, Schonfisch B et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell

carcinoma: a prospective study. Lancet Oncol 2008; 9: 713–20.
2 Figueras Nart I, Cerio R, Dirschka T et al.; Progressing Evidence in AKWG. Defining the actinic keratosis field: a literature review and discussion. J Eur Acad Dermatol Venereol 2018; 32: 544–63.
3 Stratigos A, Garbe C, Lebbe C et al.; European Dermatology Forum (EDF); European Association of Dermato-Oncology (EADO); European Organization for Research and Treatment of Cancer (EORTC). Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. Eur J Cancer 2015; 51: 1989–2007.
4 Criscione VD, Weinstock MA, Naylor MF et al.; Department of Veteran Affairs Topical Tretinoin Chemoprevention Trial Group. Actinic keratoses: Natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. Cancer 2009; 115: 2523–30.
5 Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma. Lancet 1988; 1: 795–7.
6 Quaedvlieg PJ, Tirsi E, Thissen MR, Krekels GA. Actinic keratosis: how to differentiate the good from the bad ones? Eur J Dermatol 2006; 16: 335–9.
7 Werner RN, Sammain A, Erdmann R et al. The natural history of actinic keratosis: a systematic review. Br J Dermatol 2013; 169: 502–18.
8 Smit P, Plomp E, Neumann HA, Thio HB. The influence of the location of the lesion on the absolute risk of the development of skin cancer in a patient with actinic keratosis. J Eur Acad Dermatol Venereol 2013; 27: 667–71.
9 Fernandez-Figueras MT, Carrato C, Saenz X et al. Actinic keratosis with atypical basal cells (AK I) is the most common lesion associated with invasive squamous cell carcinoma of the skin. J Eur Acad Dermatol Venereol 2015; 29: 991–7.
10 Vegter S, Tolley K. A network meta-analysis of the relative efficacy of treatments for actinic keratosis of the face or scalp in Europe. PLoS One 2014; 9: e96829.
11 Kiefer C, Sturtz S, Bender R. Indirect comparisons and network meta-analyses. Dtsch Arztebl Int 2015; 112: 803–8.
12 Dirschka T, Gupta G, Micali G et al. Real-world approach to actinic keratosis management: practical treatment algorithm for office-based dermatology. J Dermatolog Treat 2017; 28: 431–42.
13 Werner RN, Stockfleth E, Connolly SM et al. International League of Dermatological Societies; European Dermatology Forum. Evidence- and consensus-based (S3) Guidelines for the Treatment of Actinic Keratosis – International League of Dermatological Societies in cooperation with the European Dermatology Forum – Short version. J Eur Acad Dermatol Venereol 2015; 29: 2069–79.
14 Gupta AK, Paquet M, Villanueva E, Brintnell W. Interventions for actinic keratoses. Cochrane Database Syst Rev 2012; 12: CD004415.
15 Dahle DO, Grotmol T, Leivestad T et al. Association between pretransplant cancer and survival in kidney transplant recipients. Transplantation 2017; 101: 2599–605.
16 Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft DK, AWMF): S3-Leitlinie Prävention von Hautkrebs, Langversion 1.1, 2014, AWMF-Register.-Nr.: 032/052OL. Available from: https://www.awmf.org/leitlinien/detail/ll/032-052OL.html [Last accessed May 28, 2018].

