Continuing Medical Education

Actinic Keratosis and Cutaneous Squamous Cell Carcinoma

Treatment Options

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Summary

Background: Cutaneous squamous cell carcinoma (cSCC) and its precursors, actinic keratoses (AK), are common. Physicians of multiple specialties are confronted with their treatment.

Methods: This review is based on publications retrieved by a selective search in PubMed, as well as on the German guidelines on AK and cSCC, skin cancer prevention, and surgery with histologic guidance.

Results: Local treatments for AK include lesional cryotherapy, curettage, and laser ablation as well as field-directed treatments with topical agents, e.g., diclofenac plus hyaluronic acid, imiquimod, 5-fluorouracil, ingenol mebutate, and photodynamic therapy. These treatments can be administered in various sequences or combinations, depending on individual factors and the stage of the disease. The gold standard of treatment for cSCC is histologically confirmed complete resection; radiotherapy is an alternative. Locally uncontrollable or metastatic disease is treated with systemic drugs. The use of various chemotherapeutic agents, EGFR-directed therapies, and the PD-l inhibitor cemiplimab, either singly or in combination, has been described in uncontrolled trials and case series. Cemiplimab has a reported response rate of 47% and was recently approved for the treatment of advanced cSCC.

Conclusion: There are many options for the treatment of AK and cSCC that must be considered in the interdisciplinary care of these entities.

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Actinic keratosis (AK) consists of the intradermal proliferation of histologically atypical keratinocytes in an area of skin that has been chronically damaged by exposure to ultraviolet light (UV). AK presents as reddish or brownish spots or plaques with increased keratosis on areas of the skin that have been exposed to the sun. If the entire thickness of the skin contains atypical keratinocytes, but the basal membrane is preserved, this is called carcinoma in situ, or Bowen's disease (1). Multiple lesions in a contiguous area of skin with visible UV-induced skin damage (e.g., on the scalp, forehead, or dorsa of the hand) are called field cancerization *(Figure 1a)* (1). In cutaneous squamous cell carcinoma (cSCC), the atypical keratinocytes break through the basal membrane; this can manifest itself with nodular growth *(Figure 1b)* (1). cSCC can arise de novo or on the basis of preexisting AK. The probability and speed of the transition from AK to cSCC is individual, highly variable, and unpredictable. In a systematic review, the progression rate of a single AK to cSCC was variably estimated at 0% to 0.075% per lesion per year. A higher progression rate of 0.53% per lesion per year was estimated if the patient already had cSCC elsewhere. At the same time, however, single AK were found to have

The definition of actinic keratosis

Actinic keratosis (AK) consists of the intradermal proliferation of histologically atypical keratinocytes in an area of skin that has been chronically damaged by exposure to ultraviolet light.

The origin of cutaneous squamous cell carcinoma (cSCC)

In cSCC, the atypical keratinocytes break through the basal membrane; this can manifest itself with nodular growth. cSCC can arise de novo or on the basis of preexisting AK. The probability and speed of the transition from AK to cSCC is individual, highly variable, and unpredictable.

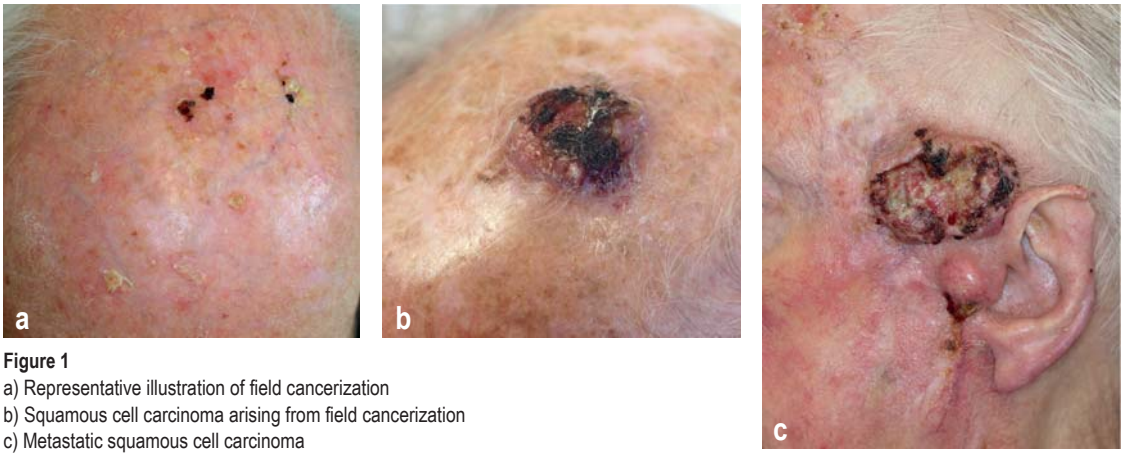


Figure 1
a) Representative illustration of field cancerization
b) Squamous cell carcinoma arising from field cancerization
c) Metastatic squamous cell carcinoma

high regression rates ranging from 15% to 53% per year, as well as long-term recurrence rates above 50% (2). In the review article, this dynamic was attributed in part to methodological weaknesses in the published studies (e.g., missing data on treatments received and on sun-screening methods, as well as high dropout rates). Yet the literature and clinical experience do, in fact, show that AK and light-induced skin damage are a dynamic rather than static pathological process (2).

The age-standardized incidence rate of cSCC in Germany in the period 2010 to 2014 was 26.90 per 100 000 persons per year, which was 30% higher than the corresponding figure for 2005 to 2009 (1). After a diagnosis of cSCC, 50% of patients go on to develop further epithelial skin tumors, most often within 1 year of the initial diagnosis (1).

Cumulative UV exposure is the main risk factor for AK and cSCC *(Box 1)*. If a patient has six or more AK, a cSCC, or field cancerization over an area of at least 4 cm^2 on a region of skin that is exposed to UV light because of the patient's work, the possible presence of an occupational disease should be assessed (no. 5103 in the German classification of occupational diseases). Immune compromise, e.g., in transplant recipients and patients with hematologic cancers such as chronic lymphocytic leukemia, is also associated with a higher incidence and a more aggressive course of cSCC (3).

The risk of recurrence and metastasis of cSCC is low with appropriate therapy. Clinical and histological risk factors have been determined *(Box 2)*. In a series of 114 patients with metastatic cSCC, 46 (40%) had locoregional metastasis in the skin and lymph nodes *(Figure 1c)*, 35 (31%) had distant metastases (usually to the lungs and pleura), and 33 (29%) had simultaneous locoregional and distant metastases (e63). Curative treatment is considered no longer possible in patients with distant metastases or a regional metastasis or local recurrence that cannot be completely controlled with surgery or radiotherapy (e63).

Learning objectives

This article is intended to enable the reader to:

- Gain an up-to-date understanding of the clinical features and prognosis of actinic keratosis and cutaneous squamous cell carcinoma
- Become familiar with the essential procedures for treatment of these lesions
- Assess the advantages and limitations of the various treatment options

Methods

This review is based on pertinent publications retrieved by a systematic review of the Medline database, as well as on the German guidelines on AK and cSCC, skin cancer prevention, and histologically guided surgery. The evidence levels are taken from the assessments contained in the German clinical practice guidelines on AK and cSCC, which employ the system of the Oxford Center for Evidence-Based Medicine in its version of 2011 (1). Evidence levels are given on a scale from 1 to 5, with 1 being the highest and 5 the lowest.

Actinic keratosis

It cannot yet be reliably determined on clinical and histological grounds which AK lesions will undergo

Rising incidence

The age-standardized incidence rate of cSCC in Germany in 2010 to 2014 was 26.90 per 100 000 persons per year, 30% higher than the corresponding figure for 2005 to 2009.

Risk factors

Cumulative ultraviolet exposure is the main risk factor for AK and cSCC.

BOX 1

Risk factors for the development of actinic keratosis and cutaneous squamous cell carcinoma (8)

- Cumulative ultraviolet light exposure
- Light skin type
- Advanced age
- Genodermatoses (e.g., epidermolysis, xeroderma)
- Chronic inflammation
- Exposure to certain toxic substances (e.g., arsenic, tar)
- Immune suppression (iatrogenic or underlying disease)
- HPV infection

BOX 2

Risk factors for unfavorable outcome of cutaneous squamous cell carcinoma*

- **Clinical**
  - Horizontal tumor size >2 cm
  - Localization on ear or lower lip
  - Immune suppression (iatrogenic/underlying disease)
- **Histological**
  - Vertical tumor thickness > 2 mm (intermediate), >6 mm (high)
  - Histological differentiation G3/G4
  - Desmoplasia
  - Perineural growth

*Elevated rate of locoregional recurrence and metastasis (40, e1, e2)

transformation into invasive cSCC and which will not. Important indicators of the individual risk of developing cSCC include immune suppression, a prior history of epithelial skin cancer, high cumulative UV exposure, and the number of lesions present. In view of this and the fact that AK is perceived as a chronic, progressive disease, adequate treatment for all cases of AK is recommended after critical evaluation of the patient's life expectancy, comorbidities, and individual preferences.

There are many treatments for AK *(Table 1, Figure 2)*. Lesion-directed treatments include procedures with the scalpel (e.g., shave excision), liquid nitrogen (cryosurgery), or laser (e.g., erbium/YAG; CO_2). These are provided directly by the physician to the patient and are appropriate for isolated, well-demarcated lesions. An advantage of the surgical approach is that it provides for histopathological control of the clinical diagnosis and the complete removal of the lesion; its disadvantages include the need for local anesthesia, bleeding, and possible scar formation. Cryosurgery and laser therapy can be performed very rapidly in experienced hands but can cause pain, blisters, and superficial wounds. Moreover, hyper- or hypopigmentation can arise during and immediately after these treatments and may be permanent. A major advantage of field-directed techniques is that they can be used to treat multiple contiguous lesions, including subclinical ones, i.e., sites of AK that cannot yet be seen or palpated. Such techniques include the topical application of agents in solution or in the form of a gel or cream, as well as photodynamic therapy (PDT). The common features of field-directed treatments are healing without scar and predominantly no more than transient local side effects such as pain, erythema, swelling, sterile pustules, erosions, and scabbing. Ten different preparations are now approved for field-directed treatment in Germany, differing in their mechanisms of action, galenic formulation, maximal area of application, duration of application, and side-effect profiles *(Table 1)*. A hierarchical ranking of the available treatments is difficult, as direct comparison studies are generally lacking. Four field-directed treatments were recently compared directly with one another in an independently financed trial published in a high-ranking journal: 5-fluorouracil was found to yield the highest rate of healing at 12 months in patients with at least five lesions on the scalp (4).

The choice of a suitable treatment depends on patient-, lesion-, and treatment-specific factors *(Table 2)*. Lesion-directed techniques can generally be carried out rapidly, but they are only effective over a small area. Field-directed techniques take a few days to months to apply and thus require high patient compliance. Some of them are not covered by health insurance in Germany (e.g., red-light PDT). Alongside the parameters listed in *Table 2,* the physician's experience, the patient's prior history, and the availability of treatments are further important factors that need to be considered in the choice of therapy.

Treatment options for actinic keratosis

Actinic keratosis can be treated with lesion-directed and field-directed methods.

The choice of treatment

The choice of treatment depends on patient-, lesion-, and treatment-specific factors.

TABLE 1

Treatments for actinic keratosis (adapted from [1])

Lesion-directed treatments	Nature and application of intervention, duration of treatment	Efficacy*1	Common side effects and tolerability / evidence level
Cryosurgery	– One or two freeze-thaw cycles with liquid nitrogen (−196°C) – Cold exposure of target lesions for 15–60 s ("bleaching") – Open spray technique or contact technique (cryostamp, cryo-probe), seconds to minutes	++/+++ Lesion-/patient-specific healing rates: 41.9–88% , 25 – 90.3%	Pain, erythema, blisters, hypopigmentation Evidence level: 2 (immune-competent patients) (e3–e8)
Operative techniques*2	– Curettage ± electrocauterization – Flat ablation (shave excision), complete excision, ca. 5–20 min	+++	Pain, bleeding, scarring Evidence level: expert consensus
Laser techniques*2	– Ablative laser techniques (e.g., CO_2, erbium-YAG laser), seconds to minutes	++/+++ Lesion-/patient-specific healing rates: 72.4–91.1% , 8–65.3%	Pain, erythema, erosions, dyspigmentation Evidence level: 2–3 (immune-competent patients) (e9, e6)
	– Non-ablative laser techniques 2 (e.g., Nd:YAG laser, fractionated 1540 nm laser), seconds to minutes	++	
Field-directed treatments	**Nature and application of intervention, duration of treatment**	**Efficacy*1**	**Common side effects and tolerability / evidence level**
Diclofenac sodium 3% Hyaluronic acid 2.5% gel	– Cyclooxygenase-2 inhibitor – b.i.d. for 60–90 days – Maximum 8 g/d – 2–3 months	++ Lesion-/patient-specific healing rates: 51.8–81.0% , 9–50%	Erythema, allergy (rare) Evidence level: 1 (immune-competent patients); evidence level: 3 (immunosuppressed patients) (e10–e18)
5-Fluorouracil 5% cream	– Cytostatic agent – b.i.d. for 4 weeks at most – Maximum 500 cm² – 4 weeks	+++/++++ Lesion-/patient-specific healing rates: 47–94% , 38–96%	Inflammatory reactions (erythema, erosions, scabbing, hyperpigmentation) Evidence level: 1 (4, e4, e19–e21)
5-Fluorouracil 0.5% with salicylic acid 10% in solution	– Cytostatic and keratolytic agent – q.d. for 6–12 weeks – 25 cm^2 – 6–12 weeks	+++ Lesion-/patient-specific healing rates: 39.4–98.7% , 55.4%	Inflammatory reactions (erythema, erosions, scabbing, hyperpigmentation) Evidence level: 2 (immune-competent patients) (e12, e5)
Ingenol mebutate gel	– Euphorbia extract (cytotoxic) – 0.015% (face and scalp): q.d. on 3 consecutive days – 0.050% (trunk, limbs): q.d. on 2 consecutive days – 25 cm^2 in each case – 2–3 days	+++ Face/scalp: lesion-/patient-specific healing rates: 62.9–87.2% , 36.4–61.6% Limbs/trunk: lesion-/patient-specific healing rates: 73–100% ,22–54-4%	Inflammatory reactions (erythema, erosions, scabbing) Evidence level: 1–2, (4, e22–e28)
Imiquimod 3.75% cream	– Toll-like receptor 7 agonist – q.d. for 2 weeks, then 2 week pause, then q.d. for 2 weeks (interval therapy) – 25–200 cm² – 6 weeks	+++ Lesion-specific healing rate: 34.0–81.8%	Inflammatory reactions (erythema, erosions, scabbing), flu-like symptoms (fever), rare Evidence level: 2 (immune-competent patients) (e29, e30)
Imiquimod 5% cream	– Toll-like receptor 7 agonist – 3×/week for 4 weeks – 25 cm² – 4 weeks	+++ Lesion-/patient-specific healing rates: 45.1–93.6% , 24–85%	Inflammatory reactions (erythema, erosions, scabbing), flu-like symptoms (fever), rare Evidence level: 1 (immune-competent patients); evidence level: 2 (immunosuppressed patients) (4, e31–e40, e20)
ALA cream for red light PDT	– Protoporphyrin precursor (photosensitizer) – Application of ALA, light-protective dressing for 3 hr or patch for 4 hr, red light illumination for ca. 10–20 min, may repeat in 4–12 weeks – Alacare 4 cm² (up to six patches at once), ca. 4 hr	+++/++++ Lesion-/patient-specific healing rates: 58.0–94.3% , 50–91%	Pain, inflammatory reactions (erythema, sterile pustules, erosions, scabbing) Evidence level: 1 (immune-competent patients) (e41–e48)
MAL cream for red light PDT	– Protoporphyrin precursor (photosensitizer) – Application of MAL, light-protective and occlusive dression for 3 hr, red light illumination for ca. 10–20 min, may repeat in 4–12 weeks, ca. 4 h	+++/++++ Lesion-/patient-specific healing rates: 67.1–90.3% , 31.4–78%	Pain, inflammatory reactions (erythema, sterile pustules, erosions, scabbing) Evidence level: 1 (immune-competent patients); evidence level: 3 (immunosuppressed patients) (4, e7, e8, e24, e43, e49–e52)
ALA or MAL cream for daylight PDT	– Protoporphyrin precursor (photosensitizer) – Application of MAL and chemical light-protective filter, exposure to sunlight for 2 hr – Conditions: outside temperature > 10°C, cloudless or cloudy sky, no rain; duration 2.5 hr	+++ Lesion-/patient-specific healing rates: 77.2–89.2% , 31.8–42.9%	Inflammatory reactions (erythema, sterile pustules, erosions, scabbing) Evidence level: 2–3 (immune-competent patients) (e23, e53−e55)

*1 Semiquantitative representation taking account of the lesion- and patient-specific response rates in randomized controlled trials (+ = not very effective, ++ = moderately effective, +++ = effective, ++++ = highly effective); *2 based on expert opinion: ALA, aminolevulinic acid; MAL, methyl aminolevulinic acid; PDT, photodynamic therapy

Combinations of treatment approaches are reasonable and are being applied more and more frequently, e.g., field-directed treatment after lesion-directed treatment. For example, laser ablation can be carried out before PDT to remove especially thick hyperkeratotic lesions, thereby making the skin surface more permeable for cream application. Other studies have shown that the combination of imiquimod and PDT leads to significantly higher healing rates than monotherapy (5–7).

Cutaneous squamous cell carcinoma

The treatment options for cSCC include surgery, radiotherapy, and medication *(Table 3, Figure 2)*.

Surgical treatment

Complete excision under histopathological guidance is the standard treatment of cSCC. There is no commonly accepted definition of an R0 resection; the desired distance from the edge of the tumor to the border of the resection varies in the literature from 0 to 6 mm (8). After resection and until the time of definitive histopathological confirmation, the wound should only be closed if the borders of the resection will remain clearly identifiable. For tumors less than 1 cm in size, shave-excision is an alternative to resection. In this situation, the diameter of the excised tissue should be no less than 5 mm to enable reliable histopathological examination (1). If the clinical diagnosis is unambiguously clear, excision can be carried out without prior biopsy. The risk factors for local recurrence and metastasis *(Box 2)* are also relevant to surgical planning, as one may want to consider wider safety margins or elective lymph node surgery (e.g., biopsy of a sentinel node) in patients at higher risk.

The technique of histopathological examination is what distinguishes conventional surgery from micrographically controlled surgery (MCS), also known as Mohs surgery (9). The latter generally involves 3D histology, i.e., once the tumor has been excised, the outer sides of the resection specimen are separately analyzed histologically to enable complete inspection of the three-dimensional edges of the resection (9). MCS allows the detection of outward extensions of the tumor with high sensitivity; consequently, the safety margin for excision can be kept relatively low. Although frozen sections are quicker to prepare, paraffin sections are superior for the detection of subclinical tumor extensions (9). MCS is to be distinguished from excision with a wide safety margin and lamellar sectioning of the specimen (the loaf-of-bread technique), in which the entire extent of the tumor is histologically examined (9). The safety margin for resection is not definitively laid down in the literature (1–4 mm, up to 50 mm under certain circumstances), but the risk of subtotal resection increases with the size of the specimen and in inverse relation to the safety margin (8). The local recurrence rate after MCS ranges from 0 to 33%, with rates of 2% to 8% reported in most studies. The local recurrence rate after resection with the loaf-of-bread technique ranges from 0% to 53%, with numbers of 2% to 13% most commonly reported (8). No method has yet been shown to be clearly superior to any other.

The identification and excision of one or more sentinel lymph nodes (sentinel lymph node biopsy, SLNB) is an option for minimally invasive lymph node diagnosis in order to detect occult metastasis while avoiding excessive lymphadenectomy. SLNB can be considered in patients with high-risk cSCC, particularly in the head and neck region, with its variable lymphatic flow. Despite high sensitivity (79%) and specificity (100%) and a negative predictive value of 96% (10), SLNB of one or more nodes has not been shown to result in significantly longer disease-specific overall or metastasis-free survival (11, 12), and it therefore cannot be generally recommended (1). Prophylactic lymphadenectomy should not be performed (1, 13). In the case of clinically or histologically apparent lymph node metastasis, therapeutic lymph node dissection should be performed, as this improves locoregional tumor control (8, 13). The extent of the therapeutic lymph node removal has not been precisely defined; if possible, selective functional resection should be carried out (1).

Resection is also the standard treatment for locoregional recurrence, as long as the conditions for local and general operability are met.

Radiotherapy

Although there have not been any prospective, randomized trials comparing primary radiotherapy with other local treatments, retrospective studies have shown a local tumor control rate of 94.0% at 5 years with radiotherapy alone (14). A prospective phase III trial compared radiation alone with radiochemotherapy for cSCC in the head and neck region. The additional administration of carboplatin was found not to have any additional effect; the rate of locoregional tumor control at 5 years was 83% after radiotherapy and 87% after radiochemotherapy, and the rates of 5-year overall survival were 76% and 79% (15).

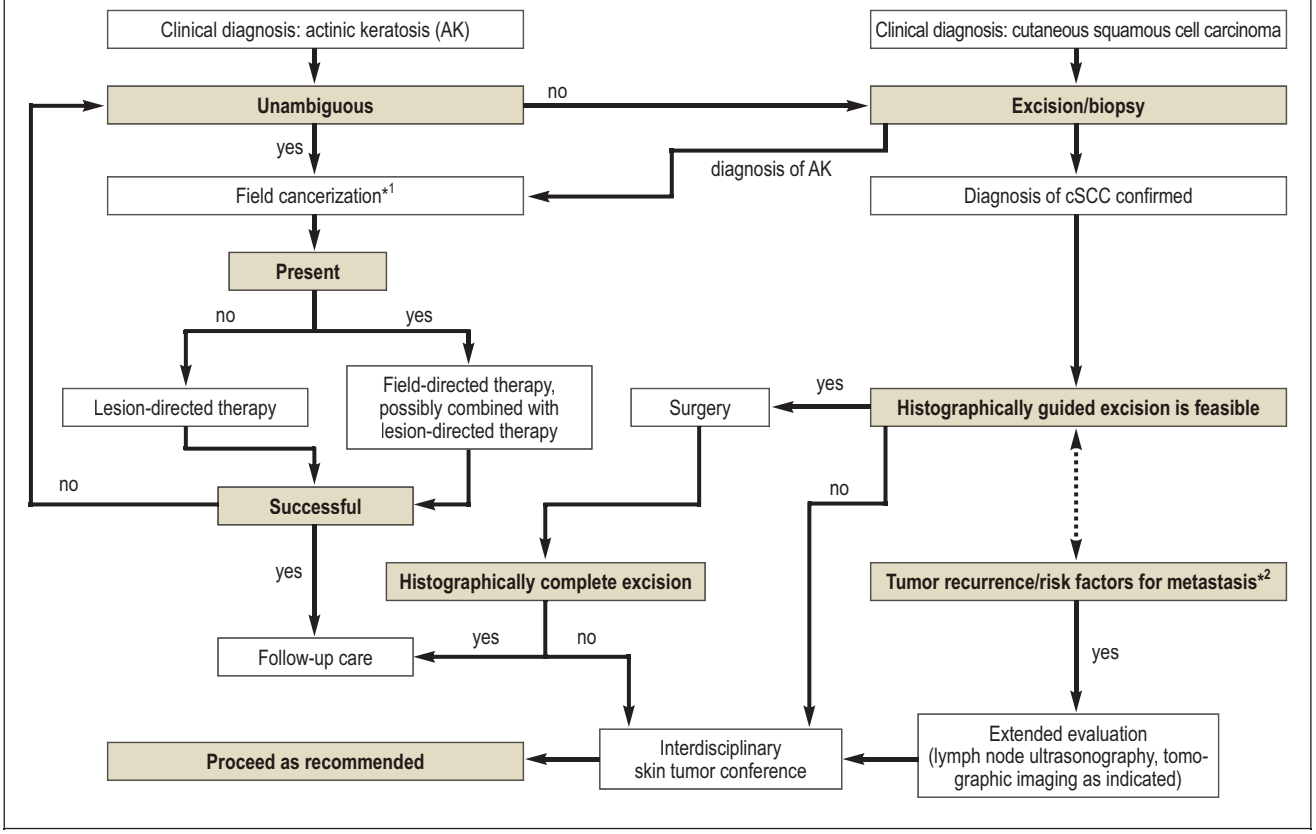
The gold standard

Complete excision is the gold standard treatment for cSCC.

Safety margins

The complete excision of cSCC should be histologically confirmed.

FIGURE 2



Diagnostic and therapeutic algorithm for actinic keratosis and cutaneous squamous cell carcinoma

*[1]Field cancerization: multiple actinic keratoses and evidence of ultraviolet-induced damage in a contiguous area of skin

*[2]Risk factors: tumor thickness >6 mm, or tumor thickness >2 mm with additional risk factors (histologic grade ≥ G3, perineural or desmoplastic growth, localization on lower lip or ear, immune suppression), or positive clinical finding (e.g., palpable regional lymph node enlargement)

Postoperative radiotherapy is indicated only in the presence of risk factors. These include R1 or R2 resection, a narrow resection margin (<2 mm), recurrent tumor, large tumor (>2 cm), deep tumor penetration (>4 mm), infiltration of adipose tissue, perineural sheath infiltration, and extensive lymphatic involvement (>1 lymph node, extension beyond capsule) (16–19). Postoperative radiotherapy should be performed after R1 or R2 resection or when the resection margin is <2 mm (1, 8, 17, 18, 20). The same holds for perineural sheath infiltration by tumor, although the extent of the infiltration is relevant here. If the infiltration is microscopic, the local control rate after surgery alone is 78% to 87%; if it is macroscopic, the local control rate after surgery is 50% to 55%, compared to 100% after postoperative radiotherapy in selected patients (19). Postoperative radiotherapy should also be performed in the case of extensive involvement of the cervical lymph nodes (> 1 lymph node, lymph node metastasis > 3 cm, extension beyond capsule, intraparotid lymph node involvement) (18, 21, 22). In a retrospective study, the local recurrence rate, 5-year disease-free survival rate, and overall survival rate after surgery alone were 55%, 34%, and 27%, respectively, while the corresponding rates after surgery and postoperative radiotherapy were 23%, 74%, and 66% (22). The procedure to be followed in the case of lymph node metastasis in the axillary or inguinal regions is analogous to the indication for postoperative radiotherapy in the head and neck

Radiotherapy

Radiotherapy should be performed if a tumor cannot be completely excised locally or is inoperable for medical reasons.

Postoperative radiotherapy

Postoperative radiotherapy is indicated if there are risk factors for local or locoregional recurrence.

TABLE 2

Factors affecting the choice of treatment for actinic keratosis

Patient factors	Lesion factors	Treatment factors
– Immune suppression – Comorbidities – Medications – Patient preference – Treatment compliance	– Site (e.g., face, scalp, lower lip, limbs) – Clinical consistency (e.g., thickness of keratinization) – Size of lesion and of affected area	– Lesion- or field-directed – Application by patient or by medical staff – Duration of application – Side effects – Availability of equipment (e.g., laser, red-light lamp) – Cost

region. Depending on the risk constellation, radiation doses ranging from 50 Gy (R1 resection, resection margin <2 mm) to 66 Gy (R2 resection) are recommended (18). For local or locoregional recurrences, the same criteria as in the primary situation apply with respect to the indication for postoperative radiotherapy (1).

Systemic drug treatment

Systemic drugs are given when local measures no longer suffice, e.g., in the case of a locally advanced lesion (usually after prior surgery and radiotherapy) or distant metastasis. In a systematic review of the literature from the years 1970 to 2011, Behshad et al. identified 28 studies (all with low-level evidence) including 119 patients with locally advanced cSCC who were treated with systemic drugs. In a large majority of cases, various chemotherapeutic agents were used either singly, in combination, or together with radiotherapy (23). The observed overall response rate was 72%, and the median response duration was 10.5 months.

In addition to chemotherapy, many publications have described the use of targeted therapies against the epidermal growth factor receptor (EGFR) to treat cSCC, but there have been only a few, uncontrolled prospective trials (24). In a trial of cetuximab on 36 patients, the response rate was 28%, and the median response duration was 6.8 months (25); in a trial of panitumumab on 16 patients, the response rate was 31%, and the median response duration was 6 months (26). In principle, EGFR blockers such as cetuximab can also be combined with chemotherapeutic drugs such as paclitaxel (27) or platinum derivatives (28), in a manner analogous to the treatment of mucosal squamous cell carcinoma.

Squamous cell carcinomas often express PD-L1 and contain tumor-infiltrating lymphocytes (29); thus, immune therapy targeted on PD-1 is another worthwhile approach. A single-armed trial of the anti-PD-1 antibody cemiplimab in 59 patients with metastatic squamous cell carcinoma yielded a response rate of 47%, and, at the time of assessment, most of these remissions had persisted longer than 6 months (30). The European Medicines Agency (EMA) has approved cemiplimab for the treatment of inoperably advanced or metastatic cSCC. Patients with inoperable cSCC are currently being recruited for a trial of cetuximab combined with the PD-L1 antibody avelumab. The PD-1 antibodies cemiplimab and pembrolizumab are being tested in placebo-controlled studies for the adjuvant treatment of patients after resection and radiotherapy of high-risk cSCC. It is particularly important that the treatment strategy for patients with cSCC should be designed on an individual basis in consideration of the patient's age, comorbidities, and personal preferences.

Special considerations for immune-suppressed patients

Patients being treated with immune-suppressant drugs, particularly organ transplant recipients, have a markedly higher risk of developing AK and of progression of AK into invasive cSCC; these cSCC also show more aggressive growth than in the usual situation, with greatly elevated morbidity and mortality (31, 32). Organ transplant recipients have a 20- to 50-fold elevation of the risk of developing a non-melanocytic skin cancer compared to immune-competent persons (32). The same holds for patients who are immunocompromised because of an underlying illness, particularly chronic lymphocytic leukemia. Such patients should be informed early of the elevated risk and taught how to examine themselves; they should undergo dermatological surveillance examinations at intervals depending on the risk, and any suspect lesions should be diagnosed and treated as early as possible.

Drug therapy

The available types of drug therapy are chemotherapy, anti-EGFR therapy, and immune therapy targeted on PD-1.

Criteria for the choice of treatment

The treatment strategy for patients with cSCC should be designed on an individual basis in consideration of the patient's age, comorbidities, and personal preferences.

TABLE 3

Treatments for cutaneous squamous cell carcinoma

Intervention	Initial situation before treatment	Efficacy	Common side effects and tolerability	Evidence level and references
Locoregional treatments				
Complete excision under histologic guidance	– All primary tumors – locoregional recurrences	Local recurrence rate 2–8%	Pain, bleeding, infection, scarring, functional limitation, nerve injury	Expert consensus (primary tumors); evidence level: 2 (recurrences) (e56, e57)
Complete excision with safety margin	– Tumor <20 mm: 4 mm safety margin – Tumor ≥ 20 mm: 6–9 mm safety margin	Local recurrence rate 2–13%	Pain, bleeding, infection, scarring, functional limitation, nerve injury	Expert consensus (e56–e58)
Deep shave-excision	Small tumors with diameter <1 cm	Local recurrence rate 0.5–3.4%	Pain, bleeding, infection, scarring	Expert consensus (e57)
Radiotherapy	– Not completely resectable tumor or inoperable patient – Narrow resection margin (<2 mm with no possibility of extending resection) or extensive perineural sheath infiltration	Local recurrence rate 3–11%	Inflammation of skin and mucous membranes, alopecia	Evidence level: 2–3 (e57)
Electrochemotherapy	Locoregional recurrence with no option for excision or radiotherapy	Response rate 46 %	Pulmonary toxicity	Expert consensus (e59)
Systemic treatments				
Chemotherapy	Tumor that cannot be controlled with locoregional measures	Response rate 72% , median response duration 9–10 months	Altered blood counts, alopecia, peripheral neuropathy, hand-foot syndrome, nephrotoxicity	Expert consensus (23)
EGFR blockers	Tumor that cannot be controlled with locoregional measures	Response rate 25–45% , median response duration 6–8 months	Papulo-pustular rash, paronychiae, hair changes, diarrhea	Expert consensus (25, 26)
PD-1 inhibitors	Tumor that cannot be controlled with locoregional measures	Response rate 39–49% , median progression-free survival 14.2–18.4 months	Autoimmune phenomena (e.g., thyroiditis, colitis, dermatitis, pneumonitis)	Expert consensus (30, e60–e62)

Data are available from randomized, controlled trials on the treatment of AK in organ transplant recipients with PDT combined with methyl aminolevulinic acid (MAL-PDT), ablative fractionated laser therapy (AFXL), diclofenac sodium 3% gel, imiquimod 5% cream, and 5-fluorouracil 5% cream: healing rates were highest with MAL-PDT and lowest with AFXL (33) *(Table 1)*. Early diagnosis and surgical resection are determinative for the successful treatment of squamous cell carcinoma (34). Radiotherapy can be used to treat advanced lesions or those with a high risk of recurrence. The drug treatments listed here must be carefully considered because of their side effects. Immune therapy, in particular, can exacerbate an existing autoimmune disease or cause transplant rejection (35, 36).

As for iatrogenic immune suppression, multiple prospective, randomized trials carried out in kidney transplant recipients have unanimously shown that switching the immune-suppressant drug from a calcineurin inhibitor to an mTOR inhibitor in high-risk patients who have had epithelial skin tumors resected significantly lowers the risk of further skin tumors (37). This effect is greatest in patients who have had only one tumor resected, rather than two or more.

Caveat: immunosuppression

The incidence and aggressiveness of AK and cSCC are higher in immune-suppressed patients.

The special case of the organ transplant recipient

In organ transplant recipients with AK or cSCC, switching the immune-suppressant drug to an mTOR inhibitor can be considered.

Prophylactic measures

In two prospective, randomized, placebo-controlled trials on patients in whom epithelial skin tumors had been resected, the development of new cSCC was shown to be significantly less common after prophylactic treatment: one study concerned topical treatment with 5% 5-fluorouracil on the face for 2 to 4 weeks (38), and the other concerned the daily taking of 1000 mg nicotinic acid amide/vitamin B3 (39). In both trials, however, the effect was lost once the treatment was terminated. It follows that permanent nicotinic acid amide treatment can be considered for high-risk patients. Topical treatment with 5% 5-fluorouracil can be repeated depending on the clinical course and the development of new lesions. In organ transplant recipients, switching the immunesuppressant drug to an mTOR inhibitor can be considered.

Conflict of interest statement

Prof. Gutzmer has served as a paid consultant for Roche, Bristol-Myers Squibb, Almirall Hermal, Amgen, Pierre Fabre, Merck Serono, Takeda, SUN, ASC, Incyte, Pfizer, Sanofi, and Novartis. He has received lecture honoraria from Roche, Bristol-Myers Squibb, MSD, Novartis, Amgen, Pierre Fabre, Merck-Serono, Almirall, AstraZeneca, Sanofi, and SUN. He has received reimbursement of congress participation fees and travel expenses from Merck-Serono, Pierre Fabre, BMS, Roche, and SUN. He has received funding from Novartis, Amgen, Merck-Serono, Pfizer, and Johnson & Johnson for a research project that he initiated.

Prof. Wiegand has served as a paid consultant for Bristol-Myers Squibb and MSD. She has received lecture honoraria from Astra Zeneca, MSD, Merck-Serono, and Bristol-Myers Squibb. She has received reimbursement of travel and accommodation expenses from Astra Zeneca, MSD, and Bristol-Myers Squibb.

PD Wermker has served as a paid member of an Advisory Board for Bristol-Myers Squibb.

Dr. Heppt has served as a paid consultant for Sanofi-Aventis.

Prof. Berking has served as a paid consultant for Almirall Hermal, Galderma, Leo Pharma, MSD, and Sanofi-Aventis. She has received lecture honoraria from Leo Pharma and Galderma. She has received funding from Leo Pharma for a research project that she initiated and third-party research funding from Biofrontera.

Prof. Kölbl states that he has no conflict of interest.

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Prophylaxis

In organ transplant recipients, switching the immune suppressant drug to an mTOR inhibitor can be considered.

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► Supplementary material

For eReferences please refer to:
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Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

Which of the following is a risk factor for the occurrence of actinic keratoses and cutaneous squamous cell carcinoma?

a) Female sex
b) Pregnancy
c) Young age
d) Dark skin type
e) Chronic exposure to ultraviolet light

Question 2

What histological finding is associated with an unfavorable prognosis of cutaneous squamous cell carcinoma?

a) Vertical tumor thickness <0.5 mm (intermediate) <4.5 mm (high)
b) Vertical tumor thickness <1 mm (intermediate) <5 mm (high)
c) Vertical tumor thickness <1.5 mm (intermediate) <5.5 mm (high)
d) Vertical tumor thickness >2 mm (intermediate) > 6 mm (high)
e) Vertical tumor thickness <2 mm (intermediate) <6 mm (high)

Question 3

In what method are all of the edges of the resection examined histologically without exception, so that narrower safety margins can be chosen?

a) Punch biopsy
b) Puncture cytology
c) Micrographically controlled histology (3D histology)
d) Hematoxylin and eosin (H&E) stain
e) Elastica–van Gieson (EvG) stain

Question 4

When should sentinel lymph node excision be considered as part of the treatment of a cutaneous squamous cell carcinoma of the head and neck region?

a) Always
b) In young patients without comorbidities
c) In patients without any already manifest lymph node metastases
d) On the initial diagnosis of actinic keratosis
e) In high-risk cSCC, especially in the head and neck region

Question 5

Which of the following is a risk factor for local or locoregional recurrence and is thus among the criteria for the indication of postoperative radiotherapy?

a) More than one involved lymph node
b) Localization on the upper arm
c) Only mild lymphatic involvement
d) Tumor depth <2 mm
e) Lymphadenitis colli

Question 6

Which of the following measures should be considered after the resection of a cutaneous squamous cell carcinoma from an organ transplant recipient?

a) Switching the immune suppressant drug to an mTOR inhibitor
b) Chemotherapy
c) Ablative fractionated laser therapy 3 times a week
d) Daily topical treatment of the site with ingenol mebutate gel
e) Increasing the immunosuppressive therapy

Question 7

How much higher is the risk of non-melanocytic skin cancer in an organ transplant recipient than in an immune-competent person?

a) 10 to 40 times higher
b) 20 to 50 times higher
c) 30 to 60 times higher
d) 40 to 70 times higher
e) 50 to 80 times higher

Question 8

How did the age-standardized incidence of cutaneous squamous cell carcinoma in Germany change from the period 2005 to 2009 to the period 2010 to 2014?

a) 10% decrease
b) 15% increase
c) 30% increase
d) 5% decrease
e) 50% increase

Question 9

Which of the following factors is relevant to occupationally associated skin cancer and makes a report to the relevant German authority mandatory (occupational disease category no. 5103)?

a) Longstanding occupational exposure to ultraviolet light
b) A light skin type
c) The appearance of two actinic keratoses within 2 years
d) Squamous cell carcinoma on the sole of the foot
e) Field cancerization <2 cm^2

Question 10

A 74-year-old kidney transplant recipient presents with an ulcerating tumor 2.5 cm in size on the left nostril extending onto the adjacent area of the cheek. A biopsy has already yielded the histopathological finding of a poorly differentiated squamous cell carcinoma, G3, with perineural invasion (Pn1), Breslow tumor thickness 6.8 mm. What is the treatment of first choice?

a) In the same operation in which the tumor is resected, the defect should be directly reconstructed with a locoregional plastic-surgical flap, even if the R status cannot yet be determined.
b) Complete excision under histopathological guidance with examination of all resection edges (micrographic surgery) and plastic-surgical defect reconstruction after histologically confirmed R0 resection
c) Locoregional photodynamic therapy
d) In the same procedure as the tumor resection, radical lymphadenectomy of the neck (neck dissection) should be performed.
e) Local topical treatment with imiquimod

Supplementary material to:

Actinic Keratosis and Cutaneous Squamous Cell Carcinoma

Treatment Options

by Ralf Gutzmer, Susanne Wiegand, Oliver Kölbl, Kai Wermker, Markus Hepp, and Carola Berking

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