S3 guideline for actinic keratosis and cutaneous squamous cell carcinoma (cSCC), short version, part 2: epidemiology, surgical and systemic treatment of cSCC, follow up, prevention and occupational disease

Ulrike Leiter, Markus V. Heppt, Theresa Steeb, Teresa Amaral, Andrea Bauer, Jürgen C. Becker, Eckhardt Breitbart, Helmut Breuninger, Thomas Diepgen, Thomas Dirschka, Thomas Eigentler, Michael Flaig, Markus Follmann, Klaus Fritz, Rüdiger Greinert, Ralf Gutzmer, Uwe Hillen, Stephan Ihrler, Swen Malte John, Oliver Kölbl, Klaus Kraywinkel, Christoph Löser, Dorothee Nashan, Seema Noor, Monika Nothacker, Christina Pfannenberg, Carmen Salavastru, Lutz Schmitz, Eggert Stockfleth, Rolf Markus Szeimies, Claas Ulrich, Julia Welzel, Kai Wermker, Claus Garbe, Carola Berking

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S3 guideline for actinic keratosis and cutaneous squamous cell carcinoma (cSCC) – short version, part 2: epidemiology, surgical and systemic treatment of cSCC, follow-up, prevention and occupational disease

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Ulrike Leiter[1]*, Markus V. Heppt[2,25]*, Theresa Steeb[2,25], Teresa Amaral[1], Andrea Bauer[3], Jürgen C. Becker[4], Eckhardt 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], Dorothee 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], Claus Garbe[1#], Carola Berking[2,25#]

(1) Department of Dermatology, Eberhard Karls University of Tübingen, Tübingen, Germany
(2) Department of Dermatology and Allergology, University Medical Center, LMU Munich, Munich, Germany
(3) Department of Dermatology, Carl Gustav Carus University Medical Center, Dresden, Germany
(4) Department of Dermatology, Essen University Medical Center, Essen, Germany
(5) Skin Cancer Center, Elbe Medical Center, Buxtehude, Germany
(6) Institute for Clinical Social Medicine, Heidelberg University Medical Center, Heidelberg, 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) 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) Department of Dermatology, Ludwigshafen Medical Center, 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, Osnabrück Medical Center, Osnabrück, Germany
(22) Dermpath, Munich, Germany
(23) Department of Dermatology, Dortmund Medical Center, Dortmund, Germany
(24) Association of Scientific Medical Societies in Germany (AWMF), Berlin, Germany
(25) Department of Dermatology, Friedrich Alexander University of Erlangen-Nuremberg, Erlangen, Germany

[†]The first two authors contributed equally to this manuscript.
[#]The last two authors contributed equally to this manuscript.

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The long version and the method report of the guideline can be found at www.awmf.org.

Summary

Actinic keratoses (AKs) 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 guidelines for actinic keratosis and cutaneous squamous cell carcinoma were developed using the highest level of methodology (S3) according to regulations issued by the Association of Scientific Medical Societies in Germany (AWMF). The guidelines are 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 AKs and cSCC. The guidelines are also aimed at affected patients, their relatives, policy makers and insurance funds. In the second part, we will address aspects relating to epidemiology, etiology, surgical and systemic treatment of cSCC, follow-up and disease prevention, and discuss AKs and cSCC in the context of occupational disease regulations.

1 Introduction

The guideline represents a short version of the complete guidelines available as online supplement and at www.awmf.org. Information on "Diagnosis" and "Interventions for actinic keratoses" can be found in part 1 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 guidelines, 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 Oncology Guidelines Program of the German Cancer Society 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 involved are designated as "expert consensus". No

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	Can

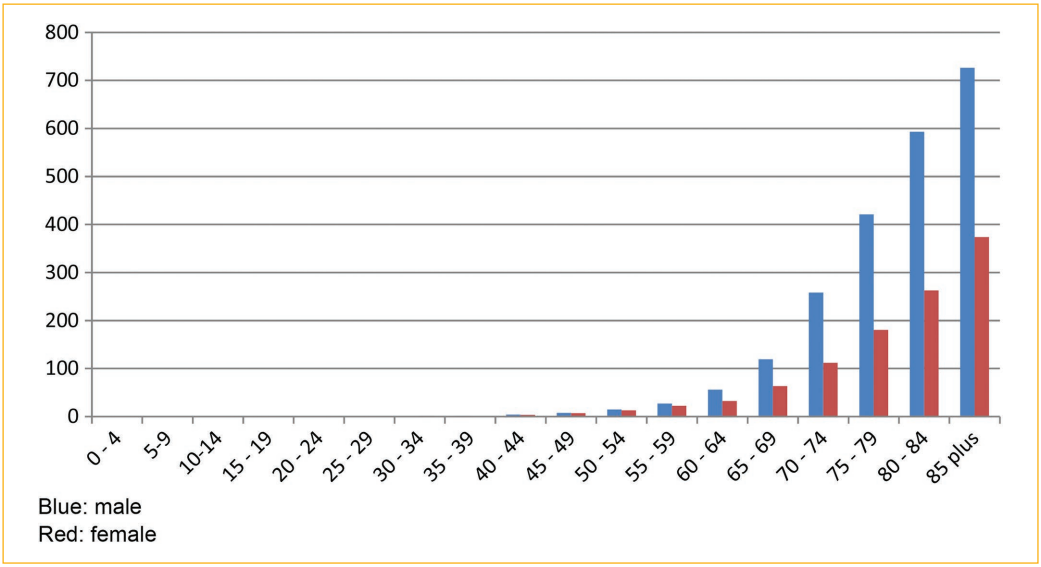

Figure 1 Raw incidence rates and extrapolated case numbers of cSCC in Germany in 2014.

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/can) (Table 2).

3 Epidemiology and etiology

3.1 Incidence

There is hardly any conclusive data on the epidemiology of AKs. Based on data from German statutory health insurance funds (2014) that included 90,800 employees, the prevalence among all age groups was calculated to be 2.7 % and showed an increase with age (11.5 % among 60–70-year-olds). Men were more commonly affected than women (3.9 % vs. 1.5 %).

The second most common type of skin cancer after basal cell carcinoma, cutaneous squamous cell carcinoma (cSCC) accounts for 20 % of all nonmelanoma skin cancer (NMSC) cases [1]. According to estimates by the Robert Koch Institute, roughly 29,300 men and 20,100 women in Germany developed cSCC for the first time in 2014 [2] (Figure 1, Table 3). It has been estimated that the incidence of cSCC in Germany has increased by a factor of four over the past 30 years [1, 3, 4]. As patients with NMSC are predominantly treated in outpatient settings in Germany, it is safe to assume that the number of cases included in most cancer registries does not reflect the actual prevalence. Thus, the epidemiological data available is incomplete, and the above-mentioned estimates are subject to a certain level of uncertainty. There is also limited international data, given that many countries do not include NMSC cases in their cancer registries.

As not all German federal states provide long-term data on the incidence of cSCC, we combined data considered to be conclusive from a number of different federal states – including Hamburg, Schleswig-Holstein, Bremen, Lower Saxony, Mecklenburg-Western Pomerania, Rhineland-Palatinate and the administrative districts of Munster (North Rhine-Westphalia), Lower Bavaria and Upper Palatinate (Bavaria) [Table 3] – to calculate 10-year incidence rates for cSCC. Depending on the region, age-standardized incidence rates are currently between 20/100,000 and 32/100,000 per year (age-standardized for the European standard population) (Table 4).

In 2016, 21 % of individuals aged 65 or older developed cSCC. Given the steady increase in the number of elderly individuals in Germany, that figure is expected to rise. The number of over-65-year-olds is going to increase from 17.4 million (2016) to approximately 20 million in 2025 and will be associated with a corresponding uptick in cSCC incidence rates.

3.2 Mortality

Mortality rates for NMSC are low and have largely remained stable in Germany over the past 25 years. According to official cause-of-death data, 464 men and 350 women died due to NMSC in 2015. The exact percentage of cSCC cases is unknown, as there is no specific ICD-10 code. Based on data from the federal statistics office, the mortality rate between 2011 and 2015 was 0.65 for men and 0.3 for women, respectively 0.62 and 0.27 between 1991 and 1995. Various publications have shown a low rate of disease-specific causes of death compared to general causes.

Table 3 Age-standardized incidence rates of cSCC in Germany between 2005 and 2014 (both genders), stratified by federal states and regions.

Incidence rates			
	2005–2009	2010–2014	Increase
Schleswig-Holstein	24.71	29.69	20 %
Hamburg	18.99	24.07	27 %
Lower Saxony	19.95	27.40	37 %
Bremen	21.59	21.67	0 %
Rhineland-Palatinate	26.41	32.09	22 %
Mecklenburg-Western Pomerania	15.39	21.63	41 %
Munster	16.15	24.45	51 %
Lower Bavaria	17.74	23.39	32 %
Upper Palatinate	17.66	20.91	18 %
All 9 regions combined	20.70	26.90	30 %

Table 4 Raw incidence rates and extrapolated case numbers in Germany in 2014.

Incidence							
	Raw rates, 2014		Population		Extrapolated case numbers		
	9 regions				*Germany 2014*		
	Male	*Female*	*Male*	*Female*	*Male*	*Female*	*Total*
0–4	0.00	0.21	1,768,121	1,679,831	0	4	4
5–9	0.00	0.00	1,790,922	1,699,097	0	0	0
10–14	0.00	0.18	1,912,951	1,813,657	0	3	3
15–19	0.16	0.00	2,085,232	1,968,411	3	0	3
20–24	0.14	0.30	2,371,714	2,252,466	3	7	10
25–29	0.27	0.00	2,615,697	2,490,930	7	0	7
30–34	0.28	1.45	2,550,763	2,484,263	7	36	43
35–39	1.35	1.06	2,374,936	2,338,925	32	25	57
40–44	3.86	3.36	2,687,988	2,646,102	104	89	193
45–49	7.68	7.14	3,444,916	3,357,094	265	240	504
50–54	14.83	12.85	3,415,839	3,366,917	507	433	939
55–59	26.97	22.24	2,870,852	2,900,161	774	645	1,419
60–64	55.94	32.28	2,489,668	2,634,296	1,393	850	2,243
65–69	119.47	63.49	1,904,860	2,061,785	2,276	1,309	3,585
70–74	258.11	111.99	2,113,109	2,432,159	5,454	2,724	8,178
75–79	421.01	180.48	1,760,828	2,242,693	7,413	4,048	11,461
80–84	593.03	262.97	928,610	1,418,596	5,507	3,730	9,237
85+	726.43	373.79	609,191	1,498,933	4,425	5,603	10,028
Total					28,171	19,745	47,915

3.3 Etiology and pathogenesis

The development of AKs is primarily caused by chronic exposure to ultraviolet (UV) radiation, in particular to UVB. Numerous studies have demonstrated a correlation between the cumulative UV dose and the occurrence of AKs. UV radiation induces mutations in the tumor suppressor gene *p53*, which is considered to be the causative event in the development of AKs. The gene plays a key role in cell cycle regulation and induces apoptosis in mutated cells. UVB radiation characteristically leads to the conversion of cytosine to thymine in *p53*, resulting in a dysfunctional gene product (p53). Subsequently, this gives rise to uncontrolled proliferation of dysplastic cells and eventually to the development of AKs.

The etiology of cSCC is multifactorial. In addition to a genetic or immunological predisposition, it primarily involves exogenous factors, in particular UV radiation. Given its oncogenic potential, UV radiation was included in the highest cancer risk category ("carcinogenic to humans") by the World Health Organization in 2009. With the newly established occupational disease BK 5103 in Germany, cumulative "natural UV radiation" has been recognized as playing a key role in terms of cSCC development. Chemical carcinogens such as polycyclic aromatic hydrocarbons or arsenic are well established carcinogens involved in the induction of cSCC.

3.4 Risk factor immunosuppression

A typical long-term complication of chronic immunosuppression, epithelial skin tumors are by far the most common malignant neoplasms among organ transplant recipients (OTRs). Similarly, these individuals also show a significantly higher risk of developing AKs. The incidence of NMSC increases with the number of years of immunosuppression and is 40–60 % after 20 years. In addition, AKs exhibit a much more aggressive growth behavior in OTRs, with early progression to cSCC.

3.5 Prognostic factors for the progression of AKs to cSCC

	Consensus-based statement
Expert consensus	The data currently available with respect to prognostic factors for the progression of AKs to cSCC is insufficient. At present, it is impossible to reliably quantify the likelihood of disease progression from AKs to SCC.
	Strong consensus (100 %)

	Consensus-based recommendation
Expert consensus	Given that existing clinical and histological classification systems (e.g., Olsen classification; keratinocyte intraepithelial neoplasia 1–3) have not been sufficiently validated in terms of their prognostic significance, new classifications should be developed.
	Strong consensus (100 %)

3.6 Prognostic factors for the development of cSCC-related metastasis

	Evidence-based recommendation
Grade of recommendation o	Prognostic factors for metastatic spread or disease-specific survival include histopathological (depth of vertical tumor infiltration, desmoplasia, degree of differentiation, perineural growth) and clinical aspects (site, horizontal tumor extent, comorbidities such as immunosuppression).
Level of evidence 4	De novo research
	Strong consensus (100 %)

Prognostic factors for metastatic spread and disease-specific survival in patients with cSCC include the following:

- vertical tumor thickness (> 6 mm),
- horizontal tumor extent (≥ 2 cm),
- histological differentiation (> grade 3),
- desmoplasia,
- perineural growth,
- site (lower lip, ear),
- immunosuppression (iatrogenic or disease-related).

The aforementioned risk factors apply to the sections "Diagnosis" (short version – part 1), "Surgical and systemic treatment of cSCC" (short version – part 2) and "Follow-up" (short version – part 2).

4 Surgical and systemic treatment of cSCC

4.1 Surgical treatment of the primary tumor

	Consensus-based recommendation
Expert consensus	Standard treatment shall consist of histologically controlled excision.
	Strong consensus (100 %)

	Consensus-based recommendation
Expert consensus	The goal of cSCC surgery shall be complete excision (R0) with histological evaluation of both peripheral and deep margins. If the diagnosis is clinically straightforward, excisional biopsy or therapeutic excision with sufficient surgical margins can be performed.
	Strong consensus (100 %)

Although there is no dispute in the literature that surgical excision is the treatment of choice for cSCC, there is little consensus as to the exact surgical approach and the subsequent histological examination. In this context, the degree of accuracy employed for histological control of excision margins has a significant impact on the surgical approach. Detailed information on surgical removal options for cSCC can be found in the long version.

	Consensus-based statement
Expert consensus	Horizontal ablation (deep "shave" excision) is an alternative approach for small tumors.
	Consensus (76.1 %)

When using horizontal ablation (shave excision) for the removal of small tumors, it is essential that dermatopathologist be provided with sufficient tissue to perform a conclusive histological examination. There are no published studies on this topic. The specimen should be no less than 5 mm in diameter and include the deep dermis or even the upper subcutis. If the tumor was thus removed completely, subsequent secondary intention healing will lead to very good aesthetic outcomes. For larger and thicker tumors, the specimen shall include deeper layers of the subcutis (approximately 6 mm deep, if possible). This enables the dermatopathologist to evaluate both tumor thickness and differentiation and thus allows for a fairly accurate prognostic assessment.

	Consensus-based recommendation
Expert consensus	As long as there is no histological confirmation that the tumor has been excised completely (R0 resection), wound closure shall only be performed if the resection margins can be unequivocally identified postoperatively (e.g., no advancement flaps).
	Strong consensus (100 %)

For very large tumors or those at unfavorable sites, reconstructive wound closure is not recommended until it has been confirmed that the resection margins are tumor free. This is especially true when local flaps are planned, as this may lead to displacement of resection margins, which complicates their subsequent identification if re-excision is required.

4.2 Sentinel lymph node biopsy (SLNB)

	Evidence-based statement
Level of evidence 3	There is currently no valid data regarding the prognostic and therapeutic significance of SLNB.
	De novo research
	Strong consensus (100 %)

Given that there is currently no sufficient and valid data regarding the prognostic and therapeutic value of SLNB, a general recommendation for this procedure cannot be issued [5–9]. Previous studies failed to demonstrate any statistically significant benefit of SLNB in terms of disease-specific and overall survival as well as metastasis-free survival [10]. Most of the data available refers to the use of SLNB in high-risk settings. Numerous studies suggest that there is a potential benefit (detection of clinically occult micrometastases, avoidance of unnecessarily extensive lymphadenectomies [with higher morbidity than SLNB]) in patients with high-risk cSCC, which is associated with a metastatic risk of > 10 %. SLNB-related complications are rare (3–5 %) and include lymphedema, infection, hematoma, seroma, cutaneous lymphatic fistula and wound dehiscence.

4.3 Prophylactic and therapeutic lymphadenectomy

	Evidence-based recommendation
Grade of recommendation A	Prophylactic lymphadenectomy shall not be performed. There is currently insufficient data regarding the value of regional lymphadenectomy following positive SLNB.
Level of evidence 3	De novo research
	Strong consensus (100 %)

For cSCC, there is as yet no evidence for a (prospective) benefit of prophylactic (elective) lymph node dissection in terms of disease-specific and overall survival [11, 12].

	Evidence-based recommendation
Grade of recommendation B	Regional (therapeutic) lymphadenectomy should be performed in cases of clinically manifest lymph node metastasis.
Level of evidence 3	De novo research
	Strong consensus (100 %)

	Evidence-based statement
Level of evidence 3	It has been reported that regional therapeutic lymphadenectomy in patients with lymph node metastasis is associated with improved locoregional disease control.
	De novo research
	Strong consensus (100 %)

Therapeutic lymph node dissection shall only be performed if such an approach is feasible and warranted by the patient's general health (general operability) and if it is deemed reasonable within the overall treatment concept. This requires that the metastasis can be completely (R0) resected (local operability). If neither general nor local operability are ensured, non-surgical treatment modalities should be given preference as determined by an interdisciplinary tumor board.

4.4 Lymphadenectomy in the head and neck region

	Evidence-based statement
Level of evidence 3	There is no general consensus regarding the required level of dissection in the head and neck region.
	De novo research
	Strong consensus (100 %)

There is no consensus in the literature regarding the required extent of lymph node dissection in the head and neck region. Especially the site of the primary tumor plays a key role. A few sites are known to be fairly consistently associated with a certain lymphatic drainage pathway. For example, the lower lip drains into the submental, submandibular and upper cervical lymph nodes (levels Ia, Ib and II according to Robbins et al. [13]) [14–16]. If feasible, selective functional neck dissection should be performed, as this approach spares functionally vital structures (especially nerves, muscles and vessels). Radical dissections are only recommended for patients with extensive metastatic disease, due to the greater morbidity associated with these procedures. Similar to the results observed in the treatment of carcinoma of the oral cavity, the outcomes achieved with selective neck dissection in terms of tumor control, disease-specific and overall survival are not inferior to those achieved with modified radical or radical neck dissection (modified after the "S3 guidelines for Carcinoma of the Oral Cavity") [17–20].

4.5 Adjuvant and postoperative radiation therapy

	Evidence-based recommendation
Grade of recommendation B	Radiation therapy should be performed in patients with locally not completely resectable or inoperable disease.
Level of evidence 3	De novo research
	Strong consensus (100 %)

	Evidence-based recommendation
Grade of recommendation B	Postoperative radiation therapy should be performed in cases of: – R1 or R2 resection (if re-excision is not feasible) – Extensive lymph node involvement (> 1 affected lymph node, lymph node metastasis > 3 cm, capsular penetration) – Intraparotid lymph node involvement
Level of evidence 2	De novo research
	Strong consensus (100 %)

	Evidence-based recommendation
Grade of recommendation B	Adjuvant radiation therapy should be performed in the presence of the following risk factors: – Surgical margins < 2 mm and re-excision is not feasible – Extensive perineural infiltration
Level of evidence 2	De novo research
	Strong consensus (100 %)

While there is no general indication for postoperative radiation therapy in patients with cSCC, it should be offered to individuals with risk factors for local or locoregional recurrence. Such risk factors (which have been subject to controversial debate) include R1 or R2 resection, narrow surgical margins (< 2 mm, and re-excision is not feasible), recurrent tumor, maximum tumor size (> 2 cm), maximum tumor invasion (> 4 mm), infiltration of subcutaneous tissue, perineural and extensive lymphatic involvement (> 1 affected lymph node, capsular penetration).

Mandatory indications for postoperative radiation therapy include R1 or R2 resection as well as cases in which re-excision is not feasible following resection with narrow surgical margins (< 2 mm). In the presence of risk factors, postoperative radiation therapy can be combined with platinum-based chemotherapy [21, 22].

4.6 Treatment of local or locoregional recurrence

	Consensus-based recommendation
Expert consensus	If clinically feasible, recurrent locoregional disease shall be managed surgically.
	Strong consensus (100 %)

	Evidence-based recommendation
Grade of recommendation A	Micrographically controlled surgery (MCS) shall be employed for this purpose.
Level of evidence 2	De novo research
	Strong consensus (100 %)

	Evidence-based recommendation
Grade of recommendation B	If, over the course of the resection, there is evidence of residual, unresectable tumor tissue (R1 or R2 resection), radiation therapy of the area thus affected should be performed.
Level of evidence 2	De novo research
	Strong consensus (100 %)

	Evidence-based recommendation
Grade of recommendation B	In case of inoperability as determined by an interdisciplinary tumor board, radiation therapy should be performed.
Level of evidence 3	De novo research
	Strong consensus (100 %)

	Consensus-based recommendation
Expert consensus	The indication for electrochemotherapy or systemic treatment should be reviewed in patients with recurrent local or locoregional disease if no surgical or radiation therapy options are available.
	Consensus (93.3 %)

Local recurrences frequently exhibit a more extensive, irregular subclinical infiltration pattern than primary tumors, a phenomenon that is difficult to completely assess using conventional bread-loaf sections. Local recurrences in the head and neck region are very often desmoplastic lesions that are characterized by high recurrence rates even following MCS [23, 24]. It is not uncommon for patients with this tumor type to die from complications caused by local tumor infiltration [25]. It is therefore recommended that patients with recurrent disease following MCS undergo postoperative radiation therapy. Studies have shown that this approach reduces recurrence rates and is associated with longer recurrence-free survival than surgery alone [7, 21, 26–32].

Patients with inoperable disease for whom radiation therapy is not feasible can be treated with electrochemotherapy to improve local tumor control; the overall response rate has been reported to be 46 % [33–35]. In addition, the indication for systemic treatment should be reviewed.

4.7 Systemic treatment for distant metastatic disease

	Consensus-based recommendation
Expert consensus	There are no controlled or randomized studies on the benefit of systemic treatment for metastatic SCC. If used, systemic treatment should preferably be administered in the context of clinical trials.
	The decision to administer systemic treatment and the choice thereof should be made by an interdisciplinary tumor board.
	Strong consensus (100 %)

Cutaneous SCC is chemosensitive and shows response rates > 50 % to platinum-based chemotherapy. While response rates are higher with polychemotherapy or chemoradiation therapy, the duration of the response remains unclear, and polychemotherapy regimens are likely associated with greater toxicity. Monotherapy with epidermal growth factor receptor (EGFR) inhibitors has achieved response rates between 25 % and 45 %.

A novel therapeutic approach for inoperable cSCC, PD1 inhibitors have been shown to be effective in tumor entities characterized by a high mutational burden (which is a feature of cSCC). Initial data from a study investigating the anti-PD1 antibody cemiplimab showed response rates of 47–50 %; after a median follow-up of 7.9 months, the median duration of response had not been reached. At that

time, 82 % of patients who had a response continued to have a response [36].

Patients with advanced or metastatic cSCC are typically older and have relevant comorbidities; for example, chronic lymphocytic leukemia is a risk factor for rapid disease progression in patients with cSCC. Irrespective of age, OTRs on immunosuppressive medication should be mentioned in this context. While several studies have shown that switching to a regimen that includes an mTOR inhibitor has positive effects in terms of primary and secondary prevention of new epithelial skin cancers in kidney transplant recipients, it remains to be elucidated whether switching to mTOR inhibitors has any effect on clinically manifest epithelial skin cancer lesions [37–40].

In summary, no treatment recommendation can be given at this time. It is recommended to administer any systemic treatment in the context of clinically controlled trials. If this is not feasible, options to be considered include chemotherapeutic agents, EGFR inhibitors and/or immunotherapeutic agents; any comorbidities and the patient's overall health should be observed.

5 Follow-up

5.1 Follow-up intervals

In order to detect disease recurrence and secondary tumors at an early stage, it is recommended that cSCC patients undergo risk-adapted follow-up. It is estimated that 30–50 % of secondary cSCC lesions occur within one year after the diagnosis of the primary tumor. While the risk is highest within the first four years after the initial diagnosis, it is still significantly increased after 15 years of follow-up [41]. The development of independent secondary tumors is a common problem, especially in high-risk patients such as individuals with field cancerization of the face, hands and balding scalp as well as OTRs on long-term immunosuppressive medication. Given that approximately 80 % of recurrences occur within the first two years after the initial diagnosis, particularly close follow-up is recommended during this period.

5.2 Examination methods

5.2.1 Clinical examination

	Consensus-based recommendation
Expert consensus	All patients with cSCC shall undergo clinical follow-up examinations on a regular basis, including inspection of the entire skin as well as inspection and palpation of the primary resection site, the in-transit pathway and the regional lymph node basin.
	Strong consensus (100 %)

5.2.2 Lymph node ultrasound

	Consensus-based recommendation
Expert consensus	Lymph node ultrasound should be performed in patients at increased risk of metastasis and in cases in which palpation has yielded ambiguous findings.
	Strong consensus (100 %)

5.2.3 Chest X-ray and abdominal ultrasound

	Consensus-based recommendation
Expert consensus	Routine chest X-ray should not be performed during follow-up. Routine abdominal ultrasound should not be performed during follow-up.
	Strong consensus (100 %)

5.2.4 Cross-sectional imaging

	Consensus-based recommendation
Expert consensus	Cross-sectional imaging should be used in the workup of recurrent disease, for example, if functional structures are suspected to be affected or if perineural tumor growth or metastasis are suspected.
	Strong consensus (100 %)

	Consensus-based recommendation			
Expert consensus	Risk-adapted follow-up should be offered to patients with cSCC* based on the following schedule:			
		Year 1–2	Year 3–5	Year 6–10
	Low-to-medium risk	Every 6 months	Annually	–
	High risk	Every 3 months	Every 6 months	Annually
	*for completely resected tumors (R0).			
	Strong consensus (100 %).			

Overall, the data currently available does not allow for a general recommendation to be made with respect to the various imaging techniques, as there are no studies investigating their use specifically in patients with cSCC. Given that there are no studies on the routine use of cross-sectional imaging in the follow-up of cSCC, these modalities are reserved for the workup of suspected metastasis. The choice of cross-sectional imaging modality in this context is guided by practical and economical aspects as well as the body region to be examined.

6 Prevention

See sections 4 (primary prevention) and 5 (secondary prevention) of the "S3 guidelines for the Prevention of Skin Cancer" [42]. As the topics "chemoprevention", "photodynamic therapy", "retinoids" and "nicotinamide" were not addressed in that particular publication, they are discussed in the long version of the present guidelines.

7 AKs and cSCC as occupational disease

7.1 Diagnostic workup and reporting of suspected occupational skin cancer

With the amendment of the German Occupational Disease Regulation on January 1, 2015, occupational disease BK 5103 ("SCC or multiple AKs of the skin caused by natural UV radiation") was newly included in the list of officially recognized occupational diseases (Table 5). The term "multiple" is defined either as the development of more than five individual AKs within a period of twelve months or as the presence of field cancerization involving more than 4 cm^2. Bowen's disease and Bowen's carcinoma are likewise recognized skin cancer entities pursuant to the requirements of BK 5103. With respect to its biological behavior and its status in terms of insurance law, extra genital Bowen's disease is considered to be equivalent to AKs. Thus, recognition as occupational

Table 5 Requirements that must be met for disease recognition pursuant to BK 5103 ("cSCC or multiple AKs of the skin caused by natural UV radiation").

Criterion	Description
Skin tumor site	Lesions must arise in areas affected by occupational exposure to UV radiation (in this context, consider whether patients with skin tumors of the scalp were protective gear, such as a hardhat, at work).
Confirmed clinical diagnosis	Cutaneous SCC (histologically confirmed) or at least 6 individual AKs diagnosed on clinical grounds within a period of 12 months (histological confirmation of one AK is recommended) or confluent AKs involving an area of at least 4 cm^2 (field cancerization). Extragenital Bowen's disease is considered to be equivalent to AKs; Bowen's carcinoma to cSCC.
Signs of chronic UV-induced skin damage/ which sites are involved?	Chronic UV- induced skin damage is not a sine qua non for recognition as occupational disease. However, the severity and distribution of UV- induced damage (occupationally vs. non-occupationally exposed skin areas) provide important clues as to causation.
Skin phototype (Fitzpatrick)	Does generally not play a role for recognition as occupational disease but should always be specified in the occupational disease report. The skin phototype is an essential risk factor for the development of skin cancer. It is modified by both occupational and non-occupational exposure to UV radiation and affects the time of disease onset.
Non-occupational risk factors	It should be specified whether there is evidence for other non-occupational risk factors, including immunosuppression, drugs that increase photosensitivity, phototherapy, pigmentary disorders, impaired DNA repair capability, exposure to carcinogens, and others.
Additional occupational UV exposure of at least 40 %.	A rough estimate is sufficient for physicians to file an occupational disease report. Actual quantification of occupational UV exposure is done by concrete calculations by the Prevention Services of the competent statutory accident insurance company.
Information whether the patient's vacation and leisure behavior differs significantly from that of the general population	The calculations done by the Prevention Services assume an average non-occupational UV exposure of the general population of 130 SED (standard erythema dose; 1 SED = 100 J/m^2) per year. Significant deviations due to the patient's individual vacation and leisure behavior should be specified.

Table 6 Behavioral and structural prevention measures for patients with occupational exposure to natural UV radiation.

Recommended measures
Institute appropriate technical and organizational UV protection measures (shady areas, work organization, break rules).
Provide information on the hazards of occupational UV radiation and motivate workers to change their behavior.
Avoid significant sun exposure during working hours and breaks: ▸ Avoid midday sun ▸ Stay in the sun for as short a time as possible ▸ Stay in the shade ▸ Avoid sunburns ▸ Observe UV index
Wear protective clothing and headgear at work (wide-brimmed headgear that also covers the nape of the neck).
Use sunscreen products suitable for the occupational activity without prolonging the exposure time. Observe individual skin sensitivity. Provide information about the various skin phototypes. Observe workplace factors.
Advise workers on individual protective measures depending on the specific occupational exposure.

disease requires multiple such lesions or involvement of an area ≥ 4 cm^2. Following its potential progression to Bowen's carcinoma, the condition is considered to be (legally) equivalent to cSCC. While the diagnosis of cSCC requires histological confirmation in order to be legally recognized, this is not the case for multiple AKs, which may be diagnosed merely on clinical grounds. Nevertheless, it is recommended to provide a pathology report for at least one of the existing AKs and to attach it to the occupational disease notification.

Detailed information on the diagnosis and reporting of occupational cSCC and AKs can be found in the long version of the guideline.

7.2 Prevention of occupational skin cancer caused by UV radiation

Primary prevention measures are paramount. Pursuant to Section 3 of the German Labor Protection Act (ArbSchG), it is the employer's responsibility to institute appropriate protective measures. Not only does this apply to hazardous materials and substances at the workplace but also to hazards caused by UV radiation from the sun (Table 6). With the revision of the German Ordinance on Preventive Occupational Health Care (ArbMedVV) currently underway, it is intended to ensure that individuals who work outdoors on a regular basis will both be required to undergo mandatory screening and also have the opportunity for voluntary screening exams. In addition, the guidelines for "Prevention of Occupational Skin Cancer" currently being developed will provide evidence- and consensus-based recommendations for primary, secondary and tertiary prevention of skin cancer pursuant to BK 5103.

Conflict of interest

The long version and the conflict of interest statements of the guideline can be found at www.awmf.org.

Correspondence to

Ulrike Leiter, MD, PhD
Center for Dermatooncology
Department of Dermatology
Eberhard-Karls University

Liebermeisterstrasse 25
72076 Tübingen, Germany

E-mail: ulrike.leiter@med.uni-tuebingen.de

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