DOI: 10.1111/ddg.15256

GUIDELINE



S3 guideline "actinic keratosis and cutaneous squamous cell carcinoma" – update 2023, part 2: epidemiology and etiology, diagnostics, surgical and systemic treatment of cutaneous squamous cell carcinoma (cSCC), surveillance and prevention

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Guidelines commissioned by: Dermatological Cooperative Oncology Group (DeCOG) (Arbeitsgemeinschaft Dermatologische Onkologie; ADO) of the German Cancer Society (DKG) and the German Society of Dermatology (Deutsche Dermatologische Gesellschaft; DDG)

Participating societies:

Arbeitsgemeinschaft Dermatologische Histologie (ADH)

Arbeitsgemeinschaft Dermatologische Onkologie der DKG und DDG (ADO)

Arbeitsgemeinschaft Dermatologische Prävention e.V. (ADP)

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Arbeitsgemeinschaft Palliativmedizin in der DKG (APM)

Arbeitsgemeinschaft Radiologische Onkologie (ARO)

Arbeitsgemeinschaft Tumorklassifikation in der Onkologie der DKG (ATO)

Arbeitsgemeinschaft Berufs- und Umweltdermatologie (ABD)

Arbeitsgemeinschaft physikalische Diagnostik in der Dermatologie in der DDG (ApDD)

Berufsverband der Deutschen Dermatologen e.V. (BVDD)

Bundesverband Deutscher Pathologen e.V. (BDP)

Deutsche Dermatologische Gesellschaft (DDG)

Deutsche Gesellschaft der Plastischen, Rekonstruktiven und Ästhetischen Chirurgen (DGPRÄC)

Deutsche Gesellschaft für Arbeitsmedizin und Umweltmedizin (DGAUM)

Deutsche Gesellschaft für Chirurgie (DGCH)

Deutsche Gesellschaft für Dermatochirurgie e.V. (DGDC)

Deutsche Gesellschaft für HNO-Heilkunde, Kopf- und Hals-Chirurgie (DGHNOKHC)

Deutsche Gesellschaft für Mund-, Kiefer- und Gesichtschirurgie (DGMKG)

Deutsche Gesellschaft für Palliativmedizin (DGP)

Deutsche Gesellschaft für Pathologie (DGPath)

Deutsche Gesellschaft für Radioonkologie e.V. (DEGRO)

Deutsche Gesellschaft für Ultraschall in der Medizin (DEGUM)

Deutsche Röntgengesellschaft (DRG)

Deutsche Gesetzliche Unfallversicherung (DGUV)

Hautkrebsnetzwerk (Patientenvertretung)

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

Valid until 01/2028 or until next guideline update.

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Summary

Actinic keratosis (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 updated and expanded by the topics cutaneous squamous cell carcinoma in situ (Bowen's disease) and actinic cheilitis. The guideline is aimed at dermatologists, general practitioners, ear nose and throat specialists, surgeons, oncologists, radiologists and radiation oncologists in hospitals and office-based settings, as well as other medical specialties, policy makers and insurance funds involved in the diagnosis and treatment of patients with AK and cSCC. A separate guideline exists for patients and their relatives. In this part, we will address aspects relating to epidemiology and etiology, diagnostics, surgical and systemic treatment of cutaneous squamous cell carcinoma (cSCC), surveillance and prevention.

INTRODUCTION

The guideline represents a short version of the complete guideline available at www.awmf.org. Information on the treatment of actinic keratosis, actinic cheilitis, cutaneous squamous cell carcinoma in situ (Bowen's disease), occupational disease and structures of care can be found in part 1 of the short version – update 2023 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. The guideline is an update of the previous version published in 2020.^{1,2}

METHODOLOGY

See long version at www.awmf.org.

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology of actinic keratosis and squamous cell carcinoma

See long version at www.awmf.org.

Mortality

See long version at www.awmf.org.

Risk factor immunosuppression

See long version at www.awmf.org.

Prognostic factors for the transition from actinic keratosis to invasive squamous cell carcinoma

See long version at www.awmf.org.

S3 GUIDELINE "AK AND CSCC", UPDATE 2023, PART 2

See long version at www.awmf.org.

Consensus-based statement	New 2022
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EC Actinic cheilitis is etiologically and morphologically the counterpart of actinic keratosis of the keratinizing squamous epithelium of the skin at the red of the lips.

Strong consensus

Consensus-based statement

Checked 2022

EC Bowen's disease is defined as an intraepidermal proliferation of highly atypical and polymorphic keratinocytes occupying the entire width of the epidermis. In this respect, Bowen's disease represents a special variant, which can progress into an invasive, then usually bowenoid differentiated (pleomorphic, low differentiated) squamous cell carcinoma (Bowen carcinoma).

Strong consensus

Classification, definition und nomenclature of invasive squamous cell carcinoma

See long version at www.awmf.org.

	Consensus-based statement	Checked 2022
EC	Squamous cell carcinoma of the skin is a malig the keratinocytes of the epidermis. The turn different degrees of differentiation (see also classification).	nors can develop
	Strong consensus	

	Consensus-based statement	Checked 2022
EC	Squamous cell carcinoma of the skin arises in not necessarily, from intraepidermal prolife keratinocytes.	,
	Strong consensus	

)22			Consensus-based statement	Checked 2022
scores J of		EC	Invasive squamous cell carcinoma of t when there is histomorphologically of the basement membrane beneat keratinocytic proliferation in no trau	demonstrable disruption h an intraepithelial
			Consensus	

Consensus-based statement

EC The data situation for reliable prognostic factors of the transition from AK to SCC is insufficient. At the moment, no reliable values for the probability of progression can be given. The following clinical factors are prognostically unfavorable: Immunosuppression

Modified 2022

Modified 2022

Therapy resistance Field cancerization

Tield cancerization

Strong consensus

Abbr.: EC, expert consensus

Consensus-based statement

EC Existing clinical and histologic systems (e.g., classification according to Olsen, graduation into keratinocytic intraepidermal neoplasia 1–3, counting of lesions) are not sufficiently validated prognostically and thus dispensable in

Consensus

clinical practice.

Prognostic factors for metastasis in invasive squamous cell carcinoma

See long version at www.awmf.org.

	Evidence-based statement Checked 2022
LoE 4	Histopathologic factors (tumor infiltration depth to be determined vertically, desmoplasia, degree of differentiation, perineural growth) and clinical factors (localization, horizontal tumor diameter, comorbidities such as immunosuppression) are considered prognostic factors for metastasis or disease-specific survival.
	4: <i>De novo</i> research
	Strong consensus

Abbr.: LoE, level of evidence

DIAGNOSTICS

Classification, definition and nomenclature of actinic keratosis

See long version at www.awmf.org.

	Consensus-based recommendation	Checked 2022
EC	The term "actinic keratosis" shall be used.	
	Strong consensus	
	Evidence-based statement	New 2022
LoE	Multiple qualitative and quantitative factor	5 5
2	(e.g., AK-FAS, AKASI) improve standardize findings for actinic keratosis.	ed reporting of

2: De novo research

Strong consensus

Consensus-based	statement
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C	neck	eu 4	2022

- **EC** The following variants of squamous cell carcinoma of the skin can be distinguished histomorphologically (some of these are reflected in the WHO/UICC classification):
 - adenosquamous squamous cell carcinoma of the skin
 - acantholytic (adenoid, pseudoglandular) squamous cell carcinoma of the skin
 - Bowen's carcinoma/ bowenoid differentiated squamous cell carcinoma of the skin
 - desmoplastic squamous cell carcinoma of the skin
 - keratoacanthoma-like squamous cell carcinoma of the skin/keratoacanthoma
 - lymphoepithelioma-like squamous cell carcinoma of the skin
 pseudovascular (pseudoangiosarcomatous,
 - pseudoangiomatous) squamous cell carcinoma of the skin • spindle cell (sarcomatoid) squamous cell carcinoma of the
 - skin • verrucous squamous cell carcinoma of the skin (epithelioma
 - cuniculatum)

Strong consensus

Consensus-based statement Checked 2022

EC Classification of squamous cell carcinoma of the skin should be based on histologic and clinical parameters according to the currently used TNM systems of the UICC or AJCC.

Strong consensus

For classification, the WHO/UICC/AJCC classification can be used. This is particularly useful for clinically very large SCC (Table 1, 2).

Field cancerization

See long version at www.awmf.org.

Consensus-based statementChecked 2022ECA generally accepted definition of field carcinization does not
exist. Field carcinization includes an area of skin with multiple
actinic keratoses surrounded by visible UV-related skin
damage.

Strong consensus

Importance of non-invasive diagnostic procedures

See long version at www.awmf.org.

	Consensus-based statement	Checked 2022
EC	Diagnosis is made by clinical examination a	nd inspection.
	Strong consensus	
	Consensus-based recommendation	Checked 2022
EC	Dermatoscopy, confocal laser microscopy, a	nd optical

coherence tomography may be used to diagnose actinic keratosis and squamous cell carcinoma of the skin when findings are clinically unclear.

Strong consensus

Histologic diagnosis

See long version at www.awmf.org.

	Consensus-based statement	Checked 2022
EC	Actinic keratosis does not require histologic d clinical findings are present.	liagnosis if typical
	Strong consensus	

EC	In case of resistance to therapy and clinically unclear findings, a
	tissue sample shall be obtained.

Consensus-based recommendation

Strong consensus

Consensus-b	ased	l recom	menda	tion	٨	Aodified 2022	

EC If squamous cell carcinoma of the skin, actinic cheilitis or Bowen's disease is clinically suspected, histology shall also be obtained to differentiate other benign or malignant neoplasia.

Preoperatively, the maximum diameter of the neoplasia should be documented for squamous cell carcinoma of the skin and Bowen's disease.

Consensus

	Consensus-based statement	Checked 2022
EC	Depending on the clinical situation, punch be ablations ("shave" excisions), or excisional appropriate.	
	Consensus	

 Consensus-based recommendation
 Checked 2022

 EC
 If the clinical picture is clear for squamous cell carcinoma of the skin, complete resection may be performed without prior probing biopsy.

 Consensus

Parameters of the histological report

See long version at www.awmf.org.

	Consensus-based recommendation	Checked 2022
EC	The following histomorphologic variant when present: • atrophic • hypertrophic • acantholytic • pigmented • lichenoid • bowenoid • actinic keratosis.	s should be designated
	Strong consensus	



Checked 2022

TABLE 1 TNM classification of SCC of the skin for the labial skin (excluding labial red), trunk, upper extremities and shoulders, lower extremities, and hip and scrotum (8th edition, 2017).

TNM classification

TNWI Classification	
T category	
ТХ	Primary tumor cannot be assessed
ТО	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest extension
T2	Tumor more than 2 cm but not more than 4 cm in greatest extent
Т3	Tumor more than 4 cm in greatest extent or superficial bone invasion or perineural invasion (PNI) or deep invasion*
T4a	Tumor with macroscopic bone invasion/ bone marrow invasion
T4b	Tumor with invasion of the axial skeleton including foramina and/or involvement of the vertebral foramen up to the epidural space

*"deep invasion" is defined as invasion beyond the subcutaneous fat or >6 mm (measured from the stratum granulosum of the adjacent epidermis to the base of the tumor).

Perineural invasion as a criterion for T3 is defined as clinical or radiologic involvement of nameable nerves without involvement of the foramina or skull base.

In the case of multiple simultaneous tumors, the tumor with the highest T category is classified and the number of delineable tumors is indicated in parentheses, e.g., T2(5).

N category				
NX	Regional lymph nodes cannot be evaluated			
NO	No regional lymph node metastases			
N1	Metastasis(s) in a regional lymph node, 3 cm or less in greatest extent			
N2	Metastasis(s) in one lymph node, more than 3 cm but not more than 6 cm in greatest extent or in multiple lymph nodes, none more than 6 cm in greatest extent			
N3	Metastasis(s) in one lymph node more that	n 6 cm in greatest extent		
M category				
MO	No distant metastases			
M1	Distant metastases			
Stage classification				
Stage 0	Tis	NO	MO	
Stage I	T1	NO	MO	
Stage II	T2	NO	MO	
Stage III	Т3	NO	MO	
	T1, T2, T3	N1	MO	
Stage IV	T1, T2, T3	N2, N3	MO	
	T4	Any N	MO	
	Any T	Any N	M1	

Consensus-based recommendation Checked 2022

EC The histologic report of squamous cell carcinoma of the skin shall include the following in addition to the diagnosis:

- histological tumor type (for specific subtypes of squamous cell carcinoma of the skin)
- description of the histological depth extension in relation to the anatomical stratification (especially from level V, corresponding to infiltration of the subcutis)
- measurement of the depth extension from an invasion depth of 2 mm (corresponds approximately to the diameter of a 10x field of view)
- in the positive case, indication of the presence of perineural spread, vascular invasion or low differentiation
- · completeness of resection of the invasive tumor portion

Strong consensus

Diagnosis of spread in invasive squamous cell carcinoma

See long version at www.awmf.org.

Cons	ensus-based recommendation	Checked 2022

EC If the presence of squamous cell carcinoma of the skin is suspected, the initial examination shall include inspection of the entire skin organ.

Strong consensus



TABLE 2	TNM classification of SCC of the head and neck according to AJCC/UICC (8th edition, 2017).
T category	
ТΧ	Primary tumor cannot be assessed
Т0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest extension
T2	Tumor more than 2 cm but not more than 4 cm in greatest extent
T3	Tumor more than 4 cm in greatest extent or superficial bone invasion or perineural invasion or deep invasion*
T4a	Tumor with macroscopic bone invasion/ bone marrow invasion
T4b	Tumor with invasion of the axial skeleton including foramina and/or involvement of the vertebral foramen up to the epidural space
the base	ion" is defined as invasion beyond the subcutaneous fat or >6 mm (measured from the stratum granulosum of the adjacent epidermis to of the tumor) vasion as a criterion for T3 is defined as clinical or radiologic involvement of named nerves without involvement of the foramina or skull
base.	
N category	
NO	No regional lymph node metastases
N1	Metastasis(s) in a regional lymph node, 3 cm or less in greatest extent
N2	Metastasis(s) as described below:
N2a	Metastasis(s) in solitary ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest extent, without extra nodal spread
N2b	Metastases in multiple ipsilateral lymph nodes, none more than 6 cm in greatest extent, without extra nodal spread
N2c	Metastases in bilateral or contralateral lymph nodes, none more than 6 cm in greatest extent, without extra nodal spread
N3a	Metastasis(s) in one lymph node, more than 6 cm in greatest extent, without extra nodal spread
N3b	Metastasis(s) in a single or multiple lymph nodes, clinically in extra nodal spread*
	ce of skin or soft tissue involvement (invasion) or clinical signs of nerve involvement is considered clinical extra nodal spread.
-	(pathological)
pN0	No regional lymph node metastases
pN1	Metastasis(s) in solitary ipsilateral lymph node, 3 cm or less in greatest extent, without extra nodal spread
pN2 pN2a	Metastasis(es) as described below: Metastasis(s) in solitary ipsilateral lymph node, 3 cm or less in greatest extent, with extra nodal spread or more than 3 cm
	but not more than 6 cm in greatest extent, without extra nodal spread
pN2b	Metastases in multiple ipsilateral lymph nodes, none more than 6 cm in greatest extent, without extra nodal spread
pN2c	Metastases in bilateral or contralateral lymph nodes, none more than 6 cm in greatest extent, without extra nodal spread
pN3a	Metastasis(s) in one lymph node, more than 6 cm in greatest dimension, without extra nodal spread
pN3b	Metastasis(s) in one lymph node more than 3 cm in greatest extent with extra nodal spread or in multiple ipsilateral, contralateral or bilateral lymph nodes with extra nodal spread
M categor	
MO	No distant metastases
M1	Distant metastases
	ories correspond to the T categories. pM1 means that distant metastases were confirmed microscopically.
Stage clas	
Stage 0	Tis NO MO
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
C 1 T 1	T1, T2, T3 N1 M0
Stage IV	T1, T2, T3 N2, N3 M0
	T4 Any N M0
	Any T Any N M1



Abbreviations/ Legends:

MCS: Micrographically controlled surgery SCC: Squamous cell carcinoma



FIGURE 1 Algorithm surgical therapy.

	Consensus-based recommendation	Checked 2022
EC	Locoregional lymph node ultrasonography when locoregional metastases are suspe Locoregional lymph node ultrasonography performed when risk factors are present	v shall be performed ected. v should be
	Consensus	
	Consensus-based recommendation	Checked 2022
EC	X-ray thoracic examination shall not be per of care when locoregional or distant me cell carcinoma of the skin is suspected o	tastasis of squamous
	Consensus	
	Consensus-based recommendation	checked 2022
EC	Abdominal ultrasonography shall not be p standard of care when locoregional or d squamous cell carcinoma of the skin is s demonstrated.	istant metastasis of
EC	standard of care when locoregional or d squamous cell carcinoma of the skin is s	istant metastasis of
EC	standard of care when locoregional or d squamous cell carcinoma of the skin is s demonstrated.	istant metastasis of
EC	standard of care when locoregional or d squamous cell carcinoma of the skin is s demonstrated.	istant metastasis of
EC	standard of care when locoregional or d squamous cell carcinoma of the skin is s demonstrated. Strong consensus	istant metastasis of uspected or Checked 2022

SURGICAL AND SYSTEMIC TREATMENT OF CUTANEOUS SQUAMOUS CELL CARCINOMA

Surgical therapy of the primary tumor

	Consensus-based recommendation	New 2022
EC	The following risk factors of SCC shall be re examining pathologist/dermatopatholo recurrence, tumor diameter > 2 cm, loca temple, immunosuppression and evider invasion, no displaceability from the sub	gist if present: alization ear, lip or nce of perineural
	Strong consensus	
	Consensus-based recommendation	New 2022
EC	Surgical therapy of the primary tumor shal according to the following algorithm (Fi	•
	Strong consensus	

Although there is no doubt in the literature that surgical excision of squamous cell carcinoma of the skin is the method of choice, there is little consensus for the exact design of the excision and subsequent histologic examination. Detailed information on surgical excision of SCC is provided in the long version of the guideline. Figure 1 shows the algorithm for surgical therapy of the primary tumor.

1429

Checked 2022

Checked 2022

Checked 2022

Lymphadenectomy in the head and neck

In the head and neck region, there is no general consensus on

For tumors that are not locally resectable in sano or inoperable

Adjuvant and postoperative Radiotherapy

patients, radiotherapy should be performed.

See long version at www.awmf.org.

Evidence-based statement

See long version at www.awmf.org.

3: De novo research

Strong consensus

LoE 2: De novo research

Evidence-based recommendation

Evidence-based recommendation

Intraparotid lymph node involvement

GoR Postoperative radiotherapy should be performed for:

R1 or R2 resection (if post resection is not possible)

Extensive lymph node involvement (> 1 affected lymph node, lymph node metastasis > 3 cm, capsule rupture)

Strong consensus

the level of dissection required.

region

LoE

GoR В

LoE

3

В

2

3

Operative procedure after R0 resection

See long version at www.awmf.org.

	Consensus-based recommendation Checked 2022
EC	As long as an R0 resection has not been histologically confirmed, wound closure shall only be performed if the resection wheels can be clearly assigned postoperatively (e.g., no displacement flaps).
	Strong consensus

Sentinel lymph node biopsy

See long version at www.awmf.org.

	Evidence-based statement	Checked 2022
LoE 3	There are no valid data on the prognostic and of SLNB.	therapeutic value
	3: De novo research	
	Strong consensus	

Prophylactic and therapeutic lymphadenectomy

See long version at www.awmf.org.

	Evidence-based recommendation	Checked 2022
GoR A	Prophylactic lymphadenectomy shall no	ot be performed
LoE 3		
	Strong consensus	
Abbr: GoP grades of recommendation		

Abbr.: GoR, grades of recommendation

metastasis.

Strong consensus

	Evidence-based statement	Checked 2022
LoE 3	There are insufficient data on the value of regi lymphadenectomy in the setting of a position node biopsy.	
	Strong consensus	

Evidence-based recommendation

	Evidence-based recommendation	Checked 2022
GoR B	Regional (therapeutic) lymphadenectomy should be performed when lymph node metastasis is clinically manifest.	
LoE 3		
	Strong consensus	
	Evidence-based statement	Checked 2022
LoE 3	Improvement in locoregional tumor control has been described for regional therapeutic lymphadenectomy for nodal	

Checked 2022

	Evidence-based recommendation Modified 2022
GoR B	Adjuvant radiotherapy should be performed in the presence of extensive perineural sheath infiltration (PNI).
LoE 2	2: <i>De novo</i> research
	Strong consensus

	Evidence-based recommendation	Modified 2022
GoR 0	Adjuvant radiotherapy may be considered in margin is narrow.	f the resection
LoE 2	2: <i>De novo</i> research	
	Strong consensus	
	Evidence-based statement	New 2022

LoE	Current data do not support a recommendation for combining
2	adjuvant radiotherapy with system therapy.

2: De novo research

Strong consensus

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Therapy of the local or loco-regional recurrence

See long version at www.awmf.org.

	ing version at www.awini.org.		
	Consensus-based recommendation	Checked 2022	
EK	Locoregional recurrence shall be surgically removed if clinically locally possible.		
	Strong consensus		
	Evidence-based recommendation	Checked 2022	
GoR A	Micrographically controlled surgery (MCS) sh	all be performed.	
LoE 2	2: <i>De novo</i> research		
	Strong consensus		
	Evidence-based recommendation	Checked 2022	
GoR B	If a R1 or R2 situation that cannot be further resected arises during the course of resection, postoperative radiotherapy should be performed at the R1 or R2 localization.		
LoE 2	2: De novo research		
	Strong consensus		
	Evidence-based recommendation	Checked 2022	
GoR B	In case of interdisciplinary determination of in radiotherapy should be performed.	noperability,	
LoE 3	3: <i>De novo</i> research		
	Strong consensus		
	Consensus-based recommendation	Checked 2022	
EC	For therapy of local or locoregional recurrence, the indication for electrochemotherapy or systems therapy should be considered if surgical or radiotherapeutic options are not		

considered if surgical or radiotherapeutic options are not available.

Consensus

Therapy in the advanced (locally advanced or metastasized) stage

See long version at www.awmf.org.

	Consensus-based recommendation	New 2022
EC	Patients with locally advanced or metastatic SCC shall be offered first-line immunotherapy with a PD-1 inhibitor approved for this indication.	
	Strong consensus	
	Consensus-based recommendation	New 2022
EC	In case of progression under PD-1 blockade contraindications to this type of immunc EGFR-directed therapy or chemotherapy	otherapy,
	Strong consensus	

New 2022

Consensus-based recommendation

EC In case of (distant) metastasis or locally advanced disease that cannot be controlled by surgical or radiotherapeutic interventions or only with major limitations of functionality, the indication for systemic therapy shall be considered.

Strong consensus

	Consensus-based recommendation	New 2022
EC	The indication for system therapy should be r interdisciplinary tumor board.	nade in an

Consensus

If there is an indication for systemic therapy, then the best data, although only from uncontrolled studies, are available for PD-1 inhibitors (Table 3).

Palliative care

Regarding palliative care aspects, reference is made to the extended S3 guideline on palliative care of the guideline program on oncology.⁸

SURVEILLANCE AND PREVENTION

Follow-up examination methods

See long version at www.awmf.org.

	Consensus-based re	Modified 2022		
EC	Follow-up of patients with SCC of the skin should be offered at risk-adjusted intervals according to the following schedule:			
		Year 1–2	Year 3–5	Year 6–10
	Primary tumor stage	9		
	Low risk	6-monthly	annually	-
	High risk	3-monthly	6-monthly	annually
	Immunosuppressed patients	3-monthly	3–6 monthly	3–6-monthly according to risk profile
	Advanced stages			
	Locally advanced/ metastatic	3-monthly (up to and including year 3)	3–6 monthly (year 4–5)	
	Strong consensus			

TABLE 3 Ongoing therapeutic trials with the use of PD1 blockers in cutaneous SCC (NBZ = next follow-up time).

Therapy	Line	Study phase	Number of evaluable patients	Median response duration (months)	Response rates	Reference	
Cemiplimab	Any	1	26	Not reached (median NBI 11.1 months)	50%	Migden et al., 2018 ³	
Cemiplimab (cohort 1, weight-adjusted dose every 2 weeks)	Any	2	59 (with metastases)	Not reached (median NBI 16.5 months).	49.2%	Migden et al., 2018 ³ Rischin et al., 2020 ⁴	
Cemiplimab (Cohort 2, weight-adjusted dose every 2 weeks)	Any	2	78 (locally advanced)	Not reached (median NBI 9.3 months)	44%	Migden et al., 2020 ⁵	
Cemiplimab (Cohort 3, fixed dose every 3 weeks)	Any	2	56 (with metastases)	Not reached (median NBZ 8.1 months)	41.1%	Rischin et al., 2020 ⁴	
Pembrolizumab (CARSKIN)	1	2	39	Not reached (median NBI 22.4 months)	41%	Maubec et al., 2020 ⁶	
Pembrolizumab	Any	2	29			NCT02964559	
Pembrolizumab + radiotherapy	Post-operative adjuvant	2	37			NCT03057613	
Pembrolizumab (Keynote 629)	Any	2	105	Not reached (median NBI 11.4 months)	34%	Grob et al., 2020 ⁷	

Consensus-based statement

New 2022

ച്ചാറ്റ

1431

CE The following examination methods are recommended depending on risk factors of the primary tumor, immunosuppression or after locally advanced and metastatic squamous cell carcinoma of the skin according to the present scheme:

	Physical examination			Lymph node sonography			Imaging examinations CT, MRT, PET-CT		
Year	1–2	3–5	6–10	1–2	3–5	6–10	1–3	4–5	6–10
Primary tumors Low risk	2x	1x	-	0–2x	-	-	-	-	-
High risk	4x	2x	1x	1-4x***	0-2x***	-	0-/2x**	-	-
Immunocompromised patients	4x	2–4x	2–4x	1-4x***	0-2x***	-	0-2x**	-	-
Locally advanced/metastasized	4x	4x	2–4x	4x	2x	-	2x	-	-

*For R0 resected stages, Low risk: TD ≤ 6 mm, ≤ 4 mm in desmoplasia, G1–2 differentiation, High risk, TD > 6 mm, > 4 mm in desmoplasia, G3–4 differentiation, perineural tumor growth, immunocompromised and patients with secondary tumors, see question I.3.

**In the case of perineural tumor growth

***Depending on the risk factors

Consensus

Consensus-based recommendation

EC Clinical examination shall be performed regularly in all patients after squamous cell carcinoma of the skin as part of follow-up and shall include inspection of the entire skin organ and inspection and palpation of the primary excision site, in-transit pathway, and regional lymph node station.

Strong consensus

Consensus-based recommendation

Modified 2022

Checked 2022

- **EC** Lymph node ultrasonography should be performed in patients at high risk of metastasis* or with unclear palpation findings and in cases of state after locally advanced and metastatic squamous cell carcinoma of the skin.
 - *High risk: TD > 6 mm, > 4 mm in desmoplasia, G3–4 differentiation, perineural tumor growth, immunosuppressed and patients with secondary tumors.

Strong consensus

Consensus-based recommendation

EC X-ray thoracic examinations and abdominal ultrasonography should not be routinely performed during follow-up.

Strong consensus

Consensus-based recommendation Modified 2022

Modified 2022

EC Cross-sectional imaging should be performed to clarify recurrences, e.g., with suspected involvement of functional structures, in cases of locally advanced or metastatic squamous cell carcinoma of the skin, or in cases of suspected perineural tumor growth or metastatic findings.

Strong consensus



Consensus-based recommendation

New 2022

EC All patients with squamous cell carcinoma of the skin (e.g., even with a tumor thickness of ≤ 2.0 mm without the presence of other risk factors) shall be followed up because of the possible development of secondary skin tumors. The frequency of follow-up should also consider the number of actinic keratoses as well as squamous cell carcinomas of the skin in the history.

Strong consensus

Measures of the primary prevention of actinic keratosis and squamous cell carcinoma of the skin

On this topic, we refer to the detailed S3 guideline "Prevention of skin cancer".⁹

Preventive measures for special risk groups

On this topic, we refer to the detailed S3 guideline "Prevention of skin cancer".⁹

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ACKNOWLEDGEMENTS

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

See long version at www.awmf.org.

REFERENCES

- 1. Heppt MV, Leiter U, Steeb T, et al. 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. *J Dtsch Dermatol Ges.* 2020.18(3):275-294.
- Leiter U, Heppt MV, Steeb T, et al. 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. *J Dtsch Dermatol Ges.* 2020.18(4):400-413.
- Migden MR, Rischin D, Schmults CD, et al. PD-1 Blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med. 2018. 379(4):341-351

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- Rischin D, Migden M, Lim A, Schmults C, Khushalani N, Hughes B, et al. Phase 2 study of cemiplimab in patients with metastatic cutaneous squamous cell carcinoma: primary analysis of fixed-dosing, long-term outcome of weight-based dosing. *J Immunother Cancer*. 2020;8(1):e000775.
- 5. Migden M, Khushalani N, Chang A, Lewis K, Schmults C, Hernandez-Aya L, et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial. *Lancet Oncol.* 2020;21(2):294-305.
- 6. Maubec E, Boubaya M, Petrow P, et al. Phase II study of pembrolizumab as first-line, single-drug therapy for patients with unresectable cutaneous squamous cell carcinomas. *J Clin Oncol*. 2020;38(26):3051-3061.
- 7. Grob J, Gonzalez R, Basset-Seguin N, et al. Pembrolizumab monotherapy for recurrent or metastatic cutaneous squamous cell carcinoma: a single-arm phase ii trial (KEYNOTE-629). *J Clin Oncol*. 2020;38(25):2916-2925.
- 8. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Palliativmedizin für Patienten mit einer nichtheilbaren Krebserkrankung. Langversion 2.2.2020.

9. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft DK. S3-Leitlinie Prävention von Hautkrebs, Langversion 21). 2021; AWMF-Registernummer: 032/052OL.

How to cite this article: Leiter U, Heppt MV, Steeb T, et al. S3 guideline "actinic keratosis and cutaneous squamous cell carcinoma" – update 2023, part 2: epidemiology and etiology, diagnostics, surgical and systemic treatment of cutaneous squamous cell carcinoma (cSCC), surveillance and prevention. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*. 2023;21:1422–1433. https://doi.org/10.1111/ddg.15256