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GUIDELINE

S3 guideline „actinic keratosis and cutaneous squamous cell carcinoma"– update 2023, part 1: treatment of actinic keratosis, actinic cheilitis, cutaneous squamous cell carcinoma in situ (Bowen's disease), occupational disease and structures of care

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For involved societies see long version at www.awmf.org.

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

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this part, we will address aspects relating to AK, actinic cheilitis, Bowen's disease, occupational disease and care structures.

INTRODUCTION

The guideline represents a short version of the complete guideline available at www.awmf.org. Information on epidemiology and etiology, diagnostics, surgical and systemic treatment of cutaneous squamous cell carcinoma (cSCC), surveillance and prevention can be found in part 2 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.

TREATMENT OF ACTINIC KERATOSIS

Indication for treatment and natural course of the disease

See long version at www.awmf.org.

General principles of treatment

See long version at www.awmf.org.

Treatment combinations

	Evidence-based recommendation	Modified 2022
GoR **B**	Concurrent or sequential combinations of distinct field- or lesion-targeted treatments should be offered for actinic keratosis.	
LoE **1**	1: De-novo-research	
	Strong consensus	

Abbr.: GoR, Grade of Recommendation; LoE, Level of Evidence

Ablative and physical procedures

Cryosurgery

See long version at www.awmf.org.

Surgical procedures

See long version at www.awmf.org.

Chemoexfoliation

	Evidence-based recommendation	Modified 2022
GoR **0**	Chemoexfoliation by chemical peelings may be offered for single or multiple actinic keratoses and field cancerization.	
LoE **3**	3: De-novo-research	
	Strong consensus	

Potassium hydroxide

	Evidence-based recommendation	New 2022
GoR **0**	Potassium hydroxide 5% solution may be offered for single or multiple actinic keratoses.	
LoE **3**	3: De-novo-research	
	Strong consensus	

Laser treatment

See long version at www.awmf.org.

Topical drugs

Diclofenac

See long version at www.awmf.org.

5-Fluorouracil

See long version at www.awmf.org.

	Evidence-based recommendation	New 2022
GoR **B**	5-Fluorouracil 4% cream should be offered for single or multiple actinic keratoses and field cancerization.	
LoE **2**	2: De-novo-research	
	Strong consensus	

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5-Fluorouracil with salicylic acid

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Ingenol mebutate

	Evidence-based recommendation	Modified 2022
GoR **A**	Ingenol mebutate shall not be offered for actinic keratosis.	
LoE **2**	2: De-novo-research	
	Strong consensus	

Imiquimod

See long version at www.awmf.org.

Tirbanibulin

	Evidence-based recommendation	New 2022
GoR **B**	Tirbanibulin 1% ointment should be offered for single or multiple actinic keratoses and field cancerization.	
LoE **2**	2: De-novo-research	
	Strong consensus	

Photodynamic therapy

See long version at www.awmf.org.

	Evidence-based recommendation	Modified 2022
GoR **B**	Photodynamic therapy using natural or simulated daylight with 5-aminolevulinic acid (ALA) or its methyl ester (MAL) should be offered for single or multiple actinic keratoses and field cancerization.	
LoE **1**	1: De-novo-research	
	Strong consensus	

Treatment on chronic immunosuppression and in organ transplantat recipients

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Other interventions

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Synopsis of interventions for actinic keratosis (balance sheet)

Intervention	TA	Type and application of the intervention	Anatomical location	Clearance rates[1]	Side-effects and tolerability[2]	Cosmesis[3]	Duration of the treatment[4]	Direct treatment costs per cycle[5]	Practicability[6]		Strength of recommendation and evidence base by subgroups[7]			
									Physician	Patient	Single AK (1–5)	Multiple AK (≥ 6)	Field cancerization	Immune suppression
Cryosurgery	L	One to two freeze-thaw cycles with liquid nitrogen (–196° C) Cold exposure of the target lesions for 15–60 seconds (whitening) Open spray method Contact method (cryo stamp, cryo probe)	Face, scalp Neck Trunk Extremities	++/+++ Lesion-specific clearance rate: 41.9%–88% Patient-specific clearance rate: 25%–90.3%	+++	+/++	⌛	€	++++	+++	↑ 2	↑ 2		
Surgical procedures[6]	L	Curettage ± electrocautery Shave excision Complete excision	Face, Scalp Neck Trunk Extremities	+++ (No data available from RCT)[8]	++ (No data available from RCT)[8]	+/++ (No data available from RCT)[8]	⌛	€–€€	+++	++	↑ EC			↑ EC
Chemo-exfoliation	L+F	Ablation of superficial skin layers using chemical agents (e.g., trichloroacetic acid, Jessner's solution, phenol)	Face, Scalp Neck Trunk Extremities	++ Lesion-specific clearance rate: 31.9% Patient-specific clearance rate: 11.8%–92%	++/+++	+++	⌛	€–€€	++	++	⇔ 3	⇔ 3	⇔ 3	
Dermabrasion[6]	L+F	Mechanical removal of the uppermost skin layers up to the dermoepidermal junction zone	Face, Scalp Neck Trunk Extremities	+ (No data available from RCT)[8]	+ (No data available from RCT)[8]	++ (No data available from RCT)[8]	⌛	€€	+/++	+				
Potassium hydroxide 5% solution (Solcera®)	L	Single and well-defined lesions < 2 cm in diameter Max. 10 lesions 1 cycle: 2 x/day over 14 days, then 14 days treatment-free interval (max. 3 cycles = 12 weeks) Availability as a medical device	Face, Scalp Neck Trunk Extremities	++ Lesion-specific clearance rate: 69.9%–83% Patient-specific clearance rate: 54.9%	+++	++	⌛⌛–⌛⌛⌛	€	+++	++++	⇔ 3	⇔ 3		

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Intervention	TA	Type and application of the intervention	Anatomical location	Clearance rates[1]	Side-effects and tolerability[2]	Cosmesis[3]	Duration of the treatment[4]	Direct treatment costs per cycle[5]	Practicability[6]		Strength of recommendation and evidence base by subgroups[7]			
									Physician	Patient	Single AK (1–5)	Multiple AK (≥ 6)	Field cancerization	Immune suppression
Laser[6]	L+F	Ablative laser treatment (e.g., CO_2 laser, Er:YAG laser)	Face, Scalp Neck Trunk Extremities	++ Lesion-specific clearance rate: 72.4%–91.1% Patient-specific clearance rate: 8%–65.3%	++	++/+++	⌛	€–€€	+++	++	⇔ 2–3	⇔ 2–3	⇔ 2–3	
	L	Non-ablative laser procedures[6] (e.g., Nd:YAG laser, fractional 1540 nm laser)	Face, Scalp Neck Trunk Extremities	++ (No data available from RCT)[8]	+++ (No data available from RCT)[8]	++ (No data available from RCT)[8]	⌛	€–€€	+++	+++	⇔ EC	⇔ EC		

[1]Semiquantitative assessment taking into account lesion- and patient-related response rates: + little effective, ++ moderately effective, +++ effective, ++++ very effective
[2]Semiquantitative assessment taking into account frequency and severity of treatment-related side effects: + poorly tolerated/ many side effects, ++ moderately tolerated, +++ well tolerated, ++++ very well tolerated
[3]Semiquantitative assessment taking into account investigator- and patient-assessed endpoints such as dyspigmentation, improvement of hyperkeratosis, global assessment: + poor, ++ moderate, +++ good, ++++ excellent
[4]⌛ short (< 1 week), ⌛⌛ medium (1–6 weeks), ⌛⌛⌛ long (> 6 weeks)
[5]€ < 100 Euro, €€ 100–500 Euro, €€ > 500 Euro; only direct treatment costs per cycle performed were considered; topical drugs were based on the public pharmacy dispensing prices in Germany (as of August 2021); procedural procedures were based on the assessments of the Gebührenordnung für Ärzte (GOÄ, as of August 2021).
[6]Taking into account expert assessments
[7]Strength of recommendation: Can ⇔, Should ↑, Shall ↑↑; indication of evidence levels according to Oxford 2011.
[8]When applying the mentioned search strategy and inclusion and exclusion criteria
Abbr.: L, lesion-directed; F, field-directed; AK, actinic keratosis; EC, expert consensus; FK, field cancerization; RCT, randomized controlled trial; TA, therapeutic approach

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										Practicability[6]		Strength of recommendation and evidence base by subgroups[7]			
Intervention	**TA**	**Mechanism of action Application**	**Recommended max. area of the treatment field**	**Approval for anatomical location**	**Efficacy[1]**	**Side-effects and tolerability[2]**	**Cosmesis[3]**	**Duration of treatment[4]**	**Immediate treatment costs per cycle[5]**	**Doctor**	**Patient**	**Single AK (1–5)**	**Multiple AK (≥ 6)**	**Field cancerization**	**Immune suppression**
Diclofenac sodium 3% gel (Solaraze®) (Solacutan®) (Diclofenac acis®) (Diclofenac AbZ®) (Diclofenac-ratiopharm®)	F	Cyclooxygenase-2 inhibitors 2 x daily for 60–90 days	8 g/d or max. 200 cm^2	Face and scalp	++ Lesion-specific clearance rate: 51.8%–81.0% Patient-specific clearance rate: 27%–50%	+++/++++	+/+++	⧖⧖⧖	€-€€	++++	++	↑ 1	↑ 1	↑ 2	↑ 3
5-Fluorouracil 5% cream (Efudix®)	F	Cytostatic agent 2 x daily until erosion stage (usually 2–4 weeks) Application with finger cloth or glove No nucleoside analogues (e.g., brivudine, sorivudine) for at least 4 weeks	500 cm^2 (approx. 23 × 23 cm)	Face and scalp Neck Trunk Extremities	+++/++++ Lesion-specific clearance rate: 47%–94% Patient-specific clearance rate: 38%–96%	++	++/++++	⧖⧖	€	+++	+++	↑ 1	↑ 1	↑ 2	
5-Fluorouracil 4% cream (Tolak®)	F	Cytostatic agent 1 x daily for 4 weeks No nucleoside analogues (e.g., brivudine, sorivudine) for at least 4 weeks	None (in studies 240–961 cm^2)	Face and scalp	+++ Patient-specific clearance rate: 80.5%	+++	+++	⧖⧖	€	+++	+++	↑ 2	↑ 2	↑ 2	
5-Fluorouracil 0.5% with salicylic acid 10% in solution (Actikerall®)	F+L	Cytostatic and keratolytic agent 1 x daily until the lesions have cleared completely (max. 12 weeks) No nucleoside analogues (e.g., brivudine, sorivudine) for at least 4 weeks	25 cm^2	Face and scalp Neck Trunk Extremities	+++ Lesion-specific clearance rate: 39.4%–98.7% Patient-specific clearance rate: 55.4%	+++	+++	⧖⧖⧖	€	+++	++	↑ 2	↑ 2	↑ 2	
Ingenol mebutate gel (Picato®)	F	Garden spurge extract (cytotoxic) 0.015% (face and scalp): 1 x daily for 3 consecutive days 0.050% (trunk, extremities): 1 x daily for 2 consecutive days	25 cm^2	Face and scalp Neck Trunk Extremities	+++ Face/scalp: Lesion-specific clearance rate: 62.9%–87.2% Patient-specific clearance rate: 36.4%-61.6% Extremities/trunk: Lesion-specific clearance rate: 73%–100% Patient-specific clearance rate: 22%–54.4%	+ (increased incidence of skin tumors in treatment fields)	++	⧖	€	+++	+++	↓↓ 2	↓↓ 2	↓↓ 2	↓↓ 2

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										Practicability[6]		Strength of recommendation and evidence base by subgroups[7]			
Intervention	**TA**	**Mechanism of action Application**	**Recommended max. area of the treatment field**	**Approval for anatomical location**	**Efficacy[1]**	**Side-effects and tolerability[2]**	**Cosmesis[3]**	**Duration of treatment[4]**	**Immediate treatment costs per cycle[5]**	**Doctor**	**Patient**	**Single AK (1–5)**	**Multiple AK (≥ 6)**	**Field cancerization**	**Immune suppression**
Imiquimod 3.75% cream (Zyclara®)	F	Toll-like receptor 7 agonist 1 x daily for 2 weeks, 2 weeks treatment-free interval, 1 x daily for 2 weeks (interval therapy), apply in the evening before going to bed. per application up to 2 sachets of 250 mg imiquimod cream per sachet	None The treatment area is the entire face or the entire hairless scalp.	Face and scalp	+++ Lesion-specific clearance rate: 34.0%–81.8%	+++	+++	⧖⧖	€€	+++	+++		↑ 2	↑ 2	
Imiquimod 5% cream (Aldara®)	F	Toll-like receptor 7 agonist 3 times a week for 4 weeks, in case of residual lesions for additional 4 weeks (max. 8 weeks), apply in the evening before going to bed (leave for at least 8 h).	Maximum dose is the contents of one sachet (250 mg)	Face and scalp	+++ Lesion-specific clearance rate: 45.1%–93.6% Patient-specific clearance rate: 24%–85%	+++	+++	⧖⧖-⧖⧖⧖	€€	+++	+++	↑ 1	↑ 1	↑ 1	⇔ 2 OLU
ALA red light PDT: ALA nanoemulsion (Ameluz®)	F	Precursor of protoporphyrin (photosensitizer) Pre-treatment, application of ALA, drying for 10 min, light-protective dressing, incubation for 3 h, illumination with suitable red light sources, second cycle after 12 weeks if necessary	Layer thickness approx. 1 mm Lesion or entire cancerized fields of up to 20 cm^2	Face and scalp Neck Trunk Extremities	+++/++++ Lesion-specific clearance rate: 58.0%–94.3% Patient-specific clearance rate: 50%–91%.	++	+++/++++	⧖	€€–€€€	++	++	↑ 1	↑ 1	↑ 1	
ALA red light PDT: ALA patch (Alacare®)	L	Precursor of protoporphyrin (photosensitizer) Apply patch for 4 h, illuminate with red light (37 J/cm^2), no St. John's wort for at least 2 weeks, second cycle if no clearance after 12 weeks	1 patch 4 cm^2 (with 8 mg ALA) Lesion max. 1.8 cm diameter (max. 6 patches per treatment session)	Face and scalp	+++/++++ Lesion-specific clearance rate: 63%–89% Patient-specific clearance rate: 62%–67%	++	++/++++	⧖	€€–€€€	+++		↑ 1	↑ 1	↑ 1	
MAL red light PDT (Metvix®)	F	Precursor of protoporphyrin (photosensitizer) Pre-treatment, application of MAL, occlusive dressing for 3 h, illumination with suitable red light sources, second cycle after 12 weeks if necessary	Layer thickness approx. 1 mm Lesion, for field cancerization up to approximately 20 cm^2	Face and scalp	+++/++++ Lesion-specific clearance rate: 67.1%–90.3 Patient-specific clearance rate: 31.4%–78%	++	+++/++++	⧖	€€–€€€	++/+++	++	↑ 1	↑ 1	↑ 1	↑ 3

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										Practicability[6]		Strength of recommendation and evidence base by subgroups[7]			
Intervention	**TA**	**Mechanism of action Application**	**Recommended max. area of the treatment field**	**Approval for anatomical location**	**Efficacy[1]**	**Side-effects and tolerability[2]**	**Cosmesis[3]**	**Duration of treatment[4]**	**Immediate treatment costs per cycle[5]**	**Doctor**	**Patient**	**Single AK (1–5)**	**Multiple AK (≥ 6)**	**Field cancerization**	**Immune suppression**
ALA daylight PDT (Ameluz®)	F	Precursor of protoporphyrin (photosensitizer) Application of chemical light protection filter, after 15 min pre-treatment, application of ALA without occlusion, within 30 min exposure to natural daylight for 2 h, second cycle after 12 weeks if necessary	None (apply thin layer) Lesion or entire cancerized fields	Face and scalp	+++ Patient-specific clearance rate: 27.5% 42.9% Lesion-specific clearance rate: 79.7% 79.8%	+++/++++	+++	⌛	€€	++	++++	↑ 1	↑ 1	↑ 1	
MAL daylight PDT (Metvix®) (Luxerm®)	F	Precursor of protoporphyrin (photosensitizer) Application of chemical light protection filter, after pre-treatment drying, application of MAL without occlusion, within 30 min exposure to natural or simulated daylight (Metvix® only) for 2 h, second cycle after 12 weeks if necessary	None (apply thin layer) Lesion and/or field cancerization	Face and scalp	+++ Patient-specific clearance rate: 27.5%–38.8% Lesion-specific clearance rate: 77.2%–89.2%	+++/++++	+++	⌛	€€	++	++++	↑ 1	↑ 1	↑ 1	
Tirbanibulin (Klisyri®)	F	Topical microtubule inhibitor 1 x/d over 5 consecutive days	25 cm^2	Face and scalp	++/+++ Patient-specific clearance rate: 44%–54% Lesion-specific clearance rate: 76%–82%	+++/++++	+++	⌛	€€	+++	+++	↑ 2	↑ 2	↑ 2	

[1] Semiquantitative assessment taking into account lesion- and patient-related response rates: + little effective, ++ moderately effective, +++ effective, ++++ very effective
[2] Semiquantitative assessment taking into account frequency and severity of therapy-mediated side effects: + poorly tolerated/ many side effects, ++ moderately tolerated, +++ well tolerated, ++++ very well tolerated
[3] Semiquantitative assessment considering investigator- and patient-assessed endpoints such as dyspigmentation, improvement of hyperkeratosis, global assessment: + poor, ++ moderate, +++ good, ++++ excellent
[4] ⌛ short (< 1 week), ⌛⌛ medium (1–6 weeks), ⌛⌛⌛ long (> 6 weeks)
[5] € < 100 Euro, €€ 100–500 Euros, €€ > 500 Euros; only direct treatment costs per cycle performed were considered; topical drugs were based on the public pharmacy dispensing prices in Germany (as of August 2021); procedural procedures were based on the assessments of the Gebührenordnung für Ärzte (GOÄ, as of August 2021).
[6] Taking into account expert opinions
[7] Strength of recommendation: May ⇔, Should ↑ Shall ↑↑; indication of evidence levels according to Oxford 2011
Abbr.: L, lesion-directed; F, field-directed; AK, actinic keratosis; OLU, off-label use; TA, treatment approach

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Treatment of actinic cheilitis

Indication for treatment and natural course of the disease

	Consensus-based recommendation	New 2022
EC	The indication for the treatment of actinic cheilitis should be made based on the clinical presentation, risk factors (e.g., immunosuppression, cumulative UV exposure, involvement of the entire lower lip, involvement also of the upper lip), comorbidities, life expectancy, and patient desire.	
	Strong consensus	

	Consensus-based recommendation	New 2022
EC	Prior to treatment, a biopsy should be obtained for diagnostic confirmation and to exclude invasive squamous cell carcinoma of the lip.	
	Consensus	

	Consensus-bases recommendation	New 2022
EC	A biopsy should be obtained if there is clinical evidence of a lack of response or incomplete response to treatment.	
	Strong consensus	

Abbr.:EC, expert consensus.

General principles of treatment

See long version at www.awmf.org.

Surgical procedures

	Evidence-based recommendation	New 2022
GoR **A**	Surgical treatment of actinic cheilitis (e.g., by vermilionectomy or lip shave with histologic assessment and analysis of resection margins) shall be offered for extensive involvement of the lip.	
LoE **1**	1: De-novo-research	
	Consensus	

Ablative procedures

Laser treatment

	Evidence-based recommendation	New 2022
GoR **0**	Ablative laser treatment (e.g., CO_2, Er:YAG) may be offered for actinic cheilitis.	
LoE **1**	1: De-novo-research	
	Strong consensus	

	Consensus-based statement	New 2022
EC	No recommendation for non-ablative laser treatment of actinic cheilitis can be made due to insufficient data.	
	Strong consensus	

Cryosurgery

	Consensus-based statement	New 2022
EC	The data available on cryosurgery do not allow a conclusive recommendation for the treatment of actinic cheilitis.	
	Strong consensus	

Chemoexfoliation

	Consensus-based recommendation	New 2022
EC	Chemical peelings should not be used for the treatment of actinic cheilitis due to a lack of evidence for clinical benefit.	
	Strong consensus	

Topical drugs

Diclofenac

	Evidence-based recommendation	New 2022
GoR **0**	Diclofenac sodium 3% gel may be offered for the treatment of actinic cheilitis.	
LoE **2**	2: De-novo-research	
	Strong consensus	

5-Fluorouracil

	Consensus-based statement	New 2022
EC	No evidence-based recommendation for the treatment of actinic cheilitis with 5-fluorouracil can be made due to insufficient data.	
	Strong consensus	

Imiquimod

	Consensus-based statement	new 2022
EC	No evidence-based recommendation for the treatment of actinic cheilitis with imiquimod 5% and 3.75% cream can be made due to insufficient data.	
	Strong consensus	

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Photodynamic therapy

	Evidence-bases recommendation	New 2022
GoR **B**	Photodynamic therapy with illumination by red light and 5-aminolevulinic acid (ALA) or its methyl ester (MAL) should be offered for the treatment of actinic cheilitis.	
LoE **1**	1: De-novo-research	
	Strong consensus	

	Evidence-based recommendation	New 2022
GoR **B**	Methyl aminolevulinate (MAL) in combination with illumination by natural or simulated daylight (MAL daylight PDT) should be offered for the treatment of actinic cheilitis.	
LoE **3**	3: De-novo-research	
	Strong consensus	

Treatment combinations

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Synopsis of interventions for actinic cheilitis (balance sheet)

Intervention	TA	Mechanism of action & application	Efficacy[1]	Side effects and tolerability[2]	Cosmesis[3]	Duration of the treatment[4]	Direct treatment costs per cycle[5]	Practicability[6]		Strength of recommendations and evidence base[7]
								Physician	Patient	
Ablative procedures										
Cryosurgery	L	1 to 2 freeze-thaw cycles with liquid nitrogen (–196° C) Cold exposure of the target lesions for 15–60 seconds "whitening) Open spray method Contact method (cryo stamp, cryo probe)	++/+++ (No data available from RCT)[8]	++	+	⌛	€	++++	+++	~ EC
Surgical procedures with histological assessment[6]	F	Complete excision, vermilionectomy, lip shave	++++ (No data available from RCT)[8]	++ (No data available from RCT)[8]	++ (No data available from RCT)[8]	⌛	€–€€	+++	++	↑↑ 1–3
Surgical procedures without histological assessment[6]	F	Electrodesiccation, dermabrasion	+ (No data available from RCT)[8]	+ (No data available from RCT)[8]	+/++ (No data available from RCT)[8]	⌛	€–€€	+/++	+	~ EC
Chemoexfoliation	F	Ablation of superficial skin layers using chemical agents (e.g., 50% trichloroacetic acid)	+ Clearance rate: 30%	+/++	++	⌛	€–€€	++	++	~ 1–4
Laser treatment[6]	F	Ablative laser treatment (e.g., CO_2 -, Erbium YAG laser)	+++ Clearance rate: 93.4%	++	++/+++	⌛	€€€	+++	++	⇔ 2–3
		Non-ablative laser treatments[6] (e.g., Nd:YAG laser, fractional 1540 nm laser)	+ (No data available from RCT)[8]	++ (No data available from RCT)[8]	++ (No data available from RCT)[8]	⌛	€€€	+++	+++	~ EC
Topical drugs and drug-based procedures										
Diclofenac sodium 3% gel (Solaraze®), (Solacutan®), (diclofenac acis®), (Diclofenac AbZ®), (Diclofenac-ratiopharm®) Off-label use	F	Cyclooxygenase-2 inhibitor 2 x daily for 60–90 days; max. 8 g/d for up to 200 cm^2	++ Clearance rate: 45.2%	+++/ ++++	+/+++	⌛⌛⌛	€-€€	++++	++	⇔ 2–3
5-Fluorouracil 5% cream (Efudix®) Off-label use	F	Cytostatic drug 2 x daily for max. 4 weeks; max. 500 cm^2 (approx. 23 × 23 cm)	+++/++++ Clearance rate: 50%–68.2%	++	++/++++	⌛⌛	€-€€	+++	+++	~ EC
Imiquimod 3.75% cream (Zyclara®) Off-label use	F	Toll-like receptor 7 agonist 1 x daily for 2 weeks, 2 weeks treatment-free interval, 1x daily for 2 weeks (interval therapy) per application up to 2 sachets of 250 mg imiquimod cream per sachet	+	++	+++	⌛⌛	€€	+++	+++	~ EC

(Continues)

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Intervention	TA	Mechanism of action & application	Efficacy[1]	Side effects and tolerability[2]	Cosmesis[3]	Duration of the treatment[4]	Direct treatment costs per cycle[5]	Practicability[6]		Strength of recommendations and evidence base[7]
								Physician	Patient	
Imiquimod 5% cream (Aldara®) Off-label use	F	Toll-like receptor 7 agonist 3 x weekly for 4 weeks Recommended maximum dose is the contents of one sachet	++ Clearance rate: 40%–73.3%	++	+++	⌛⌛	€€	+++	+++	~ EC
ALA red light PDT (Alacare®)	F, L	Prodrug of protoporphyrin (photosensitizer) Application of ALA-containing patch for 4 h, illumination with red light for approx. 10–20 min, if necessary, repeat after 4–12 weeks Alacare® 4 cm^2 (max. 6 patches)	+++/++++ Clearance rate: 66.6%–84.2%	++	+++/++++	⌛	€€-€€€	++/+++	++	↑ 2–3
ALA red light PDT (Ameluz®) Off-label use	F	Prodrug of protoporphyrin (photosensitizer) Application of ALA, light-protective bandage for 3 h, illumination with red light for approx. 10–20 min, if necessary repeat after 4–12 weeks	+++/++++ Clearance rate: 58.0%–80%	++	+++/++++	⌛	€€-€€€	++/+++	++	↑ 2–3
MAL red light PDT (Metvix®)	F	Prodrug of protoporphyrin (photosensitizer) Application of MAL, light protection and occlusive dressing for 3 h, illumination with red light for approx. 10–20 min, repeat after 4–12 weeks if necessary	+++/++++ Clearance rate: 47%–62.5%	++	+++/++++	⌛	€€-€€€	++/+++	++	↑ 2–3
MAL daylight-PDT (Luxerm®), (Metvix®)	F	Prodrug of protoporphyrin (photosensitizer) Application of chemical photoprotective filter and MAL. Daylight exposure for 2 h Conditions: > 10°C outdoor temperature, cloudless to overcast sky, no rain	+++ Clearance rate: 80%–91%	++++	+++	⌛	€€	++	++++	↑ 3

[1]Semiquantitative assessment taking into account lesion- and patient-related response rates (+ = little effective, ++ = moderately effective, +++ = effective, ++++ = very effective)
[2]Semiquantitative assessment taking into account frequency and severity of treatment-mediated side effects (+ = poorly tolerated/many side effects, ++ = moderately tolerated, +++ = well tolerated, ++++ = very well tolerated)
[3]Semiquantitative assessment considering investigator- and patient-assessed outcomes such as dyspigmentation, improvement of hyperkeratosis, global assessment (+ = predominantly poor, ++ = predominantly moderate, +++ = predominantly good, ++++ = predominantly excellent).
[4]⌛ = short (< 1 week), ⌛⌛ = medium (1–6 weeks), ⌛⌛⌛ = long (> 6 weeks)
[5]€ = < 100 Euro, €€ = 100–500 Euro, €€ = > 500 Euro; only direct treatment costs per cycle performed were considered; public pharmacy dispensing prices in Germany (as of August 2021) were used as the basis for topical drug procedures; procedural procedures were based on the valuations of the Gebührenordnung für Ärzte (GOÄ, as of August 2021)
[6]Taking into account expert opinions
[7]Strengths of recommendation: May = ⇔, Should = ↑, Shall = ↑↑; ~ no recommendation if data / evidence base is unclear; indication of evidence levels according to Oxford 2011
[8]When applying the mentioned search strategy and inclusion and exclusion criteria
Abbr.: L, lesion-directed; F, field-directed; AK, actinic keratosis; EC, expert consensus; RCT, randomized controlled trial; TA, treatment approach

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TREATMENT OF CUTANEOUS SQUAMOUS CELL CARCINOMA IN SITU (BOWEN'S DISEASE)

Clinical presentation and natural course of the disease

See long version at www.awmf.org.

Indication for treatment and treatment approaches

	Consensus-based recommendation	New 2022
EC	Prior to treatment of Bowen's disease, a biopsy should be obtained to exclude invasive squamous cell carcinoma of the skin, other skin neoplasms, or inflammatory conditions. If there is clinical evidence of a lack of response or incomplete response to treatment, a biopsy with histologic assessment should be performed.	
	Strong consensus	

Surgical procedures

	Consensus-based recommendation	New 2022
EC	Surgical removal of Bowen's disease (e.g., by shave excision or complete excision) should be offered for single lesions.	
	Strong consensus	

Ablative procedures

Cryosurgery

	Consensus-based recommendation	New 2022
EC	Cryosurgery may be offered for the treatment of Bowen's disease.	
	Consensus	

Ablative laser treatment

	Evidence-based recommendation	New 2022
GoR 0	Ablative laser treatment may be offered for the treatment of Bowen's disease.	
LoE 2	2: De-novo-research	
	Consensus	

Topical drugs

5-Fluorouracil

	Evidence-based recommendation	New 2022
GoR B	5-Fluorouracil 5% cream should be offered for the treatment of Bowen's disease.	
LoE 2	2: De-novo-research	
	Consensus	

Imiquimod

	Evidence-based recommendation	New 2022
GoR 0	Imiquimod 5% cream may be offered for the treatment of Bowen's disease in immunocompetent patients. The lack of approval for this indication should be considered.	
LoE 2	2: De-novo-Recherche	
	Consensus	

Photodynamic therapy

	Evidence-based recommendation	New 2022
GoR B	Photodynamic therapy with illumination by red light should be offered for the treatment of Bowen's disease, performed as two treatment cycles within 4 weeks.	
LoE 1	1: De-novo-research	
	Strong consensus	

	Evidence-based recommendation	New 2022
GoR 0	Pretreatment (e.g., with ablative fractional laser, microneedling) may be offered prior to photodynamic therapy with illumination by red light to enhance drug penetration.	
LoE 2	2: De-novo-research	
	Strong consensus	

OCCUPATIONAL DISEASES OF ACTINIC KERATOSIS AND CUTANEOUS SQUAMOUS CELL CARCINOMA

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Structures of care

Certified skin cancer centers

See long version at www.awmf.org.

Quality indicators

See long version at www.awmf.org.

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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.
2. 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.

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