Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2018-B-050 Cemiplimab

Stand: Mai 2018

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Cemiplimab
[Behandlung des kutanen Plattenepithelkarzinoms]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Keine zugelassenen Arzneimittel*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*Strahlentherapie*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	*Es liegen keine Beschlüsse im Anwendungsgebiet vor.*
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Cemiplimab N.A. N.A.	<u>Geplantes Anwendungsgebiet laut Beratungsanforderung:</u> „Cemiplimab ist indiziert als Monotherapie zur Behandlung von Patienten mit metastasiertem kutanen Plattenepithelkarzinom (metastatic cutaneous squamous cell carcinoma, mcSCC) oder Patienten mit lokal fortgeschrittenem kutanen Plattenepithelkarzinom (locally advanced cSCC, lacSCC), die für eine Operation nicht in Betracht kommen.“
keine zugelassenen Arzneimittel im Anwendungsgebiet	

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2018-B-050 (Cemiplimab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	25. April 2018

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DAHTA	DAHTA Datenbank
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Monotherapie zur Behandlung von Patienten mit metastasiertem kutanen Plattenepithelkarzinom (metastatic cutaneous squamous cell carcinoma, mcSCC) oder Patienten mit lokal fortgeschrittenem kutanen Plattenepithelkarzinom (locally advanced cSCC, lacSCC), die für eine Operation nicht in Betracht kommen.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation Plattenepithelkarzinom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 27.03.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 400 Quellen, die anschließend in einem zweistufigen Screening Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 7 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 IQWiG Berichte/G-BA Beschlüsse

Es wurden keine relevanten Quellen identifiziert.

3.2 Cochrane Reviews

Es wurden keine relevanten Quellen identifiziert.

3.3 Systematische Reviews

Es wurden keine relevanten Quellen identifiziert.

3.4 Leitlinien

Breuninger H et al., 2013 [1].

Deutsche Krebsgesellschaft (DKG), Deutsche Dermatologische Gesellschaft (DDG), Arbeitsgemeinschaft Wissenschaftlicher Medizinischer Fachgesellschaften (AMWF)

Kurzleitlinie - Plattenepithelkarzinom der Haut; Update 2012

Leitlinienorganisation/Fragestellung

Leitlinien zur standardisierten Diagnostik, Therapie und Nachbehandlung sollen dazu beitragen, den Wissensstand der behandelnden Ärztinnen und Ärzte* zu aktualisieren und damit die Ergebnisqualität bei der Versorgung von Patienten mit dieser Erkrankung zu verbessern. Insbesondere soll der Anteil nicht sachgerecht exzidierter oder anderweitig nicht sachgerecht behandelter Plattenepithelkarzinome der Haut, und damit die Lokalrezidivrate, gesenkt werden.

Methodik

Grundlage der Leitlinie

- Vielzahl an beteiligten Berufsgruppen
- Patientenbeteiligung nicht gegeben, da keine Selbsthilfegruppe identifizierbar
- Evidenzbasierung: Formulierung von Schlüsselfragen, keine formale methodische Bewertung der Literatur
- Formulierung der Empfehlungen, Konsensfindung: Die Verabschiedung und Graduierung von Empfehlungen in sprachlicher Form (soll /sollte / kann) erfolgte im Rahmen von Konsensuskonferenzen unter Verwendung eines formalen Konsensusverfahren (nominaler Gruppenprozess). Pro Empfehlung/Statement fand eine Abstimmung statt
- Darlegung der Leitliniengruppe; Interessenskonflikte dargelegt; Finanzierung dargelegt

Recherche/Suchzeitraum:

- keine systematische Literaturrecherche, orientierende Recherchen in Medline

LoE

- Da keine systematische Recherche, Selektion, Bewertung und Synthese der Evidenzgrundlage erfolgte, wurden keine Evidenzlevel vergeben.

GoR

Beschreibung	**Syntax**
Starke Empfehlung	soll
Empfehlung	sollte
Empfehlung offen	kann

Sonstige methodische Hinweise

- Gültigkeit der LL bis 30.12.2018 verlängert, geprüft am 20.04.2016
- Ein Upgrade der Leitlinie nach S3 ist geplant
- keine systematische Literaturrecherche, orientierende Recherchen in Medline, keine formale methodische Bewertung der Literatur
- „Leitlinie erfüllt nicht die methodischen Anforderungen einer S3 Leitlinie. Die LL wurde jedoch aufgrund fehlender höherwertiger Evidenz ergänzend dargestellt."

1. Lokoregionäre Therapie

Statement

Verschiedene histologische Subtypen des Plattenepithelkarzinoms der Haut wurden beschrieben. Derzeit ist keine hinreichend evidenzbasierte Aussage darüber möglich, ob diese mit einer erhöhten Metastasierungswahrscheinlichkeit einhergehen. Daher sollten alle histologischen Subtypen des Plattenepithelkarzinoms der Haut gleichartig therapiert werden.

Empfehlung („kann"-Empfehlung offen)

Die vollständige chirurgische Exzision mit topografisch zugeordneter histologischer Kontrolle der Schnittränder (mikroskopisch kontrollierte Chirurgie – MKC) ist die Therapie der ersten Wahl für das Plattenepithelkarzinom der Haut. Alternativ kann eine Operation mit tumoradaptiertem Sicherheitsabstand und konventioneller Histologie erfolgen, bei superfiziellen Plattenepithellkarzinomen auch durch Horizontalexzision („Shave-Exzision") mit konventioneller Histologie.

Empfehlung („sollte"-Empfehlung offen)

Bei lokal nicht in sano resezierbaren Tumoren oder inoperablen Patienten sollte die Strahlentherapie als Behandlungsmethode der ersten Wahl durchgeführt werden.

Empfehlung („sollte"-Empfehlung offen)

Alternative Therapieverfahren – bei multiplen oder superfiziellen Plattenepithelkarzinomen - wie die Elektrodesikkation, Kürettage, Kryotherapie, Lasertherapie und photodynamische Therapie sowie lokale medikamentöse Behandlungen mit Imiquimod oder 5-Fluorouracil sollten Einzelfällen vorbehalten bleiben.

1.1. Strahlentherapie

Empfehlung („kann“-Empfehlung offen)

[…]. Bei Inoperabilität oder non in sano-Resektion besteht die Indikation einer Strahlenbehandlung. Dies gilt auch für die Karzinome der Hautanhangsgebilde. Bei zu erwartender R1, R2 Resektion oder wenn eine Nachresektion nicht möglich ist, kann einer alleinigen oder zusätzlichen Bestrahlung der Vorzug gegeben werden. Die Brachytherapie kann eine sinnvolle Alternative zur konventionellen Strahlentherapie darstellen. Eine Strahlenbehandlung bei Karzinomen auf vorgeschädigter Haut und bei immusupprimierten Patienten ist im Hinblick auf Indikationsstellung und Strahlendosis kritisch zu bewerten. Plattenepithelkarzinome an Ohr, Lippe oder Nasenspitze sollten primär nicht bestrahlt, sondern einer chirurgischen Therapie zugeführt werden.

Quelle:
15. Mendenhall WM, Amdur RJ, Hinerman RW, et al.: Radiotherapy for cutaneous squamous and basal cell carcinomas of the head and neck. Laryngoscope 119:1994-1999, 2009

Systemische Therapie bei inoperablen Metastasen

Statement

Derzeit existiert keine ausreichend evidenzbelegte systemische Therapie für das metastasierte Plattenepithelkarzinom der Haut.

Empfehlung 1 („sollte“-Empfehlung)

Eine systemische Therapie des metastasierten Plattenepithelkarzinoms der Haut sollte möglichst im Rahmen von klinischen Studien erfolgen.

Empfehlung 2 („sollte“-Empfehlung)

Die Polychemotherapie mit Cisplatin und 5-Fluorouracil (oder orale Analoga) sollte die Therapie der ersten Wahl für das metastasierte Plattenepithelkarzinom der Haut sein. Bei Patienten mit eingeschränktem Allgemeinzustand kann eine Monochemotherapie mit 5-Fluorouracil (oder orale Analoga) in Erwägung gezogen werden. Bei Nichtansprechen der Therapie kann eine Therapie mit Cetuximab in Erwägung gezogen werden.

Erläuterung:

Die Ansprechraten von metastasierten Plattenepithelkarzinomen der Haut auf chemotherapeutische Behandlungen sind hoch. Die Remissionsraten betragen bei Monotherapie mit 5-Fluorouracil ca. 60% und sind bei der Verwendung von Polychemotherapieschemata mit bis zu 80% deutlich höher (Tabelle 4) (17-19). Die historisch anzusehende Monotherapie mit Methotrexat zeigt exemplarische Ansprechraten von 20-40%. Sie sind durch entsprechend Studien jedoch nicht belegt. Die Behandlung ist nicht kurativ, Rezidive sind regelhaft. Hinsichtlich des Gesamtüberlebens scheint die Anwendung der kombinierten Schemata gegenüber den Monotherapien keine Vorteile zu bieten. Neuere Therapieschemata zielen auf die Blockade des „Epidermal Growth Factor“- Rezeptors ab. Der Tyrosinkinase-Inhibitor Gefitinib zeigte in einem Kollektiv von 15 auswertbaren Patienten keine objektiven Ansprechraten (Stabilisierung in 27%) (20). Der monoklonale IgG1-Antikörper Cetuximab erzielte in einer Studie mit 36 Patienten eine objektive Ansprechrate von 28% (6% CR, 22% PR) und eine Stabilisierung in 42% (Tabelle 4) (21), ist jedoch in Deutschland nicht für das Plattenepithelkarzinom der Haut zugelassen. Da kein Standardschema existiert, sollte eine Chemo- bzw. Immuntherapie möglichst im Rahmen von Studien erfolgen. Zur Vermeidung von Toxizitäten sollte insbesondere die Chemotherapie bei älteren Patienten von

einer intensiven Supportivtherapie begleitet werden. Insbesondere bei einer eingeschränkten Nieren oder Leberfunktion müssen die Dosen angepasst werden und bei aggressiven Kombinationstherapien kann der Einsatz von hämatopoetischen Wachstumsfaktoren notwendig werden. Überdies ist auf eine ausreichende Antiemese und Schmerztherapie zu achten.

Quellen:
17. Cartei G, Cartei F, Interlandi G, et al.: Oral 5-fluorouracil in squamous cell carcinoma of the skin in the aged. Am J Clin Oncol 23:181-184, 2000 18. Sadek H, Azli N, Wendling JL, et al.: Treatment of advanced squamous cell carcinoma of the skin with cisplatin, 5-fluorouracil, and bleomycin. Cancer 66:1692-1696, 1990
19. Khansur T, Kennedy A: Cisplatin and 5-fluorouracil for advanced locoregional and metastatic squamous cell carcinoma of the skin. Cancer 67:2030-2032, 1991
20. Glisson BS, Kim ES, Kies MS, et al.: Phase II study of gefitinib in patients with metastatic/recurrent squamous cell carcinoma of the skin. J Clin Oncol ASCO Annual Meeting Proceedings Part I. Vol 24, 2006
21. Maubec E, Petrow P, Scheer-Senyarich I,Duvillard P, et al.: Phase II Study of Cetuximab as first-line single-drug therapy in patients with unresectablesquamous cell carcinoma of the skin: J Clin Oncol 29,3419-26, 2011

SIGN, 2014 [6].

Scottish Intercollegiate Guidelines Network (SIGN)

Management of primary cutaneous cell carcinoma. A national clinical guideline

Leitlinienorganisation/Fragestellung

k.A.

Methodik

Grundlage der Leitlinie

- The evidence base for this guideline was synthesised in accordance with SIGN methodology
- The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline.
- Statement of all members of the guideline group (name and affiliation)
- Declaration of interest
- Consultation and peer review process and internal review of the recommendations

Recherche/Suchzeitraum:

- A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2007-2012. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence evaluated each of the selected papers.

LoE

KEY TO EVIDENCE STATEMENTS AND RECOMMENDATIONS	
LEVELS OF EVIDENCE	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GoR

RECOMMENDATIONS	
Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation). The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher quality evidence is more likely to be associated with strong recommendations than lower quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation. Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.	
R	For '**strong**' recommendations on interventions that 'should' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm.
R	For '**conditional**' recommendations on interventions that should be 'considered', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.
GOOD PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group

Sonstige methodische Hinweise

- This guideline was published in 2014 and will be considered for review in three years.

1. surgical techniques

standard surgical excision (LoE: 3)

R	**For high-risk tumours a clinical peripheral margin of 6 mm or greater is indicated, where surgically achievable and clinically appropriate.** **For low-risk tumours a clinical peripheral margin of 4 mm or greater is indicated where surgically achievable and clinically appropriate.**

Mohs micrographic surgery (LoE: 3)

R	**Mohs micrographic surgery should be considered at the multidisciplinary team meeting, for selected patients with high-risk tumours where tissue preservation or margin control is challenging, and on an individual case basis for patients with any tumour at a critical anatomical site.**

2. destructive techniques

CURETTAGE AND CAUTERY (LoE: 3)

R	**Curettage and cautery can be considered for patients with low-risk SCCs, if healthcare professionals have had appropriate training with a blunt curette.**
✓	Curettage and cautery is not suitable for high-risk SCC and should not be used where there are any high-risk clinical features.

A meta-analysis identified eight retrospective case series examining outcomes following curettage (with a blunt curette) plus cautery (also referred to as electrodessication). Pooled average recurrence (the nature of which was unspecified) from seven of the studies (n=1,131) was 1.7% (95% CI 0.6% to 3.4%). In this pooled analysis 91% of the tumours had a horizontal diameter <20 mm. One series reported using two treatment cycles and one using three but most series did not indicate the number of treatment cycles.[69]

Quelle:
69. Lansbury L, Bath-Hextall F, Perkins W, Stanton W, Leonardi-Bee J. Interventions for non-metastatic squamous cell carcinoma of the skin: a systematic review and pooled analysis of observational studies. BMJ 2013 347:f6153.

photodynamic therapy (LoE: 2+)

R	Photodynamic therapy should not be used for treatment of primary squamous cell carcinoma.

A meta-analysis identified 14 small prospective studies of photodynamic therapy using topical or systemic photosensitisers. Eight of the studies examined outcomes following apparent complete response and the pooled odds of recurrence at six to 38 months were 26.4% (95% CI 12.3% to 43.7%) based on 119 tumours.[69]

Quelle:
69. Lansbury L, Bath-Hextall F, Perkins W, Stanton W, Leonardi-Bee J. Interventions for non-metastatic squamous cell carcinoma of the skin: a systematic review and pooled analysis of observational studies. BMJ 2013 347:f6153.

3. chemotherapy

systemic chemotherapy (LoE: 4)

✓	Systemic chemotherapy for the management of patients with primary cutaneous SCC should not be used outside of a clinical trial. Systemic chemotherapy may be appropriate for patients with metastatic SCC.

Evidence on the use of systemic chemotherapy, either alone or in combination with radiotherapy in the management of cutaneous SCC is mainly from small case series. A review highlights how chemotherapy has been used neoadjuvantly, either prior to surgery or radiotherapy for advanced high-risk tumours. This strategy has been applied to squamous cell cancers at other sites such as the head and neck and anus but the evidence in cutaneous SCC is based on small case series. Agents that have been used include cisplatin, vindesine, mitomycin C, 5-fluorouracil, methotrexate, bleomycin, interferon and doxorubicin. The review included one small randomised study (n=36) of adjuvant 13-cis-retinoic acid and interferon in patients with high-risk features following surgery, which failed to demonstrate any benefit compared to a control group.[79] Chemotherapy has been added to postoperative radiotherapy in patients with high-risk tumours but the only randomised controlled studies pertain to head and neck tumours and there is insufficient evidence to recommend this for cutaneous SCC.[30]

Quellen:
30. Bonerandi JJ, Beauvillain C, Caquant L, Chassagne JF, Chaussade V, Clavere P, et al. Guidelines for the diagnosis and treatment of cutaneous squamous cell carcinoma and precursor lesions. J Eur Acad Dermatol Venereol 2011;25 Suppl 5:1-51.
79. DeConti RC. Chemotherapy of squamous cell carcinoma of the skin. Semin Oncol 2012;39(2):145-9.

4. radiotherapy

primary radiotherapy

R **Primary radiotherapy should be considered for individual patients where surgical excision would be extremely challenging or difficult to perform or would be likely to result in an unacceptable functional or aesthetic outcome.**

✓ Radiotherapy should be delivered by a clinical oncologist with a special interest in the management of skin cancer including SCC.

A meta-analysis identified one prospective and 13 retrospective studies of primary radiotherapy in patients with SCC. Radiation sources included orthovoltage, megavoltage or electron therapy. Dose, fractionation and fields were not uniformly reported and were variable. Follow up ranged from less than six months to over ten years and the prognostic features (size, site and stage) of the tumours varied widely. Local recurrence was 6.4% (95% CI 3.0% to 11.0%) based on seven studies (n=761). Disease-specific death was 9.1% (95% CI 1.4% to 22.8%) based on five studies (n=191).[69] LoE: 2+

A meta-analysis identified four prospective and two retrospective studies (n=88) examining a range of brachytherapy techniques. Local recurrence was 5.2% (95% CI 1.6% to 10.5%) with a range of follow-up periods with a median of 55 months.[69] LoE: 2+

Previous guidelines recommend that radiotherapy should be used with caution on sites where the intervention is poorly tolerated such as the back of the hand, lower limb and where the tumour invades bone or cartilage. There are contraindications related to long term cosmesis in younger patients and the potential for radiation-induced second malignancy.[37] LoE: 4

Radiotherapy is contraindicated in patients with previously irradiated sites and with genodermatoses predisposing to skin cancer.[37] LoE: 4

Radiotherapy may be particularly indicated in older patients where comorbidities or significant risks associated with general anaesthetic prevent consideration of surgery. It may also be suitable where a patient has anxiety disorder or is intolerant to local anaesthetic.[30] LoE: 4

Quellen:
30. Bonerandi JJ, Beauvillain C, Caquant L, Chassagne JF, Chaussade V, Clavere P, et al. Guidelines for the diagnosis and treatment of cutaneous squamous cell carcinoma and precursor lesions. J Eur Acad Dermatol Venereol 2011;25 Suppl 5:1-51.
37. Motley RJ, Preston PW, Lawrence CM. Multi-professional Guidelines for the Management of the Patient with Primary Cutaneous Squamous Cell Carcinoma. London: British Association of Dermatology (BAD); 2009.
69. Lansbury L, Bath-Hextall F, Perkins W, Stanton W, Leonardi-Bee J. Interventions for non-metastatic squamous cell carcinoma of the skin: a systematic review and pooled analysis of observational studies. BMJ 2013 347:f6153

Sapijaszko M et al., 2015 [5].

Non-melanoma Skin Cancer in Canada Chapter 5: Management of Squamous Cell Carcinoma

Siehe auch Guenther, LC et al., 2015 [2].

Leitlinienorganisation/Fragestellung

The aim of this document is to provide guidance to Canadian health care practitioners on NMSC management.

Methodik

Grundlage der Leitlinie

- The Canadian Non-Melanoma Skin Cancer Guidelines Committee comprises 10 dermatologists and dermatologic surgeons tasked with the development of evidence-based guidelines on the prevention and management of AKs, SCCs, and BCCs.
- The relevant publications were categorized according to type of lesion (eg, high-risk SCC) and treatment modality (eg, photodynamic therapy). Each study was formally evaluated by 3 members of the Committee, using GRADE
- Studies rated as “moderate” quality or better by at least 1 Committee member served as the core literature for each of the treatment chapters
- The final document was finalized by the chairs, after community review, and approved by all 10 Committee members.
- Patientenbeteiligung nicht gegeben
- Endorsers and sponsors were not party to the development of the guidelines and were not involved in the literature search, the selection of Committee members, or the drafting of text, recommendations, or algorithms.
- The final guidelines chapters were circulated to potential endorsing bodies, which made no changes to the text.

Recherche/Suchzeitraum:

- systematische Literaturrecherche in PubMed (im August 2012)

LoE

Table 2. The GRADE System for Classifying the Quality of Evidence.[a]

Level of Evidence	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Abbreviation: GRADE, Grading of Recommendations Assessment, Development and Evaluation.
[a]In addition, for statements based purely on biologic plausibility or other indirect arguments, the level of evidence could be identified as "NA," indicating that direct support for the claim is not available.

GoR

Table 3. Rating the Strength of Recommendations.

Strength of Recommendation	Definition
Strong	For intervention: desirable effects outweigh undesirable effects Against intervention: undesirable effects outweigh desirable effects
Weak	For intervention: desirable effects probably outweigh undesirable effects Against intervention: undesirable effects probably outweigh desirable effects, but appreciable uncertainty exists

Sonstige methodische Hinweise

- Evidenzbasis: Randomized controlled trials for SCC are uncommon, especially head-to-head comparison studies. Recurrent and otherwise high-risk SCCs are not well studied.
- „Leitlinie erfüllt nicht die methodischen Anforderungen einer S3 Leitlinie. Die LL wurde jedoch aufgrund fehlender höherwertiger Evidenz ergänzend dargestellt."

Empfehlungen:

The complete removal of the SCC lesion along with preservation of function and cosmesis is best achieved through surgical methods that allow identification of tumour margins via histologic assessment. Specifically, fixed-margin surgical excision and MMS are the cornerstone treatments of low and high-risk SCCs, respectively. When available, a number of second-line options can also be used in the management of low-risk SCCs, with nearly equivalent 5-year clearance rates. Although not currently approved for this indication, both PDT and topical therapy have shown promise in managing SCC in situ lesions, and these options may be particularly advantageous for lesions located on the lower leg. Treatment options for high-risk lesions are limited to MMS, fixed-margin surgical excision, and radiation therapy. Recurrence and metastasis of these lesions remain possible despite best efforts. A number of emerging therapies may provide promise in the management of high-risk SCC; patients with inoperable SCC lesions may be candidates for clinical trials.

Zusammenfassung der Empfehlungen siehe Tabelle und Abbildung:

Table 3. Treatment Recommendations.

Recommendation	Level of Evidence[a]	Strength of Recommendation[b]
1. Suspected SCCs should be biopsied according to the criteria outlined in chapter 1.[86]	NA	Strong
2. Risk of recurrence should be established using the criteria in Table 1.	NA	Strong
3. Selected patients with high-risk SCCs may be considered for sentinel lymph node biopsy in consultation with a multidisciplinary skin cancer clinic.	Low[32, 33]	Weak
4. Primary low-risk SCC lesions of the skin, including SCC in situ and keratoacanthomas, may be treated with the following options:		
• Surgical excision with approximately a 4- to 5-mm margin (only if functionality/cosmesis of the treated site is not a concern)	Moderate[3,36,40,42,45]	Strong
• Electrodesiccation and curettage (performed by physicians trained in the technique; to be used when long-term follow-up is planned)	Moderate[3,59]	Weak
• Cryosurgery (performed by physicians trained in the technique; to be used when other options are not appropriate)	Moderate[3,64,65]	Weak
• Radiation therapy (in selected patients with contraindications to surgery, when surgery would be disfiguring, or when radiation therapy is needed for palliation)	Moderate[3]	Strong
5. The following off-label modalities can be also considered in the treatment of SCC in situ:		
• Photodynamic therapy	Moderate[70,71,73]	Strong
• 5-Fluorouracil	Low[75]	Weak
• Imiquimod	Moderate[75]	Weak
6. Treatment options for recurrent or otherwise high-risk SCC lesions include the following:		
• Mohs micrographic surgery	High[3,50]	Strong
• Surgical excision with a 6- to 13-mm margin	Moderate[3,41,42]	Strong
• Radiation therapy (in selected patients with contraindications to surgery, when surgery would be disfiguring, or when radiation therapy is needed for palliation)	Moderate[41]	Strong
7. Adjuvant radiation therapy may be added to the surgical treatment of high-risk SCCs, such as those with perineural invasion.	Moderate[44,67,68]	Weak
8. Patients with select high-risk SCCs may be considered for a referral to a multidisciplinary clinic.	NA	Strong

Abbreviations: NA, not available; SCC, squamous cell carcinoma.
[a]Level of evidence is evaluated as high, moderate, low, or very low, corresponding to the likelihood that the benefits of the therapeutic approach will stand up to further testing. Therapeutic approaches supported by meta-analyses or multiple randomized controlled trials that are free from significant bias have a high level of evidence. Studies based on intraindividual comparisons may also have a high level of evidence. Options supported by methodologically weaker studies (non–randomized controlled trials) and those with weak effects or inconsistent data across studies have a low or very low level of evidence. Statements that are based on biological plausibility or other indirect arguments are listed as *NA*, indicating that direct support for the claim is not available. (See chapter 1 for general methods.[86])
[b]Strength of recommendation is evaluated as strong or weak, depending on the confidence that the treatment is more helpful than the alternative(s), including nontreatment. Hence, therapies with a high level of evidence regarding efficacy may receive a weak recommendation if the risk of adverse response is high or if this risk is not well known. Conversely, approaches with no likelihood of doing harm may receive a strong recommendation, even if they are supported by limited evidence. (See chapter 1 for general methods.[86])

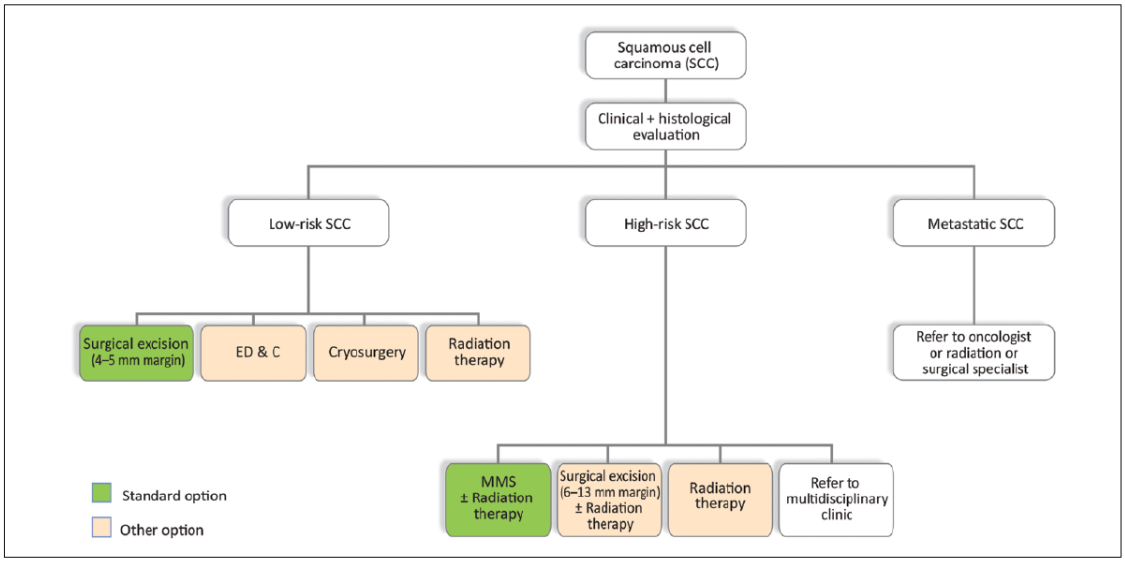

Figure 1. SCC management algorithm.
ED&C, electrodesiccation and curettage; MMS, Mohs micrographic surgery; SCC, squamous cell carcinoma.

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European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC)

Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline

Leitlinienorganisation/Fragestellung

The guidelines address in detail all aspects of cSCC management, from the clinical and histological diagnosis of primary tumour to the systemic treatment of advanced or metastatic disease.

Methodik

Grundlage der Leitlinie

- Items that were agreed upon by our expert panel were adapted within our guideline proposal with appropriate reference. Items that differed from previously published guidelines or were originally recommended by our working group were clearly stated as proposed by the EADO consensus group.
- The guideline draft was circulated between panel members from EADO, EDF and EORTC before reaching its final form.

Recherche/Suchzeitraum:

- extensive search with terms ‘cutaneous squamous cell carcinoma’ using the PubMed, EMBASE and Cochrane Library was conducted (until 31st October).
- Articles included systematic reviews, pooled analyses and meta-analyses.
- search was restricted to English-speaking language publications
- We also searched for existing guidelines on cutaneous squamous cell carcinoma and precursor lesions in the databases mentioned above as well as in relevant websites (national agencies, medical societies).
- the panel looked for concordances and differences among recently published guidelines

Sonstige methodische Hinweise

- „Leitlinie erfüllt nicht die methodischen Anforderungen einer S3 Leitlinie. Die LL (S2k) wurde jedoch aufgrund fehlender höherwertiger Evidenz ergänzend dargestellt.“

LoE

Table 2. The GRADE System for Classifying the Quality of Evidence.[a]

Level of Evidence	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Abbreviation: GRADE, Grading of Recommendations Assessment, Development and Evaluation.
[a]In addition, for statements based purely on biologic plausibility or other indirect arguments, the level of evidence could be identified as "NA," indicating that direct support for the claim is not available.

GoR

Table 3. Rating the Strength of Recommendations.

Strength of Recommendation	Definition
Strong	For intervention: desirable effects outweigh undesirable effects Against intervention: undesirable effects outweigh desirable effects
Weak	For intervention: desirable effects probably outweigh undesirable effects Against intervention: undesirable effects probably outweigh desirable effects, but appreciable uncertainty exists

Sonstige methodische Hinweise

- *Evidenzbasis:* Randomized controlled trials for SCC are uncommon, especially head-to-head comparison studies. Recurrent and otherwise high-risk SCCs are not well studied.

Treatment of locally advanced and metastatic SCC

Our comprehensive literature research only retrieved a few reports, which are strictly limited to cSCC, particularly for stage IV disease; indeed, most reports were on in studies performed in head and neck SCC (HNSCC). It is however likely, that despite a lower probability of distant metastases, once they occur they should be managed as for those of any SCC of the head and neck.

Surgery/radiation therapy/electrochemotherapy

Satellite or in-transit metastases around the primary site should be removed surgically if the number, size and location allow a complete removal of the metastatic sites. RT alone or in combination with chemotherapy may be used as an alternative option when surgery is not feasible. RT is particular helpful as a palliative treatment, […]

Electrochemotherapy is a treatment modality that can find indication in locally advanced lesions. It helps to control the progression of inoperable loco-regional SCC recurrences with

the benefit of controlling bleeding lesions and of reducing painful symptoms when present. The two most commonly used drugs in electrochemotherapy are bleomycin and cisplatin.

Chemotherapy

Stage IV cSCC can be responsive to various chemotherapeutics, however, there is no established standard regimen. The following chemotherapeutic agents that have been used in cSCC: platin derivates (i.e. cisplatin or carboplatin), 5-fluorouracil, bleomycin, methotrexate, adriamycin, taxanes, gemcitabine or ifosfomide alone or in combination. Notably, remission rates of up to 80% have been reported for combined treatments and monochemotherapy still may achieve remissions in up to 60% (e.g. with 5-fluorouracil) [79–83].

Biologic response modifiers

Currently there is no supporting evidence for the use of biologic response modifiers in advanced cSCC outside the framework of clinical trials as first line treatment.

Targeted therapies – EGFR inhibitors

EGFR inhibitors such as cetuximab, currently approved for the treatment of metastatic head and neck SCC, should be discussed as second line treatments after mono- or polychemotherapy failure and disease progress. Participation of patients with metastatic cSCC in clinical trials should be encouraged as treatment of choice if possible, taking into consideration the limitations of chemotherapeutic regiments due to associated toxicity and advanced age of the patients.

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National Comprehensive Cancer Network

Squamous Cell Skin Cancer, Version 2.2018

Leitlinienorganisation/Fragestellung

k.A.

Methodik

Grundlage der Leitlinie

- Keine näheren Informationen zur Methodik und zur Erstellung der Leitlinie verfügbar.

Recherche/Suchzeitraum:

- k.A.

Sonstige methodische Hinweise

- „Leitlinie erfüllt nicht die methodischen Anforderungen einer S3 Leitlinie. Die LL wurde jedoch aufgrund fehlender höherwertiger Evidenz ergänzend dargestellt."

LoE/ GoR

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical Trials: NCCN believes that the best management for patients with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus

Local Treatment for SCC

The primary goals of treatment of squamous cell skin cancer are the complete removal of the tumor and the maximal preservation of function and cosmesis. All treatment decisions should be customized to account for the particular factors present in the individual case and for the patient's preference. Localized cSCC, (ie, without clinically or radiographically concerning regional lymph nodes) is most commonly treated with surgery. Traditional techniques such as C&E are mostly supported by older studies, and data from prospective trials with long-term follow-up are limited. Although surgical approaches often offer the most effective and efficient means for accomplishing cure, consideration of function, cosmetic outcome, and patient preference may lead to the choice of radiation therapy (RT) as primary treatment in order to achieve optimal overall results.

Radiation Therapy

Radiation as Primary Therapy

Although surgery is the mainstay of local treatment for SCC, patient preference and other factors may lead to the choice of RT as primary therapy for local disease without lymph node involvement. A large meta-

other modalities (eg, surgery/MMS alone, RT alone, chemotherapy), patients with other types of skin cancer (BCC and metatypical BCC), patients with lymph node metastases, and a mix of patients with primary and recurrent skin lesions, with and without positive margins.[168,169,195,263,264] These studies suggest that postoperative RT for patients with PNI may improve local control and disease-free survival, but there is likely no survival benefit.

Radiotherapy Safety

RT is often reserved for patients older than 60 years because of concerns about long-term sequelae, including secondary malignancies.[159,256,259,265-276] Large cohort and population-based studies (n > 1000) have shown by multivariate analysis that rates of NMSCs are significantly higher in those who received prior RT (either for a benign condition or for cancer) compared with those who have no history of therapeutic RT exposure.[271-273,275] In patients who developed NMSC after prior RT, most NMSC lesions occurred within the radiation field, with elevated risk of NMSC confined to the site of RT exposure. The risk of NMSC was particularly high in patients who received therapeutic RT early in life.

Radiotherapy can result in poor cosmetic outcomes, including telangiectasia, changes in skin pigmentation, and fibrosis. More serious long-term complications include non-healing ulcers; soft tissue, cartilage, bone, or brain necrosis; decreased sensation; and cataracts (for lesions in the periorbital region).[254,256,259,261,268-270] For SCC in situ, a few studies have reported that RT treatment can result in non-healing ulcers in up to 25% of lesions.[258-260]

Administration of Radiation

Specifics about the application of RT, including total doses, treatment duration, and contraindications, are described under *Principles of*

Radiation Therapy in the algorithm. RT is contraindicated in patients with genetic conditions predisposing to irradiation-related skin cancer (eg, basal cell nevus syndrome[277-283]), and relatively contraindicated in patients with connective tissue diseases (eg, lupus, scleroderma).[284-287] Given higher rates of poor cosmesis and complications with increasing cumulative radiation dose,[256,270,288] reirradiation should not be routinely utilized for recurrent disease within a prior radiation field. As described in the previous section, RT is often reserved for patients >60 years of age due to concerns about risk of RT-related subsequent malignancies. Protracted fractionation is associated with improved cosmetic results,[268,270,289-291] and should be utilized for poorly vascularized or cartilaginous areas. Retrospective studies have found that for patients with cSCC and PNI, failures tend to occur along involved nerves, suggesting that extending the radiation field along involved nerves may help reduce risk of recurrence.[169,292,293] The NCCN panel recommends that for extensive PNI, clinically evident perineural involvement, or involvement of named nerves, (particularly in the head and neck region), consider including the course of the local nerves proximally.

Selection of target area margins and RT modality is left to clinical judgement and based on the experience and expertise available at the treating institution. A variety of external beam options have been shown to be effective for treating cSCC and have similar cosmetic/safety results,[256,270,289,294-296] and are generally accepted as standard of care. Brachytherapy, however, is not considered a standard-of-care approach for treatment of skin cancer. There are insufficient long-term efficacy and safety data to support the routine use of electronic surface brachytherapy, and radioisotope brachytherapy should only be considered in highly selected cases.

Superficial Therapies

Given the limited penetration beyond epidermis and lower cure rates than with surgical techniques, superficial therapies should be reserved for those patients with SCC in situ.[297-299] Recommended superficial therapies include topical fluorouracil (5-FU), topical imiquimod, photodynamic therapy (PDT), and cryotherapy.

Topical Therapies

Retrospective studies, meta-analyses, and an open-label phase II trial have shown that imiquimod was effective for treating patients with SCC in situ, with reasonably high rates of initial clearance (70%–100%) and low rates of recurrence.[300-305] One small (n = 31) double-blind randomized trial showed that imiquimod led to the resolution of 73% of lesions compared to 0% of lesions resolving with vehicle control ($P <$ .001).[306] Side effects include inflammatory skin reactions, such as erythema, pruritus, and pain, and often lead to discontinuation of imiquimod before the treatment course is complete. [302,304] Discontinuation after lesion clearance has not been shown to lead to recurrence.

5-FU is another agent used topically to treat SCC in situ. Clearance rates with 5-FU tend to be lower than those for topical imiquimod, and vary widely, ranging from 27% to 93%.[302,305,307-309] Toxicities are similar to imiquimod, being primarily inflammatory skin reactions such as severe eczematous reactions, ulceration, and erosions.[302,308,309]

Cryosurgery/Cryotherapy

Cryosurgery, which destroys tumors cells by freeze-thaw cycles, has been used for many years as a fast and cost-effective means for removal of SCCs. Prospective and retrospective studies, including large meta-analyses, have shown recurrence rates of 0% to 4% for invasive SCCs treated with cryotherapy.[48,310-313] For SCC in situ, recurrence rates

after cryotherapy range from 1% to 13% in retrospective studies[258,298,299,313] and 0% to 50% in prospective studies.[297,309,312,314,315] Variability in reported recurrence rates may be due in part to patient selection, variable follow-up durations, and differences in technique and operator skill. Common adverse events associated with cryosurgery include edema/blistering, scabbing, ulceration, loss of pigment, and postoperative pain. [297,314,316] Less common adverse events include scarring and infection.[297,312,314-316] One prospective comparative study reported that patients were much more likely to experience pain with cryotherapy compared with curettage and cautery, and time to complete healing was also significantly longer with cryotherapy.[297] A randomized controlled trial showed that cryotherapy was associated with poorer cosmetic outcomes compared with topical 5-FU for treatment of SCC in situ.[309]

Photodynamic Therapy

PDT involves the application of a photosensitizing agent on the skin followed by irradiation with a light source. Photosensitizing agents often used include methyl aminolevulinate (MAL) and 5-aminolevulinic acid (ALA). For SCC in situ, rates of initial complete clearance following PDT with ALA or MAL range between 52% and 98% according to prospective studies (n = 23–96 lesions).[308,317-328] Most of these studies report recurrences, such that durable complete response rates range from 48% to 89%.[308,309,317-320,322-326,328,329] Small randomized trials have shown that differences in PDT techniques can cause significant differences in clearance rate for SCC in situ,[318,326] which likely contributes to the broad range of rates reported in the literature. One small randomized trial showed that fewer treatments were required for complete clearance with PDT versus cryotherapy, and two randomized trials showed that durable complete response rates were higher with PDT.[309,314] Another small randomized trial in patients with SCC in situ

showed that PDT was associated with higher rates of initial complete clearance compared with 5-FU, and two randomized trials showed that and durable complete response rates were higher with PDT.[308,309]

PDT is associated with itching, tingling, stinging, burning during the application of the topical agent, and mild to moderate pain during the phototreatment.[318-323,325,330,331] Other less common toxicities include severe pain, ulceration, crusting, edema, erythema, scarring, and pigmentary alterations.[320-323,325,331-333] Most of these resolve within days or weeks of treatment, but there have been reports of long-term scarring and pigmentary alterations.

Results from randomized trials in patients with SCC in situ suggest that 5-FU may be associated with lower risk of adverse events compared with PDT or cryotherapy, but due to inconsistent results across trials it is unclear whether risk of toxicity differs between cryotherapy and PDT.[308,309,314] All three treatment modalities are associated with risk of pain and various manifestations of inflammation at the treated site, including erythema, burning, crusting, stinging, itching, edema/blistering, and ulceration/erosions. All three also occasionally lead to pigmentary changes, or scarring.

Currently, PDT is being utilized at some NCCN Member Institutions for SCC in situ lesions. Although MAL is an approved photosensitizer for PDT, it is no longer produced in the United States.

Low-Risk Local SCC

Primary treatment options for low-risk local SCC include: 1) C&E in areas without hair growth (ie, excluding terminal hair-bearing regions, such as the scalp, pubic and axillary regions, and beard area in men), provided that the treatment be changed to excision if the adipose tissue is reached; 2) standard excision if the lesion can be excised with 4- to 6-mm clinical margins and repaired with linear closure, secondary intention healing, or skin graft; and 3) RT for non-surgical candidates, generally limited to those older than 60 years of age because of risk of long-term toxicity.

If margins are positive after excision, patients should receive additional therapy. MMS, resection with CCPDMA with frozen or permanent section, or standard re-excision for area L regions (trunk and extremities, excluding pretibia, hands, feet, nail units, and ankle) are recommended, while radiation may be administered to non-surgical candidates.

The NCCN panel discussed the use of alternative therapies for first-line treatment in patients with SCC in situ (Bowen's disease). Although cure rates may be lower than with surgical treatment modalities, alternative therapies the panel recommends considering include 5-FU, imiquimod, PDT with porfimer sodium or ALA, or vigorous cryotherapy. Data suggest that the cure rates of these approaches may be lower compared with surgery.[297-299] On the other hand, panelist experience indicates that they may be effective for anatomically challenging locations, and recurrences are often small and manageable.

High-Risk Local SCC

Recommended options for high-risk lesions include: 1) standard excision, using wider margins with linear or delayed repair; 2) MMS or resection with CCPDMA with frozen or permanent section; and 3) RT for non-surgical candidates.

Due to the wide variability of clinical characteristics that may define a high-risk tumor, it is not feasible to recommend a defined margin for standard excision of high-risk SCC. Keen awareness of the subclinical extension of SCC is advised when selecting a treatment modality without complete margin assessment for a high-risk tumor. These margins may need to be modified based on tumor- or patient-specific factors. If negative margins are not achieved after standard excision, patients should undergo MMS or resection with CCPDMA, or receive RT. If residual disease is still present after second-line treatment and

Treatment of SCC with Regional Lymph Node Involvement

Data on SCC with nodal metastasis are limited to retrospective or observational studies. Some of these studies have shown that treating regional disease with RT alone results in poorer survival and/or regional/local control than those who received surgery plus adjuvant RT.[145,488-491] This was true for patients with parotid involvement, neck lymph node metastases, or a combination of the two, which is why the NCCN panel recommends resection of regional disease over radiation or chemotherapy. Radiation with or without concurrent therapy is reserved for patients who are not surgical candidates.

Most studies of patients with regional involvement of cSCC focus on treatment of parotid and/or cervical nodes either with surgery alone (parotidectomy and/or neck dissection) or surgery plus adjuvant radiotherapy.[51,145-149,151,152,488-507] In these studies the extent of resection and whether adjuvant RT was given depended on the treating clinician's assessment of the extent of the disease and risk of recurrence. Although some institutions have standard practices guiding treatment, published data from studies at these institutions may include cases in which the clinician deviated from that standard practice. Many of these studies used highly heterogeneous patient populations, including a wide range of levels of lymphatic and/or parotid involvement, a mix of primary and recurrent disease, and a mix of immunosuppressed and immunocompetent patients. In addition, some studies included a few patients treated with adjuvant chemotherapy, [147-149,494,500-502,507] and a few included patients who received RT or chemotherapy alone (no surgery).[51,145,489-492]

For studies where the majority of patients receive at least surgery plus adjuvant RT for parotid and/or neck LN metastases, recurrence rates are usually between 20% to 35%,[145-147,149,488,491,493,494,496,497,506,507] and

estimates of 5-year disease-free survival and disease-specific survival are between 59% to 83%[147,149,151,500] and 63% to 83%,[145,148,149,151,152,488,489,491-497,499], respectively.

Due to the heterogeneity of study populations and treatment selection bias in these retrospective/observational studies, direct comparison of treatment outcomes is not appropriate. However, multivariate analyses provide some insight into factors and treatment options associated with better outcomes.

Studies of patients with cSCC metastases to the parotid and/or lymph nodes in the neck from several Australian centers (ie, Royal Prince Alfred Hospital, Westmead Hospital, Peter MacCallum Cancer Centre) have found by multivariate analysis that adjuvant RT improved local regional control or disease-free survival.[493,497,501] This finding was corroborated by a study from University of Texas Southwestern Medical Center.[503] Another study from Westmead Hospital that included patients with LN metastases of the neck but excluded those with parotid involvement found by multivariate analysis that adjuvant RT improved disease-free survival.[147] In contrast, studies from 2 different centers (ie, Toowoomba Hospital, Greenlane Hospital) found no significant association between adjuvant RT and improved disease-free survival or recurrence rate in patients with involvement of the parotid and/or cervical nodes.[149,150] Survival results are also mixed. Whereas several studies showed by multivariate analysis that adjuvant RT improved overall survival in patients with parotid and/or neck lymph node involvement,[146,151,501,505], and one study showed that this was also true for the subset of patients with neck lymph node involvement alone (no parotid involvement),[147] data from the Royal Prince Alfred Hospital showed no significant association between adjuvant RT and overall survival.[494]

Such variability in results across studies suggests that there may be subsets of patients who derive more clinical benefit from adjuvant RT than other patients. Based on these retrospective and observational analyses, it is difficult to determine distinguishing features for identifying patients most likely to derive clinical benefit from adjuvant RT. Adjuvant RT is therefore a recommended option for all patients following resection of regional cSCC.

Many retrospective and observational studies have attempted to identify prognostic factors and determine how to best risk stratify patients with regional cSCC. Even among studies with multivariate analyses, results vary for all of the prognostic factors frequently considered, including patient characteristics (age, current/prior immunosuppression), features of the primary tumor (size, LVI, PNI, differentiation, positive margins after excision), and features of the regional disease (LN size, extracapsular extension (ECE), number of involved nodes, involvement of parotid, neck nodes, or both).[145-149,151,152,488,489,492-494,499,501,505,508] For each of these there are some analyses showing that they are significantly associated with regional control or survival, and other analyses showing no significant association.

Several staging systems have been proposed for regional cSCC, as shown in Table 1. O'Brien proposed a staging system that separated parotid involvement from neck LN involvement based on multivariate analysis showing improved local control for P1 compared with P2/P3.[493] Multivariate analysis of 126 patients corroborated the finding that P2/P3 were associated with reduced locoregional control,[145] but two other multivariate analyses found that P-stage was not significantly associated with disease-free survival.[489,500] Results from multivariate analyses of survival also yielded mixed results regarding the prognostic value of O'Brien P-stage.[145,146,151,152,493,500] O'Brien also showed by multivariate analysis that survival was significantly better for patients with N0/N1 compared with N2.[493] One other multivariate analysis (n = 170) supported this result,[151] but several other multivariate analyses did not find a significant association with survival or locoregional control.[145,146,152,489,500]

The AJCC 7th edition staging for regional cSCC reflects the results from multiple studies, and therefore does not separate parotid from cervical lymph node involvement. The AJCC 7th edition staging includes both 3-cm and 6-cm cutoffs for largest lymph node dimension. A subsequent analysis by Forest and colleagues in 2010 found that lymph node size was related to ECE, and that the 3-cm cutoff was significantly associated with survival as long as ECE was excluded from the model.[494] Their multivariate analysis did not confirm the 6-cm cutoff, so they proposed a new staging system that only includes the 3-cm cutoff. Risk stratification per the NCCN Guidelines takes into account data from multivariate analyses showing that ECE and margin status after resection are prognostic for recurrence and/or survival.[146,489,493,499,500,508] The recent update of the AJCC staging system also now includes extranodal extension as a criterion for determining N-stage.[129] It should be noted that there are other multivariate analyses that showed no significant association between outcomes and ECE or margin status.[151,489,500,501]

Systemic Therapy for Regional Disease

Systemic Therapy for Regional Disease

Regional cSCC has been shown to respond to systemic cytoxic therapies and to EGFR inhibitors in a number of prospective (noncomparative) and retrospective studies.[341,343,352,509-512] However, in the absence of prospective comparative trial data it is unclear whether these systemic therapies provide additional clinical benefit when used postoperatively in combination with RT. Several retrospective studies were unable to show that the addition of chemotherapy to postoperative RT significantly improved any disease-related outcome in patients with regional disease,[148,508] but at least one retrospective study showed improved relapse-free survival by multivariate analysis.[345]

A wide variety of cytotoxic therapies have been tested in patients with regional or distant metastatic cSCC. Those most commonly used are cisplatin, carboplatin, and 5-FU, either as monotherapy or combination regimens.[148,341,343-345,508-511,513,514] Among EGFR inhibitors, cetuximab is most commonly used in this setting,[347-349,352,508,512,515-517] but there have also been prospective studies on gefitinib,[351] erlotinib,[350] panitumumab,[518] and lapatinib.[346] Results from retrospective studies and meta-analyses attempting to compare platinum-based cytotoxic therapy with cetuximab have yielded inconsistent results,[348,511,519] so it is not clear which of these agents is more effective at treating regional or distant metastatic cSCC. Several studies have reported on patients treated with combinations of EGFR inhibitors and cytotoxic agents,[347,510,516] but it is not yet clear whether the combination improves outcomes in patients with regional or distant metastatic cSCC.

NCCN Recommendations for Treatment of Regional Disease

The preferred treatment for cSCC with lymph node involvement is excision of the primary tumor and regional lymph node dissection unless the patient is not a surgical candidate. Because surgery is the preferred treatment approach, surgical candidacy should be assessed by a clinician with experience in performing regional lymph node dissections.

Patients treated with dissection of nodes in the trunk and extremities should consider adjuvant RT of the nodal bed, especially if multiple nodes are involved or if ECE is present. Dosage information can be found in the *Principles of Radiation Therapy for Squamous Cell Skin Cancer* section of the algorithm.

For patients with nodal metastasis to the head and neck, the extent of surgery should depend on the number, location, and size of effected nodes. Patients with a solitary positive lymph node should receive ipsilateral selective neck dissection. Comprehensive ipsilateral neck dissection is recommended for patients with a solitary positive node larger than 3 cm and those with multiple positive ipsilateral nodes. For patients with bilateral positive nodes, comprehensive bilateral neck dissection is appropriate. If parotid nodes are involved, the panel recommends superficial parotidectomy and ipsilateral neck dissection as indicated.

Truly radical neck dissection is no longer used and is not recommended. Because the definition of modified radical neck dissection varies across institutions, the NCCN Guidelines use the term "comprehensive neck dissection" to refer to all types of modified radical neck dissections, provided that they are more extensive procedures compared with selective neck dissections.

For patients with nodal metastasis to the head and neck, postoperative adjuvant treatment should depend on the pathologic findings after surgery—namely the extent resection, number of positive nodes, and presence or absence of ECE. Postoperative radiation is recommended

in all cases, although observation is a reasonable alternative for patients with only one small (≤3 cm) node and no ECE. Patients with ECE or incompletely excised nodes are at high risk of recurrence. They should receive adjuvant RT and also consider concurrent systemic therapy depending on individual toxicity tolerance. Multidisciplinary consultation is recommended for these cases and should consider the systemic therapies used to treat head and neck squamous cell carcinomas as indicated in the NCCN Guidelines for Head and Neck Cancers.

Patients with inoperable nodal disease should be treated with radiation of the nodal bed and multidisciplinary consultation to consider concurrent systemic therapy. Systemic therapies recommended for use with radiation to treat head and neck squamous cell carcinomas should be considered.

Patients should be re-evaluated for surgical candidacy for lymph node dissection after radiation. CT with contrast may be indicated to evaluate the extent of residual disease.

Recurrence and Metastasis

Systemic Therapy for Distant Metastatic Disease

Cutaneous SCC with distant metastasis, while rare, is more common than metastatic BCC. A 10-year cohort study involving 985 patients with SCC found that patients with 1 primary cSCC have a 3.7% risk of lymph node metastasis and 2.1% risk of disease-specific death.[17] Risk of nodal disease is even lower in patients with only one primary cSCC.[107] Risk of distant metastatic disease is only 0.4%.[17] Unfortunately, evidence regarding systemic therapy for the condition is limited. There are no prospective phase III studies available. Whereas a number of small studies have reported responses to cytotoxic therapy in patients with local or regional cSCC (See *Systemic Therapy for Local High-Risk SCC* and *Systemic Therapy for Regional Disease*),[334,342,343,509,511,513,520] few of these studies included patients with distant metastatic cSCC.[340,341,344,510] Cisplatin either as a single agent or combined with 5-FU or vindesine has occasionally produced useful responses in patients with distant metastases from cSCC, but data supporting efficacy are limited.[340,341,510] In the only phase II study of biochemotherapy with interferon alfa, cis-retinoic acid, and cisplatin, 35 patients were assessed for response, 11 of whom had distant metastases.[344] One of the 11 patients experienced a complete response. This lends some credence to a cisplatin-based regimen for distant metastatic disease.

The status of evidence supporting EGFR inhibitors for treatment of distant metastatic cSCC is similar to that for cytotoxic therapy. Multiple small studies, including some phase II trials, have shown responses to EGFR inhibitors in patients with locally advanced or regional disease,[338,347,351,516] but only a few have reported responses in patients with distant metastases, including 2 responses reported in phase II trials.[346,352,512,515,518] The low toxicity profile of cetuximab holds an advantage over the toxic cisplatin regimen.

Neoadjuvant systemic therapy in preparation for subsequent surgery and/or radiation has been used for locoregional cSCC that is very large and/or deeply invasive. For locoregional disease for which surgery or RT are unlikely to be curative, both cytotoxic and EFGR inhibitor systemic therapy (monotherapy or combination) have been successfully used to reduce tumor load, which in some cases enabled complete resection or complete response after RT.[334,341,343,347,351,352,511,512,516] The efficacy of this approach has not been demonstrated for patients with distant metastatic cSCC.

In addition to several trials testing new approaches to treating locally advanced unresectable or metastatic cSCC with cytotoxic or targeted agents,[521-524] checkpoint immunotherapies are also being tested in this setting.[525-530] Preliminary data from these studies and case reports have shown responses to anti-PD-1 (nivolumab, pembrolizumab, REGN2810) and anti-CTLA-4 (ipilimumab) agents.[526,531-537] FDA recently approved nivolumab and pembrolizumab monotherapy for the treatment of patients with recurrent or metastatic head and neck squamous cell cancer with disease progression on or after platinum-containing chemotherapy.[538,539] However, neither the phase 3 trial supporting the nivolumab approval (Checkmate 041; NCT02105636) nor the phase 1b trial supporting the pembrolizumab approval (KEYNOTE-012; NCT01848834) included any patients with *cutaneous* SCC.[540-542]

NCCN Recommendations

For the management of local tumor recurrence or new regional disease, the algorithm directs clinicians to follow the appropriate pathways for primary treatment. Complicated high-risk tumors, regional recurrence, or the development of distant metastases should be managed by a multidisciplinary tumor board.

The NCCN panel encourages participation in a clinical trial for patients with metastatic cSCC. Unfortunately such trials are scarce. Possible agents include cisplatin monotherapy, cisplatin plus 5-FU, EGFR inhibitors such as cetuximab, or immune checkpoint inhibitors. Currently there are insufficient published data to support recommending any specific immunotherapies for treatment of cSCC. If the patient is a solid organ transplant recipient taking immunosuppressive therapy, one should consider reducing the doses of immunosuppressive agents where appropriate or minimizing the doses of calcineurin inhibitors and/or antimetabolites in favor of mTOR inhibitors.[543] For symptomatic sites, palliative RT or surgery should be considered. Stereotactic body RT (SBRT) may be appropriate in select patients.

Alam M et al, 2016 [3].

Guidelines of care for the management of cutaneous squamous cell carcinoma

Leitlinienorganisation/Fragestellung

This guideline addresses the management of patients with cutaneous squamous cell carcinoma

(cSCC) from the perspective of a US dermatologist.

The primary focus of the guideline is on the most commonly considered and utilized approaches for the surgical and medical treatment of cSCC, but it also includes

recommendations on appropriate biopsy techniques, staging, follow-up, and prevention of cSCC.

Methodik

Grundlage der Leitlinie

- expert work group was convened to determine the audience and scope of the guideline, and to identify important clinical questions in the biopsy, staging, treatment, and follow-up of cSCC
- Clinical questions used to structure the evidence review:
  - What is the standard grading system for BCC and cSCC?
  - What are the standard biopsy techniques for BCC and cSCC?
  - What pathologic and clinical information is useful in the pathology report for BCC and cSCC?
  - What are the benefits harm and effectiveness/efficacy of available treatments for BCC and cSCC?
  - What are effective treatment options for the management of advanced BCC and cSCC?
  - What are the effective methods for follow-up and preventing recurrence and new primary keratinocyte cancer formation?
- Work group members completed a disclosure of interests that was updated and reviewed for potential relevant conflicts of interest periodically throughout guideline development.
- If a potential conflict was noted, the work group member recused himself or herself from discussion and drafting of recommendations pertinent to the topic area of the disclosed interest.
- This guideline has been developed in accordance with the AAD/AAD Association Administrative Regulations for Evidence-Based Clinical Practice Guidelines, which includes the opportunity for review and comment by the entire AAD membership and final review and approval by the AAD Board of Directors
- An additional multidisciplinary panel of invited reviewers was utilized to provide crossspecialty comments on the draft guideline. This guideline will be considered current for a period of 5 years from the date of publication, unless reaffirmed, updated, or retired at or before that time

Recherche/Suchzeitraum:

- An evidence-based approach was used and available evidence was obtained by using a systematic search and review of published studies from PubMed from January 1960 through April 2015
- secondary search was subsequently undertaken to identify and review published studies from April 2015 to August 2016 to provide the most current information.
- limited to publications in the English language
- The available evidence was evaluated by using a unified system called the Strength of Recommendation Taxonomy (SORT), which was developed by editors of the US family medicine and primary care journals (ie,American Family Physician, Family Medicine, Journal of Family Practice, and BMJ USA).

LoE

Evidence was graded using a 3-point scale based on the quality of study methodology (eg, randomized control trial [RCT], case-control, prospective/ retrospective cohort, case series, etc), and the overall focus of the study (ie, diagnosis, treatment/ prevention/screening, or prognosis) as follows:

- I. Good-quality patient-oriented evidence (ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life).
- II. Limited-quality patient-oriented evidence.
- III. Other evidence, including consensus guidelines, opinion, case studies, or disease-oriented evidence (ie, evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes).

GoR

Clinical recommendations were developed on the basis of the best available evidence tabled in the guideline. These are ranked as follows:

- A. Recommendation based on consistent and goodquality patient-oriented evidence. Recommendation based on consistent and good-quality patient-oriented evidence.
- B. Recommendation based on inconsistent or limited-quality patient-oriented evidence.
- C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence.

Nonsurgical Therapy

Table X. Recommendations for the nonsurgical therapy of cSCC

If surgical therapy is not feasible or preferred, radiation therapy (eg, superficial radiation therapy, brachytherapy, external electron beam therapy, and other traditional radiotherapy forms) can be considered when tumors are low risk, with the understanding that the cure rate may be lower.
Cryosurgery may be considered for low-risk cSCC when more effective therapies are contraindicated or impractical.
Topical therapies (imiquimod or 5-FU) and PDT are not recommended for the treatment of cSCC on the basis of available data.
There is insufficient evidence available to make a recommendation on the use laser therapies or electronic surface brachytherapy in the treatment of cSCC.

cSCC, Cutaneous squamous cell carcinoma; *5-FU*, 5-fluorouracil; *PDT*, photodynamic therapy.

Table XI. Level of evidence and strength of recommendations for the nonsurgical treatment of cSCC

Recommendation	Strength of recommendation	Level of evidence	References
Cryosurgery	B	II	54
Radiation therapy			
• Traditional radiotherapies and modern superficial radiation therapy	B	II, III	54,70-75
• Electronic surface brachytherapy	C	III	76,77
Against topical therapy alone			
• Imiquimod	C	III	54,78,79
• 5-FU	C	III	54
Against photodynamic therapy alone	B	II	54
Laser therapy	C	III	54

cSCC, Cutaneous squamous cell carcinoma; *5-FU*, 5-fluorouracil.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 27.03.2018

#	Suchfrage
1	[mh “Skin Neoplasms”/DT,RT,SU,TH]
2	[mh “Carcinoma, Squamous Cell”/DT,RT,SU,TH]
3	[mh Skin]
4	(skin or hide or derm* or epiderm* or cutaneous):ti,ab,kw
5	(neoplasm* or cancer* or tumor* or tumour* or carcinom*):ti,ab,kw
6	(squamous next cell):ti,ab,kw
7	(nonmelanoma or non-melanoma):ti,ab,kw
8	(#3 or #4) and #5 and #6
9	#1 or (#3 or #4) and #5
10	#9 and (#6 or #7)
11	#2 and (#3 or #4)
12	(#1 or (#3 or #4)) and #5 and #6
13	#8 or #10 or #11 or #12
14	#13 from Publication Year from 2013 to 2018

SR, HTAs in Medline (PubMed) am 27.03.2018

#	Suchfrage
1	Skin Neoplasms[mh]
2	Carcinoma, Squamous Cell[mh]
3	Skin[MeSH]
4	skin[tiab] OR hide[tiab] OR derma[tiab] OR dermis[tiab] OR epiderm*[tiab] OR cutaneous[tiab]
5	(((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR neoplasm*[tiab]) OR cancer*[tiab]
6	squamous[tiab]
7	nonmelanoma[tiab] OR non-melanoma[tiab]
8	(#3 OR #4) AND #5 AND #6
9	#1 OR (#3 AND #5)
10	#9 AND (#6 OR #7)
11	#2 AND (#3 OR #4)
12	(#3 OR #4) AND #5 AND #7
13	(#1 OR (#3 OR #4)) AND #5 AND #6
14	#8 OR #10 OR #11 OR #12 OR #13
15	(#14) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR

	technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
16	((#15) AND ("2013/03/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 27.03.2018

#	**Suchfrage**
1	Skin Neoplasms[mh]
2	Carcinoma, Squamous Cell[mh]
3	skin[tiab] OR hide[tiab] OR derma[tiab] OR dermis[tiab] OR epiderm*[tiab] OR cutaneous[tiab]
4	(((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR neoplasm*[tiab]) OR cancer*[tiab]
5	squamous[tiab] AND cell[tiab]
6	nonmelanoma[tiab] OR non-melanoma[tiab]
7	#1 AND #5
8	#2 AND #3
9	#1 AND #6
10	#3 AND #4 AND #5
11	#7 OR #8 OR #9 OR #10
12	(#11) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[tiab])*
13	(((#12) AND ("2013/03/01"[PDAT] : "3000"[PDAT])) NOT ((comment[Publication Type]) OR letter[Publication Type])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))
14	(#13) NOT retracted publication[ptyp]

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