Leitlinienprogramm Onkologie

Evidenztabellen zur S3-Leitlinie Aktinische Keratose und Plattenepithelkarzinom der Haut

Evidenztabellen 2.0 – Dezember 2022
AWMF-Registernummer: 032/022OL

Evidenztabellen

DKG KREBSGESELLSCHAFT
Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN.
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Inhaltsverzeichnis

1. Informationen zu dieser Leitlinie

1.1. Herausgeber

Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF), Deutschen Krebsgesellschaft e.V. (DKG) und Stiftung Deutsche Krebshilfe (DKH).

1.2. Federführende Fachgesellschaft(en)

Deutsche Dermatologische Gesellschaft (DDG)

Deutschen Krebsgesellschaft (DKG) vertreten durch die Arbeitsgemeinschaft Dermatologische Onkologie (ADO) von DKG und DGG

1.3. Finanzierung der Leitlinie

Diese Leitlinie wurde von der Deutschen Krebshilfe im Rahmen des Leitlinienprogramms Onkologie gefördert.

1.4. Kontakt

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1.5. Zitierweise

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3 Leitlinie Aktinische Keratose und Plattenepithelkarzinom der Haut, Evidenztabellen 2.0, 2022, AWMF Registernummer: 032/022OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/aktinische-keratosen-und-plattenepithelkarzinom-der-haut/ (abgerufen am: TT.MM.JJJJ)

2. Working group: Epidemiology and etiology

(AG Epidemiologie und Ätiologie)

2.1. Question I.1. Which prognostic factors are important for the transition from AK to SCC?

(Frage I.1. Welche prognostischen Faktoren sind bei der AK für den Übergang in ein PEK von Bedeutung?) Beantwortung durch Orientierende Recherche

Introductory chapter with presentation of the incidence, prevalence and mortality, clinical epidemiology, risk factors, pathogenesis and molecular aberrations of AK and PEK in Germany.

Einführungskapitel mit Darstellung der Inzidenz, Prävalenz und Mortalität, der klinischen Epidemiologie, Risikofaktoren, Pathogenese und molekulare Aberrationen von AK bzw. PEK in Deutschland.

2.1.1. PICO

PICO – Scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Patients with actinic keratosis	n.a. (no intervention)	n.a. (no intervention)	Rate of progression to invasive SCC (iSCC), time to progression to iSCC, prognostic factors of progression (clinical or histological)

2.1.2. Database, search strategy, number of results

Database	Search strategy	Date	Number of results
1. Search			
Medline	((actinic*[title] OR solar*[title]) AND keratos*[title]) AND (evolu*[Title/Abstract] OR develop*[Title/Abstract] OR progres*[Title/Abstract] OR transform*[Title/Abstract]) NOT "case report" AND "squamous"[Title/Abstract] AND (English[Language] OR German[Language])	12 January 2017 (initial search) Update 17th May 2017	270 278
Remarks and notes: -			

2.1.3. Selection criteria

Literature selection	
Number of total results	278
Inclusion criteria	Observational studies with defined outcomes, cohort (longitudinal) studies, retrospective studies (case control)
Exclusion criteria	Case reports, case series, narrative reviews, small sample size (n<10), experimental or exploratory histological staining reports, reports of genetic prognostic factors (experimental), studies without relevant outcomes
Number of results after abstract searching	25
Number of full texts reviewed	8

2.1.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Fernández-Figueras et al 2014	To evaluate the prevalence of classic and differentiated pathways in the development of cutaneous invasive SCC (iSCC).	Histological examination of the epidermis adjacent to and overlying 196 skin biopsy specimens showing cutaneous iSCC. Thickness of the epidermal proliferation of atypical keratinocytes overlying the tumour was studied independently by three pathologists, score assigned (AK I – AK III)	196 skin biopsy specimens showing iSCC from 79 women and 117 men, mean age: 77.3 years Inclusion criteria: sun-exposed skin biospies >3mm, containing invasive tumours <25mm in diameter	Prevalence of AK I-III lesions, ulceration and adnexal involvement overlying cutaneous iSCC	AK I, AK II and AK III lesions overlying iSCC: present in 63.8%, 17.9% and 18.4% of cases respectively. The corresponding percentages in the epidermis adjacent to iSCC were 77.9%, 6.6% and 8.3% respectively (stage could not be assessed in 8.1% of cases). Focal epidermal ulceration overlying iSCC was seen in 32% of AK I, 28.6% of AK II and 33.3% of AK III instances. Adnexal involvement by atypical keratinocytes: more frequently present in cases with	Conclusion: All AK lesions have a potential risk of invasive progression, regardless of the thickness of epidermal changes.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					overlying AK I (39/125, 31.2%) than with AK II (8/35, 22.9%) and AKIII (5/36, 13.9%)		
Fuchs et al 2007	To determine the time scale of AK progression.	Retrospective electronic medical record review	n=91 patients with histopathologically confirmed AK at the same site as the subsequent SCC (subset of 6.691 patients with pathologically confirmed SCC in a 2-year time frame)	1) Length of time of AK to progress to SCC [months] 2) mean time to conversion according to sex, age and location of lesion [months]	1) 24.6 (95% CI: 21.04–28.16, range:1.97 to 75.6) 2) extremities: 15.56 (n=9), eyebrow: 15.86 (n=6),temple: 16,75 (n=5), scalp: 22.54 (n=17), cheek: 23.18 (n=14), ear: 25.51 (n=4), nose: 28.24 (n=19), trunk: 28.54 months (n=3), forehead: 33.57 (n=15) no sign.difference in time to progression based on sex (p=0.323) or age (p=0.77) of patient or location of the lesion	Possible lag time to biopsy and diagnosis of the AK or SCC Previous data has been excluded from the study (electronic medical records have been introduced in 1997): selection bias likely Only patients with extensive, descriptive matching locations were included: selection bias likely The paper charts of patients with SCC, but without pathology proven precursor	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						AK, were not examined due to the large number of medical records in the study: selection bias, over/understimation of the results possible	
Heerfordt et al 2016	To investigate whether AK thickness correlates with dysplasia or expression of p53.	Correlation study Clinical thickness of AK measured by: scale bars (0.5mm an 1mm) and measurement of stratum corneum hydration via non-invasive capacitance measurement Histological measurements included thickness of the stratum corneum, the cellular epidermis and total epidermis thickness (mm)	n=24 patients with 66 lesions (21 from the trunk, 37 from the upper limbs and 8 from the lower limbs) 9 women age range: 53 – 89	Clinical and histological thickness Severity of Dysplasia according to Roewert-Huber classification Percentage of p53 positive nuclei	Positive correlation between clinical thickness of AKs and the histological thickness of total epidermis (r=0.72, p<0.0001) No correlation between clinical thickness and severity of dysplasia (p=0.7) No correlation between clinical thickness and expression of p53 (p=0.5). Clinical thickness	Intra-observer agreement of the scale bars: substantial (kappa=0.8) Inter-observer agreement: moderate (kappa=0.5) Median % of p53 positive nuclei was 54%. Therefore, AKs where more than 54% of nuclei were p53 positive were considered to have high expression of p53. The rest were considered to have low expression of	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Anti-p53 (Bp53-11) primary antibody was used to stain p53 protein			cannot predict aggressiveness.	p53.	
Jiyad et al 2016	To identify clinical features of actinic change that correlate with an increased risk of SCC or intraepidermal carcinoma (IEC) in the short-medium term (18 months) as guidance for prioritizing field treatment.	Nested case-control study among participants of the STAR cohort (skin tumours in allograft recipients) (Australia)	Cases: n=39 RTRs (renal transplant recipients) who developed an incident SCC or IEC On the face/forearms/ hands within 18 months following baseline examination and photography Controls: N=39 RTRs without SCC/IEC within 18 months of the baseline examination Matching (1:1) according to age, sex, time since first transplantation, and pre-defined skin	OR: Association of actinic damage (as defined as presence of AK patch, number of AK Patches, number of AKs and area affected by AK) and the development of either SCC and IEC, or SCC alone.	Presence of an AK patch (AK greater than 1cm²): 18-fold higher risk of SCC alone (OR=18.00, 95% CI 2.84-750) and a 6-fold increased risk of SCC/IEC combined (OR=6.6, 95% CI 2.56-21.66). Number of AK patches (n>3 vs n<3): 5-fold higher risk of developing SCC/IEC (OR=5.68, CI 95% 1.64-30.18) Number of AK (n>3 vs n<3): 4-fold higher risk of developing SCC/IEC (OR=4.63, 95% CI 2.12- 11.45)	Study only assessed Caucasian OTRs (at least one year post-transplant with stable immunosuppression, or at least 10 years of immunosuppressive therapy) Generalisabilty questionable: exclusion of immune-competent patients and small number of cases Only one researcher extracted the photography data: comparison and assessment of inter-observer reliability not possible	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			sites				
					% of area involving AK (>25% vs <25%): 5-fold higher risk of SCC/IEC (OR=5.33, 95% CI 1.53-28.56) Features of actinic damaged skin **not** associated with an significant higher risk of developing SCC or IEC within 18 months: % of area involving erythema (>25% vs <25%): SCC/IEC (OR=2.00, 95% CI 0.81-5.40) and SCC alone (OR=1.17, 95% CI 0.34-4.2) % of area involving pigmentation change (>25% vs <25%): SCC/IEC (OR=1.6, 95% CI 0.46-6.22), SCC alone (OR=1.50, 95% CI 0.17-	Various facial and upper limb skin sites were not of equal size	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					17.96)		
Pandey et al 2012	To examine the prognostic significance of follicular extension of atypical keratinocytes in AKs.	Retrospective, case-controlled study	104 cases of AK with follicular extension and 104 cases of AK without follicular extension out of a randomly selected pool of 1.000 biopsies. Follicular extension: presence of atypical keratinocytes extending into the isthmus of the hair follicle.	Correlation of AK with follicular extension with history of prior SCC	OR=1.18, 95% CI 0,67-2.04, p=0.57 i.e. no increased likelihood that patients with AK with follicular extension would have past SCCs compared to those without follicular extension	short follow-up Only one lesion per patient was chosen → might undererstimate the results Selected cases were examined by two board-certified Dermatopathologists	4
Smit et al 2013	To answer the clinical question whether the location of the AK influences the risk on skin cancer.	Systematic review	N=7 records; the two highest on scoring on relevance and validity were selected: Study 1: n=83 white patients with 98 biopsy-proven AK lesions (mean age: 69 years, 43 female)	Study 1: data to calculate the AR on skin cancer for the different locations in a time period between 6 and 60 months (mean duration 37 months) Study 2: 'time to progression to SCC' as main (prognostic)	Study 1: patients with AKs on the head/ upper extremities: lower AR to develop skin cancer than patients with lesions on the neck, trunk or lower extremities Study 2: no difference between time to conversion	Both studies have a limited sample size No risk of bias assessment performed Reliability of results is questionable. No statistical comaprisons provided for the results from study 1	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			Study 2: n=91 patients with 92 pathologically confirmed AKs at the same site of the subsequent SCC. (45 women, 59 patients were older than 69 years)	outcome. The study provided no data to calculate the absolute risk.	from AK to SCC among the different lesion sites (ANOVA, p=0.26)		
Vilcea et al 2012	To establish the value of the histopathologic examination in the diagnosis of AK, the assessment of the histopathologic type of AK, and the percentage of the malignant transformation.	Retrospective study	n=208 patients diagnosed with different types of cutaneous precancers	Gender, age, living environment, lesion's topography, the clinical diagnosis and results of the histopathologic examination of patients with AK or other precancerous lesions % of the malignant transformation of AK lesions	Gender, lesion's topography, environment: no relevant data with regard to AK transformation into SCC reported Mean age (years): benign AKs vs AKs with carcinomas: 66.2±12.45 vs 67.73±8.51, p=0.18	Cutaneous horn and actinic cheilitis were excluded Authors report most data on 'precancerous lesions' (including Bowen disease, keratoacanthoma) instead on AK Selection bias likely	4
Wallingford et al 2015	To estimate the risk of developing SCC in the short to medium term in renal transplant recipients (RTRs)	Multicentric cohort study	n=452 white RTRs mean age 53 years, mean duration of immunosuppression was 11 years	Risk of developing SCC in the short to medium term (OR, 95% CI)	RTRs with AKs and field change (OR=93, 95% CI 9,7-890, n = 15) RTRs with AKs but	Representative population (all RTRs are referred to these clinics after transplantation for follow-up)	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					no field change (OR 20, 95% CI 2.1-195, n =4) compared with the one person with SCC but no prevalent keratotic lesions. 58 RTRs with AKs but no field change, 4 (7%) developed SCCs, compared with 15 (21%) of the 70 with AKs and field change 55% of SCC RTRs developed the malignancy directly in an area of field change The predominant site for SCC in an area of field change was the scalp (n = 5) and the face (n = 3)	Lack of knowledge of partcipants' history of skin cancer and AKs prior to immunosuppression	

Papers not included (n=17)

Author, year	Grund
Dika et al. 2016	No relevant prognostic facotrs reported
Choi et al. 2010	n=4 SCC (small sample size)
Werner et al. 2013	No relevant outcomes reported
Criscione et al. 2009	No relevant outcomes reported
Atasoy et al. 2009	No relevant prognostic facotrs reported
Giuffrè et al. 2008	Histological staining report
Mittelbronn et al. 1998	Histological staining, no relevant outcomes reported
Suchniak et al. 1997	No relevant information reported
Kazama et al. 1994	No relevant prognostic facotrs reported
Marks et al. 1988	No relevant prognostic facotrs reported
Berhane et al. 2002	Histological staining report
Ruini 2015	Case report
Helfand et al. 2001	No relevant prognostic facotrs reported
Harvey et al. 1996	No relevant data reported with regard to research question
Thompson et al. 1993	No relevant data reported with regard to the research question
Marks et al. 1986	No relevant data for research question reported
Mostow et al. 1992	No relevant prognostic facotrs reported

2.1.5. Literature

Fernandez-Figueras MT, Carrato C, Saenz X, et al. Actinic keratosis with atypical basal cells (AK I) is the most common lesion associated with invasive squamous cell carcinoma of the skin. Journal of the European Academy of Dermatology and Venereology : JEADV 2015;29(5):991-7. doi: 10.1111/jdv.12848 [published Online First: 2014/11/28]
Fuchs A, Marmur E. The kinetics of skin cancer: progression of actinic keratosis to squamous cell carcinoma. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al] 2007;33(9):1099-101. doi: 10.1111/j.1524-4725.2007.33224.x [published Online First: 2007/09/01]
Heerfordt IM, Nissen CV, Poulsen T, et al. Thickness of Actinic Keratosis Does Not Predict Dysplasia Severity or P53 Expression. Scientific reports 2016;6:33952. doi: 10.1038/srep33952 [published Online First: 2016/09/28]
Jiyad Z, O'Rourke P, Soyer HP, et al. Actinic keratosis-related signs predictive of squamous cell carcinoma in renal transplant recipients: a nested case-control study. The British journal of dermatology 2016 doi: 10.1111/bjd.15019 [published Online First: 2016/09/02]
Pandey S, Mercer SE, Dallas K, et al. Evaluation of the prognostic significance of follicular extension in actinic keratoses. The Journal of clinical and aesthetic dermatology 2012;5(4):25-8. [published Online First: 2012/06/19]
Smit P, Plomp E, Neumann HA, et al. The influence of the location of the lesion on the absolute risk of the development of skin cancer in a patient with actinic keratosis. Journal of the European Academy of Dermatology and Venereology : JEADV 2013;27(6):667-71. doi: 10.1111/jdv.12008 [published Online First: 2012/10/13]
Vilcea AM, Vilcea ID, Georgescu CV, et al. The value of the histopathologic examination in the diagnosis and management of the actinic keratosis. Romanian journal of morphology and embryology 2012;53(4):927-34. [published Online First: 2013/01/11]
Wallingford SC, Russell SA, Vail A, et al. Actinic keratoses, actinic field change and associations with squamous cell carcinoma in renal transplant recipients in Manchester, UK. Acta dermato-venereologica 2015;95(7):830-4. doi: 10.2340/00015555-2098 [published Online First: 2015/03/19]

2.2. Question I.2. Which prognostic factors are important for metastatic SCC?

(Frage I.3. Welche prognostischen Faktoren sind für die Metastasierung beim PEK von Bedeutung?) Beantwortung durch Orientierende Recherche

2.2.1. PICO

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Patients with metastatic SCC	n.a. (no intervention)	n.a. (no intervention)	Rate of progression to metastatic SCC Time to metastization Prognostic factors of metastization (clinical or histological)

2.2.2. Databases, search strategy, number of results

Databases	Searching strategy	Date	Number of results
1. Search			
Medline	(squamous[Title] AND (skin[Title] OR cutaneous[Title])) AND prognos*[title/abstract] NOT case report AND (English[Language] OR German[Language])	15th December 2016 (initial search) Update 30th May 2017	209 225

Databases	Searching strategy	Date	Number of results

2.2.3. Selection criteria

Literature selection	
Total number of results	225
Inclusion criteria	Observational studies with defined outcomes, cohort (longitudinal) studies, retrospective studies (case control)
Exclusion criteria	Case reports, small sample size (n<10), studies without relevant outcomes
Number of results after abstract searching	65
Number of full texts reviewed	57

2.2.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Abhikair et al. 2017	Identification of tumor-specific antigens as therapeutic targets in squamous cell carcinoma (SCC) patients	Retrospective review; n=31 (7 healthy participants and 24 SCC patients)	SCC patients with available formalin-fixed paraffin embebed-samples for whom long-term clinical follow-up was available	To draw correlations between MAGEA gene expression, tumor characteristics and clinical outcomes	9 of 24 SCC patients showed MAGEA3 positivity. 7 of the 9 developed perineural invasion either within the index lesion or at a	Cancer testis antigens as MAGEA3, MAGEA4 and MAGEA6 are selectively up-regulated in SCC. MAGEA3 may be a	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					separate site. All patients who subsequently developed metastasis of SCC (n=3) or disease specifc death (n=2) showed MAGEA3 positivity. 12 patients had stage 2B or higher tumor (Brigham and Woman's Hospital staging system-BWH), and 10 of them had perineural invasion on histology or eventuating metastasis or death related with SCC. Marked upregulation of MAGEA3 expression was observed in BHW stage 3. MAGEA3 expression was significantly associated with BWH	useful biomarker of high risk and poor prognosis in aggressive cutaneous SCC. If patients could be identified early enough, MAGEA3 vaccine could potential be beneficial.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					stage 2B or higher. 10 of 24 patients showed a high expression of MAGEA3 protein in at least one of their tumors. 7 of these had either perineural invasion, metastasis or death related to SCC. High MAGEA3 expression on immunohistochemistry had a positive predicted value of 91% for tumor invasiveness with 10 out of 11 highly staining tumors being invasive on histological examination. MAGEA3 protein expression was significantly associated with poor histological		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					differentiation ($p<0.05$) and advanced BWH tumor stage ($p<0.001$). MAGEA3 positive cells co-expressed pankeratin and ki67, confirming expression of MAGEA3 in rapidly deviding keratinocytes.		
Ashford et al. 2017	This review outlines the clinical problems in high-risk and metastatic cutaneous SCCs, the known genetic events and molecular mechanisms, and identify avenues for further investigation and potential therapy	Review	Patients with metastatic cutaneous SCC	To report the known genetic events and molecular mechanisms in high-risk primary cutaneous SCC and metastasis To identify avenues for further investigation and potential therapy.	The authors report data from the following genes/genetic alterations available for SCC: TP53 family, NOTCH family, RAS family, CDKN2A, And the following topics: Protein tyrosine phosphatase		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					receptors Epigenetic changes in cutaneous squamous cell carcinoma Stromal influences and epithelial-mesenchymal transition in the tumor microenvironment The limited exploration of the mutational landscape has identified a very high rate of mutation, but principally inactivation of tumor suppressors, rather than activation of oncogenes.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Sophisticated sequencing regimens and the use of expanded bioinformatic capabilities promise to further unlock key details around metastasis of cutaneous SCC. By doing so, reliable diagnostic measures of risk of metastasis can be developed. Such tests would ideally stratify risk in the primary cutaneous SCC, so that surveillance can be better targeted and curative treatment can be tailored to the biology of the tumor.		
Bachar et al. 2016	To analyze independent prognostic factors for metastasis and	Retrospective monocenter study; n=71	Patients with metastatic cutaneous SCC over a 15-year period treated in one	Disease free survival (DFS) and OS	Poorly differentiated carcinoma was an independent predictor of poorer		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	survival		center		DFS, and older age was found to be an independent predictor of poorer OS No significant difference in DFS or disease-specific survival was found among patients with parotid involvement, neck involvement, or both The site of nodal involvement appeared to have no prognostic significance in patients with metastatic cutaneous SCC of the head and neck		
Barksdale et al. 1997	To discuss general prognostic factors for nonmelanocytic skin cancers (SCC and BCC)	Review article	Patients with SCC and BCC	Risk of recurrence, metastasis, and development of subsequent skin cancers	Risk factors are solar radiation, Ionizing radiation, skin type, immuno-suppression, HPV, chemical exposures,		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					scars, ulcers, and sinus tracts, geno-dermatosis. Many observers have not found a correlation between histologic subtypes of BCC and metastasis. Recurrence rates are less for Mohs micrographic surgery. Develop-ment of one skin cancer is a warning that others will develop. 52 % of patients with a history of SCC develop a new primary NMSC within 5 years.		
Bota et al. 2017	To review and compare the risk factors and clinical behavior of cSCC, omSCC, and lip SCC, review tumor biology of squamous cell carcinoma, and compare work-up	A comprehensive PubMed and MEDLINE database search was performed with comparison of primary literature on cSCC, omSCC,	Comparison of primary literature on cSCC, omSCC, and lip SCC	To review and compare the risk factors and clinical behavior of cSCC, oral mucosal SCC, and lip SCC, review tumor biology of squamous cell carcinoma, and	The American Joint Committee on Cancer (AJCC) has developed separate staging guidelines for both cSCC and omSCC. In 2010, the guidelines for cSCC	Lip SCC exhibits rates of nodal metastasis and death that are intermediate between cSCC and omSCC. Lip SCC is an	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	and treatment algorithms for lip SCC	and lip SCC.		compare work-up and treatment algorithms for lip SCC	were revised to include high-risk features of cSCC for T-staging. Tumors with origin on the mucosal lip are staged concomitantly with the omSCC AJCC staging guidelines. These 2 sets of guidelines are largely similar with the exception of T2 definition, where the AJCC guidelines for omSCC defines T2 as any tumor between 2 and 4 cm diameter. The impli-cations of this difference are unclear. The Brigham and Women's Hospital (BWH) staging system was developed to risk stratify patients with	overlapping entity that poses many challenges to clinicians. Although there is evidence to suggest that lip SCC may have biochemical roots in either cSCC or omSCC, practitioners in both dermatology and otolaryngology should be mindful that lip SCC behaves differently than similar SCCs in their respective fields. Dermatologists should consider that lip SCC may be more aggressive than cSCCs and portends a more worrisome outlook. Likewise, otolaryngologists should remember that while omSCC may benefit from elective LND, the current evidence	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					T2 tumors. Patients in this study were staged by both AJCC and BWH criteria, with a similar number of patients comprising AJCC T2 and BWH T2a/T2b stages. There remains debate over the optimum staging system for cSCC, and risk stratification of cSCC has been limited given the lack of standard reporting and larger population- based studies. Recommendations and modalities of imaging for lip SCC are continuously evolving. In the cutaneous NCCN guidelines, imaging	does not support this intervention for lip SCC. Accurate staging modalities of SCC are evolving, and it is essential to be aware of the practice guidelines as well as imaging and treatment recommendations to optimize patient care and maximize outcomes.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					is recommended for patients who have a clinically positive lymph node examination, extensive local disease, or perineural invasion on histopathology. In contrast, the NCCN guidelines for head and neck cancer recommend that imaging be considered in the initial work-up for patients presenting with lip or omSCC, but these recommendations are left intentionally broad. Imaging modalities include computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), and positron emission tomography (PET).		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					For assessment of the primary tumor, it has been shown that MRI more accurately estimates tumoral depth. Evidence directly comparing CT versus MRI for omSCC is limited. The MRI is superior with respect to soft-tissue imaging capabilities; however CT is adequate for T staging and may be more readily available. Detection of bony invasion is important as it upstages primary tumors to a T4 by the AJCC guidelines. The MRI has high sensitivity and specificity of 93% and 93%, respectively, for detection of bony		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					invasion. The MRI was found to have a higher sensitivity than CT—94% versus 83%. Despite the limitations in current evidence, the authors feel that MRI may offer an advantage over CT with regard to invasion of bone, but further studies are needed. Contrast CT, MRI, and ultrasound (US) are widely used in the detection of nodal involvement. Contrast CT and MRI have been shown to be equivalent in assessing extent of nodal disease and extranodal extension. There is a need for detection of		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					microscopic nodal involvement; however it has been demonstrated that PET/CT cannot predict the need for surgical LND and should not be used to guide management. Nonetheless, it has been suggested that PET/CT may have a role in surveillance of the N0 neck.		
Brantsch et al. 2008	To prospectively analyse the key factors predicting metastasis and local recurrence in cutaneous SCC	Prospective monocenter study; n= 615	White patients who underwent surgery for cutaneous SCC between Jan 1, 1990, and Dec 31, 2001	Primary endpoints were time to metastasis and time to local recurrence, defined as the time from date of diagnosis of the primary tumour to the date of diagnosis of metastasis or local recurrence	During a median follow-up period of 43 months, 26 (4%) of 615 patients developed metastases and 20 patients developed local recurrence (3%). Tumours 2.0 mm or less in thickness did not metastasise. Metastases occurred in 12 (4%) of 318 tumours between	Only SCC greater than 2.0 mm in thickness are associated with a significant risk of metastasis. Tumours greater than 6.0 mm are associated with a high risk of metastasis and local recurrence. Desmoplastic growth is an independent risk factor for local	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					2.1 mm and 6.0 mm in thickness, and in 14 (16%) of 90 tumours with a thickness greater than 6.0 mm. On multivariate analysis, key prognostic factors for metastasis were increased tumour thickness (hazard ratio 4.79 [95% CI 2.22–10.36]; p<0·0001), immunosuppression (4.32 [1.62–11.52]; p=0.0035), localisation at the ear (3.61 [1.51–8.67]; p=0.0040), and increased horizontal size (2.22 [1.18–4.15]; p=0.0128). The risk of local recurrence depended on increased tumour thickness (6.03 [2.71–13.43];	recurrence.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					p<0·0001) and desmoplasia (16.11 [6.57–39.49]; p<0.0001).		
Brinkman et al 2015	To investigate a possible correlation between cutaneous SCC differentiation, local recurrence, metastasis, and patient survival	Retrospective study; n= 131; n (SCC)= 155	Patients with SCCs treated between 2001 and 2008	Association of different tumor characteristics with survival Overall survival (OS) Metastasis-free survival	No significant correlation between tumor differentiation grade and local recurrence could be found. Tumor differentiation was an independent prognostic factor for metastatic disease and OS. Incomplete excision of the first tumor showed an increased relative risk of dying of SCC of 4.0 (95% confidence interval, 2.4-6.6; P < 0.001) compared to excision with clear margins. Metastasis-free survival at 5 years was significantly	Tumor differentiation grade is an independent prognostic factor for OS. This finding suggests poor differentiation of cutaneous SCC alone is sufficient to upstage the primary tumor in the TNM classification system. Although the introduction of a unified N system for mucosal SCC and cutaneous SCC has added complexity, it does not translate into optimal distribution and stratification for metastatic cutaneous SCC.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					higher in well-differentiated tumors (70%) compared to moderately (51%) and poorly differentiated SCCs (26%; P = 0.012); identical percentages were found for OS (P = 0.005).		
Brunner et al 2014	Assessment of the new nodal classification for cutaneous squamous cell carcinoma and its effect on patient stratification	Retrospective study; n= 672	Patients with metastatic cutaneous SCC from 2 prospective cancer center databases, treated with curative intent between 1980 and 2010	Disease-specific survival (DSS) and OS.	The differentiation between N1 and N2 subgroups demonstrate little prognostic importance in cutaneous SCC, whereas survival is significantly worse for N3 DSS and OS. Immunosuppression radiotherapy, the treating institution, and the radiotherapy–institution	Although the current AJCC cutaneous SCC nodal staging system is much more descriptive, the added complexity does not necessarily provide clinicians with a higher degree of useful prognostic information.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					interaction were found to be significant covariates. The majority of patients were classified N1 (44%) or N2b (39%). N2c was rare (2%) and there was no particular relevance to being assigned to this group.		
Campoli et al 2014	Investigate clinical, histologic and treatment characteristics associated with incidental PNI, histologic PNI extending beyond the tumor bulk	Multicenter prospective analysis of a 5-year follow-up study; n= 753	Patients with CSCC undergoing Mohs micrographic surgery	Association of different tumor characteristics with PNI	The incidence of PNI was 4.6% in 753 CSCC an 653 Patients. PNI was significantly associated with tumors of the head and neck (P = .039), larger tumor diameter (P<.001), presence of clinically palpable lymphadenopathy (P = .012), and recurrent (P<.001) and painful (P<.001)	PNI may serve as a marker to improve the precision in the prognostic assessment of patients with CSCC.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					tumors. PNI was significantly associated with poor tumor differentiation (P<.001), greater tumor thickness (P<.001), a greater number of Mohs stages (P<.001), and larger estimated maximum Mohs margin (P<.001) required to clear the tumor.		
Canueto et al 2016	Investigation of clinical and histopathological features including EGFR expression by immunohistochemistry, FISH, QPCR and events of bad clinical evolution, in CSCC	Retrospective study; n=94	Patients with CSCC	Lymph node metastasis and progression EGFR expression	EGFR were detected in 85 (90.4%) cases, with overexpression in 33 (35.1%) cases, and aberrant EGFR expression in the cytoplasm in 50 (53.1%) cases. EGFR overexpression in the primary tumours was associated with lymph node progression, TNM stage progression	EGFR overexpression has prognostic implications associated with lymph node metastasis and progression in CSCC	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					and proliferation (Ki-67 staining) in CSCC. EGFR overexpression and poor grade of differentiation were the strongest independent variables defining lymphnode metastasis and progression in CSCC in a logistic regression model. EGFR overexpression in the primary tumours was associated with lymph node progression, TNM stage progression and proliferation (Ki-67 staining) in CSCC.		
Canueto et al 2016	This study provides further evidence regarding	Retrospective study; n=94	Patients with SCC	Nodal progression (NP) and short DFS	Podoplanin expression was observed in 48.9% of	This article provides evidence supporting the implication of	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	the prognostic implications of podoplanin expression in primary CSCCs, and highlights its relevance in predicting DFS				the cases, the expression was considered moderate to intense in 19 of the cases. Moderate/intense podoplanin was associated with infiltrative growth pattern, desmoplasia, lymphovascular invasion, higher risk of nodal progression (NP) and short DFS, specifically with a short latency to NP	podoplanin expression as a marker of bad prognosis of CSCC	
Chen et al 2014	To investigate p300 expression in cutaneous squamous cell carcinoma cSCC tissues and its effect on the outcome of patients with cSCC	Retrospective study; n=165	SCC patients	Lymph node metastasis Recurrence free-survival	High expression of p300 was positively correlated with lymph node metastasis (P = 0 006) and advanced clinical stage (P < 0 001). In univariate survival analysis, high expression of p300	High p300 expression is associated with aggressive features of cSCC and will be a promising biomarker for predicting clinical outcomes.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					was correlated with poor patient outcomes in terms of recurrence-free survival (P = 0 006) and OS (P < 0 001). Moreover, p300 expression was evaluated as an independent prognostic factor in a multivariate analysis		
Cerpelis et al 2002	To characterize tumors with the greatest tendency to metastasize.	Retrospective study; n=200	Patients diagnosed with invasive SCC managed by Mohs surgery from 1988 to 1998	Recurrence and development of metastasis	Size, Clark's level, degree of differentiation, the presence of small tumor nests, infiltrative tumor strands, single-cell infiltration, perineural invasion, acantholysis, and recurrence all correlated strongly with metastasis. Location, ulceration, inflammation, and	Patients with tumors that exhibit certain clinical and histologic features are more likely to metastasize and need close follow-up to detect recurrence and metastasis early, allowing for appropriate life-saving intervention. Sentinel lymph node biopsy should be considered in patients with high-	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Breslow depth did not correlate with the development of metastasis.	risk SCC	
Ch'ng 2013	To assess whether primary tumor characteristics are independent prognostic factors.	Retrospective study; n= 239	Patients treated for metastatic cutaneous SCC from 1978 to 2010	DSS, OS	On multivariable analysis, tumor differentiation (HR, 0.2; 95% CI, 0.1–0.8; p= .03) was found to be significantly associated with DSS, unlike margin status (p=.23), tumor size (p=.21), and thickness (p=.11). Patient, treatment, and nodal factors were confirmed to be important predictors of survival	Pathological features of the primary lesion bear little importance in the presence of established nodal metastasis, other than tumor differentiation	4
Ch'ng et al 2008	Clinical outcome of patients with head and neck metastatic cutaneous SCC treated at the four major head & neck surgical oncology centers in New	Retrospective study; n=174	Patients treated with a curative intent from 1990 to 2005 were identified and re-staged.	DSS, recurrence DFS and OS Prognostic impact of impact of each proposed P and N sub-group	The 5-year DSS rate was 69%, and the locoregional recurrence rate was 36%. The presence of parotid (P<0.01) or		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	Zealand and tests the proposed staging system, with modifications for pathological staging				neck (P<0.01) disease, immunosuppression (P<0.01) and the uptake of radiotherapy (P<0.01) impacted significantly on survival. Increasing P or N category worsened the prognosis significantly.		
Clark et al. 2013	To compare the 7th edition AJCC staging of nodal metastases from cSCC with the N1S3 staging system	Retrospective study; n=603	Patients from two prospective cancer center databases	DSS according to N stage compared to AJCC N- stage	The N1S3 staging system functioned well in terms of distribution and stratification of patients. The distribution of patients within the AJCC staging system was problematic with three groups (N2a, N2c, and N3) containing less than 10 % of patients without any prognostic	The 7th edition of the AJCC Staging Manual for cSCC is a major advance over the 6th edition; however, the AJCC staging system does not stage patients as well as the N1S3 staging system despite being more complicated.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					relevance. The estimated HR for N1S3-IInand N1S3-III was 1.4 and 2.1, respectively, indicating anclinically useful, monotonic, and linear increase in risk. The estimated HR for N2a, N2b, N2c, and N3 was 1.1, 1.5, 1.4,nand 2.1, indicating that the increase in risk was neither clinically useful nor monotonic. Stratification of patients within the AJCC staging system was poor in terms of monotonicity (N2c) and distinctiveness (N2a). The performance of the AJCC		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					and N1S3 staging systems was similar despite the AJCC staging being more complex. The N1S3 staging system for cSCC is preferred on the grounds of better distribution, stratification, and parsimony. (Kolmogorov–Smirnov test, p = 0.06).		
Czerwonka et al 2017	The purpose of this study was to validate this staging system using a North American cohort, and to compare it to the O'Brien P (Parotid) and N staging system	Database search; n=136	All patients with cSCC metastasis to the parotid gland treated at three major Canadian tertiary referral centers from December 1999 to March 2015	OS PFS	Of 136 patients identified, 80% had a documented history of previously treated head and neck cSCC an average of 27 months prior to presentation. Average size of the parotid lesion at recurrence was 4.5 cm. Ninety-six percent of patients underwent surgical		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					resection of the parotid metastasis. Five-year overall and DSS is 79% and 55%, respectively. Only cSCC staging and cSCC-N category had statistically significantdifferences between groups. cSCC staging had the largest percentage of variation in OS explained.		
de Lima Vasquez et al 2008	To identify risk factors for lymph node metastasis and outcome in cSCC	Retrospecitve study; n=57	Patients with locally advanced SCC of the trunk and extremities treated from October 1987 to November 2005	Lymph node metastasis at presentation (N1) or during follow up (N1f) OS	Fifteen patients presented with previous skin lesions. Thirty-six were classified as T3 tumors and 21 as T4; 46 were N0, and 11, N1. Eleven N0 patients presented lymph node metastasis during follow up. Univariate analysis	Local advanced tumors are at risk of lymph node metastasis. Increased risk is associated to previous lesions at tumor site. T4 classification have worse prognosis. Lymph node recurrences in N0 patients, once treated, did not affect survival.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					identified previous skin lesions (ulcers and scars) as risk factor for lymph node metastasis (p = 0.047). Better overall survival was demonstrated for T3 (p = 0.018) classification. N0 patients who presented lymph node metastasis during follow up (submitted to lymphadenectomy) had similar survival to patients without lymph node recurrence (p = 0.219).		
Erkan et al. 2017	To analyze the outcomes of multimodal treatment entailing the en bloc surgical resection and post-operative	Retrospective review; n =21	Patients with the diagnosis of clinical perineural invasion (PNI) from a cutaneous HNSCC	DFS OS Correlation of OS and DFS with surgical factors,	Of 21 patients with clinical PNI from cutaneous HNSCC, 7 patients (33%) were previously treated for their disease with primary	The retrospective study of this rare clinical entity demonstrates that multimodal treatment can achieve favorable	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	radiotherapy for previously untreated patients as well as the outcomes of the salvage treatment for previously treated patients with clinical perineural invasion (PNI) of the trigeminal and facial nerves from cutaneous HNSCC at a single institution			such as margin status, previous treatment, zone involvement, and trigeminal involvement (branch-specific), as well as the pretreatment and post-treatment pain scores	radiotherapy. Negative tumor margins were achieved in 18 patients (86%). Three of the 7 patients (43%) undergoing salvage surgery had positive margins. One-year and 3-year DFS for previously untreated patients was 91% and 67%, respectively, whereas 1-year and 3-year DFS was 72% and 28%, respectively, for the previously treated patients. Previous radiotherapy, ophthalmic nerve involvement, and positive mar- gins portended poorer survival outcomes in this study.	survival outcomes.	
Farasat et al 2011	To describe the AJCC cSCC staging	Review for the rationale for and	Available published studies on	Classification of patients into	A new AJCC cSCC T classification is	The data available for analysis are still	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	system and rationale for the T (tumor characteristics) staging	characteristics of the new AJCC staging system	prognostic factors for cSCC were reviewed and analyzed over a period of 3 years from 2005 through 2008. For nodal (N) criteria, prospective data from randomized trials, case controlled studies, or multivariate analyses were prioritized over case series and retrospective reviews	primary tumor (T), regional lymph nodes (N), and distant metastasis (M).	presented. The T classification is determined by tumor diameter, invasion into cranial bone, and high-risk features, including anatomic location, tumor thickness and level, differentiation, and perineural invasion.	suboptimal, with limited prospective outcomes trials and few multivariate analyses. The new AJCC staging system for cSCC incorporates tumor-specific (T) staging features and will encourage coordinated, consistent collection of data that will be the basis of improved prognostic systems in the future	
Gof et al 2012	This study evaluates the St Vincent's Hospital, Sydney experience between 1996 and 2006	Retrospective monocenter study; n=67	Patients with metastatic cSCC to the parotid gland who were treated with curative intent during a 10-year period (1996 to 2006)	OS and DSS Multivariate analysis of factos influencing OS and DSS	The two-year and five-year DFS rate was 0.91 and 0.83 respectively. OS was only significantly correlated to the extent of parotidectomy (superficial versus total; P = 0.0256).	Very small group of patients. This study confirmed the association of adverse prognostic implication of positive margins on DFS. Immune compromise was not a significant factor	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					The only parameter that significantly correlated with DFS was margin status (close/negative versus positive P = 0.0348). Other parameters of immune suppression, perineural invasion, extra capsular extension, degree of tumour differentiation, number of positive nodes, extent of neck dissection and radiotherapy dosage delivered did not confer prognostic significance. Adverse prognostic implication of positive margins on DFS	in this small group. Further studies are warranted in this population	
Gonzalez-Guerrero et al. 2017	To assess the correlation of tumor budding with the	Retrospective study, n= 98	Samples from 49 primary nonmetastatic and	To assess the relationship between tumor budding,	Tumor budding was observed in 45 cases of 98 (46%).	This was a retrospective study limited to cSCCs of	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	clinicopathologic features and the prognostic value of tumor budding in cutaneous squamous cell carcinoma (cSCC).		49 primary metastatic cSCCs to regional lymph nodes	clinicopathologic parameters, and patient survival	High-intensity budding (>=5 tumor buds) was observed in 20 tumors. Presence of tumor buds was a significant risk factor for nodal metastasis with crude and adjusted hazard ratios (HRs) of 8.92 (95% CI, 4.39-18.1) and 6.93 (95% CI, 3.30-14.5), respectively, and for reduced OS time (crude and adjusted HRs of 2.03 [95% CI, 1.26-3.28] and 1.72 [95% CI, 1.05-2.83], respectively).	the head and neck. Examined tumors were >2 mm thick, and all were from a primary excision. These results indicate an increased frequency of nodal metastasis and risk of death in patients with tumor buds.	
Griffiths et al 2002	Prognostic factors for primary squamous cell carcinoma of the skin treated by conventional surgery	Retrospective monocenter study; n= 71	A 6 year (1990-1995) cohort	OS and DFS Prognostic factors related to histologic parameters.	64 (41%) died within 5 years of treatment from causes other than squamous cell carcinoma, and were therefore defined as inde-terminate. The remaining 93 patients were		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					determinate patients; 85 lived without recurrence or metastasis for at least 5 years after treatment, and eight died of their disease. Comparing the groups who were alive or had died of disease at 5 year follow-up, the tumour diameter and tumour thickness were significantly greater in the eight patients who died (P = 0.02 and P =0.0057, respectively) but there were no significant differences between the two groups with regard to age, deep resection margin clearance, lateral epidermal resection margin clearance, lymphocyte response or degree		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					of tumour differentiation.		
Haisma et al 2016	To identify independent risk factors for LN metastasis in patients with HNcSCC and to evaluate the impact of LN metastasis on prognosis	Retrospective monocenter study; n=363	Patients with cHNSCC	The primary endpoint was time to LN metastasis. Further endpoints: LN metastasis-free survival, DSS, and OS.	Three hundred thirty-six patients with 545 primary HNcSCCs were included. The median follow-up period was 43 months (range, 1-176 months). LN metastasis occurred in 55 patients (16.4%). The following independent risk factors of HNcSCC for the development of LN metastasis were identified: location on the ear, tumor diameter >50 mm, moderate and poor differentiation, and tumor thickness >2 mm. There was a		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					significant decline in DSS and OS in patients with LN metastasis compared to patients without LN metastasis		
Halifu et al 2016	To investigate the expression of Wnt1 and SFRP1 to understand the role of the Wnt signaling pathway in skin development and function	Prospective monocenter study; n=35	Patients with cSCC recruited between January 2012 and February 2014 from the Dermatology Department of the Xinjiang Uygur Autonomous Region People's Hospital at Urumchi City, China	Quantification of Gene and protein expressions of Wnt1 and SFRP1 by immunohistochemistry and western blotting	Wnt1 expression was significantly higher ($P < 0.05$) in CSCC samples than in normal skin cells of the control subjects; in contrast, SFRP1 expression was significantly lower in CSCC tissues than that in tissues of control subjects ($P < 0.05$). Wnt1 expression ($P < 0.05$) was found to be correlated with histopathological differentiation in CSCC, and negatively correlated with SFRP1 expression in CSCC	The authors concluded that Wnt1 and SFRP1 play important roles in the development of CSCC and could be potent markers for diagnosis, prevention, and therapy of CSCC	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(rs = -0.473, P = 0.015).		
Hesse et al 2016	To characterise the invasion of cSCC by correlating the expression of the potential biomarker with metastatic risk and prognosis and investigated if there are prognostic parameters for metastasis	Retrospective study; n=98	102 samples of metastatic and non-metastatic cSCC and 18 corresponding skin and lymph node metastases	E-cadherin and podoplanin expression	E-cadherin was highly expressed in metastatic and non-metastatic cSCC and skin metastases. This suggests collective cancer invasion. However, E-cadherin was downregulated in poorly differentiated cSCC and lymph node metastases, suggesting partial EMT. Podoplanin was significantly upregulated in metastatic (p=0.002) and poorly differentiated (p=0.003) cSCC. Overexpression of podoplanin represented a statistically independent prognostic factor for	Collective cancer invasion is likely in cSCC. In lymph node metastases and poorly differentiated cSCC, partial EMT is possible.Podoplanin is an independent prognostic parameter for metastasis.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					DFS (p= 0.014).		
Hirshore, et al. 2017	To describe the clinical outcomes and prognostic factors for patients with node-positive head and neck cutaneous SCC (cHNSCC) who underwent lymphadenectomy	Retrospective single center study; n=149 lymphadenectomies	Patients with node-positive cHNSCC who underwent lymphadenectomy	OS Locoregional control rates	The median number of positive lymph nodes from 149 lymphadenectomies was 2 in the neck and 1 in the parotid gland. The 5-year OS and locoregional control rates were 50% and 77%, respectively. OS was worse among older patients (hazard ratio [HR], 1.04; p =.015), immunosuppressed patients (HR, 2.06; p=.034), and patients with a high total lymph node ratio calculated from the number of positive lymph nodes divided by the total number of nodes; multivariate analysis [MVA]; HR, 1.13; p=.019.	Low total lymph node ratio is associated with improved out-comes in node-positive cHNSCC	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Hong et al 2005	To analyze the outcome of patients with parotid area lymph node metastasis from primary scalp and facial cutaneous cancers	Retrospective monocenter study; n=20	Patients with a malignant parotid lymph node metastases diagnosed between1989 and 1999 from the University of Wisconsin Tumor Registry and Head and Neck Oncology Tumor Board	Outcome according to different treatment modalities (surgery vs surgery and ratdiotherapy).	Approximately 20% of patients (20 of 102) in this series with a malignant parotid mass had presumed metastasis from an identifiable skin primary tumor. The mean time from index lesion to presentation of regional spread was 13.5 months. Seventy percent of the patients (14 of 20) underwent surgery followed by radiation as locoregional therapy, whereas 30% underwent surgery alone. Six (30%) of 20 patients required some degree of facial nerve sacrifice. Three patients (15%) experienced sub-sequent loco-regional failure. Two	Parotid area lymph node metastases from scalp and facial cutaneous carcinomas require aggressive therapy to optimize loco-regional control. The addition of radiotherapy after parotidectomy is important and should be considered for optimal disease control. Selective neck dissection or radiation may be warranted at the time of parotidectomy. This combined approach is associated with high locoregional control rates and is generally well tolerated	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					of six patients from the surgery alone group and one of 14 patients who received surgery plus radiation therapy experienced loco-regional relapse.		
Jambusaria-Pahlajani et al 2013	To identify risk factors for poor outcomes in CSCC and evaluate the 2010 American Joint Committee on Cancer (AJCC) tumor (T) staging system's ability to stratify occurrence of these outcomes	Retrospective cohort study-, n=256	Patients having primary CSCC with 1 or more risk factors from January 1, 1998, through June 30, 2005. Patients without risk factors were excluded since the risk of recurrence and metastasis in this group is low. Recurrent tumors were also excluded.	Outcomes of interest were local recurrence, nodal metastasis, disease-specific death, and all cause death.	83% of nodal metastases, 92% of deaths from CSCC occurred in AJCC stage T2 cases. Four risk factors were found to be statistically independent prognostic factors for at least 2 outcomes of interest in multivariate modeling. These factors (poor differentiation, perineural invasion, tumor diameter 2 cm, invasion beyond subcutaneous fat)	The proposed alternative tumor staging system offers improved prognostic discrimination via stratification of stage T2 tumors. Meanwhile, stage T2b tumors are responsible for most poor outcomes and may be a focus of high-risk CSCC study.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					were incorporated in the alternative staging with 0 factors indicating T1, 1 factor indicating T2a; 2 to 3 factors, T2b; and 4 factors or bone invasion, T3. Stages T2a and T2b significantly differed in incidences of all 4 end points. Stage T2b tumors comprised only 19% of the cohort but accounted for 72% of nodal metastases and 83% of deaths from CSCC.		
Jensen et al 2010	To better define prognostic criteria for cSCC	Retrospective case-control single center analysis; n=165	165 consecutive patients with documented aggressive cutaneous SCC in the Aggressive Squamous Cell Carcinoma database at the Southern	Comparisons included demographics, histology, immunohistochemical protein expressions (Ki-67, p53, E-cadherin, cyclin D1).	Demographic features were similar between cases (n=30) and controls (n=30). Non-well differentiated tumors were larger (1.8 cm versus 1.3	Tumor differentiation and depth are important pathologic and prognostic criteria for cutaneous squamous cell carcinoma. Immunohistochemis	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			Arizona Veterans Affairs Health Care System from January 29, 2001 to February 10, 2006	Clinical outcomes	cm, P=0.08), deeper (0.81 cm versus 0.32 cm, P < 0.0001), and had greater recurrence (P=0.003). Non well-differentiated tumors showed increased proliferation rate, Ki-67 index (77% versus 61%, P=0.001); no significant difference in activity of p53, E-cadherin, and cyclin D1 between the two groups.	try helps describe patterns of biomarker protein expression and may exemplify aggressive subtypes	
Kelder et al 2012	To evaluate the prognosis of patients with soft tissue metastases (STM) from head and neck cSCC, and to compare this with that of node metastases with and	Retrospective monocenter study; n= 164	Patients with cSCC metastatic to the parotid and/or neck treated by primary surgical resection between 1987 and 2007	OS and DFS	The population included 164 patients with a median follow-up of 26 months. There were 8 distant and 37 regional recurrences. There were 22 cancer-		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	without extra nodal spread (ENS).				specific deaths, and 29 patients died. Soft tissue metastase (STM) was a significant predictor of reduced OS (hazard ratio 3.3; 95% confidence interval 1.6–6.4; P = 0.001) and DFS (hazard ratio 2.4; 95% confidence interval 1.4–4.1; P = 0.001) when compared to patients with node disease with or without extranodal spread. After adjusting for covariates, STM and number of involved nodes were significant independente predictors of overall and DFS.		
Krediet et	To quantify	Retrospective	Patients diagnosed	The association	Lymphatic vessel	Small colective	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
al 2016	lymphangiogenesis in SCC. Vascular parameters were evaluated and compared with respect to their predictive power for tumor metastasis.	monocenter case-control study; n=30 tumors	with SCC, who had surgery between January 2005 and September 2009 at the Department of Dermatology, Charité University Hospital, Berlin. Fifteen metastatic patients were compared to 15 non-metastatic patients	between the parameter tumor thickness and the lymphangiogenesis parameters LVD, LVA, and D2-40-Chalkley count.	density, relative lymphatic vessel area, and lymphatic Chalkley count were significantly elevated in metastatic SCC. Tumor thickness was significantly higher in metastatic SCC, and had the highest predictive power for metastatic disease. Tumor thickness was a significant predictor of lymphangiogenic parameters.		
Kreppel et al 2013	To assess the impact of podoplanin expression on regional lymph node metastasis, locoregional recurrence, and prognosis	Monocenter retrospective study; n=63	Podoplanin expression was examined immunohistochemically in treatment-naive patients with cHNSCC	OS and locoregional control	In 40 patients (63.5%), podoplanin was expressed in the tumor cells. The x2-test revealed that podoplanin expression was associated with the	Small colective	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					number of tumorous lymph nodes (P< 0.001). The OS was significantly influenced by podoplanin expression (P< 0.001). None of the patients with high levels of podoplanin expression survived, whereas the 5-year OS for patients with podoplanin-negative tumors was 91.3%.		
Kusters-Vandevelde et al 2010	To assess the frequency of CDKN2A and TP53 in metastatic CSCCs, to study possible relations between mutation status and protein expression of both tumor suppressors	Multicenter retrospective study; n=35	Patients with metastatic CSCC from 14 pathology departments in the Netherlands	OS DSS	CDKN2A was mutated in 31% of the metastases and their primary tumors, while the TP53 gene was mutated in 51% of the metastases. P53 protein expression was significantly associated with missense type of	Small collective	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					mutations (p=0.002). CDKN2A mutations were significantly associated with disease-specific death (p=0.001). A significant difference was observed in DSS between patients with or without a CDKN2A mutation (p=0.010), while this was not the case for TP53. At univariate Cox's regression analysis tumor size (p=0.010), invasion depth (p=0.030) and CDKN2A mutations (p=0.040) were significantly related to shorter DSS. At multivariate Cox's regression only tumor size had an		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					adverse effect on survival (p=0.002)		
Li et al 2015	To evaluate the prognostic significance of CD200 in cutaneous squamous cell carcinoma (CSCC) compared to normal tissue	Monocenter retrospective study; n=120	CSCC patients who were confirmed by pathological and clinical diagnoses in General Hospital of Beijing Military Region from October 2009 to February 2015	OS of the patients according to the CD200 expression. Association between CD200 expression and the clinical features were estimated by chi-square test.	Patients with high expression level of CD200 had a shorter OS than those with low expression (31.3 months vs. 41.9 months) and there was a significant difference between them (log-rank test, P<0.001). Increased expression of CD200 was detected in the tumor tissues compared with the corresponding normal tissues both at mRNA and protein level. And CD200 expression level was associated with tumor differentiation grade (P=0.041) and clinical stage (P=0.004).		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Cox regression analysis indicated that CD200 could be an independent marker for the prognosis of CSCC.		
Manyam et al 2017	The current study is an effort to validate preliminary findings in a large cohort from 3 institutions and to further elucidate the association between immune status and disease-related outcomes in patients with cutaneous HNSCC (cHNSCC)	Multi-institutional study; n=205	Patients from 3 institutions who underwent surgery and also received postoperative RT for primary or recurrent, stage I through IV cHNSCC between 1995 and 2015. 138 patients were immunocompetent and 67 were immunosuppressed	Locoregional RFS and PFS OS	RFS (47.7% vs 86.1%) and PFS (38.7% vs 71.6%) were significantly lower in immunosuppressed patients at 2 years. OS rate in immunosuppressed patients demonstrated a similar trend but did not meet significance. Immunosuppressed patients with cSS-HN had dramatically lower outcomes	Immunosupressed status is strongly associated with inferior locoregional control and PFS in patients with high-risk cHNSCC who undergo surgery and receive postoperative RT. This findings underscores the need for improved prognostic systems, increased multidisciplinary management and clinical trials investigating methods of intensified therapies for these patients.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Maruyama et al 2016	To present our experience of SLNB in patients with cutaneous SCC (cSCC) and compared the outcomes with those in cSCC patients who did not undergo concurrent SLNB	Retrospective analysis; n=169	240 patients with cSCC that were evaluated in the Department of Dermatology, Tsukuba University Hospital, for medical treatment, etween 2004 and 2015	Metastasis-free and DSS	Patients with clinical lymph node metastases had a higher risk compared with those without. Patients with T2–T4 tumors had a higher risk compared with those with T1 tumors. When selecting for those with T2 tumors or greater, the same lack of relationship was observed. In patients with cSCC, there were no significant differences in metastasis-free and DSS rates between those who did or did not undergo sentinel lymph node biopsy, regardless of T stagin		3
McLaughlin et al. 2017	To determine the rate of regional lymph node	Retrospective chart review; n= 30 solid organ	All solid organ transplant recipients who underwent	Rate of regional lymph node involvement;	The average age of the patient was 63. Seven patients (5%)	This is the largest study to date of cutaneous SCC in	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	involvement in a large cohort of solid organ transplant patients with cutaneous head and neck squamous cell carcinoma (cHNSCC)	transplant patients; 383 cHNSCC ressections	surgery between 2005 and 2015 for a cHNSCC at the Hospital of the University of Pennsylvania Department of Dermatology and/or Otorhinolaryngology	Time from first diagnosis to regional lymphatic disease	developed regional lymph node metastases (3 parotid, 4 cervical lymph nodes). The mean time from primary tumor resection to diagnosis of regional lymphatic disease was 6.7months. Six of these patients underwent definitive surgical resection followed by adjuvant radiation; one patient underwent definitive chemoradiation. 6 of the 7 patients died of disease progression with a mean survival of 15months. The average follow up time was 3years (minimum 6months). Solid organ	solid organ trans-plant patients. In addition, all of these lesions were limited to the head and neck. Despite the low rate of regional lymph node involvement demonstrated in these patients, their extremely poor prognosis makes managing a N0 neck in an immunocompromise d patient a difficult clinical dilemma.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					transplant recipients with cutaneous squamous cell carcinoma of the head and neck develop regional lymph node metastasis at a rate of 5%. Regional lymph node metastasis in this population has a poor prognosis and requires aggressive management and surveillance.		
McLean et al 2013	To determine whether alternative clinicopathologic prognostic factors should be applied to a patient cohort: patients with cSCC-HN in which nodal metastases present concurrently with the primary lesion	Retrospective analysis; n=95	Patients with concurrent primary and nodal metastatic cSCC-HN from prospective databases of 2 large head and neck cancer units in Sydney, Australia	OS DSS	OS was adversely affected by immunosuppression (p=.011) and nodal extracapsular spread (ECS) (p=.006). Immunosuppression (p=.005) and ECS (p=.005) indicated a worse outcome for DSS.		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					ECS and immunosuppression remained significant in the multivariable analysis.		
Mizrachi et al 2012	To indentify the prognostic significance of nodal ratio in cutaneous squamous cell carcinoma of the head and neck	Retrospective analysis; n=71	Patients with cutaneous head and neck squamous cell carcinoma and regional lymph node metastasis who attended a tertiary medical center between 1990 and 2008	OS DSS DFS	On univariate analysis, the only variables significantly associated with OS were the N -ratio (hazards ratio 9.98; 95 % CI 2.03–49.07, p = 0.005) and patient age (hazards ratio 1.06; 95 % CI 1.02–1.10, p = 0.002). Patient sex, number of positive nodes, number of nodes removed, radiation therapy, and pathological stage showed no association with OS. On multivariate analysis, N-ratio and age were found	The log-rank test was used to determine the appropriate cutoff value for the N -ratio. Two subgroups with different survival rates were identified. Patients with an N -ratio smaller than 0.1 had a 5-year OS of 66.3 %, and patients with an N -ratio to 0.1 or more had a 5-year OS of 43.1 % (p = 0.058). The N -ratio is a potentially valuable prognostic index in cutaneous SCC because it takes into account both the	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					to be significant predictors of OS (Nratio: hazards ratio 7.60, 95 % CI 1.64–35.30, p = 0.01; age:hazards ratio 1.06, 95 % CI 1.02–1.10, p = 0.002. The N-ratio was the only factor significantly associated with DSS (hazards ratio 12.86, 95 % CI 1.64–100.56, p = 0.015). Multivariate analysis confirmed that the N-ratio was the only statistically significant predictor of DSS. On multivariate analysis, pathological stage (poorly differentiated vs. well differentiated) and radiation	extent of the neck dissection, represented by the number of lymph nodes removed, as well as the regional tumor burden (number of positive nodes in the specimen). The present study found it to be a significant predictor of OS and DSS.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					therapy were found to be significant predictors of DFS (pathological stage:hazards ratio 8.01, 95 % CI 1.02–61.39, p = 0.048; radiation: hazards ratio 2.96, 95 % CI 1.17–7.49, p = 0.022; The 5-year DSS rate was 91.3 % for patients with an N - ratio of less than 0.1 and 67.8 % for patients with an N - ratio of 0.1 or more (p = 0.037)		
Oddone et al 2009	To propose a prognostic score model in patients with regional metastatic cutaneous squamous cell carcinoma of the head and neck	Prospective study; n=250	Patients between 1980 to 2005 who had metastatic cSCC to lymph nodes of the HN (parotid and/or cervical) and who were treated with curative intent. Patients must have undergone	OS and progression-free survival Risk factors for survival	All patients underwent either surgery alone (28 of 250 patients; 11%) or surgery and adjuvante radiotherapy (222 of 250 patients; 89%). At a median follow-up of 54 months	Patients who underwent surgery and received adjuvant radiotherapy had a better outcome compared with patients who underwent surgery alone. Patients who	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			surgery and had to have biopsy-proven cSCC to HN lymph nodes		(range, 1.3-212 months) 70 of 250 patients (28%) developed recurrent disease: Most were regional recurrences (51 of 70 patients; 73%) in the treated lymph node basin. After regional recurrence, a majority (73%) died of disease. The following 4 variables were associated significantly with survival: immunosuppression (hazard ratio [HR], 3.13; 95% confidence interval [CI], 1.39-7.05), treatment (HR, 0.32; 95% CI, 0.16-0.66), extranodal spread (HR, 9.92; 95% CI, 1.28-77.09), and margin status (HR, 1.85; 95% CI, 1.85-	had moderate- or high-risk ITEM scores, usually because of extranodal spread and involved excision margins, had a poor outcome.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					3.369); Immuosuppression, treatment, extranodal spread, and margin status were used to calculate the ITEM score. The 5-year risk of dying from disease for patients with high-risk (>3.0), moderate-risk (>2.6-3.0), and low-risk (2.6) ITEM scores were 56%, 24%, and 6%, respectively.		
Petter et al 1999	To make a precise difinition of high- and low-risk carcinomas possible and can thus influence therapy and follow-up procedures	Retrospective monocenter study; n=184	Patients with cSCC	DFS	An increased malignancy was found in carcinomas with the following features: clinical diameter greater than 2 cm, low degree of keratini-zation, high degree of cellular poly-morphism, high mitotic index and		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					high tumor thickness index (metastases only from tumor thickness 2,4 mm and subcutaneous infiltration), desmoplasia and ulceration.		
Picard et al 2017	To search for somatic mutations of the HRAS, KRAS, NRAS, BRAF and EGFR genes in patients with advanced cSCC treated with cetuximab; and to investigate the efficacy and tolerance of cetuximab according to these mutations	Multicenter retrospective study; n=31	Patients with confirmed advanced cSCC treated in two medical oncology departments in France between January 2008 and December 2014	Incidence of somatic mutations of the RAS, BRAF and EGFR genes and association with cetuximab efficacy with these mutations – Fisher test Disease control rate at week 6 PFS OS Safety	31 samples of cSCC from 31 patients were analyzed. Only 2 RAS muated samples (6.5%) were identified. The firs harbored a NRAS point mutation (c.35G>A) in codon 12, resulting in a p.G12D substitution. The second sample presented a HRAS point mutation (c.38G>T) in codon 13, resulting in p.G13V substitution. No mutation of KRAS, BRAF and EGFR genes at the	Even in elderly patients (median age 86 years; range 48-96 years) cetuximab was efficacious and well-tolerated. This suggests that cetuximab is certainly warranted in the treatment of cSCC. However, it is also important to identify tumor specific mutations that may determine response to treatment and prognosis for the disease. We have identified here that	3 3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					investigated loci was found. Two patients with NRAS and HRAS mutations showed a partial and complete response to cetuximab, respectively. The mean duration of follow-up was 19 months. At week 6, the disease control rate was 67.8%. The median OS was 13 months and the median PFS was 9 months. All patients could continue cetuximab treatment without dose reduction.	the incidence of RAS, BRAF and EGFR mutations is low in cSCC. The authors concluded that the incidence of RAS, BRAF and EGFR mutations is very low in cSCC. The search for mutations appears unnecessary before initiating a cetuximab treatment for advanced cSCC, but ultimately mutational data are needed to better define the genetic landscape of this disease. Dr. Frederic Peyrade is a Merck board Member.	
Roozeboom et al	To identify clinical and	Retrospective monocenter	Patients diagnosed with cSCC between 1	DFS, local recurrence-free	The cumulative probabilities of		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
2013	histopathological prognostic factors for local recurrence and metastasis in cSCCs at any body site.	study; n=224	January 2005 and 31 December 2007 at Maastricht University Medical Centrum (MUMC).	survival	recurrence-free survival at 1, 2 and 4 years post-treatment were 98.0%, 96.9%, and 94.7%, respectively, and for metastasis-free survival 98.1%, 97.0% and 95.9%, respectively. In univariate survival analyses, significant predictors for local recurrence were tumour diameter and tumour thickness. For metastasis this was invasion of deeper structures, location on the ear, poor differentiation, tumour diameter and tumour thickness. In multivariate survival analysis, every millimetre increase in both		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					tumour diameter and tumour thickness were independent predictors for local recurrence as well as for metastasis.		
Ruiz et al. 2017	To review utilization of radiologic imaging of high-stage cutaneous SCC (cSCC) to evaluate whether imaging impacted management and outcomes.	Retrospective study; n=98 patients; 108 high-stage cSCC	Patients diagnosed with cSCC from January 1, 2000, through May 30, 2013 treated in the Brigham and Women's Hospital.	Disease-related outcomes (DRO): local recurrence, nodal metastasis, death from disease	Imaging (mostly computed tomography, 79%) was utilized in 45 (46%) patients and management was altered in 16 (33%) patients who underwent imaging. Patients that received no imaging were at higher risk of developing nodal metastases (nonimaging, 30%; imaging, 13%; P = .041) and any DRO (nonimaging, 42%; imaging, 20%; P = .028) compared to the imaging group. Imaging was associated with a	Limitations: Single institution retrospective design and changes in technology overtime. Radiologic imaging of high-stage cSCC may influence management and appears to positively impact outcomes. Further prospective studies are needed to establish which patients benefit from imaging.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					lower risk for DRO (subhazard ratio, 0.5; 95% CI 0.2-0.9; P = .046) adjusted for BWH T stage, sex, and location.		
Schmults et al 2013	To identify risk factor independently associated with poor outcomes in primary CSCC	A 10-year retrospective monocenter cohort study; n= 985 patients; n= 1832 tumors	Patients with primary CSCC	Subhazard ratios for local recurrence, nodal metastasis, disease-specific death, and all-cause death adjusted for presence of known prognostic risk factors.	The median follow-up was 50 (range, 2-142) months. Local recurrence occurred in 45 patients (4.6%) during the study period; 36 (3.7%) developed nodal metastases; and 21 (2.1%) died of CSCC. In multivariate competing risk analyses, independent predictors for nodal metastasis and disease-specific death were a tumor diameter of at least 2 cm (subhazard ratios, 7.0 [95% CI, 2.2-21.6] and 15.9 [4.8-52.3],	In this study, patients with CSCC had a 3.7% risk of metastasis and 2.1% risk of disease specific death. Tumor diameter of at least 2 cm, invasion beyond fat, poor differentiation, perineural invasion, and ear, temple, or anogenital location were risk factors associated with poor outcomes	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					respectively), poor differentiation (6.1[2.5-14.9] and 6.7 [2.7-16.5], respectively), invasion beyond fat (9.3 [2.8-31.1] and 13.0 [4.3-40.0], respectively),and ear or temple location (3.8 [1.1-13.4] and 5.9 [1.3-26.7], respectively). Perineural invasion was also associated with disease-specific death (subhazard ratio, 3.6 [95% CI, 1.1-12.0]), as was anogenital location, but few cases were anogenital. Overall death was associated with poor differentiation (subhazard ratio, 1.3 [95% CI, 1.1-1.6]) and invasion beyond fat (1.7 [1.1-2.8]).		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Seddon et al. 2011	To assess circulating and tumor-localised neutrophil and G-MDSC populations for associations with high-risk tumor characteristics and OS in CSCC patients	Retrospective monocenter study; n=282 cases	Patients with primary CSCC and 47 patients with prospectively collected blood and primary CSCC tumor samples were analysed to determine frequencies of circulating G-MDSC and tumor localised CD66b+ and CD8+ leukocytes	Association between cell populations and high-risk tumor characteristics OS	In the clinical audit of non-TII, high circulating neutrophil counts were associated with tumor thickness 5 mm, Clark level V and high T-stage. Univariate analysis showed elevated neutrophil count was a significant marker of poor OS, whilst tumor thickness remained the only independent histological predictor of OS after adjusting for age and immuno-suppression. Tumors ≥ 5 mm thick had significantly increased total and peri-tumorally localised CD66b+ Leukocytes		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(comprising neutrophils and/or G-MDSC) and that elevated circulating G-MDSC numbers were associated with high T-stage tumors. The presence of high risk CSCC is associated with increased numbers of both circulating and tumor resident populations of neutrophils and/or G-MDSC.		
Skulsky et al 2017	To review the high-risk features included in NCCN and AJCC guidelines, as well as their notable discrepancies and omissions. To provide a brief overview of current prophylactic measures, surgical options, and	Embase, CENTRAL, and MEDLINE were searched for published studies, clinical trials, and guidelines on high- risk cutaneous SCC of the head and neck. Reference lists from the	Patients with high-risk cSCC	To compare two different guidelines (NCCN and AJCC) in what concerns SCC high risk features discrepancies and omissions. The following aspects were evaluated: Tumor size Depth of invasion	The AJCC TNM staging system considers the following high-risk features when determining the primary tumor (T) classification: depth (>2mm thickness or Clark level≥IV), anatomic location, poor histological differentiation, and	Future studies are required to evaluate the extent to which the inclusion of these additional high-risk features would improve tumor staging and prognostic outcomes. Ultimately, a consensus on the definition of high-	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	adjuvant therapies for high-risk cutaneous SCC (cSCC).	relevant articles acquired were also searched. The search date range used January 2016 as the end date; no start date was specified. The following terms are examples of terms that were combined in the database searches: “high-risk cutaneous squamous cell carcinoma, guidelines, excision margins, organ transplant, immuno-suppression, depth, recurrence, sirolimus, cyclosporine, azathioprine, sentinel lymph node biopsy,		Recurrent setting Poorly differentiated lesions Histopathologic subtype Perineural invasions Lymphovascular invasion High-risk anatomical location Immunosuppressed sate Incomplete excision	perineural invasion (PNI). Tumors are classified as T2 in 2 ways: (1) tumors > 2 cm in greatest dimension, or (2) any size tumor with ≥2 high-risk features. NCCN has also identified several high-risk features of cSCC. High-risk cSCC, as per NCCN Guidelines refers to a greater propensity for local recurrence and/or metastasis. NCCN classifies cSCC as high-risk if≥1 feature is present. Currently, there is no unanimous consensus on the high-risk features of cSCC. Although NCCN Guidelines and the AJCC TNM classification system share some	risk features of cSCC needs to be reached in order to produce accurate and practical treatment guidelines that will enhance patient care.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		superficial parotidectomy, elective neck dissection, and Mohs micrographic surgery." All records obtained from our searches were screened by title and abstract for selection.			overlapping high-risk features of cSCC, significant discrepancies exist. In comparison with NCCN Guidelines, the AJCC omits several high-risk features associated with poor clinical outcomes, including immunosuppression , lymphovascular invasion, recurrent tumors, and certain prominent high-risk anatomic locations. Notably, neither NCCN nor the AJCC include incomplete excision as a feature warranting a tumor's treatment as high-risk cSCC. As a compounding factor, there are no guidelines for managing the deep tumor margin.		
Stevenson	Review metastatic	Retrospective	Patients with	Comparison	Seven of 16 patients	The modified BWH	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
et al. 2016	cSCC at the study institution to evaluate whether the modified BWH staging system improved prognostication of the patients with poor outcomes	monocenter study; n= 16; n= 32 control subjects	metastatic cSCC were identified at the New York University Dermatologic Associates and Cancer Associates from 1998 to 2013.	between two staging systems	were identified as Stage T2 by AJCC criteria and Stage T2b by BWH criteria; two patients were on Stage T1, three patients were on more advanced T stages, and four patients lacked primary tumor data. Five patients had hematologic malignancy, and one patient had a solid-organ transplant. Using the BWH staging system, the odds ratio for the presence of a high-risk lesion (defined as Stage T2b or higher) in patients with metastases versus control subjects was 75 (95% confidence interval, 7.2–973). Under the AJCC staging system, the	criteria aims to better prognosticate the large group of T2 AJCC tumors, resulting in the majority of mortality. In the experience of the authors, the majority of patients with metastatic disease were on T2, stratifying to stage T2b by BWH criteria, or more advanced T stages. The findings of this study support BWH stratification of T2 tumors and also indicate that hematologic malignancy is a significant comorbidity associated with a poor outcome. **Sehr kleine Fallzahl, unbrauchbar, rein decriptiv**	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					odds ratio for high-risk lesions (defined as T2 or higher) between the same groups was 8.3 (95% confidence interval, 1.4–87).		
Szewczyk et al 2015	To evaluate the risk factors of developing neck metastases in a group of patients with head and neck cSCC.	Retrospective monocenter study; n=100	Patients treated for head and neck cSCC at the Department of Head and Neck Surgery of the University of Medical Sciences in Poznan, Poland.	Risk factors of developing neck metastases	Local recurrence, degree of cell differentiation, tumour dimension and/or location, can increase the risk of neck metastases. For this reason, the authors suggest that in patients with such risk factors, neck dissection should be considered to evaluate for metastatic lesions. Neck ultrasound is a valuable supplement to clinical examination and can aid in selecting patients for	Rein dekriptiv, kleine Anzahl von metastasierten Patienten	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					subsequent neck dissection.		
Takeda et al 2013	To predict lymph node metastases prior to surgery	Retrospective monocenter study; n=164	Patients with cutaneous SCC	Factors which contribute to the development of lymph node metastases.	Lymph node metastasis was observed in 17 cases (10.4%). Lower lip SCC was observed only in the higher metastasis rate. Significant local recurrence occurred more frequently in the lymph node metastasis group. For other factors, no significant difference was observed between the lymph node metastasis group and the non metastasis lymph node group. A sentinel lymph node biopsy was performed in 21 cases, two false-negative cases were		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					observed, and local recurrence and lymph node metastasis were observed postoperatively. Operation should be given to the lower lip SCC and local recurrence cases considering lymph node metastasis.		
Tseros et al 2016	To analyze the correlation between lymph node ratio (LNR) and outcome in patients who have undergone surgery for metastatic cutaneous nodal SCC of the head and neck	Retrospective monocenter study; n=238	Patients who had undergone nodal surgery (parotidectomy and/or neck dissection) for metastatic cutaneous nodal SCC of the head and neck were identified from a prospective computer database maintained at Crown Princess Mary Cancer Centre (Westmead Hospital), Sydney	Time to disease progression (TTDP) Secondary endpoint was OS	In total, 193 males and 45 females with a median of age 68 years were identified, with a mean recorded LNR of 0.15. On multivariate analysis, an LNR cutpoint of 0.21 was a significant predictor of decreased TTDP [hazard ratio (HR) 2.34, 95 % confidence interval (CI) 4.40–0.49; p = 0.009] and OS	LNR is potentially an independent predictor of outcome in patients with metastatic cutaneous nodal SCC.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(HR 2.75, 95 % CI 1.57–4.82;p<0.001). 21% of the patients developed recurrence, with most recurrences being regional (29 of 49; 59%). A total of 17% of patients with an LNR≤ 0.21, recurred compared with 40% for patients with an LNR >0.21. On multivariate analysis, LNR (HR 2.75, 95 % CI 1.57–4.82; p<0.001), female sex (HR 2.83, 95 % CI 1.11–7.22; p=0.029) and age (HR 1.05, 95 % CI 1.03–1.08; p<0.001) were all significant independent predictors of decreased OS. Mean OS was 42 months		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					for patients with an LNR≤0.21 and 36 months for patients with an LNR >0.21 (HR 2.91, 95 % CI 1.66–5.08; p<0.001)		
Vinicius de et al. 2011	To evaluate prognostic and risk factors and the expression of markers such as the HER family, E cadherin, and Podoplanin in patients with locally advanced cutaneous squamous cell carcinoma of the trunk and extremities	Retrospective monocenter study; n= 55	Patients with locally advanced (American Joint Committee on Cancer staging T3 and T4) CSCC of the trunk and extremities admitted to two cancer institutions in Brazil (Barretos Cancer Hospital and Amaral Carvalho Hospital) between 1997 and 2006	Association between clinical variables and lymph node metastasis. Lymph node metastasis -free survival. Cancer specific survival.	Primary tumor positivity was 25.5% for EGFR, 87.3% for HER-3, and 48.1% for HER4. Metastases were positive for EGFR in 41.7%, for HER-3 in 83.3%, and HER-4 in 43.5%. HER-2 was negative in all samples. Membrane E-cadherin and cytoplasmic E-cadherin were positive in 47.3% and 30.2% of primary tumors and 45.5% and 27.3% of metastases. Podoplanin was positive in 41.8% of primary tumors and 41.7% of		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					metastases. Intratumoral lymphocytic infiltrate was the only prognosticator of lymph node metastasis (92% versus 66.6%; p = 0. 046). The mean and median follow-up was 9.6 (SD 25.0) and 25.0 months, respectively. At last follow-up, 19 patients were alive with no evidence of disease (34.5%), one was alive with disease (1.8%), 19 were dead of disease (34.5%), 9 dead from other causes (16.4%), and 7 lost to follow-up (12.7%). Patients with T3 tumors had better		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					cancer-specific survival (CSS) than those with T4 tumors; patients with no lymph node involvement had better CSS than patients with N1 tumors. Undifferentiated tumors and hyperexpression of podoplanin were negative prognostic indicators on multivariate analysis		
Wermker et al 2014	To establish a prediction model for LNM in patients with cSCC of the ear	Retrospective monocenter study; n= 353 patients	Patients with cSCC of the ear who were treated surgically between 2005 and 2011	DSS Lymph node metastases-free survival	Five-year DSS was significantly lower in the LNM group than in the control group (59% vs. 99%; $p < 0.001$). Recurrence number, invasion of cartilage, tumour depth, and tumour grading were the most important predictors for LNM, with correct prediction of LNM in	The prediction score stratified patients into high and low risk groups ($p < 0.001$) with a sensitivity of 89.2%, a specificity of 94.6%, and an overall accuracy of 94.1%.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					94.0% of cases.		

2.2.5. Literature

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3. Working group: Diagnostics

(AG Diagnostik)

3.1. Question II.1 Which classification, definition and nomenclature should be used for the actinic keratosis classification?

(Frage II.1. Welche Klassifikation, Definition und Nomenklatur soll für die Einteilung der aktinischen Keratose angewendet werden?)
Beantwortung durch systematische Recherche

3.1.1. PICO

PICO scheme			
Population	**Intervention**	**Comparison**	**Outcome/ Measures of interest**
Patients with actinic keratosis	no specific intervention	no specific comparison	Clinical or histopathologic classification, scoring systems, grading systems, scaling systems

3.1.2. Database, search strategy, number of results

Database	Search strategy	Date	Number of results
1. Search			
Medline	((actinic*[title] OR solar*[title]) AND keratos*[title]) AND (classification[Title/Abstract] OR class*[Title/Abstract] OR scor*[Title/Abstract] OR stag*[Title/Abstract] OR scal*[Title/Abstract] OR assess*[Title/Abstract]) AND (English[Language] OR	01 January 2021	439
	German[Language]) NOT "case report" NOT "trial"		

3.1.3. Selection criteria

Literature selection		
Number of total results		439
Inclusion criteria	Clinical or histopathological studies investigating any classification system for actinic keratosis	
Exclusion criteria	Specific interventions, case reports, trials investigating a specific intervention	
Number of results after title and abstract screening		33
Number of full texts included		17

3.1.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
Chen et al 2013	To assess the reliability of four different methods used to quantify AKs and to investigate whether a consensus meeting affects the reliability.	Single-blinded, cross- sectional study of 12 experienced dermatologist raters counting AKs on the face and ears of nine subjects before and after a consensus meeting To compare the degree of agreement of (i) AK count of discrete lesions > 0.25 cm (big), (ii) AK count of discrete lesions < 0.25 cm (small); (iii) total count, irrespective of size, and (iv) the body surface area method	N=12 board-certified dermatologists 67% were women Mean age: 47 years ± 9 N=9 consecutive subjects with extensive AKs on their face and ears were invited to participate in a research kick-off meeting for AK assessment, 100% male	intraclass correlation coefficient (ICC) among raters for pre- and post-consensus evaluations	total count' method had the greatest ICC for both pre- (0.18, P=0.04) and post-consensus (0.66, P≤ 0.0001) assessments. Total count was also the only pre-consensus ICC for which the null hypothesis of no association among assessments was rejected.	Small sample size No histological confirmation of AK was obtained Patients with AK to be rated were only male	2

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
Cockerell 2000	To propose criteria for grading keratinocytic intraepidermal (malignant) neoplasia.	Modification of an existing classification system based on a literature review □ expert review/opinion	-	Classification system	Proposed criteria for grading keratinocytic intraepidermal (malignant) neoplasia. <u>Grade I:</u> *Clinical:* Flat, pink macule or patch on solar-damaged skin; background mottling; no roughness or hyperkeratosis. *Histologic:* Focal atypia of basal keratinocytes of **lower one third** of the epidermis. <u>Grade II:</u> *Clinical:* Pink to red papule or plaque with rough, hyperkeratotic surface; variable induration. *Histologic:* Focal atypia of keratinocytes of **at**	No validation with real-world data of the system No inter-rater reliability or other measure were investigated Only expert review	5

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					least the lower two thirds of the epidermis; focal hyperkeratosis, alternating orthokeratosis and parakeratosis with sparing of acrotrichia and acrosyringia; prominent acanthosis and buds of keratinocytes into the upper papillary dermis; may see some involvement of upper acrotrichia and acrosyringia. Grade III: *Clinical:* Red, scaly indurated plaques on sun-damaged skin; may be pigmented. *Histologic*: Diffuse atypical keratinocytic proliferation involving the **full thickness** of the epidermis		

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					diffusely; parakeratosis, acanthosis, papillomatosis, the involvement of adnexal structures.		
Cockerell et al 2005	To propose a classification for AK analogous to that used for cervical intraepithelial neoplasia.	Modification of an existing classification system based on a literature review □ expert review/opinion	-	Classification system	Criteria for grading keratinocytic intraepidermal (malignant) neoplasia. <u>Grade I:</u> *Clinical:* Flat, pink macule or patch on solar-damaged skin; background mottling; no roughness or hyperkeratosis. *Histologic:* Focal atypia of basal keratinocytes of **lower one third** of the epidermis. <u>Grade II:</u> *Clinical:* Pink to red papule or plaque with rough,	No validation with real-world data of the system No inter-rater reliability or other measure were investigated Only expert review	5

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					hyperkeratotic surface; variable induration. *Histologic:* Focal atypia of keratinocytes of **at least the lower two thirds** of the epidermis; focal hyperkeratosis, alternating orthokeratosis and parakeratosis with sparing of acrotrichia and acrosyringia; prominent acanthosis and buds of keratinocytes into the upper papillary dermis; may see some involvement of upper acrotrichia and acrosyringia. <u>Grade III:</u> *Clinical:* Red, scaly indurated plaques on sun-damaged skin; may be pigmented. *Histologic*: Diffuse atypical		

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					keratinocytic proliferation involving the **full thickness** of the epidermis diffusely; parakeratosis, acanthosis, papillomatosis, involvement of adnexal structures.		
Dirschka et al 2017	To develop and perform an initial pilot validation of a new easy-to-use quantitative tool for assessing AK severity on the head.	review of other severity scoring systems in dermatology, in particular the psoriasis area and severity index (PASI) Initial validation was performed by 13 physicians assessing AK severity in 18 AK patients and two controls using a physician global assessment (PGA) and AKASI. To determine an AKASI score, the head was divided	N=18 patients with AK on the head [mean age (range): 73 years (60–80); 10 men and eight women] and two controls without AK (62-year old man and 70-year-old woman) N=13 physicians were involved in the rating	AKASI & PGA scores Correlation between AKASI and PGA (Pearson correlation coefficient)	AKASI & PGA scores mean (SD) PGA score was 0.08 (0.27) for the controls and 1.74 (0.80) for the patients. The mean (SD) AKASI score was 0.11 (0.38) for the controls and 4.75 (2.51) for the patients strong correlation between AKASI and	This work was funded by Centroderm GmbH. An initial 30-min training on AKASI was provided, and the physician participants were provided with a handout containing detailed instructions on AKASI. Small-medium sample size of both patients and physicians.	2

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
		into four regions (scalp, forehead, left/right cheek ear, chin and nose). In each region, the percentage of the area affected by AKs was estimated, and the severities of three clinical signs of AK were assessed: distribution, erythema and thickness.			PGA scores (Pearson correlation coefficient: 0.86). AKASI was able to discriminate between different PGA categories: mean (SD) AKASI increased from 2.88 (1.18) for 'light' to 5.33 (1.48) for 'moderate', 8.28 (1.89) for 'severe', and 8.73 (3.03) for 'very severe' PGA classification. The coefficient of variation for AKASI scores was low and relatively constant across all PGA categories.		
Dréno et al 2017	To develop, test, and validate an Actinic Keratosis Field	<u>Development:</u> initial draft of the AK- FAS was based on a combination of Olsen criteria for AK.	The final AK-FAS was tested separately on face and scalp areas (on 66 and 30 photographic cases,	Inter-rater reproducibility	<u>Validation of the AK- FAS by investigators</u> *Inter-rater*	Assessment for each area was repeated (with at least 1 h between assessments) to	2

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	Assessment Scale (AK- FAS) based on photographic clinical cases.	This draft was then dynamically modified in a face-to-face meeting on 15 July 2016. <u>Validation:</u> 108 standardized photographs of patients representing the full range of AK severity were collected. Six investigators (involved in the development) and 2 untrained investigators independently rated each photograph according to 3 criteria (**AK-FAS scale**): AK area (total skin area affected by AK lesions), hyperkeratosis and sun damage.	respectively) by 6 trained (testing) and 2 untrained investigators (validation).		*reproducibility:* For face and scalp combined, the inter- rater κ scores were 0.69, 0.71 and 0.51, respectively substantial agreement for 2 criteria (AK area and hyperkeratosis) and moderate agreement for the third criteria (sun damage) *Intra-rater reproducibility:* good for all criteria (AK area, hyperkeratosis and sun damage) substantial agreement range for all investigators for AK area, almost perfect or substantial agreement range for all but one of the investigators for hyperkeratosis and moderate agreement range	allow evaluation of inter- and intra-rater agreement. The order of the photographic cases was randomly Ch'nged in the repeat assessment, in order to minimize grading by memory. The investigators had not previously seen any of the cases provided by their colleagues and were not allowed to confer during the assessment. This study was funded by LEO Pharma.	

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					for the majority of the investigators for sun damage <u>Validation of the AK- FAS by untrained investigators</u> κ scores of 0.59, 0.54 and 0.38, respectively, for AK area, hyperkeratosis and sun damage, indicating moderate agreement (good reproducibility) for AK area and hyperkeratosis, and fair agreement for sun damage; s imilar results were obtained for the face and scalp analysed separately □Validation of the AK-FAS showed good		

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					reproducibility for AK area and hyperkeratosis, even for dermatologists untrained on use of the scale.		
Fernández-Figueras et al 2015	To evaluate the prevalence of classic and differentiated pathways in the development of cutaneous iSCC.	The epidermis adjacent to and overlying iSCC, assumed to be representative of pre- existing lesions, was histologically studied in 196 skin biopsy specimens showing iSCC by three pathologists.	N=196 skin biopsy specimens showing iSCC (79 women and 117 men) mean age:77.3 years (±10.1) Most lesions (108 out of 196) were located on the face. selected biopsy specimens was 19.30 mm [median, 17 mm ± 13.01 mm; interquartile range (IQR), 10.00–27.50 mm]. The mean width of iSCC areas was 9.05 mm (median, 7 mm; ±7.17 mm; IQR, 3.50–13.00 mm). The anatomic level of	Features of the epidermis overlying iSCCs and at the edge of iSCCs, distributed according to the degree of involvement and the presence of ulceration (number of cases and corresponding percentages of total) Adnexal involvement by atypical cells (proliferative AK) according to the thickness of atypical Ch'nges in the epidermis overlying iSCCs	AK I, AK II and AK III lesions overlying iSCC were present in 63.8%, 17.9% and 18.4% of cases respectively. The corresponding percentages in the epidermis adjacent to iSCC were 77.9%, 6.6% and 8.3% respectively (stage could not be assessed in 8.1% of cases). Focal epidermal ulceration overlying iSCC was seen in 32%	Almirall has provided financial support for this study but has not participated in the elaboration and discussion of results. Baseline characteristics of included participants were unbalanced.	2

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
			infiltration was II in two cases (1.0%), III in 14 cases (7.1%), IV in 127 cases (64.8%), and V in 53 cases (27.0%). The mean maximum depth of infiltration was 3.83 mm (median, 3.00 mm; ±2.85 mm; IQR 2.00–5.00 mm). mean diameter of the		of AK I, 28.6% of AK II and 33.3% of AK III instances. Adnexal involvement by atypical keratinocytes (proliferative AK) was present more frequently in cases with overlying AK I (39/125, 31.2%) than with AK II (8/35, 22.9%) and AKII I (5/36, 13.9%).		
Fernández-Figueras et al 2018	To demonstrate that follicular extension of an AK is associated with the depth of invasion (Breslow) of	retrospective histologic review of 193 biopsy specimens of iSCC with an associated AK by three dermatopathologists assessment of the presence and depth	N=193 biopsy specimens	Follicular extension	Follicular extension was present in 25.9% of the cases (50 cases), usually extending into the lower follicular segment. . In 12 of them, the atypia reached the upper	all biopsy specimens smaller than 3 mm and larger than 2.5 cm in size and those specimens with poor architectural preservation (i.e. superficial or	2

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	iSCC.	of follicular extension of atypical keratinocytes in the AK, using tumour (Breslow) thickness and the follicular unit level (infundibular, isthmic and subisthmic), as well as iSCC being present directly adjacent to the follicular basalis			portion of the follicle (infundibulum), and in three of them (25%), there was evidence of invasive squamous cell carcinoma (iSCC) originated from the follicular basalis. In 33 cases, the atypical cells reached the isthmic portion, and in 21 of them (63.6%), iSCC originated from the follicular basalis. In five cases, the atypical cells reached the isthmic portion and in all of them iSCC originated from	fragmented specimens and tumours with extensive exulceration) were excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					the follicular basalis. The iSCC was present directly adjacent to the follicular basalis in 58% of the cases (29 cases), correlating highly with the depth of follicular extension (infundibular: 3/12; isthmic: 21/33; subisthmic 5/5).		
Ianhez et al 2013	To evaluate the actinic keratoses counting by various raters and suggest approaches to increase the reliability.	Cross-sectional study: forty-three patients were evaluated by four raters (inter- and intra-rater assessment) on the face and forearms. rating: two board-certified	N=43 patients Age: 63.1 years (range: 50–80 years) 25 females mean actinic keratoses counts on the face and forearms were 7.7 and 9.1	Inter-rater agreement Intra-rater agreement	The overall agreement among the raters for the facial and forearm actinic keratoses was 0.74 and 0.77. The intra-rater assessment showed high rates of agreement for	All evaluators received a specific training session on counting AKs for the study.	2

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
		dermatologists and two residents of Dermatology			the face (ICC = 0.93) and forearms (ICC = 0.83). The intra-rater agreement for 0–5, 6– 10 and 11–20 counted lesions were: 0.66, 0.29 and 0.30.		
Jiyad et al 2017	To provide a detailed evaluation of the consistency of AK counts on digital photographs with clinical examination in renal transplant recipients, using defined areas of skin.	Skin sites of renal transplant recipients were examined clinically and on digital photographs by independent dermatologically-trained examiners.	N=28 patients with 138 skin sites Mean age: 57 ± 9 years, the majority were male (67%) mean ± SD length of time since transplantation was 9 ± 7 years number of AKs per skin site ranged from 0 to 14 and overall 305 AKs were diagnosed in total across all skin sites	Specificity, sensitivity, and Kendall's tau-b correlation coefficient were calculated based on exact photographic AK counts as well as counts with ± 1 AK tolerance.	When 138 skin sites with 305 clinical AK counts were examined for total count ± 1 AK, the sensitivity and specificity of photography was 95% and 100%, respectively. There was a significant positive correlation between AK counts on photographs and clinical examination (Tb = 0.537) and	Blinding was performed	2

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
			mean ± SD number of AKs on any single skin site was 2 ± 3		correlation was even higher for total count ± 1 AK (Tb = 0.758). moderate to strong concordance between AK counts on digital photographs and clinical examination		
Röwert-Huber et al 2007	To propose a system that classifies an AK as an SCC, in conjunction with an atypia grading system.	Review based on existing classification systems; modification of the existing system of Cockerell Expert opinion	-	-	The authors recommend an AK classification system that describes these lesions as squamous cell carcinomas (SCCs), using the terminology 'early in situ SCC Type AK I', 'early in situ SCC type AK II' and 'in situ SCC type AK III'.	No validation of the system; only expert opinion	4

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
Schmitz et al 2018a	To determine the association between chronically UV-induced tumours such as basal cell carcinomas or squamous cell carcinomas and AKASI.	retrospective analysis of patients who had undergone oncological surgery due to UV- induced tumours and who were assessed for AKASI and Physician's global assessment (PGA) before surgery. AKASI assessment and PGA were performed by one investigator. Statistical analysis of the correlation between AKASI, PGA and invasive carcinomas	N=210 patients were included Median age: 77 years (42–95) 66.2% were male 61.9%: FST II 52.4%: history of NMSC N=626 lesions Histological evaluation revealed AKs in 298 (46.9%), BD in 88 (13.8%), SCC in 32 (5.0%), BCC in 118 (18.6%) and other tumours such as seborrhoeic keratosis in 104 (16.4%) cases	AKASI PGA Statistical differences Correlation (Spearman)	patients exclusively presenting AKs (n = 106) showed a median (range) AKASI of 4.6 (0–15.5) and PGA of 2.0 (0–4.0) Patients with solely noninvasive tumours (n = 43) such as AKs and BD had a median (range) AKASI of 5.0 (0.6–11.2). Significantly higher AKASI in patients with SCC compared to patients with non- invasive lesions like AK and Bowen disease (BD) (P=0.0275). Spearman's coefficient of rank correlation between AKASI and PGA indicates that these	Large sample size; retrospective design AKASI and PGA have been evaluated by only one investigator	2

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					measures of AK severity were strongly correlated ($P < 0.0001$; $r = 0.90$; 95% CI 0.865–0.920).		
Schmitz et al 2018b	To determine whether there is a correlation between the commonly used histological classification scheme for AK lesions proposed by Röwert-Huber and basal epidermal growth patterns of AK. To investigate accompanying factors such as vascular density,	Retrospective analysis of histologically confirmed AK lesions occurring on the head/face from patients seen in routine practice Determination of histological grade (AK I-III), basal growth patterns of atypical keratinocytes (crowding, budding and papillary sprouting) and accompanying parameters by two investigators independently from each other.	N=246 lesions were included Median age: 79 (56–94) years 92.3% male 30.9% of lesions located on the scalp	histological grade (AK I-III) basal growth patterns of atypical keratinocytes (crowding, budding and papillary sprouting) accompanying parameters correlation of basal growth patterns and histological AK grades	Of the 246 lesions included, 28.0% were histologically classified as AK I, 46.7% as AK II and 25.2% as AK III. Approximately 26.4% of the basal growth patterns were classified as crowding (pro I), 49.6% as budding (pro II), 17.9% as papillary sprouting (pro III) and 6.1% without basal directed growth. No significant correlation of the histological AK IIII grading and underlying growth	-	2

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	inflammation and involvement of adnexal structures.				patterns was observed (P = 0.4666). However, adnexal structure involvement (OR = 2.37; 95% CI 1.21–4.65), infiltration (OR = 2.53; 95% CI 1.31–4.90) and increased number of vessels (OR = 2.56; 95% CI 1.42–4.65) were independent positive predictive markers for pro II and pro III basal growth patterns.		
Schmitz et al 2019a	To investigate a possible relationship between basal growth patterns of AKs adjacent to iSCC.	Retrospective study Histological assessment of the epidermis overlying and adjacent to iSCCs Determination of the histological grade (AK I–III), basal growth pattern (PRO	N= 307 iSCC lesions were included 73.6% male Median age: 81 (76–86) Tumour thickness (mm), median: 1.9 (IQR 1.1–3.9) 59.6% of patients with a history of more	histological grade (AK I–III), basal growth pattern (PRO I–III) and accompanying parameters	Among 307 lesions, 52.4% of AKs were histologically classified as AK grade I, 38.1% as AK II and 6.8% as AK III (v2-test, P < 0.001). Only 2.6% of adjacent epidermal samples did not	adjacent and overlying AKs were assessed, but the investigators were not able to evaluate the original AK from which the iSCC had originated. Ch'nges at the mutational level most probably	2

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
		I–III) and accompanying parameters such as adnexal involvement. Assessments were performed by two investigators independently from each other.	than one iSCC Most of the tumours were well differentiated (85.3%) and invaded into the reticular dermis (75.9%)		show any atypical keratinocytes. The epidermis adjacent to iSCCs was classified as having a PRO I basal growth pattern in 25.7%, PRO II in 31.9% and PROIII in 39.4% of cases. Only 2.9% of AKs showed no basal growth (v2- test, P < 0.001). In total 118 AKs (48.8%) showed extension into adnexal structures. These AKs were graded as PRO I in 18.6% of cases, PRO II in 30.5% and PRO III in 50.8%. The epidermis above iSCCs could be assessed only for upwards- directed growth and showed no significant differences in the three AK grades (P = 0.42).	lead to the final progression of this distinct subtype of AK.	

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
Schmitz et al 2019b	To compare the inter-rater reliability of the established classification of upwards directed growth of AKs (AK I–III) and the recently established classification of basal growth pattern of AKs (PRO I–III).	Retrospective study Histological images of 54 AKs were classified by 21 independent dermatopathologists with regard to basal proliferation (PRO I–III), histological grade (AK I–III) and assumed risk of progression into invasive carcinoma.	N=54 AKs Raters: 21 expert dermatopathologists, thereof 12 dermatologists (57.1%) and nine pathologists (42.9%) mean age: 43.4 (±9.6) years and a mean experience in dermatopathology of 10.9 (±8.6) years	Classification of AK images with regard to basal proliferation (PRO I–III), histological grade (AK I–III) and assumed risk of progression into invasive carcinoma Inter-rater reliability	16.7% of AK (9/54) were classified as AK I, 66.7% (36/54) as AK II, and 16.7% (9/54) as AK III. With regards to basal growth pattern, 25.9% (14/54) were classified as PRO I, 42.6% (23/54) as PRO II, and 31.5% (17/54) as PRO III. We observed a highly significant inter-rater reliability for PRO-grading ($P < 0.001$) which was higher than for AK-grading (Kendall's W coefficient: AK = 0.488 vs. PRO = 0.793). We found substantial	-	2

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					agreement for assumed progression risk for AKs with worsening basal proliferation (k = 0.759) compared to moderate agreement (k = 0.563) for different AK-gradings.		
Schmitz et al 2016	Determine whether there is a correlation between the commonly used clinical classification scheme for AK lesions proposed by Olsen et al. with that of the histological classification	Retrospective analysis One AK lesion from patients in three pivotal clinical studies and routine practice was assessed clinically and histologically. A match in grading was defined as Olsen grade 1 being classified histologically as AK I,	N=892 patients Mean age: 71.6±7.3 83.4% male 64.0% of lesions located on face/forehead	Classification of AK according to Olsen and Röwert-Huber correlation between clinical and histological classification	29.0% of lesions were classified as Olsen grade 1, 59.6% as Olsen grade 2 and 11.3% as Olsen grade 3; 19.2% were histologically classified as AK I, 69.6% as AK II and 11.2% as AK III. Only 480 lesions	-	2

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	system developed by Roewert-Huber et al.	Olsen grade 2 as AK II and Olsen grade 3 as AK III. Patient population for this study came from three randomized clinical trials (ALA-AK- CT002, ALA-AK-CT003 and ALA-AK-CT007) and routine clinical practice.			(53.8%) had a matching clinical and histological classification. Of these matches, most were 'Olsen grade 2 = AK II' (83.1%). The Spearman's rank correlation coefficient for clinical and histological classification was r=0.0499 (P=0.137).		
Sinnya et al 2015	To compare the inter-observer agreement between trained observers for AK counts based on photographs compared with clinical AK counts.	Clinical AK counting was carried out in 2 sessions by 4 dermatologically trained clinicians with 6 months or more of dermatological experience and a senior consultant dermatologist with over 25 years of experience, whose counts served as practical reference	N=6 patients (n=3 immunocompetent, n=3 OTRs) 84% male Mean age: 60 years±15	Agreement of AK counts: interclass and intraclass correlation coefficients (ICC)	ICC for agreement across 5 observers for the photographic AK counts was 0.63 (95% CI 0.48–0.78) compared with 0.79 (95% CI 0.68–0.88) for clinical counts ICC for agreement between	Small sample size; Reference standard was the assessments of the senior consultant	3

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
		standard. The observers repeated counting from the same photographic images, 2 weeks later.			photographic AK counts and clinical counts ranged from 0.66 (95% CI 0.48–0.81) to 0.84 (95% CI 0.73–0.91) across the 5 observers interclass correlation coefficient for agreement between AK counts based on the same photographs but counted on 2 separate occasions ranged from 0.86 to 0.99		
Yantsos et al 1999	To propose a classification system for AK.	Expert review/opinion	-	Classification system	<u>Criteria for Grading KIN</u> <u>Grade I:</u> *Clinical:* Undetectable or fiat, pink macule or patch on solar damaged skin; background	No validation of the system with real-world data or assessment of inter-rater reliability Only expert opinion	5

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					mottling; no roughness or hyperkeratosis. *Histological:* Focal atypia of basal keratinocytes of lower one-third of the epidermis. <u>Grade IIa:</u> *Clinical:* Pink to red papule or plaque with rough, hyperkeratotic surface; minimal induration. *Histological:* Focal atypia of keratinocytes of the lower two thirds of the epidermis; alternating orfho and parakeratosis with sparing of acrotrichia and acrotrichia. <u>Grade IIb:</u> *Clinical:* Similar to IIa but more		

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					induration, more hyperkeratosis and/or more erythema; all KIN lesions (other than KIN III) on lip and conjunctiva. *Histological:* Focal atypia of keratinocytes of at least the lower two-thirds of the epidermis; focal hyperkeratosis, often greater than IIa; one or more additional features such as acantholysis, the involvement of adnexal structures, prominent acanthosis and buds of keratinocytes into the upper papillary dermis present. <u>Grade III:</u> *Clinical:* Red, scaly indurated plaques		

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					on sun-damaged skin; may be pigmented; seen on other sites such as mucosa in Bowenoid papulosis and erythroplasia of Queyrat; non sun-damaged skin in squamous cell carcinoma in situ induced by arsenic. *Histological:* Diffuse atypical keratinocytic proliferation involving the full thickness of the epidermis; parakeratosis, acanthosis, papillomatosis, involvement of adnexal structures.		

3.1.5. Full texts not included with reasons

Author, year	Reason for exclusion (n=16)
Anwar et al 2004:	narrative review

Author, year	Reason for exclusion (n=16)
Bakshi et al 2020:	does not match review question
Ehrig et al 2006	does not match pico
Epstein 20014	review
Fernández-Figueras et al 2017	review
Giuffrè et al 2008	experimental design
Heerfordt et al 2016	does not match pico
Jiyad et al 2017	does not match review question
Lee et al 2020	does not match review question
Queen et al 2020	does not match review question
Rongioletti 2019	commentary
Schmeusser et al 2020	no classification
Schmitz et al 2018a	now additional classification; does not match review question
Schmitz et al 2018b	Intervention-specific analysis
Tokez et al 2020	does not match review question
Zalaudek et al 2014	review, no additional data

3.1.6. Literature

Chen SC, Hill ND, Veledar E, et al. Reliability of quantification measures of actinic keratosis. Br J Dermatol 2013;169(6):1219-22. doi: 10.1111/bjd.12591 [published Online First: 2013/09/17]
Cockerell CJ. Histopathology of incipient intraepidermal squamous cell carcinoma ("actinic keratosis"). J Am Acad Dermatol 2000;42(1 Pt 2):11-7. doi: 10.1067/mjd.2000.103344 [published Online First: 1999/12/22]
Cockerell CJ, Wharton JR. New histopathological classification of actinic keratosis (incipient intraepidermal squamous cell carcinoma). J Drugs Dermatol 2005;4(4):462-7. [published Online First: 2005/07/12] Dirschka T, Pellacani G, Micali G, et al. A proposed scoring system for assessing the severity of actinic keratosis on the head: actinic keratosis area and severity index. J Eur Acad Dermatol Venereol 2017;31(8):1295-302. doi: 10.1111/jdv.14267 [published Online First: 2017/04/13]
Dréno B, Cerio R, Dirschka T, et al. A Novel Actinic Keratosis Field Assessment Scale for Grading Actinic Keratosis Disease Severity. Acta Derm Venereol 2017;97(9):1108-13. doi: 10.2340/00015555-2710 [published Online First: 2017/05/26]
Fernández-Figueras MT, Carrato C, Sáenz X, et al. Actinic keratosis with atypical basal cells (AK I) is the most common lesion associated with invasive squamous cell carcinoma of the skin. J Eur Acad Dermatol Venereol 2015;29(5):991-7. doi: 10.1111/jdv.12848 [published Online First: 2014/11/28]
Fernández-Figueras MT, Saenz-Sardà X, Vargas P, et al. The depth of follicular extension in actinic keratosis correlates with the depth of invasion in squamous cell carcinoma: implication for clinical treatment. J Eur Acad Dermatol Venereol 2018;32(10):1657-61. doi: 10.1111/jdv.14901 [published Online First: 2018/03/01]
Ianhez M, Fleury Junior LF, Bagatin E, et al. The reliability of counting actinic keratosis. Arch Dermatol Res 2013;305(9):841-4. doi: 10.1007/s00403-013-1413-y [published Online First: 2013/09/21] Jiyad Z, O'Rourke P, Soyer HP, et al. Assessing the Concordance of Actinic Keratosis Counts on Digital Photographs with Clinical Examination in Organ Transplant Recipients. Acta Derm Venereol 2017;97(3):351-53. doi: 10.2340/00015555-2539 [published Online First: 2016/10/05]
Röwert-Huber J, Patel MJ, Forschner T, et al. Actinic keratosis is an early in situ squamous cell carcinoma: a proposal for reclassification. Br J Dermatol 2007;156 Suppl 3:8-12. doi: 10.1111/j.1365- 2133.2007.07860.x [published Online First: 2007/05/10]
Schmitz L, Gambichler T, Gupta G, et al. Actinic keratosis area and severity index (AKASI) is associated with the incidence of squamous cell carcinoma. J Eur Acad Dermatol Venereol 2018;32(5):752-56. doi: 10.1111/jdv.14682 [published Online First: 2017/11/09]
Schmitz L, Gambichler T, Gupta G, et al. Actinic keratoses show variable histological basal growth patterns - a proposed classification adjustment. J Eur Acad Dermatol Venereol 2018;32(5):745-51. doi: 10.1111/jdv.14512 [published Online First: 2017/08/11]
Schmitz L, Gambichler T, Kost C, et al. Cutaneous squamous cell carcinomas are associated with basal proliferating actinic keratoses. Br J Dermatol 2019;180(4):916-21. doi: 10.1111/bjd.16536 [published Online First: 2018/03/12]
Schmitz L, Gupta G, Stücker M, et al. Evaluation of two histological classifications for actinic keratoses - PRO classification scored highest inter-rater reliability. J Eur Acad Dermatol Venereol 2019;33(6):1092- 97. doi: 10.1111/jdv.15580 [published Online First: 2019/03/20]
Schmitz L, Kahl P, Majores M, et al. Actinic keratosis: correlation between clinical and histological classification systems. J Eur Acad Dermatol Venereol 2016;30(8):1303-7. doi: 10.1111/jdv.13626 [published Online First: 2016/03/10]
Sinnya S, O'Rourke P, Ballard E, et al. Counting actinic keratosis - is photographic assessment a reliable alternative to physical examination in clinical trials? Acta Derm Venereol 2015;95(5):604-5. doi: 10.2340/00015555-2040 [published Online First: 2015/01/13]
Yantsos VA, Conrad N, Zabawski E, et al. Incipient intraepidermal cutaneous squamous cell carcinoma: a proposal for reclassifying and grading solar (actinic) keratoses. Semin Cutan Med Surg 1999;18(1):3- 14. doi: 10.1016/s1085-5629(99)80003-0 [published Online First: 1999/04/03]

3.2. Question II.2-2: How is actinic cheilitis defined and how should it be classified?

(Wie ist die Definition und Klassifikation der Cheilitis actinica?) De-novo-Recherche

3.2.1. PICO

PICO scheme			
Population	**Intervention**	**Comparison**	**Outcomes/ Measures of interest**

PICO scheme			
Patients with actinic cheilitis	no specific intervention	no specific comparison	Clinical or histopathologic classification, scoring systems, grading systems, scaling systems

3.2.2. Database, search strategy, number of results

Database	Search strategy	Date	Number of results
1. Search			
Medline	((actinic*[title] OR solar*[title]) AND (cheilitis[title] OR cheilosis[title] OR cheil*[title])) AND (defin*[title] OR classification[Title/Abstract] OR class*[Title/Abstract] OR scor*[Title/Abstract] OR stag*[Title/Abstract] OR scal*[Title/Abstract] OR assess*[Title/Abstract]) AND (English[Language] OR German[Language]) NOT "case report" NOT "trial"	5th January 2021	61

3.2.3. Selection criteria

Literature selection	
Number of total results	61

Literature selection	
Inclusion criteria	Clinical or histopathological studies investigating any classification system for actinic cheilitis
Exclusion criteria	Specific interventions, case reports, trials investigating a specific intervention
Number of results after title and abstract screening	9
Number of full texts included	5

3.2.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
Câmara et al 2016	To evaluate comparatively the influence of histopathological features on epithelial dysplasia (ED) and the effectiveness in usage of WHO and binary grading systems in actinic cheilitis (AC).	Cytological and architectural alterations established by WHO for ED were evaluated in 107 cases of AC. Epithelial dysplasia was graded using WHO (no, mild, moderate, and severe ED) and binary systems (low risk and high risk for malignant transformation).	Lower lip biopsies from 107 cases of AC were retrieved from Universidade Federal Fluminense. Sample was composed of 60 males (56.1%) and 47 females (43.9%) with ages ranging from 21 to 86 years (mean of 59 years).	presence and grade of ED	Most cases were classified as mild ED (44.5%) in the WHO system and as low risk for malignant transformation (64.5%) in the binary system. There was a positive correlation between WHO and binary systems ($k = 0.33$; $P < 0.0002$). Loss of basal cell polarity ($P < 0.001$) was associated	No calibration exercises were attempted by the evaluators. Unclear whether blinding was performed.	3

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
		The comparisons were performed using kappa, chi-square, and phi coefficient tests (P < 0.05).	There are only light-skinned types (phototypes I, II, or III)		with severity of ED grade in the WHO system. Anisonucleosis (P < 0.0001), nuclear pleomorphism (P < 0.0001), anisocytosis (P = 0.03), cell pleomorphism (P = 0.002) increased nuclear/cytoplasm ratio (P < 0.0001), increased nuclear size (P < 0.0001), increased number of mitotic figures (P = 0.0006), and dyskeratosis (P = 0.008) were associated with severity of ED grade in the binary system.		
Cavalcante et al 2008	To analyze the clinical and histological features of actinic cheilitis (AC).	Clinical evaluation of 29 patients with AC, incisional biopsies for confirmation of clinical diagnosis. Histological features were analyzed, and	N=29 patients 72.41% male, 75.86% were over age 40 years 93.10% were	Histological features Classification of dysplasia (mild, moderate, severe) Associations with baseline	Clinical findings: Dryness (100%), atrophy (72.41%), scaly lesions (65.52%), swelling of	Unclear whether blinding was performed.	3

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
		dysplasia was classified as mild, moderate, or severe. The x^2 test was used for the following variables: gender, age, race, and smoking habits. The degree of dysplasia was related to these variables (Fisher's test) to test for independence between them ($P<0.05$).	white 72.41% were nonsmokers	demographic features	the lip (62.07%), erythema (58.62%), ulceration (58.62%), blurred demarcation between the lip vermilion border and the skin (58-62%), marked folds along with the lip vermilion (48.28%), white spots or plaque (41.3%)s, crusts (34.48%), blotchy areas (27.59%), and areas of pallor (17.24%). Histological findings: Dysplasia (100%), Elastosis (100%), inflammatory infiltrate (100%), vasodilatation (100%), Hyperplasia and/or acanthosis (86.21%),		

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					hyperparakeratosis (58.62%), hyperorthokeratosis (55.17%), epithelial atrophy (55.17%), granulosis (37.92%, hypergranulosis (37.93%), parakeratosis (17.24%), orthokeratosis (3.45%) Dysplasia was mild in 10.34% of the patients, moderate in 27.59%, and severe in 62.07%. Gender, age, race, or smoking habits were not related to the degree of dysplasia in the sample.		
Pilati et al 2008	To determine the histopathologic findings in actinic cheilitis (AC) and lip squamous cell	Histopathologic features were evaluated according to the World Health Organization	N= 58 cases of AC	Histological features according to the WHO classification and binary system classification	presence of dyskeratosis and keratin pearls was found to be strongly associated	Unclear whether blinding was performed.	3

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	carcinomas (LSCC) to attempt to predict the evolution from AC to LSCC based on the comparison of two dysplasia classification systems.	classification of dysplasia and binary system of classification. Also, in LSCC, pattern, stage of invasion, and degree of keratinization were evaluated. A total of 58 cases of AC and 70 cases of LSCC were studied, and data correlation was performed using statistical analysis.			with severe dysplasia and could represent higher proximity between the severe dysplasia in AC Ch'nges related to the nuclei, such as hyperchromasia, nuclear pleomorphism, anisonucleosis, increase in the number and size of nucleoli, increased number of mitoses, and atypical mitoses, indicate progression in dysplasia spectrum		
Poitevin et al 2017	To make a proposition of a clinical score to actinic cheilitis (Grade I starting from dryness of vermilion to endured ulcers representing Grade IV) and to assess its	Fifty subjects were assessed Obtained data were analyzed by means of descriptive statistics and by Kappa test to assess the interexaminer and	N=35 patients 20 men and 15 women, 32 Caucasians, 2 mixed ethnicities and 1 black. 28 were farmers, 2	interexaminer and the clinical Golden-Pattern concordance	During calibration, 15 patients were examined three times a week by each examiner (4) until Kappa test observed k= 0.8 or more. In the main experiment, the	Calibration: four examiners studied and discussed it before its application. The examiners were composed of two professors of oral medicine, one student finishing	2

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	Lo E
	reproducibility.	the clinical Golden-Pattern concordance (95% CI). AC Grade I. Dryness and desquamation on the vermilion of lips. AC Grade II. Atrophy on the vermilion's border, presenting soft superficies and pallid areas with eruptions. Blurred limit between the lip's vermilion border and the skin, or a dark line demarking that limit can be seen. This melanotic line should be different from ephelides or other pigmented lesions. AC Grade III. Rough and squamous areas on the drier parts of the vermilion and hyperkeratotic areas, especially when they spread to the wet lip's mucosa (border between mucosa and semimucosa).	were business people, 2 were homemakers and 3 were students average age of 46.12 (18–74) years		inter-examiner concordance was classified between good (k= 0.779; Po0.05) and very good (k= 0.925; Po0.05) from the 35 examined subjects. With the Golden-Pattern, it was considered very good (k= 0.812; Po0.05 to k= 0.925; Po0.05).	dental School and one dentist with 2 years of general dentistry practice. The study was conducted in Brazil.	

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
		AC Grade IV. Ulceration present in one or more sites of the lip's vermillion or Leukoplakia, mainly in more traumatic places, due to the history of pipe or cigarettes consumption. These lesions could suggest that a malignization process would be in progress, especially when they are accompanied by endured areas on palpation.					
Santana et al 2020	To summarize the results of published studies on immunohistochemical biomarkers in lip carcinogenesis, to evaluate if there is a marker that can distinguish the different histological grades of AC.	Systematic review of retrospective studies that investigated immunohistochemical biomarkers in AC defined on standardised histological assessment Systematic literature	N=27 retrospective studies were included in the systematic review and n=3 in the meta-analysis number of AC cases in each study varied from	type of histological grading performed; immunohistochemical biomarkers that were analyzed; expression of biomarkers in each subgroup	Among the studied biomarkers, the ones that were most investigated were DNA repair proteins, with 12 antibodies assessed. The inflammatory markers were the second most assessed group.	Most studies had a high risk of bias. Studies from Brazil were overrepresented. High heterogeneity among studies.	2

Study	Aims	Design	Population	Outcomes	Results	Comments and methodological assessment	Lo E
		search in 5 databases until 25 April 2017: PubMed, Scopus, Web of Science, ScienceDirect and Scielo Partial grey literature search was conducted as well. Meta-analysis of protein Ki-67 Qualitative appraisal using the Critical Appraisal Tools from SUMARI.	10 to 70		Other groups of proteins were also analyzed, including apoptosis markers, metalloproteins, cell cycle markers, growth factors, neural and muscle markers: The proliferation marker Ki-67 was the most studied biomarker and we observed, through meta-analysis, that it was differently expressed between AC and lip cancer, but not in AC subgroups. Ki- 67 mean expression was similar in control groups and was higher in LSCC than in AC. N=5 articles used the binary classification system		

3.2.5. Full texts not included with reasons

Author, year	Reason for exclusion (n=4)
Dancyger et al 2018	study does not match review question/PICO
Fontes et al 2009	experimental design
Menta Simonsen et al 2007	surgery was included as interventio
Santana et al 2020	experimental design

3.2.6. Literature

Câmara PR, Dutra SN, Takahama Júnior A, et al. A comparative study using WHO and binary oral epithelial dysplasia grading systems in actinic cheilitis. Oral Dis 2016;22(6):523-9. doi: 10.1111/odi.12484 [published Online First: 2016/03/31]
Cavalcante AS, Anbinder AL, Carvalho YR. Actinic cheilitis: clinical and histological features. J Oral Maxillofac Surg 2008;66(3):498-503. doi: 10.1016/j.joms.2006.09.016 [published Online First: 2008/02/19] Pilati S, Bianco BC, Vieira D, et al. Histopathologic features in actinic cheilitis by the comparison of grading dysplasia systems. Oral Dis 2017;23(2):219-24. doi: 10.1111/odi.12597 [published Online First: 2016/10/21]
Poitevin NA, Rodrigues MS, Weigert KL, et al. Actinic cheilitis: proposition and reproducibility of a clinical criterion. BDJ Open 2017;3:17016. doi: 10.1038/bdjopen.2017.16 [published Online First: 2018/04/03] Santana T, Matuck B, Tenório JR, et al. Can immunohistochemical biomarkers distinguish epithelial dysplasia degrees in actinic cheilitis? A systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal 2020;25(1):e106-e16. doi: 10.4317/medoral.23223 [published Online First: 2019/12/28]

3.3. Question II.2 Which classification, definition and nomenclature should be used for the squamous cell carcinoma classification?

(Frage II.2. Welche Klassifikation, Definition und Nomenklatur soll für die Einteilung des Plattenepithelkarzinoms angewendet werden?) Beantwortung durch Expertkonsens

3.4. Question II.3. How should field cancerization be defined? Terminology definition?

(Frage II.3. Wie definiert sich die Feldkanzerisierung (Definition der Begrifflichkeiten)?) Beantwortung durch Leitlinienadaptation

3.5. Question II.4. Which non-invasive diagnostic tools/procedures are suitable for actinic keratosis and squamous cell carcinoma diagnosis?

(Frage II.4. Welche nicht-invasiven diagnostischen Verfahren sind geeignet, die Diagnose von AK und PEK zu stellen?)

Beantwortung durch systematische Recherche

3.5.1. PICO

PICO – Scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Patients with actinic keratosis and/or cutaneous SCC	Diagnosis with non-invasive techniques	normal skin, skin conditions other than AKs or cSCC comparison with histopathology as gold standard	Accuracy indicated by quantitave measures (sensitivity, specificity, positive and negative predictive value, odds ratios, percent counts)

3.5.2. Database, search strategy, number of results

Database	Search strategy	Date	Number of results
1. Search			
Medline	(keratos*[Title] AND (solar[Title] OR actinic[Title])) OR (squamous[Title] AND (skin[Title] OR cutaneous[Title])) AND diagnos*[Title/Abstract] NOT “case report” AND (English[Language] OR German[Language])	12nd January 2017 (initial search)	512

Database	Search strategy	Date	Number of results
		Update 17th May 2017	524
Remarks and notes: -			

3.5.3. Selection criteria

Literature selection	
Number of total results	524
Inclusion criteria	Comparative trials (randomized, non-randomized), observational trials, cross-sectional trials, sample size of investigated patients n>10, quantitative outcomes measures
Exclusion criteria	Case reports, case series, narrative reviews, sample size n<10, qualitative reports without quantified accuracy measures, experimental studies
Number of results after abstract searching	45
Number of full texts reviewed	24

3.5.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Akay et al 2010	To investigate the frequency	Prospective, single-centre	n=80 patients (50 men, mean age:	Distribution and frequency of	Essential dermatoscopic features in facial AKs and	Lack of information	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of dermatoscopic findings suggestive of lentigo maligna /lentigo maligna melanoma (LMM) in the other facial pigmented skin lesions (FPSL) and to assess the distinguishing dermoscopic criteria of pigmented actinic keratoses (PAK) and LM.	study	66years, range=22-89 years) n=89 FPSL were evaluated with conventional dermoscopy PAK: n=67, LM/LMM: n=20 lichen planus-like keratosis (LPLK): n=2	dermatoscopic criteria in the sample	their frequency in the sample: slate-grey dots (70%); annular-granular pattern (39%); rhomboidal structures (36%); pseudonetwork (36%); black globules (34%); slate-grey globules (33%); black dots (30%); asymmetrical pigmented follicular openings (25%); hyperpigmented rim of follicular openings (21%); slate-grey areas (18%); streaks (3%) Presence of brown to grey pseudonetwork: highly specific (90%) for PAK (p=0.028)	regarding observers' blinding Conclusion: Histopathology still remains the gold standard for correct diagnosis.	
Boone et al 2015	To design an algorithm for AK classification with high-definition optical coherence tomography	Cross sectional study to model an algorithm	N=53 histopathologically confirmed lesions (37 AKS, 16 SCCcs) from 25 men and 28 women. Skin types I-III, mean age=65.5	Parameters to discriminate SCC/AK from normal skin Sensitivity (Se), specificity (Sp), phi-coefficient (Phi)	Discrimination of SCC from AK and normal skin: Absence of dermo-epidermal junction (Phi=0.84), Se=100%, Sp=94% Discriminate AK from normal skin: Presence of disarranged	Severe (>300 µm) hyperkeratotic AKs not included: selection bias likely	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(HD-OCT) that could (i) distinguish SCC from AK and normal skin, (ii) differentiate AK from normal skin and (iii) discriminate AKs with adnexal involvement from those without.		years (range 38-93) Reference= 53 images of healthy skin; matching according to age, skin type, anatomic site		epidermal architecture (Phi=1, Se=100%, Sp=100%) and atypical honeycomb pattern (Phi=1, Se=100%, Sp=100%)		
Di Carlo et al 2014	To examine, by means of video thermography (VTG) and dermoscopy, the head and trunk regions of chronic sun-exposed individuals showing clinical lesions suspected to be AK or BCC, in order: (i) to	Single centre, prospective, diagnostic study	n=36 participants with 145 lesions (48 were BCC, 87 were AK) 12 women Mean age: 64.3 years, range: 55-75 All participants: history of prolonged sun exposure	Sensitivity (Se) Presence of characteristic patterns for BCC/AK	VTG showed the presence of a hyperthermic pattern in all AK cases, in all BCC cases a hypothermic pattern was present. <u>Dermoscopy AK:</u> Se=74% (65/87) 22% were undiagnosed: false negative result <u>Main dermoscopic criteria for AK:</u> strawberry pattern, with a red pseudonetwork pattern, and	Small sample size Moderate interobserver agreement (k=0.4-0.6 in 5 of 7 criteria)	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	evaluate the diagnostic accuracy of VTG; and (ii) to compare the validity of each of these two methods as diagnostic tool for the clinicians.				keratotic hair follicles		
Friis et al 2017	To investigate the current existing optical coherence tomography (OCT) features of AK, including both conventional OCT and high definition -OCT (HD-OCT) studies.	Systematic review was perfomed in PubMed, Medline, EMBASE, Chochrane and Svemed.	n=21 studies were included range of number of AK lesions: 4-113	Morphological characteristics of AKs described in the studies	<u>Conventional OCT (cross-sectional images):</u> -disruption of layers consistent with absence of normal layered architecture in the skin (16/16 studies) -thickened epidermis (14/16 studies) -white (hyperreflective) streaks and dots (11/16) <u>HD-OCT:</u> -disarranged epidermis (cross-sectional images) along with an atypical honeycomb pattern (en-face images) (5/5 studies)	Many of the included studies are small with less than 20 AKs No bias assessment of the individual studies reported No information about the design of the included studies provided No information regarding the data/information extraction process	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					-well-demarcated dermo-epithelial junction (cross-sectional images) (3/5 studies)	of the 21 included studies records in this review that are also available in the evidence table: Boone et al. 2015 Maier et al. 2013 Markowitz et al. 2016 Marneffe et al. 2016 Schuh et al. 2016 Olsen et al. 2016	
Horn et al 2008	To validate the diagnostic confocal examination of AKs.	Prospective, observer-blinded, single centre, intrapatient study	N=30 AKs among 26 patients 17 males, 13 females Mean age: 79.7 years, range: 68-92 30 skin fields from the contralateral side served as controls.	Sensitivity (Se) Specificity (Sp) Positive predictive value (PPV) of the observers Negative predictive value (NPV) of the observers Frequency of each confocal feature in the	<u>Dermatooncologists</u> Se=93.34%, Sp=88.34%, PPV=88.94%, NPV=93.15% <u>Dermatopathologist</u> Se=88.34%, Sp=66.67%, PPV=72.35%, NPV=87.04% <u>All 4 observers:</u> Se=90.84% Sp=77.50% PPV=80.65% NPV=89% <u>Frequency of each confocal feature:</u>	Small sample size Moderate interobserver agreement (k=0.4-0.6 in 5 of 7 criteria)	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			15 AKs were histpathologically confirmed, 15 AKs were diagnosed according to clinical and conventional dermoscopic criteria.	sample	AK vs normal skin: -inhomogenous, irregular stratum coneum: 86.67% vs 26.67% -irregular honeycomb pattern of keratinocytes: 80% vs 26.67% -loss of regular stratification of epidermal layers: 86.67% vs 26.67% -dyskeratotic areas: 90% vs 40% -different size and shape of the nuclei of keratinocytes: 76.67% vs 26.67% -irregular borders of keratinocytes: 86.67% vs 13.34% -irregular intercellular keratinocyte connections: 63.34% vs 10%		
Huerta-Brogeras et al 2012	To estimate the sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio	Prospective, diagnostic validation study Independent blinded comparison by expert dermoscopist.	n=178 patients with 178 confirmed lesions 64.6% men, mean age: 67 years (range 37-9)	Concordance (dermoscopy results and histopathological findings) sensitivity, specificity, LR+, LR- of dermoscopy	Concordance: K=0.917 Se=98.7% Sp=95.0% PPV=99.4% NPV=90.5% LR+=19.74 LR-=0.01	Lack of interobserver reliability (only one observer) Study was supported in part by a grant from the	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(LR+), or negative likelihood ratio (LR-) of dermoscopy as a real-time non-invasive diagnostic imaging technique for AK.	Histopathological diagnoses were used as gold standard		sensitivity and specificity of a diagnostic algorithm	Diagnostic algorithm that combined follicular openings and erythematous pseudonetwork: sensitivity: 95.6%, specificity: 95.0%	Carlos III Health Institute Research Fund for Research in Health Technology and by the Mutua Madrilen Foundation for Medical Research.	
Jiyad et al 2016	To examine accuracy of AK counts on digital photographs when compared with clinical examination counts.	Nested diagnostic study Observer of digital images was blinded to results of clinical examination.	n=138 skin sites with 305 clinical AK counts among 28 RTRs (STAR cohort), majority male, mean age 57 years±9	Number of AKs identified within pre-defined skin sites on digital photographs compared to number of AKs identified on clinical examination. Sensitivity (Se) Specificity (Sp) Kendall's tau-b correlation coefficient (Tb) based on exact photographic AK counts as well as counts with ± 1 AK tolerance	Sensitivity of detecting AK on digital photographs (given min. 1 AK clinically) was 88% and increased to 95% with tolerance of ± 1 AK. Specificity of digital photographs for not identifying AK where no AK was present on clinical examination was 65%, and 100% with ±1 AK tolerance. Significant positive correlation between AK counts on photographs and clinical examination: Tb=0.537. With tolerance by	Observers had different degrees of experience. P-values for the correlation according to skin sites missing: selective reporting bias likely Lack of inter-rater reliability. AKs were only diagnosed clinically.	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					± 1 AK: Tb=0.758. Correlation regarding skin sites: lower face: Tb=0.816 forearm: Tb=0.408		
Lallas et al 2015	To evaluate whether specific dermoscopic criteria can predict the diagnosis of poorly differentiated SCC compared with well- and moderately differentiated SCC.	Retrospective, multicentre evaluation of clinical and dermoscopic images of SCCs for the presence of pre-defined criteria.	n=143 patients with SCCs mean age: 77 years±11.9, 106 men) 48 well, 45 moderately and, 50 poorly differentiated SCCs Based on clinical image analysis: 50=flat, 54=elevated and 39=nodular	OR: predictors of poorly/moderately/well-differentiated SCCs	<u>Poor differentiation:</u> red colour: (OR=13.33, 95% CI 1.04-170.63, p=0.05) flat tumours: (OR=4.23, 95% CI 1.45-12.41, p=0.01) <u>Positive predictors of poorly differentiated SCC:</u> bleeding (OR=11.67, 95% CI 30.80) increased vessel quantity, small vessel caliber (OR=3.16, 95% CI 1.05-9.50, p=0.040) Decreased Odds of poor differentiation by 97% for white colour (OR= 0.03 95% CI 0.00-0.28, p<0.01) and white yellow colour (OR= 0.03 95% CI 0.00-0.24, p<0.01) <u>Well/moderately differentiation:</u>	Exclusion: cases lacking clinical/dermoscopic images or information about differentiation grade → selection bias Retrospective design: possibility of recall/observer bias Broad confidence intervals Results for ROC are not presented: selective reporting bias likely This study was supported, in part,	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					predictors: scales/keratin, central distribution of scales/keratin, white structure-less areas, white halos, white circles, large vessel caliber	by the Italian Ministry of Health (RF-2010-2316524).	
Lallas et al. 2016	To investigate the diagnostic accuracy of established dermoscopic criteria for pigmented actinic keratosis (PAK), lentigo maligna (LM) and seborrheic keratosis (SK).	Retrospective, multicentre morphological study Evaluation by 3 blinded investigators according to predefined clinical and dermoscopic criteria based on available literature. Addition of new dermatoscopic criterion: „evident follicles“	Participants with histopathologically diagnosed PAK (n=56), LM (n=70) and SK (n=18) in the face. Mean age: 67.7±12.3 years.	Clinical and dermoscopic predictors of PAK (OR for PAK compared with LM or SK) Sensitivity Specificity AUC	**Multivariate analyses:** White circles (OR: 13.52, 95% CI 2.11-86.55, p=0.006), scales (OR: 7.67, 95% CI 2.24-26.28, p=0.001) and red colour (OR: 3.60 95% CI 1.07-12.10, p=0.039) represent main diagnostic clues for PAK. Heavy pigmentation intensity (OR: 0.31 95% CI 0.13-0.75, p=0.009) not suggestive for PAK. **Univariate analysis:** Evident follicles (OR 12.45, 95% CI 5.34-29.06). sensitivity=78.6% specificity=94.3% AUC=0.94	Small sample size Study was supported by the Italian Ministry of Health (RF-2010-2316524).	2
Lee et al 2014	To evaluate the dermoscopic features of AK	Retrospective study with a follow-up of 6-12	n=34 AK lesions among 25 Korean subjects (4 men,	Frequency of dermoscopic features of AK	Keratin/scales (79.4%) Red pseudonetwork (73.5%) Targetoid-like appearance	Scaling might also be observed in SCC	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	in Asians. To assess Ch'nges in dermoscopic features following treatment, and to compare dermoscopic results with histopathologic al results.	months	21 women, mean age: 77.8 years, range 62-88 years)		(55.9%) Rosette sign (38.2%) Absence of fissures/ridges, cryps and milia-like cysts After treatment with PDT, cryotherapy or imiquimod: dermoscopic features of 33 AK lesions were decreased/disappeared. Skin biopsies confirmed the disappearance of atypical keratinocytes.	Sample consists only of Asians, no control group → limited generalizability to other populations Some results are presented in the discussion section Study was supported by a grant of the Dermatology Alumni Fund of the Catholic University of Korea.	
Maier et al 2013	To evaluate non-invasively the clinical diagnosis of AK in correlation with the histological diagnosis using high-definition optical coherence tomography	Diagnostic study HD-OCT: Lesions examined by an experienced investigator Histological evaluation: board-certified dermatopathologi st	n=20 clinically suspicious AKs of 13 subjects (4 women, age range: 50-82 years)	HD-OCT features in en-face and slice mode compared with matching criteria in routine histology and their sensitivity and specificity	Specificity: 0% (95% CI: 0-84%) Sensitivity: -Parakeratosis in histology and disruption of stratum corneum in the en-face mode: 88% -Pleomorphic keratinocytes in histology and cellular/nuclear	Small sample size results in broad confidence intervals No statistically significant results No information regarding blinding of investigators	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(HD_OCT) in the en-face (horizontal) and slice (vertical) imaging modes.				polymorphism in en-face mode: 80% -Parakeratosis in histology and irregular entrance signal in slice mode: 77% -Destruction of epidermal structure in histology with architercural disarray in stratum granulosum and stratum spinosum en-face and destruction of epidermal structure in histology with destruction of layer in in slice: 68% (each)	Work supported by the Curd-Bohnewand-Fonds of the University of Munich, by the Matthias Lackas Foundation and the Dr Helmut Legerlotz Foundation. Conflict of interest: The HD-OCT Skintell device used in this study was provided by Agfa HealthCare GmbH. Dr. Maier served as lectures for Agfa Healthcare GmbH.	
Markowitz et al 2016	To assess the ability of optical coherence tomography to detect clinical and scubclinical AKs.	Single-center, single-arm, open-label, split-face study Lesions were imaged using noninvasive OCT	Caucasian male subjects (n=30) with at least seven clinically appearing AKs on the face on three separate areas, mean age: 76	Sensitivity (Se) of OCT	Clinical AKs (including SCC in situ): Se=100% (95% CI 88-100%) (28/28) Subclinical AKs: Se=73% (95% CI 52-87%) (16/22)	Small sample size with similar demographics Results based on examination of only one observer.	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		and were biopsied. Diagnosis based on imaging was compared with histopathology as standard reference.	years, range: 67-93			Lack of information regarding Sp, PPV, NPV Two authors (including the main author) report conflict of interests mainly with respect to Michelson Diagnostics (Producer of the used OCT-scanner VivoSight®).	
Marneffe et al. 2016	To determine the accuracy of a high-definition optical coherence tomography (HD-OCT)-based algorithm in AK and SCC classifications.	In vivo non-invasive diagnostic study 3 observers with different levels of experience in HD-OCT (6 months to 3 years) assessed images according to a diagnostic algorithm. All were blinded to histopathology and clinical	106 HD-OCT images of histopathologically proven AKs (n=38), SCCs (n=16) and normal skin (n=52) were collected from 71 patients	Sensitivity (Se) Specificity (Sp) Positive predictive value (PPV) Neagtive predictive value (NPV)	**AK:** (p<0.001) Se: 57.9-81.6% Sp: 58.8-92.6% PPV: 44.0-86.1% NPV: 71.4-90.0% **SCC:** (p<0.001) Se: 43.8-93.8% Sp: 90.0-98.9% PPV: 43.8-93.8% NPV: 90.0-98.9% Classification of AKs in subtypes according to adnexal	Hyperkeratotic AKs were excluded Overall moderate interobserver agreement: k=0.63 (95% CI 0.55-0.70) >AK diagnosis: k=0.52 (95% CI 0.32-0.72) >SCC diagnosis: k=0.53 (95% CI 0.15-0.92)	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		appearance of the lesions.			involvement associated with poor reliability [k=0.54 (95% CI 0.19-0.91)] (kappa statistics: k=0-1 with 0=no agreement, 1=complete agreement)		
Nascimento et al. 2014	To explore clinical usefulness of the dermoscopic feature “inner gray halo” (IGH) and to identify its histologic correlation through in vivo confocal microscopy and histologic transverse sectioning.	Diagnostic study Gold standard: histopathological diagnosis	n=58 pigmented AKs (PAK), n=21 LM in 40 men and 39 women, mean age=67 years (range 49-96) All lesions were located on the face.	Presence of IGH Sensitivity (Se) Specificity (Sp)	Presence of IGH in 53/58 (94.1%) PAK Se: 91.4% (95% CI 81.4-96.3%) Sp: 71.4% (95% CI 50.0-86.2%) PPV: 89.8% (95% CI: 79.5-95.3%)	Excellent interobserver agreement (k=0.846) (kappa statistics: k=0-1 with 0=no agreement, 1=complete agreement)	2
Nguyen et al. 2016	To evaluate the accuracy of in vivo reflectance confocal microscopy (RCM) for AKs	Systematic review Literature search in PubMed, Embase, Cochrane library and Web of	Overall inclusion of n=25 studies of which n=3 report relevant separate data on AKs and n=1 on SCC.	Sensitivity (Se) and Specificity (Sp) of RCM diagnoses relative to histopathological examination	Se AK: 91-100% Sp AK: 78-100% (results out of 3 studies) Se SCCs: 100%	Conclusions mostly based on case series and case control studies with low to moderate	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	and SCCs relative to histopathology.	Science databases. Quality assessment of the eligible studies performed with the STROBE criteria.			Sp SCCs: not reported (results out of 1 study of which only 74% of the clinically suspicious lesions were biopsied)	methodological quality. Small sample size in all studies Confidence intervals of Se/Sp not reported	
Olsen et al. 2016	To estimate the diagnostic accuracy of optical coherence tomography in AKs.	Retrospective observer-blinded diagnostic study. Two observer groups (OCT-skilled and -unskilled) reviewed a data set consisting of OCT images of histologically verified AK as well as clinically defined healthy skin of the same region. 20 minutes lecture about OCT features of AK	n=30 patients with AK lesions mean age: 72.2 years ±11.0, 13 female n=71 patients with healthy skin Mean age: 69.2 years±11.9, 40 female	Sensitivity (Se) Specificity (Sp)	<u>Unskilled observers (n=5):</u> Se AK: 69% (95% CI 54-83%) Sp AK: 58% (95% CI 52-65%) <u>Skilled observers (n=5):</u> Se AK: 76% (95% CI 56-96%) Sp AK: 68% (52-83%) No significant differences between skilled and unskilled observers for AK (Se p=0.20 and Sp p=0.06)	Only good quality OCT images were used for the evaluation Both groups overdiagnosed (especially overdiagnosis of AK) → leads to a high sensitivity and mediocre specificity ROC for AKs planned, but not presented -> selective reporting bias likely Funded by the	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		and normal skin prior to evaluation for all observers				European Union.	
Peppelman n et al. 2015	To determine whether there are reflectance confocal microscopy (RCM) features that are specific for making an in vivo distinction between AK and SCC.	Retrospective evaluation Two observers evaluated RCM images according to literature-based list of RCM features	n=24 patients (12 male, mean age of 67 years, range =53-80) with 30 lesions (24 AK, 6 invasive non-pigmented SCC) Control group of n=2 without skin condition to compare vascular RCM features	Predictors for the diagnosis of AK/SCC: OR	-Architectural disarray in the statum granulosum (OR=24.0, p=0.013) -Architectural disarray in the spinous layer (OR=15, p=0.023) -Nest-like structures in the dermis (OR=11, p=0.029) -Presence of architectural disarray in granular layer: correct diagnosis in 84.6% of SCC cases (6 cases) Combination of architectural disarray in the granular layer with architectural disarray in stratum spinosum and/or dermal nest-like structures: correct prediction of 88.5% of SCC cases	Small sample size Study is underpowered Obserevers: not blinded for the final diagnosis Inter-observer agreement (starting vs. experience): poor to no agreement Financial support: grant of the Dutch Ministry of Economic Affairs, Agriculture and Innovation and the provinces Gelderland and Overijssel	3
Rishpon et al. 2009	To identify criteria for the diagnosis of	Prospective, single centre study	n=38 lesions in 34 patients (7AKs, 25 SCCs in situ, 3	Presence of dermoscopic and RCM features	Presence of the features in SCCs vs AKs:	Small sample size overestimates the results (only 7 AKs	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	SCC and AK by reflectance confocal microscopy (RCM)	RCM imaging of lesions suspected clinically and/or dermoscopically to be SCC or AK, followed by RCM assessment of the biopsy-proven SCCs and AKs. Evaluation by 3 observers.	invasive SCCs, 3 keratoacanthomas), mean age =69 years, range 30-91		-Scales at the stratum corneum: 95% vs 100% -Polygonal nucleated cells at the stratum corneum: 10% vs 14% -Atypical honeycomb and/or disarranged pattern of the spinous-granular layer of epidermis: 100% vs 100% -Round nucleated cells in the spinous-granular layer: 65% vs 14% -Round blood vessels in the superficial dermis: 90% vs 72%	in the sample)	
Schuh et al. 2016	To objectively diagnose AKs and BCC through standardized measurement of signal intensity and layer thickness in optical coherence tomography (OCT)	Experimental diagnostic study Only OCT images of clinically and dermoscopically unequivocal or histopathologicall y confirmed lesions were taken in vivo. Perilesional unaffected skin served as control.	n=301 lesions (188 BCCs and 113 AKs) of 125 patients (74 male. Median age: 70.5 years, range 39-95)	1) Mean thickness and signal intensity of the stratum corneum and epidermis compared to perilesional healthy skin measured by OCT. 2) Spearmans correlation coefficient to correlate OCT findings with histology.	1) Compared to normal skin, AKs (n=113) showed a stronger decline of signal intensity from stratum corneum towards dermis, but a strong increase in the thickness of the stratum corneum and epidermis ($p<0.0001$). A subgroup of histologically confirmed AKs (n=23) showed the same results. 2)>Stratum corneum: $r=0.894$ ($p<0.0001$)	Not all AK lesions were histologically assessed and confirmed Due to maximum penetration of 2 mm in OCT, tumours with >2 mm depth could not be completely measured No blinding of observer reported	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					>Epidermis:r=0.951(p<0.0001)		
Tan et al. 2016	To correlate reflectance confocal microscopy (RCM) features of photodamaged skin (PD) and AK with histopathology (HP).	Diagnostic correlation study	n=20 participants (mean age: 64 years, skin phototype I and II, 30% female) Setting: Australia 57/60 (95%) of the areas included as they met histopathological criteria for PD or AK. Of these, 75% (43/57) were PD and 25% (14/57) AK, both histopathologically confirmed.	Sensitivity of discernible histopathological and RCM features for the diagnosis of AK	HP vs RCM >Parakeratosis: 71.4% (10/14) vs 88.9% (8/9) >Hyperkeratosis: 57.1% (8/14) vs 45.5% (5/11) >Severe keratinocyte pleomorphism HP: marked keratinocyte atypia in all HP confirmed AKs RCM: diffuse irregularity of honeycomb pattern, increased variation in size and shape of keratinocyte nuclei in all HP confirmed AKs >Architectural disruption: 100% (14/14) vs 91.7% (11/12) >Inflammatory cells in the upper dermis: 28.6% (4/14)	Small sample size RCM: partly increased sensitivity compared to histopathology → might lead to false positive results Exclusion of hyperkeratotic AKs (due to limited penetration depth of RCM) Study was funded by LEO Pharma.	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					vs 21.4% (3/14) >Inflammatory cells in epidermis: 50% (7/14) vs 71.4% (10/14)		
Ulrich et al. 2008	To evaluate the applicability of reflectance confocal microscopy (RCM) in the diagnosis of AK in correlation with routine histology.	Prospective, single center, diagnostic study Evaluation consisted of clinical examination, RCM, and routine histology. RCM images were evaluated by two blinded, independent experts. Prior to this, evaluation by an expert who was not blinded. RCM features of AK: parakeratosis, architectural disarray, and keratinocyte pleomorphism.	n=46 AKs among 44 Caucasians (age range: 56-79 years, skin photo types II-III) Exclusion of lesions with hyperkeratosis 10 normal skin sites served as control group.	Correct identifications of two observers Sensitivity (Se) and specificity (Sp) for each RCM parameter compared to routine histology	Observer 1: correct identification of AK by RCM: 46/46 lesions (100%) Observer 2: correct identification in 45/46 lesions (97.8%) RCM parameters with highest sensitivity and specificity reported: -epidermal pleomorphism at the level of spinous layer (Se=100%, Sp=100%, p<0.0001) and granular layer (Se=97.8%, Sp=100%, p<0.0001) -architectural disarray at the level of spinous layer (Se=91.2%, Sp=95.2%, p<0.0001) RCM parameters with the lowest sensitivity reported: Lymphocyte rolling:	No calculation of PPV, NPV, Confidence intervals High inter-observer agreement, concordance values from 87% to 98.2%. Acknowledgements: The Vivascope 1500 used in this study was loaned by MAVIG. One author has served as a lecturer for MAVIG GmbH.	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Se=14.3%, Sp=100%, p=0.123 Exocytosis in the stratum granulosum: Se=35.1%, Sp=100%, p=0.0001		
Ulrich et al. 2007	To evaluate the reflectance confocal microscopy (RCM) morphologic features of clinically diagnosed AKs and to correlate the findings with routine histopathology	Prospective, blinded, single centre, diagnostic study RCM parameters: parakeratosis, architectural disarray, keratinocyte pleomorphism	n=44 AKs among 44 Caucasians (FST I-III)	Sensitivity of RCM in identifying AKs	97.7% 2.3% were incorrectly identified as normal skin	Lack of participants' socio-demographic characteristics Conflict of interest: S. Astner has acted as a lecturer for MAVIG GmbH. E. Stockfleth has acted as a lecturer and consultant for Shire Pharmaceuticals.	2
Xiang et al. 2017	To assess the potential of reflectance confocal microscopy (RCM) to predict the histology of the debrided and non-debrided skin lesions of	Diagnostic, monocentric study Following RCM imaging, a biopsy was obtained from the skin site within the lesion. Follow-up: after 2	n=25 patients with histologically confirmed SCC. Lesions without obvious keratosis (n=14) underwent direct RCM examinations. Lesions with obvious keratosis	Correlation of RCM features with invasive SCC	-Atypical keratinocytes arranged in nests and islands and disarrangement patterns (80%, (12/15) debrided lesions, 14.3% (2/14) non-debrided lesions) -an atypical honeycomb pattern (20% (3/15) debrided lesions, 85.7% (12/14) non-debrided	Small sample size/small number of lesions, only 1 patient with healthy skin as comparison No information about participants' skin types	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	invasive SCC before and after therapy (PDT or surgery).	months and every 6 months thereafter for 2 years.	(n=15) were gently debrided for further RCM. For comparison, 1 participant without dermatosis was recruited.		lesions) -non-edged dermal papillae (100%) -absence of a cobblestone pattern (100%) -"Bright dots" = inflammatory cell infiltration in 40% (6/15) debrided lesions, 57.1% (8/14) non-debrided lesions) -keratin pearl structures: closely associated with well differentiated SCC (4/15 debrided lesions)	Blinding of obersevers unclear: detection bias likely Research was supported by Science and Technology Commission of Hangzhou, National Natural Science Foundation of China	
Zalaudek et al. 2006	To investigate the dermoscopic features of nonpigmented AKs located on the head/neck that may assist the clinical diagnosis.	Prospective, multicentre diagnostic pilot study Histopathological diagnosis served as gold standard	n=41 nonpigmented AKs on facial sites in 32 patients (24 men, mean age=69 years, range 48-91)	Presence of dermoscopic features in facial AKs	Essential dermoscopic features: (i) erythema, revealing a marked pink-to-red pseudonetwork surrounding the hair follicles (95%) (ii) white-to-yellow surface scale (85%) (iii) fine, linear-wavy vessels surrounding the hair follicles	Limitation: lack of testing of the specificity of the dermoscopic criteria in differentiating nonpigmented AKs from other nonpigmented skin lesions at this site Examination of the	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(81%) (iv) hair follicle openings filled with yellowish keratotic plugs (66%) (i-iv) combined produced in 95% of cases a peculiar strawberry appearance	lesions by two investigators, no information about blinding or correlation available	

Remarks and notes: Papers not included

Author, year	Grund
Seyed et al. 2016	Relevant ouctomes not reported, objectives of study not adequate, no diagnostic values reported
Malvehy et al. 2016	Relevant ouctomes not reported, objectives of study not adequate, no diagnostic values reported
Boone et al. 2016	Relevant ouctomes not reported, no diagnostic values reported
Zalaudek et al. 2015	Narrative review
Ulrich et al. 2015	Case series with n=8
Malvehy et al. 2015	No relevant outcomes reported, narrative review
Ishioka et al. 2015	Small sample size (n=9), no focus on diagnostics
Fox et al. 2014	Experimental design,
Mittal et al. 2013	Relevant ouctomes not reported, objectives of study not adequate, no diagnostic values reported, experimental study
Aghassi et al. 2000	Small sample size
Zalaudek et al. 2005	Case reports
Peris et al. 2007	Narrative review
Bae et al. 2011	Relevant ouctomes not reported, objectives of study not adequate, no diagnostic values reported, experimental

Author, year	Grund
	study
Zalaudek et al. 2012	Not suited according to PICOT question
Boone et al. 2013	No relevant outcomes reported, qualitative character
Çayirli et al. 2013	Relevant ouctomes not reported, objectives of study not adequate, no diagnostic values reported
Richtig et al. 2010	Small sample size (n=6)
Ortonne et al.	Relevant ouctomes not reported, objectives of study not adequate, no diagnostic values reported
Mogensen et al. 2009	Data not sperately reported for actinic keratosis
Ulrich et al. 2007	Relevant ouctomes not reported, objectives of study not adequate, no diagnostic values reported
Klemp et al. 2016	Not suited according to PICOT question

3.5.5. Literature

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3.6. Question II.5. When, how and using which criteria should the histologic sample be obtained?

(Frage II.5. Wann, bei welchen Kriterien und wie soll die Gewinnung der Histologie erfolgen?) Beantowrtung durch orientierende Recherche und Expertenkonsens, systematische Recherche für Zytologie, ggf Adaptation zu bestehenden Leitlinien

3.6.1. PICO

PICO – Scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Patients with actinic keratosis and cSCC	Cytology	n.a. (no specific intervention)	Diagnostic accuracy

3.6.2. Databases, search strategy, number of results

Database	Search strategy	Date	Number of results
1. Search			
Medline	(keratos*[Title] AND (solar[Title] OR actinic[Title])) OR (squamous[Title] AND (skin[Title] OR cutaneous[Title])) AND cytol*[Title/Abstract] NOT "case report" AND (English[Language] OR German[Language])	15th December 2016 (initial search) Update 30th May 2017	20 20
Remarks and notes:			

3.6.3. Selection criteria

Literature selection	
Number of total results	20
Inclusion criteria	Comparative trials (randomized, non-randomized), observational trials, cross-sectional trials, sample size of investigated patients n>10, quantitative outcomes measures
Exclusion criteria	Case reports excluded; oral and esophageal carcinomas were also excluded.
Number of results after abstract searching	8
Number of full texts reviewed	4

3.6.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Bilen et al. 2000	To evaluate if cytology of skin scrape material of cutaneous lesions suspected of malignancy can be used as a rapid and reliable diagnostic method.	n.a; total number of patients evaluated not reported	Patients with suspected malignant lesions of the head	To evaluate if cytology of skin scrape material of cutaneous lesions suspected of malignancy can be used as a rapid and reliable diagnostic method.	Cytologic examination revealed malignancy in 18 cases. All were histopathologically confirmed. The rate of false negatives was thus 1/19 (5.3%). No false positive results occurred. Of the	There are certain limitations of cytodiagnosis that may cause problems in differential diagnosis and that should be borne in mind. Flattened or ulcerated seborrheic keratosis may be	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					malignant cases, eight were classified as BCC and five as SCC. No discrepancy between cytology and histopathology was found in any of the cases so categorized. The remaining five cases could not be subclassified cytologically.	confused with BCC or SCC Scraping cytology may fail in crusted, hyperkeratotic and tough cutaneous lesions.	
Christensen et al. 2008	To compare and evaluate the diagnostic performance of scrape cytology using two different cytological staining techniques, and to evaluate additional touch imprint cytology, with that of histopathology of basal cell carcinoma (BCC) and actinic	Prospective trial; n= 50 BCC cases (41 patients) and 26 AK cases (25 patients)	Samples from patients with BCC and SCC	To compare and evaluate the diagnostic performance of scrape cytology using two different cytological staining techniques, and to evaluate additional touch imprint cytology, with that of histopathology of basal cell carcinoma (BCC) and actinic	Scrape cytodiagnosis agreed with histopathology in 48 (Pap) and 47 (MGG) of the 50 BCC cases, and in 26 of 28 (Pap) and 21 of 26 (MGG) AK cases, yielding sensitivities of 96%, 94%, 93% and 81%, respectively. No significant difference in		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	keratosis (AK).			keratosis (AK).	sensitivity between the two staining methods was found but a trend towards higher Pap sensitivity for AK was noted (P = 0.10). Touch imprint cytology confirmed histopathology in 38 of the 77 cases of BCC and AK.		
Pellacani et al. 2015	To evaluate the strength of the correlation between keratinocyte atypia, as detected by Reflectance Confocal Microscopy (RCM) and histopathology, and to develop a more objective atypia grading scale for RCM quantification, through a discrete ranking	Prospective trial; n= 48 AK samples	48 samples from AK plus 2 control samples	To evaluate the strength of the correlation between keratinocyte atypia, as detected by Reflectance Confocal Microscopy (RCM) and histopathology, and to develop a more objective atypia grading scale for RCM quantification, through a discrete ranking	Good interobserver correlation was obtained for RCM and histopathology grading, with high concordance between RCM and histopathology grading.		2
Vega-Memije et al.	Evaluate the	Prospective trial; n=	Samples from	Evaluate the	Imprint cytology		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
2000	diagnostic accuracy of cytologic examination in basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs), in order to assess its clinical value.	45; 15 BCC patients; 30 SCC patients.	patients with BCC and SCC	diagnostic accuracy of cytologic examination in basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs), in order to assess its clinical value.	demonstrated to be of help in the rapid diagnosis of skin tumors. Cytologic examination is easy to perform, saves time, provides a rapid diagnosis, and can be considered, under experienced hands, reliable in the confirmation of malignant skin tumors. Cytology does not give much information about tumor patterns or subtypes which can be related to aggressive behavior and can be very important in further therapeutic decisions. Therefore, histopathologic confirmation is mandatory before		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					any therapeutic maneuver		

Remarks and notes:

3.6.5. Literature

Bilen N, Dal H, Kaur AC. Scraping cytology in the diagnosis of malignant squamous neoplasms of the skin. Acta cytologica 2000;44(1):101-3. [published Online First: 2000/02/10]
Christensen E, Bofin A, Gudmundsdottir I, et al. Cytological diagnosis of basal cell carcinoma and actinic keratosis, using Papanicolaou and May-Grunwald-Giemsa stained cutaneous tissue smear. Cytopathology : official journal of the British Society for Clinical Cytology 2008;19(5):316-22. doi: 10.1111/j.1365-2303.2007.00483.x [published Online First: 2007/10/06]
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Vega-Memije E, De Larios NM, Waxtein LM, et al. Cytodiagnosis of cutaneous basal and squamous cell carcinoma. International journal of dermatology 2000;39(2):116-20. [published Online First: 2000/02/26]

3.7. Question II.6. Which parameters should be included in the actinic keratosis and squamous cell carcinoma histological report?

(Frage II.6. Welche Parameter sollten Bestandteile des histologischen Befundberichtes bei AK und PEK sein?) Beantwortung durch Expertenkonsens

3.8. Question II.7. Which staging procedures are recomend for patients with squamous cell carcinoma, considering the different stages?

(Frage II.7. Welche Ausbreitungsdiagnostik ist bei Patienten mit PEK in welchem Stadium indiziert?) Beantwortung durch De novo Recherche

3.8.1. PICO

PICO – Scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Patients with SCC	Imaging techniques	n.a.	Accuracy

3.8.2. Databases, search strategy, number of results

Database	Search strategy	Date	Number of results
1. Search			
Medline	(squamous[Title] AND (skin[Title] OR cutaneous[Title])) AND staging [Title/Abstract] NOT "case report" AND (English[Language] OR German[Language])	15th December 2016 (initial search)	114

Database	Search strategy	Date	Number of results
	(squamous[Title] AND (skin[Title] OR cutaneous[Title])) AND (staging [Title/Abstract] or lymph node sonography or imaging [title/Abstract]) NOT “case report” AND (English[Language] OR German[Language]) ("lymph nodes"[MeSH Terms] OR ("lymph"[All Fields] AND "nodes"[All Fields]) OR "lymph nodes"[All Fields] OR ("lymph"[All Fields] AND "node"[All Fields]) OR "lymph node"[All Fields]) AND ("ultrasonography"[MeSH Terms] OR "ultrasonography"[All Fields] OR "sonography"[All Fields]) AND SCC[All Fields]	Update 30th May 2017	118
Remarks and notes:			

3.8.3. Selection criteria

Literature selection		
Number of total results		118
Inclusion criteria	Complementary diagnosis such us lymph node ultrasound, CT/MRT and PET TC	
Exclusion criteria	Exclusion of oral and esophageal/larynx carcinomas, SLNB and lymphatic mapping (already discussed in questions IV 2 and 3)	
Number of results after abstract searching		15
Number of full texts reviewed		*15*

3.8.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Bota et al. 2017	To review and compare the risk factors and clinical behavior of cSCC, omSCC, and lip SCC, review tumor biology of squamous cell carcinoma, and compare work-up and treatment algorithms for lip SCC	A comprehensive PubMed and MEDLINE database search was performed with comparison of primary literature on cSCC, omSCC, and lip SCC.	Comparison of primary literature on cSCC, omSCC, and lip SCC	To review and compare the risk factors and clinical behavior of cSCC, oral mucosal SCC, and lip SCC, review tumor biology of squamous cell carcinoma, and compare work-up and treatment algorithms for lip SCC	The American Joint Committee on Cancer (AJCC) has developed separate staging guidelines for both cSCC and omSCC. In 2010, the guidelines for cSCC were revised to include high-risk features of cSCC for T-staging. Tumors with origin on the mucosal lip are staged concomitantly with the omSCC AJCC staging guidelines. These 2 sets of guidelines are largely similar with the exception of T2 definition, where the AJCC guidelines for omSCC defines T2 as any tumor between 2 and 4 cm diameter. The impli- cations of	Lip SCC exhibits rates of nodal metastasis and death that are intermediate between cSCC and omSCC. Lip SCC is an overlapping entity that poses many challenges to clinicians. Although there is evidence to suggest that lip SCC may have biochemical roots in either cSCC or omSCC, practitioners in both dermatology and otolaryngology should be mindful that lip SCC behaves differently than similar SCCs in their respective fields. Dermatologists	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					this difference are unclear. The Brigham and Women's Hospital (BWH) staging system was developed to risk stratify patients with T2 tumors. Patients in this study were staged by both AJCC and BWH criteria, with a similar number of patients comprising AJCC T2 and BWH T2a/T2b stages. There remains debate over the optimum staging system for cSCC, and risk stratification of cSCC has been limited given the lack of standard reporting and larger population- based studies.	should consider that lip SCC may be more aggressive than cSCCs and portends a more worrisome outlook. Likewise, otolaryngologists should remember that while omSCC may benefit from elective LND, the current evidence does not support this intervention for lip SCC. Accurate staging modalities of SCC are evolving, and it is essential to be aware of the practice guidelines as well as imaging and treatment recommendations to optimize patient care and maximize outcomes.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Recommendations and modalities of imaging for lip SCC are continuously evolving. In the cutaneous NCCN guidelines, imaging is recommended for patients who have a clinically positive lymph node examination, extensive local disease, or perineural invasion on histopathology. In contrast, the NCCN guidelines for head and neck cancer recommend that imaging be considered in the initial work-up for patients presenting with lip or omSCC, but these recommendations are left intentionally broad. Imaging modalities include computed		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), and positron emission tomography (PET). For assessment of the primary tumor, it has been shown that MRI more accurately estimates tumoral depth. Evidence directly comparing CT versus MRI for omSCC is limited. The MRI is superior with respect to soft-tissue imaging capabilities; however CT is adequate for T staging and may be more readily available. Detection of bony invasion is important as it upstages primary tumors to a T4 by the AJCC guidelines.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					The MRI has high sensitivity and specificity of 93% and 93%, respectively, for detection of bony invasion. The MRI was found to have a higher sensitivity than CT—94% versus 83%. Despite the limitations in current evidence, the authors feel that MRI may offer an advantage over CT with regard to invasion of bone, but further studies are needed. Contrast CT, MRI, and ultrasound (US) are widely used in the detection of nodal involvement. Contrast CT and MRI have been shown to be equivalent in assessing extent of nodal disease and extranodal extension.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					There is a need for detection of microscopic nodal involvement; however it has been demonstrated that PET/CT cannot predict the need for surgical LND and should not be used to guide management. Nonetheless, it has been suggested that PET/CT may have a role in surveillance of the N0 neck.		
Cho et al. 2005		Exhaustive collaborative database search	All patients with cSCC metastasis to the parotid gland treated at three major Canadian tertiary referral centers from December 1999 to March 2015	OS DFS TNM	Of 136 patients identified, 80% had a documented history of previously treated head and neck cSCC an average of 27 months prior to presentation. Average size of the parotid lesion at recurrence was 4.5 cm. 96% of patients	Patients with cSCC metastasis to the parotid gland proved to have a moderate survival rate, despite presenting with advanced disease. cSCC staging in the setting of parotid metastasis, despite its limitations,	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					underwent surgical resection of the parotid metastasis. Five-year OS and DFS is 79% and 55%, respectively. Only cSCC staging and cSCC-N category had statistically signify-cant differences between groups. cSCC staging had the largest per-centage of variation in OS explained. TNM cSCC staging in the setting of parotid metastasis, notwithstanding its limitations (N2a patients did worse than N2b patients), currently offers the most predictive staging system available.	currently offers the most predictive staging system available.	
Czerwonka et al. 2017	To report on the usefulness of FDG PET as a baseline	Retrospective study; n=12 patients	Patients with SCC and hight risk SCC in whom PET CT	To report on the usefulness of FDG PET as a baseline	Primary lesions were detected in nine cases (83.3%), lymph		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	workup study for patients with cutaneous SCC (cSCC)		was performed between May 2000 and September 2003	workup study for patients with cSCC	node involvement in three cases (25.0%), and distant organ (lung) involvement in one case (8.3%). All of the patients with high-risk SCC showed FDG uptakes of the primary lesions, and the patients with FDG uptakes in lymph nodes and distant organ had high-risk SCC. There have been no comparative studies on the cost-effectiveness between sentinel lymph node biopsy and FDG PET in SCC patients. However, considering the noninvasiveness and thoroughness in checking the whole body, including distant organs, FDG PET may have clinical value as a baseline		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					workup study for patients with high-risk SCC		
Ebrahimi et al. 2010	To analyze the distribution of regional nodal metastases according to primary tumor location in patients with cutaneous squamous cell carcinoma of the head and neck (cHNSCC).	Retrospective study; n= 295 neck dissections	Patients with clinically evident regional metastases from cSCCHN between 1987 and 2009	To analyze the distribution of regional nodal metastases according to primary tumor location in patients with cHNSCC.	Level I involvement in the absence of level II or III only occurred in patients with facial primaries. In patients with clear nodes in level II–III, the risk of level IV–V involvement was 0.0% for external ear primaries, 2.7% for face and anterior scalp, and 15.8% for posterior scalp and neck. In patients undergoing parotidectomy for metastatic cHNSCC with a clinically negative neck, the results of this study support selective neck dissection		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					including level I–III for facial primaries, level II–III for anterior scalp and external ear primaries, and levels II–V for posterior scalp and neck primaries.		
Forest et al. 2010	Review of clinical and pathological information of patients treated for metastatic cutaneous SCC (cSCC) to the parotid and/or neck was conducted. Potential prognostic factors were analyzed using univariate and multivariate analyses. A staging system was elaborated and externally validated.	Retrospective study; n=215 patients	Patients treated with curative intent between 1987 and 2007 for metastatic HN cSCC to the parotid and/or neck were identified.	To identify potential prognostic factors using univariate and multivariate analyses. To elaborate a staging system and validated it externally.	All patients had surgery as their primary treatment; 148 had parotidectomy with neck dissection, 50 parotidectomy alone, and 18 neck dissection alone. One hundred seventy-five patients received postoperative radiotherapy. On univariate analysis, the number of involved lymph nodes (P < .001), maximal size (P=.01), and extracapsular spread (P=.003) were found to be		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					significant predictors of survival. On Cox regression, the number of involved lymph nodes as single or multiple (P =.006) was significant. The N1S3 staging system incorporates involved lymph nodes from parotid and neck (single or multiple) and the size (< or >3 cm). This system demonstrates significant predictive capacity for locoregional control (P < .001), DSS (P<.0001), and OS (P<.0001). N1S3 was tested on a different cohort of 250 patients, and the results confirmed those obtained from our primary analyses. The N1S3 system stages patients		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					according to the number of involved lymph nodes and size, and incorporates parotid as 1 of the regional levels. These 2 predictors are easily applied on both clinical and pathological data.		
Fujiwara et al. 2016	To evaluate the 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging to assess lymph node (LN) metastasis of high-risk cutaneous SCC (cSCC) patients	Prospective study; n= 26	Patients with primary cSCC treated in one center	To evaluate the 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging to assess lymph node (LN) metastasis of high-risk cSCC patients	The maximum standardized uptake value (SUVmax) of more than 2.5 is generally evaluated as a positive PET finding indicative of malignancy. On the basis of the histopathological and PET findings, 30 LN from 26 patients were categorized into four groups: (i) histologically negative and PET negative (true-negative; n = 22); (ii) histologically positive		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					and PET negative (false-negative; n = 0); (iii) histologically positive and PET positive (true-positive; n = 3); and (iv) histologically negative and PET positive (false-positive; n = 5). The mean SUVmax was significantly higher in the true-positive cases (11.0±2.8) than in the false-positive cases (3.4 ±0.6). In the false-positive cases, the number of tumor-infiltrating inflammatory cells at the primary skin site was highest among the four groups, suggesting that inflammation contributed to the false-positive uptake of FDG.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Ghafoori et al. 2015	To determine valuable sonographic features for differentiating metastasis from benign nodes using gray scale and Doppler sonography.	Prospective study; n= 63	Patients with head and neck SCC treated and referred to surgery clinic of Hazrat Rasoul Akram hospital from November 2010 to June 2012, with complaint of palpable cervical lymph node.	To determine valuable sonographic features for differentiating metastasis from benign nodes using gray scale and Doppler sonography.	The number of metastatic lymph nodes was 47, while the remaining 16 were reactive. There were significant differences in length ($P = 0.037$), width ($P = 0.001$), resistance index ($P < 0.001$), pulsatility index ($P < 0.001$) and systolic velocity ($P < 0.001$) of metastatic and reactive lymph nodes. Cut points for resistive and pulsatility indexes and systolic velocity were calculated as 0.695, 1.35 and 16.5, respectively. The most valuable factor for defining a lymph node as metastatic was circulation pattern with accuracy, sensitivity and specificity of 94%, 85% and 93%,		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					respectively.		
Gonzalez et al. 2017	To compare the AJCC-7 and BWH staging systems for cutaneous SCC (cSCC) in immunosuppressed patients	A single-institution retrospective cohort study; n=106	cSCC in immunosuppressed patients	Risks of local recurrence nodal metastasis in-transit metastasis To report poor outcomes	One hundred six patients had 412 primary invasive cSCC. Eighty-five percent were AJCC-7 T1, and 15% T2. Risks of NM and PO for AJCC-7 T1 versus T2 were 0.9% versus 5% and 12.8% versus 23.3%, respectively, $p < .05$. Eighty-one percent of tumors were BWH T1, 18% T2a, 1% T2b, and 0.2% T3. Risk of LR for BWH T1 versus T2a was 11.4% versus 20.3%, $p < .01$. Risk of NM increased from 0.3% for T1 to 4.1%, 25%, and 100% for T2a, T2b, and T3, $p < .05$. Ninety percent of PO occurred in low-stage BWH T1/T2a.	Low T-stage cSCC account for most poor outcomes. Brigham and Women's Hospital staging criteria better risk stratifies cSCC in immunosuppressed patients for risk of nodal metastasis and local recurrences. Additional studies are needed to quantify the increase in risk of por outcomes for same T-stage cSCC in immunocompetent versus immunocompro-mised patients. Better risk stratification of low T-stage cSCC in immunosuppressed	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						patients is needed. Alternatively, immune status can potentially be included as part of the staging criteria to reflect the inherent higher risk of poor outcomes associated with immuno-suppression. In the meantime, vigilant detection and definitive treatment of even low T-stage cSCC in immunosuppressed patients are recommended.	
Kim et al. 2010	To access the probabibily of metastasis of small atypical cervical lymph nodes, detected on US in patients with head and neck SCC (HNSCC)	Retrospective study; n=148 patients (US were blindly reviewed)	Patients with HNSCC who underwent curative neack dissection between January 2006 and December 2008 in one center	To access the probabibily of metastasis of small atypical cervical lymph nodes, detected on US in patients with HNSCC	Small atypical nodes were found on US in 63 cervical levels of 48 patients, of which 18 (28,6%) were proven to be metastatic nodes. The probability of metastasis was significantly higher in		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					with than without a large (>3cm) ipsilateral metastatic node (0.50 vs 0.20; p=0.38) and marginaly higher with than without an ipsilateral metastatic node.(0.42 vs 0.16; p=0.61) but not significantly associated with the T from the primary tumor (p=0.238) or the presence of an ipsilateral tumor (p=0.904). Metastais was found in about 30% of small atypical cervical nodes on US in patients with SCC. The results show that small atypical nodes must be interpreted with consideration of metastatic nodes in the ipsilateral neck.		
Marrazzo et al.	To investigate the	Retrospective	Patients from a	To investigate the	Twenty-nine percent		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
2015	clinical and pathologic features predictive of bony invasion, perineural invasion, or lymphadenopathy in patients that had undergone head and neck imaging for high-risk cutaneous squamous cell carcinoma (hrSCC).	study; n=82 patients	single center that had undergone head and neck imaging for hrSCC.	clinical and pathologic features predictive of bony invasion, perineural invasion, or lymphadenopathy in patients that had undergone head and neck imaging for high-risk cutaneous squamous cell carcinoma (hrSCC).	(24/82) of patients in the study had positive findings on radiologic imaging. Immunocompromised patients were more likely to have the radiologic finding of lymphadenopathy (p = .04). Tumor size was found to correlate with the radiologic finding of bony invasion (correlation coefficient = 0.40, p = .0002). There was no relationship between either high risk location or high risk histopathology and positive radiologic findings.		
Ruiz et al. 2017	To review utilization of radiologic imaging of high-stage cutaneous SCC (cSCC) to evaluate whether imaging	Retrospective study; n=98 patients; 108 high-stage cSCC	Patients diagnosed with cSCC from January 1, 2000, through May 30, 2013 treated in the Brigham and Women's Hospital.	Disease-related outcomes (DRO): local recurrence, nodal metastasis, death from disease	Imaging (mostly computed tomography, 79%) was utilized in 45 (46%) patients and management was altered in 16 (33%)	Limitations: Single institution retrospective design and Ch'nges in technology overtime.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	impacted management and outcomes.				patients who underwent imaging. Patients that received no imaging were at higher risk of developing nodal metastases (nonimaging, 30%; imaging, 13%; P = .041) and any DRO (nonimaging, 42%; imaging, 20%; P = .028) compared to the imaging group. Imaging was associated with a lower risk for DRO (subhazard ratio, 0.5; 95% CI 0.2-0.9; P = .046) adjusted for BWH T stage, sex, and location.	Radiologic imaging of high-stage cSCC may influence management and appears to positively impact outcomes. Further prospective studies are needed to establish which patients benefit from imaging.	
Shetty et al. 2015	To evaluate the accuracy of preoperative clinical methods such as palpation, ultrasonography (USG), and computed	Prospective study; n= 26 patients	Patients who were incisional biopsy proven cases of oral carcinoma requiring resection of tumor and neck dissection treated in one	Accuracy of preoperative clinical methods To assess whether combining these techniques increases the	Palpation, USG, and CT findings were compared with histopathologic findings by Fisher's exact test and the "P" value for palpation, US and CT were		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	tomography (CT) in comparison with postoperative histopathological findings in determination of metastatic cervical lymph nodes and also to assess whether combining these techniques increases the specificity and sensitivity of lymph node metastasis in oral SCC.		center	specificity and sensitivity of LN metastasis diagnostic	0.003, 0.000, 0.000, respectively, which are statistically significant. US examination combined with CT gives a better assessment of the neck for nodal metastasis		
Supriya et al. 2014	To evaluate the impact of whole-body positron emission tomography in comparison to staging by conventional methods alone in management of patients with head and neck cutaneous SCC (cHNSCC) with confirmed regional	Retrospective case cohort study; n= 31	Patients with cHNSCC and regional nodal metastasis treated at Peter MacCallum Cancer Centre (PMCC), from 1st January 2009 to 31st December 2010.	To compare staging PET-CT with staging by conventional methods alone in management of patients with cHNSCC.	Addition of 18F-FDG PET–CT did not Ch'nge the management in 24/31 (77%) of patients. In four cases the 18F-FDG PET–CT failed to pick up biopsy proven metastatic disease. Two patients who had reduced extent of surgery have shown no features of		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	nodal metastasis.				regional failure after one year of follow-up. Overall the management in majority of cHNSCC patients with regional metastasis does not Ch'nge by addition of 18F-FDG PET–CT over conventional imaging.		
Yoon et al. 2009	To compare the diagnostic value of four different imaging methods CT, MR imaging, US, and FDG PET-TC and their combined use for preoperative detection of cervical nodal metastases in head and neck SCC (HNSCC)	Retrospective study; n=67 patients	Patients with SCC of the head and neck underwent CT, MR, US, and PET/CT for staging of the tumor, between February 2006 and September 2007 in one center	To compare the diagnostic value of four different imaging methods CT, MR imaging, US, and FDG PET-TC and their combined use for preoperative detection of cervical nodal metastases in HNSCC.	Results were verified, on a level-by-level basis, with histopathologic findings. Histopathologic examination revealed nodal metastases in 74 of 402 nodal levels. The sensitivity, specificity, and accuracy were 77.0%, 99.4%, and 95.3% for CT and MR; 78.4%, 98.5%, and 94.8% for US; and 81.1%, 98.2%, and 95.0% for PET/CT, respectively.		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					The comparison of these modalities showed no statistically significant difference among them (p>0.05). The combination of CT, MR, US, and PET/CT improved sensitivity (86.5%), without loss of specificity (99.4%) and accuracy (97.0%), although the difference failed to reach statistical significance.		

Remarks and notes:

3.8.5. Literature

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4. Working group: Actinic keratosis treatment

(AG Therapie der AK)

4.1. Question III.1. Which actinic keratosis treatment modalities/options are recomended, based on severity and clinical context?

(Frage III.1. Welche Therapieformen sind für die Behandlung der AK nach Schweregrad und klinischem Kontext geeignet?)
Beantwortung durch De novo Recherche

4.1.1. PICO

PICO – Scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Patients with actinic keratoses (any grade, any clinical or histologic type)	Any intervention (except for sequential or combination therapy) such as: • Cryotherapy • Curettage or shave-excision • Laser • Diclofenac Natrium 3% in 2.5% Hyaluronic Acid • 5-FU, 5-FU and 10% SA • Ingenolmebutate • Ingenoldisoxat	placebo, vehicle only, active control therapy	At least one of the following **efficacy** outcomes: • Mean reduction in lesion counts from baseline to assessment (indicated as absolute values or percentages) • Participant complete clearance (rate of participants with a complete clearance of all lesions within a predefined field) • Participant partial clearance

PICO – Scheme			
	• Imiquimod • Resiquimod • MAL-PDT, ALA-PDT • Retinoids Tbc.		(rate of participants with 75% reduction in the AK lesions within a predefined field) • Investigator global improvement index (IGII, rate of participants rated as completely improved by the investigator) • Participants global improvement index (PGII, rate of participants self-assessed as completely improved) **Optional:** safety, tolerability, cosmesis optional

4.1.2. Database, search strategy, number of results

Database	Search strategy	Date	Number of results
1. Search			
Medline	(keratos*[Title] AND (actinic[Title] OR solar[Title] OR senil*[Title] OR hyperkeratos*[Title])) AND (randomized controlled trial[Title/Abstract] OR controlled clinical trial[Title/Abstract] OR random* [Title/Abstract] OR clinical trial	12nd January 2017 (initial search)	269

Database	Search strategy	Date	Number of results
	[Title/Abstract] OR placebo[Title/Abstract] OR trial[Title/Abstract]) NOT case report AND (German[language] OR English[language])	First update 17th May 2017	280
		Second update 12th February 2021	395
Remarks and notes: Some of the studies were already thoroughly analyzed in a Cochrane Review by Gupta, Paquet et al. (2012). The review served as supporting document for the evidence tables displayed here. Articles which were included in the review are highlighted with an asterisk (★).			

4.1.3. Selection criteria

Literature selection	
Number of total results	395
Inclusion criteria	**Study design**: RCTs, systematic reviews or meta-analyses of RCTs, total sample size N≥10, inter- and intraindividual design **Outcomes:** At least one of the following efficacy outcomes reported (according to Werner 2015, Gupta 2012) • Mean reduction in lesion counts from baseline to assessment (indicated as absolute values or percentages) • Participant complete clearance (rate of participants with a complete clearance of all lesions within a predefined field)

Literature selection	
	• Participant partial clearance (rate of participants with 75% reduction in the AK lesions within a predefined field) • Investigator global improvement index (IGII, rate of participants rated as completely improved by the investigator) • Participants global improvement index (PGII, rate of participants self-assessed as completely improved) Other outcomes regarding safety, tolerability, cosmesis optional
Exclusion criteria	**Study design**: Observational studies (retrospective and prospective), controlled studies without randomization, case series, case reports, experimental studies, RCTs with a total sample size N<10, dose-finding studies, experimental studies **Outcomes**: only per-lesion-efficacy reported without information on the subject of randomization (participant in inter-individual studies **Intervention:** Combination treatments allowed
Number of results after title and abstract screening	213 (186+27)
Records excluded after full text review	**89 (88+1)**
Records included	124

4.1.4. Evidence table

4.1.4.1. Systematic reviews and meta-analysis (n=7)

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
Askew et al 2009	To systematically review and critically appraise the evidence supporting the use of 5-FU to treat AK.	Systematic review of RCTs of treatment of AK with 5-FU Databsases searched: Medline, EMBASE, and the Cochrane Central register of Controlled trial as well as cross-references Inclusion of RCTs on humans comparing the treatment of AK with 5-FU, placebo, or another active treatment, or investigated different 5-FU dosage regimens.	n=13 RCTs number of participants: range: 17-75 N=1: comparison of the efficacy of a 1-week treatment with 0.5% 5-FU cream followed by cryotherapy on the remaining lesions at 4 weeks post-treatment with cryotherapy alone. N=8: Comparison of 5% 5-FU cream with other treatments (imiquimod, cryotherapy, diclofenac sodium 3% gel (DFS), facial resurfacing, PDT,	Reduction in mean or median number of lesions Lesion complete clearance rate Participant complete clearance rate OR to achieve 100% lesion clearance Cosmetic outcome Patient preference Number of patients	<u>Reduction in mean or median number of lesions (N=8):</u> 5% 5-FU: 79.5% (59.2%-100%) 0.5% FU: 86.1% (77.9-91.7%) Laser surfacing: 94.5% (92.9-96.6%) Placebo: 28.0% (21.6-34.4%) <u>Lesion complete clearance rate:</u> 5% 5-FU: 93.8% (606/646) at 24 weeks, 98.0% (124/126) at 4 weeks Imiquimod: 65.9% (323/490) DFS: 89% (111/125)	Only 5 studies provided information about randomization, only two described allocation concealement Unclear risk for publication bias Only one study was double-blinded and 4 were single blinded Most studies: small sample size Most of the included studies were at moderate to high risk of bias <u>Records in this review, that are also available in the evidence table:</u> Jorizzo et al. 2002	2

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
			5% 5-FU augmented with tretinoin, and 0.5% 5-FU (twice daily for 3 weeks vs. twice daily f-or 1 day per week for 12 weeks) N=3: comparison of 0.5% 5-FU with placebo N=1: Comparison of 5% 5-FU with 5-ALA PDT	withdrawing from the study as a result of adverse events	0.5% 5-FU; 79% ALA-PDT (blue light): 80%, with pulsed laser: 60% <u>Participant complete clearance rate:</u> 5% 5-FU: 49.0% (0-96%) 0.5% 5-FU: 34.8% (14.9-57.8%) Placebo: 0-4.3% Acid peel/ALA PDT (red light): in no patient reported CO2 laser resurfacing: 37.5% (3/8) ALA-PDT (blue light): 50% (6/12) Imiquimod: 54.5% (24-85%) Cryotherapy: 68% <u>OR to achieve</u>	Krawtchenko et al. 2007 Ostertag et al. 2006 Smith et al. 2003 Weiss et al. 2002 Statement regarding potential conflict of interest is missing.	

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					100% lesion clearance (N=4): 5% 5-FU vs cryotherapy: OR=10.8 (95% CI: 1.2-94.9) 0.5% 5-FU vs placebo: OR=30.0 (95% CI: 1.7-516.5) 0.5% 5-FU vs ALA-PDT (pulsed laser light): OR=11.0 (95% CI: 1.1-114.1) Cosmetic outcome (N=1, assessed at 3 months): no difference between the groups treated with 5% 5-FU, cryotherapy, or imiquimod; however, at 12 months, 4% of patients treated with 5% 5-FU or		

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					cryotherapy and 81% of patients treated with imiquimod showed an excellent cosmetic outcome (based on scarring, atrophy, and induration). Patient preference (N=2): 0.5% vs 5% FU: 85% (17/20) in favour of 0.5% 5-FU DFS vs 5% 5-FU: 79% very/completely satisfied with DFS, 68% with 5% 5-FU Number of patients withdrawing from the study as a result of		

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					adverse events (N=3): 1.9% (4/213) of patients using 0.5% 5-FU and 5.9% (1/17) of patients using 5% 5-FU		
Ezzedine et al 2021	To qualitatively and quantitively assess the comparative efficacy and acceptability of AK interventions, including the most recently approved intervention, 5-FU 4%, for the treatment of head-region lesions in immunocompetent patients with AK.	Systematic literature search of RCTs including immunocompetent patients ≥ 18 years with head region lesions of AK who were treated with field-directed, lesion-directed and other therapies. MEDLINE, MEDLINE In-Process and Embase databases and the Cochrane Central Register of Clinical Trials) as well as conference proceedings and clinical trials were searched. Network meta-analysis was used to quantitatively evaluate field-directed therapies (5-fluorouracil formulations, diclofenac sodium, imiquimod, ingenol	N=75 RCTs from 151 publications were included; patients' age ranged from 56.5 to 76 years, and the majority were male¸The majority (n = 62) included patients with ≥ 5 lesions N=31 trials were included in the NMA	Participant complete clearance Participant partial clearance adverse event-related withdrawals as a proxy of acceptability	Participant complete clearance: 5-FU 4%:OR 22.58 (95% CI 5.44-101.10) 5-FU 0.5%: OR 12.66 (95% CI 3.39-61.28) 5-FU/SA: OR 5.88 (95% CI 1.26-26.42) 5-FU 5%: OR 28.84 (95% CI 6.81-134.10) ALA-PDT: OR: 16.59 (95% CI 1.21-207.9) DIC: OR 2.53 (95% CI 0.53-11.64) IMQ 2.5% OR 6.93 (95% CI 0.77-64.08) IMQ 3.75 OR 8.70 (95% CI	Only records published in English were eligible for inclusion. Language is bias is likely. No risk of bias assessment was undertaken Imprecision: Wide confidence intervals Clinical heterogeneity among the included trials.	2

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
		mebutate, 5-aminolevulinic acid or methyl aminolevulinate plus photodynamic therapy).			0.96-79.84) IMQ 5% OR 14.26 (95% CI 3.66-53.22) IMB 0.015% OR 11.34 (95% CI 2.04-64.28) MAL-PDT OR 8.71 (95% CI 1.16-60.10) Placebo+PDT: OR 0.59 (95% CI 0.05-5.56) Participant partial clearance: 5-FU 4%: OR 59.12 (95% CI 17.66-305.20) 5-FU/SA: OR 4.37 (95% CI 0.53-34.47) 5-FU 5%: OR 57.73 (95% CI 12.42-336.60) DIC 3%: OR 7.74 (0.44-129.20) IMQ 2.5% OR 3.19 (95% CI 0.43-24.91) IMQ 3.75% OR 5.05 (95% CI 0.64-38.04) IMQ 5% OR 7.33 (95% CI 1.70-30.58)		

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					IMB 0.015% OR 22.51 (95% CI 3.00-173.70) ALA-PDT OR 16.60 (95% CI 1.21-223.60)		
Fu et al 2019	To investigate if PDT in combination with BF-200 ALA is superior to PDT with MAL for AK.	Systematic Review and Meta-Analysis Databases: PubMed, Cochrane Library, Web of Science and EMBASE databases were searched to select eligible randomized controlled trials until 1st April 2019. Cochrane Risk of Bias Tool was used to estimate the risk of bias.	N=5 RCTs with a total of 2953 lesions treated with BF-200 ALA and 3035 lesions treated with MAL Most participants in these comparative trials were older and tended to favor male enrollment. Mean age of study participants ranged from 70.7 to 79.8 years with the fraction of male participants ranging from 54% to 96%. Locations included the face and scalp in the selected trials. Daylight illumination was applied in three trials.	Participant complete clearance rate Lesion specific recurrence rate Pain reported on a visual analog scale (VAS) from 0 to 10.	ALA-PDT vs. MAL-PDT Participant complete clearance rate RR: 1.07, 95% CI 1.02–1.12, p=0.01, I^2=72% At 3 months: RR 1.09 (95% CI 1.06-1.12, p=0.5, I^2=0%) At 12 months: RR 1.10 (95% CI 0.99-1.23, p=0.04, I^2=68%) Subgroup analysis: increased complete clearance rates of grade II-III lesions: RR: 1.24, 95% CI 1.05–1.46,	Recurrence was reported in the results section, although not defined as outcome in the methods section. Selective reporting bias is thus likely. Most studies were rated as low risk of bias. Statistical heterogeneity	1

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					p=0.01 Lesion specific recurrence rate at 12 months: 0.67 (95% CI 0.48-0.92, p=0.01; I^2=26%) Pain: MD: 0.21, 95% CI 0.05-0.37, p=0.008; I^2=6%		
Gupta et al 2012	To assess the effects of topical, oral, mechanical, and chemical interventions for AK.	Systematic review performed in the following databases up to March 2011: the Cochrane Skin Group Specialised Register, CENTRAL in the Cochrane Library, MEDLINE (from 2005), EMBASE (from 2010), and LILACS (from 1982)	N=83 RCTs comparing the treatment of actinic keratoses with either placebo, vehicle, or another active therapy with a total of 10036 participants The RCTs covered 18 topical treatments, 1 oral treatment, 2 mechanical interventions, and 3 chemical interventions, including PDT.	Participant complete clearance Comparative risks in terms of number of participants completely cleared per 1000 Adverse events	Participant complete clearance: favoured four field-directed treatments compared to vehicle or placebo: 3% Diclofenac in 2.5% hyaluronic acid (RR 2.46, 95% CI 1.66-3.66; 3 studies with 420 participants) 0.5% 5-	Most of the studies lacked descriptions of some methodological details, such as the generation of the randomisation sequence or allocation concealment, and half of the studies had a high risk of reporting bias.	1

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					fluorouracil (RR 8.86, 95% CI: 3.67-21.44; 3 studies with 522 participants) 5% imiquimod (RR 7.70, 95% CI 4.63-12.79; 9 studies with1871 participants) 0.025% to 0.05% ingenol mebutate (RR 4.50, 95% CI 2.61-7.74; 2 studies with 456 participants) It also significantly favoured the treatment of individual lesions with PDT compared to placebo PDT with the		

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					following photosensitisers: ALA (blue light): RR 6.22, 95% CI 2.88-13.43; 1 study with 243 participants ALA (red light): RR 5.94, 95% CI 3.35-10.54; 3 studies with 422 participants) MAL (red light): RR 4.46, 95% CI 3.17-6.28; 5 studies with 482 participants) ALA-PDT was also significantly favoured compared to cryotherapy (RR 1.31, 95% CI 1.05 to 1.64) <u>Number of participants completely cleared per 1000:</u>		

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					313 with 3% diclofenac compared to 127 with 2.5% hyaluronic acid; 136 with 0.5% 5-fluorouracil compared to 15 with placebo; 371 with 5% imiquimod compared to 48 with placebo; 331 with ingenol mebutate compared to 73 with vehicle; 527 to 656 with ALA/MAL-PDT treatment compared to 89 to 147 for placebo-PDT; and 580 with ALA-PDT compared to 443 with cryotherapy. 5% 5-fluorouracil		

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					efficacy was not compared to placebo, but it was comparable to 5% imiquimod (RR 1.85, 95% CI 0.41 to 8.33) <u>Adverse events:</u> 144 participants affected out of 1000 taking 3% diclofenac in 2.5% hyaluronic acid, compared to 40 participants affected out of 1000 taking 2.5% hyaluronic acid alone, and 56 participants affected out of 1000 taking 5% imiquimod compared to 21 participants affected out of 1000 taking placebo.		

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
Gupta et al 2013: Network meta-analysis of the outcome "participant complete clearance" in non-immunosuppressed participants of 8 interventions for AK (follow-up Gupta 2012):	To determine the relative efficacies of eight main AK treatments in non-immunosuppressed participants.	Network meta-analysis: mixed treatment comparison combining both indirect and direct eveidence from multiple trials by using a Bayesian approach and Markov chain Monte Carlo methods. Inclusion of parallel-group RCTs reporting the outcome "participant complete clearance" Literature search can be obtained from the Cochrane Review Gupta 2012	n=32 studies were included: n=number of individual or pooled studies; N=total number of participants: 5-FU 0.5% (n=4, N=169), 5-FU 5.0% (n=2, N=44), ALA-PDT (n=6, N=739), cryotherapy (n=2, N=174), DCF/HA (n=5, N=299), IMI (n=14, N=1411), IMB (n=3, N=560), MAL-PDT (n=7, N=557) and placebo (n=32, N=2520).	Participant complete clearance	The interventions were ranked as follows based on calculated probabilities and odd ratios: 5-FU > ALA-PDT ~ IMI ~ IMB ~ MAL-PDT > cryotherapy > DCF/HA > placebo (~equal to)	The ranking might Ch'nge based on the analysed outcome. Most of the studies lacked descriptions of some methodological details, such as the generation of the randomisation sequence or allocation concealment, and half of the studies had a high risk of reporting bias.	1
Hadley et al 2006	To evaluate the efficacy and safety of imiquimod 5% cream for the treatment of AK.	Systematic review and meta-analysis Eligible records were identified from Medline, the Cochrane Library, and PubMed using the terms: (imiquimod or aldara) and	n=5 randomized, double-blind trials Lasted 12-16 weeks and treated 1293 patients 90% were men Mean age: range: 64-71 years	Participant complete clearance rate Number needed to treat (NNT) for one patient to	Imiquimod vs vehicle Participant complete clearance rate: 50% vs 5%	Quality scores were high; all trials reported being both randomized and double blind, scoring 3 or more of the maximum 5 points.	1

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
		((actinic or solar) and keratosis) and (random OR randomized). Review articles and reference lists were used as well.	All studies diagnosed AK by clinical examination, supplemented by biopsy and histology in two trials. All five trials used one sachet of 5% imiquimod cream or vehicle cream (placebo) twice or three times a week; none used an active control. Cream was applied to specified areas of sun-exposed skin, usually 20–25cm² on the face and balding scalp, but including neck, forearms, and hand in one trial.	have their AK completely or partially (≥75%) cleared after 12-16 weeks Number needed to harm (NNH) for one additional AE with imiquimod over 12-16 weeks Incidence of adverse events for imiquimod group (available information on over 1200 patients) Relative risk for serious adverse events (RR sAE)	NNT for complete clearance: 2.2 (95% CI: 2.0-2.5) NNT for partial clearance: 1.8 (95% CI: 1.2-2.0) NNH: range: 3.2-5.9 Adverse events: erythema (28%), scabbing or crusting (21%), flaking (9%), erosion (6%), edema (4%), and weeping (3%) RR sAE: 1.2 (95% CI: 0.7-2.0) NNT to cause one additional withdrawal: 20 (95% CI: 12-55) RR withdrawal:	Limitations: Two of the five studies used histological rather than clinical diagnoses of AK. QORUM guidelines were followed Unclear risk for publication bias	

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
				NNT to cause one additional withdrawal Relative risk to withdraw due to adverse events	1.5 (95% CI: 0.8-2.7)		
Heppt et al 2019	To summarize the current evidence for nonsystemic treatments of AKs in OTRs.	systematic literature search in MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL); trial register were hand-searched for eligible RCTs until 22 August 2018. The risk of bias was estimated using the Cochrane Risk of Bias Tool. Qualitative synthesis	N=8 RCTs with 242 OTRs (range 8–81)	Participant complete clearance Lesion specific clearance rates Local skin reactions Allograft rejections	Participant complete clearance MAL-PDT: (40–76.4%) IMQ: 27.5–62.1% DIC: 41% 5-FU: 11% Lesion specific clearance rates cMAL-PDT: 60.99% DL-MAL PDT: 57% AFXL-assisted cMAL-PDT: 73% AFXL-assisted daylight MAL-PDT: 78% AFXL: 16-31% IMQ: 73.7% DIC: 53%	The overall risk of bias was high. Potential language bias Clinical heterogeneity of included studies Limited evidence is available for the treatment of AKs in OTRs. MAL-PDT is currently the best-studied intervention.	1

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					5-FU: 79% Cryotherapy: 74% Local skin reactions: most intense in participants treated with a combination of AFXL and daylight MAL-PDT no therapy-related transplant rejections or worsening of graft function in any trial		
Mei et al 2019	To compare the efficacy and safety of dPDT versus conventional photodynamic therapy (cPDT) in patients with AK	Systematic search of PubMed, Embase, and the Cochrane Library until 15th June 2018 Meta-analysis: fixed or random-effect model was applied, depending on the heterogeneity Cochrane risk of bias tool was used to assess risk of bias	N=6 RCTs with 369 patients with 5,556 AK undergoing dPDT or cPDT with red light and methyl aminolevulinate were included	Complete response Pain Adverse events	dPDT vs. cPDT Incidence of complete response: RR: 0.93, 95% CI 0.86-1.01, p=0.07, I^2=80% reduced maximal pain score: MD= -4.51, 95% CI -	No grey literature was included in the search; publication bias likely. Data presented in the results section and Figure 2 do not match (complete response outcome) Studies had an increased risk of bias, especially in the	2

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					5.12- - 3.89, p < 0.001, I^2=71% lower risk of adverse events: RR=0.70, 95% CI 0.58-0.85; p < 0.001, I^2=0%	domains blinding of participants and reporting bias Only inter-individual trials were included. Only MAL was allowed as photosensitizer. High statistical heterogeneity.	
Rahvar et al 2012	To assess the efficacy of 0.5% 5-fluorouracil in treating actinic keratosis.	Systematic review of randomized, vehicle-controlled trials PubMed and EMBASE were searched from 1965 to April 2012 Key words: actinic keratosis, solar keratosis, topical 5-fluorouracil, topical 5-FU, double-blind, controlled trial, vehicle controlled trial, and precancerous skin lesions The medication names were also incorporated.	N=4 trials with 399 (active treatment) and 269 participants (vehicle) The mean age of the active treatment groups was 62.7 years. The majority of patients were male (85.4%) and 89% had a Fitzpatrick skin type of either I or II. In the vehicle treatment groups, the mean age was 62.9 years, 85.8%	Absolute clearance and mean % reduction in lesion count after 4 weeks of treatment Percentage of patients achieving complete clearance of their AKs Percentage reductions in AK counts	Active vs vehicle Total clearance: 52.6 vs 0.85 Mean lesion count reduction: 90.2% vs 28.3% Percentage of patients achieving complete clearance of their AKs in the 5-FU group: 19, 28.2, and 52.6% in the 1-, 2-, and 4-week	No bias assessment reported Only randomized, double-blind, vehicle-controlled clinical trials written in English evaluating the efficacy of topical 5-FU in treatment of AK were included. The included studies only evaluated the treatment of AKs present on the face, and therefore the results may not be relevant to the	1

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
		Two trials assessed a once-daily regimen for 1, 2 and 4 weeks, while the other two trials assessed a once-daily regimen for 1 week	of the patients were male and 93.6% had a Fitzpatrick skin type of I or II.		treatment groups, resp.; vehicle: 0.85% Percentage reductions in AK counts: 68.2, 84.2, 90.2, and 28.3% in the 1-, 2-, 4-week 5-FU and vehicle groups Author's Conclusion: 0.5% 5-FU is significantly efficacious in the treatment of AKs as compared with its vehicle cream. Increasing the length of the therapy appears to add to its efficacy. Improving the rate of total clearance and	treatment of AKs on other anatomical regions. All records from this review are also available in the evidence table: Weiss et al. 2002 Jorizzo et al. 2002	

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					number of lesions present by increasing the length of therapy may indicate that patients would benefit from prolonging therapy for up to 4 weeks. Moreover, the fact that no serious side effects were reported demonstrates the safety of this medication for its use in the populations evaluated in these studies.		
Stockfleth et al 2016	To compare the relative efficacy of 5-fluorouracil 0.5% in salicylic acid 10% (5-FU/SA), ingenol mebutate (IMB, all	Systematic review of RCTs, other systematic reviews and meta-analysis 11 studies were included, related to 7 RCTs	Immunocompetent adults (>18 years) with grade I-II AKs on the face, forehead, and scalp	Complete clinical clearance Sustained clinical	<u>Complete clinical clearance:</u> -5-FU/SA vs vehicle/ placebo: 55.4% vs 15%	No sequential or combination treatments included Risk of bias assessment with the	2

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
	concentrations: 0.0025%, 0.005%. 0.01%, 0.015%, or 0.05%), and imiquimod 2.5%/3.75% (IMI) for AKs on the face, forehead, and scalp.	Systematic search was performed in the The Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and BIOSIS. Cross-references and conference websites were searches as well.	5-FU/SA (1 study and 1 long-term follow-up of the same study): age slightly older (>70 years) IMB (7 studies) and IMI (2 studies): age range 63-70 years In all studies, most patients were white or Caucasian with a higher proportion of males (>70%) Patients with treatment for AKs on other areas than scalp, face, and forehead were excluded Patients with hyperkeratotic or hypertrophic AKs excluded in IMB studies	clearance (recurrence rate)	-IMI vs vehicle/ placebo: 25.0-35.6% vs 5.5%-6.3% -IMB vs vehicle/ placebo: 42.2% vs 3.7% <u>Sustained clinical clearance:</u> -recurrence rate for 5-FU/SA after 12 months: 32.7% -recurrence rate for IMB after 12 months 53.9%	Cochrane Collaboration “risk of bias” assessment tool with risk of bias being mostly low to unclear High heterogeneity Differences in the duration of the follow-up periods High heterogeneity of study design, population, treatment duration, and vehicle composition Literature search was limited: only records that have been published between January 2011 and January 2014 were included: selection bias likely The study was funded by Almirall S.A.	

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
						Records in this review that are also available in the evidence table: Lebwohl et al. 2013 Stockfleth et al. 2012 Lebwohl et al. 2012 Hanke et al. 2010 Swanson et al. 2010 Stockfleth et al. 2011	
Steeb et al 2020	To systematically review and synthesize the current knowledge on chemically exfoliative peelings as interventions for AK.	systematic literature research in Medline, Embase, and CENTRAL and trial register were searched until 5 August 2019. Results from individual studies were pooled using a random-effects model or described in a qualitative synthesis. The risk of bias was estimated with the tools provided by the Cochrane Collaboration (randomized and non-randomized trials) and the Evidence Project (single-arm trials).	N=8 studies were included in the qualitative synthesis and n=4 studies in the meta-analysis. Two studies investigated a combination of TCA 35% peeling in combination with Jessner's solution in comparison with 5-fluorouracil (5-FU) 5% cream for AKs located on the face. One study assessed glycolic acid 70% in combination with 5-FU 5% solution compared to	Participant complete clearance Lesion clearance rate Pain	COMBINATION APPROACHES TCA + Jessner's solution v.s 5-FU 5% cream participant complete clearance: RR 0.36, 95% CI: 0.14–0.90, two studies, I^2 = 0%, P = 0.03 Lesion clearance rate: RR 0.92, 95% CI: 0.85–0.99, one study, P = 0.03 5-FU plus glycolic acid vs. GA monotherapy:	All studies had a high risk of bias: neither the participants were blinded in the trials nor were sham interventions performed in any of the controlled studies High heterogeneity among included trials. RCTs as well as single-arm trials were included.	1

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
			glycolic acid monotherapy for AKs on the face. Another study investigated 5-FU 5% followed by chemical peeling with glycolic acid 70% in patients with AK in the head and neck area.		Participant complete clearance: RR 9.00 (95% CI 0.52–155.86) Lesion clearance rate: RR 5.87 (95% CI 4.39–7.85) 5-FU + GA (single-arm trial): Participant complete clearance: 30% (6/20) Lesion complete clearance: 92% (322/350) MONOTHERAPY TCA monotherapy vs. PDT: Participant complete clearance: RR 0.75, 95% CI: 0.69–0.82, two studies, I^2 = 7%, P < 0.001 Pain cPDT vs. TCA: MD -1.71		

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					95% CI: -3.02 to -0.41, two studies, I^2 = 55%, P = 0.01 Phenol peeling: participant complete clearance: 90.6%		
Steeb et al 2020b	To synthesize the current knowledge of interventions for AK in non-scalp and non-face localizations.	Systematic review and network meta-analysis Randomized controlled trials (RCTs) reporting data for these localizations were searched in Medline, Embase, and the Cochrane library CENTRAL as well as in pertinent trial registers until 25 March 2020. Network meta-analysis: Five treatment modalities were evaluated and compared to placebo in a frequentist network meta-analysis (NMA), including cryosurgery, ingenol mebutate, photodynamic therapy, colchicine and 5-fluorouracil.	N=13 RCTs with 1,380 patients	participant complete clearance rate (dichotomous) and the participant partial clearance rate (dichotomous), defined as the rate of participants who had all (100%) or at least 75% of their lesions cleared, respectively lesion-specific complete clearance rate (dichotomous) defined as the proportion of	Indirect comparisons: participant complete clearance rates compared to placebo: cryosurgery: RR 7.73, 95% CI 3.21-18.61; 10 studies; I^2=20.3%; GRADE ++-- IMB: RR 7.00, 95% CI 3.06-15.98, GRADE ++--) PDT: RR 3.87, 95% CI 2.14-6.97; GRADE +++-) Participant partial clearance	The certainty of the evidence varied from very low to high and was limited by imprecision and study limitations. Risk of bias was heterogenous among included studies.	1

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
				cleared lesions after the end of treatment in comparison to baseline safety, defined as number of participants who experienced any treatment-related adverse event	rates in comparison to placebo: IMB: RR 7.12, 95% CI 4.36-11.64; 5 studies; I2=0%; GRADE +++- PDT: RR 6.59, 95% CI 2.94-14.75, GRADE +++- 5-FU: RR 6.59, 95% CI 2.60-16.68, GRADE +---), Colchizine: RR 4.39, 95% CI 1.76-10.96, GRADE ++-- lesion clearance rates compared to placebo: cryosurgery: RR 2.97, 95% CI 2.45-3.59; 4 studies; I2=0%; GRADE ++-- PDT: RR 2.59, 95% CI 2.16-3.09, GRADE ++++ Imiquimod: RR 0.67, 95% CI 0.43-1.05,		

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					GRADE ++-- Direct comparison: MAL-PDT, 63-67% of participants reported adverse events (photosensitivity reactions), followed by 43% for cryosurgery (cold exposure injury), 33.3% for ingenol mebutate (erythema, flaking, scaling, crusting), and 27.2% for placebo (infection or infestation)		
Stockfleth et al 2016	To compare the relative efficacy of 5-fluorouracil 0.5% in salicylic acid 10% (5-FU/SA), ingenol mebutate (IMB, all concentrations: 0.0025%, 0.005%. 0.01%, 0.015%, or	Systematic review of RCTs, other systematic reviews and meta-analysis 11 studies were included, related to 7 RCTs Systematic search was performed in the The	Immunocompetent adults (>18 years) with grade I-II AKs on the face, forehead, and scalp 5-FU/SA (1 study and 1 long-term follow-up of the	Complete clinical clearance Sustained clinical clearance (recurrence rate)	<u>Complete clinical clearance:</u> -5-FU/SA vs vehicle/ placebo: 55.4% vs 15% -IMI vs vehicle/ placebo: 25.0-35.6% vs 5.5%-	No sequential or combination treatments included Risk of bias assessment with the Cochrane Collaboration “risk of bias” assessment tool	2

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
	0.05%), and imiquimod 2.5%/3.75% (IMI) for AKs on the face, forehead, and scalp.	Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and BIOSIS. Cross-references and conference websites were searches as well.	same study): age slightly older (>70 years) IMB (7 studies) and IMI (2 studies): age range 63-70 years In all studies, most patients were white or Caucasian with a higher proportion of males (>70%) Patients with treatment for AKs on other areas than scalp, face, and forehead were excluded Patients with hyperkeratotic or hypertrophic AKs excluded in IMB studies		6.3% -IMB vs vehicle/ placebo: 42.2% vs 3.7% <u>Sustained clinical clearance:</u> -recurrence rate for 5-FU/SA after 12 months: 32.7% -recurrence rate for IMB after 12 months 53.9%	with risk of bias being mostly low to unclear High heterogeneity Differences in the duration of the follow-up periods High heterogeneity of study design, population, treatment duration, and vehicle composition Literature search was limited: only records that have been published between January 2011 and January 2014 were included: selection bias likely The study was funded by Almirall S.A. <u>Records in this review that are also available in the evidence table:</u>	

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
						Lebwohl et al. 2013 Stockfleth et al. 2012 Lebwohl et al. 2012 Hanke et al. 2010 Swanson et al. 2010 Stockfleth et al. 2011	
Vegter et al 2014	To compare different treatments for mild to moderate AKs on the face and scalp available in clinical practice in Europe.	A Bayesian network meta-analysis (NMA) of RCTs (random-effects Bayesian model) 11 different treatment modalities were investigated: -3 with ALA-PDT (gel or patch) -1 with MAL-PDT -3 with imiquimod cream (IMI), as 4-week application 5%, 16-week course 5%, and 2/3-week course 3.75% -1 cryotherapy -1 diclofenac 3% in 2.5% hyaluronic acid (DCF) -1 0.5% fluoruracil (5-FU) -1 ingenol mebutate (IMB)	N=5562 from 25 studies were included Average age 63.2-71.9 years 81.4% male patients with mild to moderate AK lesions on the face and scalp (5-20) Immunosuppressed patients were excluded	Primary outcome: complete patient clearance (total clearance of all patient's lesions) The probability to achieve complete patient clearance was indicated by a log OR relative to the other treatments or placebo Surface under	Complete clearance rates, OR, SUCRA score (%) -BF-200 ALA-PDT (2 studies, N=156): 75.8% (95% CI: 55.4–96.2%), 45.9 (95% CI: 13.9-151.8), 92.1% -ALA-PDT patch (2 studies, N=205): 56.8% (95% CI: 30.5–83.1%), 18.1 (95% CI: 5.6-58.9), 62.8% -MAL-PDT (3 studies, N=232):	Combination treatments were excluded A Cochrane review (Gupta et al. 2012) was used to identify studies, but no new systematic research was performed Study covariates were not taken into consideration in the Bayesian NMA No uniform time point of outcome evaluation (4-12 weeks post trial) Repeated applications were not studied in the NMA	2

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
				the cumulative ranking curve (SUCRA), ranking from 0-1 (0=worse treatment with no uncertainty, 1=best treatment with no uncertainty)	54.8% (95% CI: 33.6–76.0%), 16.5 (95% CI: 6.5-42.1), 57.2% -Cryotherapy (2 studies, N=169): 38.2% (95% CI: 12.1–64.3%), 8.0 (95% CI: 2.4-26.9), 30.6% -IMI 5% 16 weeks (5 studies, N=966): 63.3% (95% CI: 45.5–81.1%), 23.8 (95% CI: 10.4-54.2), 74.2% -IMI 5% 4 weeks (3 studies, N=278): 56.3% (95% CI: 33.8–78.8%), 17.6 (95% CI: 6.5-47.6), 60.9% -IMI 3.75% 4 weeks (2	The research was funded by Biofrontera (Germany) records in this review that are also available in the evidence table: Szeimies et al. 2009 Dirschka et al. 2012 Szeimies et al. 2010 Hauschild et al. 2009 Szeimies et al. 2004 Korman et al. 2005 Lebwohl et al. 2004 Jorizzo et al. 2007 Alomar et al. 2007 Krwatchenko et al. 2007 Weiss et al. 2002 Jorizzo et al. 2002 Stockfleth et al. 2011 Wolf et al. 2001 Rivers et al. 2002 Gebauer et al. 2003 Lebwohl et al. 2012 Swanson et al. 2010 Hanke et al. 2010	

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					studies, N=322): 39.9% (95% CI: 15.6–64.2%), 8.7 (95% CI: 2.9-26.2), 33.2% -DCF (5 studies, N=413): 24.7% (95% CI: 12.4–37.0%), 4.3 (95% CI: 2.1-8.6), 14.0% -5-FU 0.5% (3 studies, N=262): 59.9% (95% CI: 38.9–80.9%), 20.7 (95% CI: 7.7-55.7), 66.8% -IMB (2 studies, N=309): 54.5% (95% CI: 27.8–81.2%), 16.4 (95% CI: 5.0-53.6), 58.1% -Placebo (23 studies, N=2250): 6.9%		

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					(95% CI: 5.5–8.3%), 1 (reference), 0.0%		
Wu et al 2018	To compare the efficacy of 5-fluorouracil (5-FU) with that of other treatments of actinic keratosis (AK). Evaluation of 0.5% 5-FU with 10% salicylic acid [5-FU/SA], 5% 5-FU cream, 3% diclofenac sodium, cryosurgery, and vehicle	Systematic literature review of five databases (OVID, PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and MANTIS) was first performed to identify RCTs from their inception to May 2018. A total of n=731 publications were initially identified. The search key terms were “actinic keratosis/5-fluorouracil,”“actinic keratosis/fluorouracil,”“actinic keratosis/randomized study,” and “fluorouracil/randomized study.” network meta-analysis (NMA) based on a random-effects Bayesian model	N=11 studies of 10 RCTs with 2.256 patients with AK were included in the NMA a total of 1,105 cases were treated with 5-FU, 58with cryosurgery, 200with diclofenac sodium, and 893 with a vehicle. In most of the studies (except for two studies), the mean age was between 70 and 75 years	Total lesion clearance Lesion reduction from baseline	OR total lesion clearance: 5-FU 0.5%/10% % vs. vehicle: OR 3.1 (95% Ci 1.2-9.1) 5-Fu 0.5% vs. vehicle OR 2.8 (95% CI 1.5-5.7) diclofenac vs. vehicle OR 1.4 (95% CI 0.52 – 3.5) Cryosurgery vs. vehicle OR 0.27 (95% CI 0.049-1.3) MD lesion reduction from baseline 5-FU 0.5%/10% % vs. vehicle MD 5.2 (95% CI 3.2-6.5) 5-Fu 0.5% vs. vehicle MD 1.8 (95% CI 0.74 – 2.7) diclofenac vs. vehicle	Lesion number at baseline varied among the studies; heterogeneity across studies is likely Overall risk of bias of included studies was low No grey literature/unpublished studies were searched. Search string does not seem to be sensitive as “only” n=731 citations have been initially identified. Immunosuppressed patients were excluded	2

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					MD 0.91 (95 CI -0.82 – 2.1) Cryosurgery vs. vehicle MD 2.5 (95% CI 0.090-4.4)		
Zhao et al 2019	To evaluate the safety and efficacy of DLPDT in treating patients with AKs as compared to conventional photodynamic therapy (CPDT).	Systematic literature review and meta-analysis PubMed, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials were searched for relevant randomized controlled trials (RCTs) published before November 2017, based on the following search terms: “solar keratoses”, “actinic keratoses”, “photodynamic therapy”, “daylight photodynamic therapy”, “conventional photodynamic therapy”, and “randomized”. The literature search initially identified 457 records. AK had to be histopathologically confirmed and localized on the face or scalp.	N=8 RCTs with 424 patients all patients were aged >60 years, and the majority were male	complete response rate—with response rates based on individual lesions as opposed to treatment areas patient satisfaction: assessed by convenience of the procedure at baseline, and a subject satisfaction questionnaire regarding the treatment outcome at the final visit pain	DLPDT vs. cPDT RR: Complete response rate: RR, 0.892; 95% CI, 0.818–0.973; P = 0.01; n=244 Man lesion response: SMD, -0.221; 95% CI, -0.395 to -0.027; p= 0.024; n=237 Patient satisfaction RR 4.001; 95% CI, 2.017–7.938; p< 0.001; n=318 Pain SMD -2.544; 95% CI, -3.57 to -1.632; p<0.001; n=424	Only MAL was allowed as photosensitizer. Publication/language bias likely as only English publications were eligible. The authors only considered trials with low risk of bias for the meta-analysis, thus, nearly all domains in the assessment were rated as low risk of bias (Fig. 2), which seems unrealistic and thus, the true risk of bias assessment might be overestimated. Besides, the authors explicitly state that there were 2 single-blinded studies and 3 investigator-blinded studies; however, risk	4

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
		Only MAL was allowed as photosensitizer.				of bias was only assessed as unclear for 2 studies, although this should be rated as high for all studies for the respective domain. The amount of studies identified in the initial literature search is low; it seems as if the search string was not sensitive. Furthermore, the authors misinterpreted the results and stated that results were not significant although they were significant.	

4.1.4.2. Individual studies (n=91 + 18)

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
Akar et al 2001★	To compare the efficacy and safety of two different	Randomized, active-controlled, double-blind, parallel-group study	n=16 patients with AKs (10 male, mean age=64 years, range:50-82 years) Majority: photo skin types	Complete healing Reduction rate	1% colchicine group vs 0.5% colchicine group	Insufficient detail reported about the method used to generate the	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	concentrations of colchicine cream, 0.5% and 1% for the therapy of AKs. Intervention: Application of 0.5% or 1% colchicine cream twice daily for 10 days.	N=8: 1% colchicine cream twice daily for 10 days N=8: 0.5% colchicine cream twice daily for 10 days Washout period: 3 months Follow up of 1, 2 and 6 months after treatments Examination by the same investigator	II and III Exclusion criteria: Patients with ≥15 lesions or with very extensive lesions	in number of AKs at 1 month Mean reduction of lesions counts at 1 month	Complete healing: 6/8 vs 7/8 Reduction rate in number of AKs: 73.9% (48/65) vs 77.7% (52/67), p<0.001 Mean reduction of lesion counts: 0.7±1.3 vs 0.66 ±1.7,p > 0.05	allocation sequence. lesions on the face: more responsive to treatment than those on the scalp and upper extremities The drug was provided by Dr. F Frik Drug Company. Statement regarding potential conflict of interest is missing.	
Akarsu et al 2011	To compare the effects of topical 3% diclofenac sodium plus hyaluranon (DFS) gel, 5% imiquimod (IMQ) cream, and base cream (BC) in	Single-centre, open label, evaluator-blinded, randomized study, follow-up=24 weeks	n= 61 patients with AKs 3 treatment groups: DFS (twice daily for 12 weeks): n=21, mean age=65.71 years ±11.60, disease duration (years): 2.68±2.34 Basal TTS: 3.95±0.22	Complete clearance rates =CR Total Thickness Score=TTS from 0-4 Patient Global	CR at the end of the treatment vs follow-up: DFS: 19.1% vs. 14.3% IMQ: 20% vs. 45% BC: 0% Average TTS value	Results not generalizable due to use of TTS and PGII (self-report scale) Efficacy of DFS seemed to decrease after	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	patients with AK. Intervention: Application of diclofenac sodium plus hyaluronan gel twice daily for 12 or 16 weeks or vehicle twice daily for 12 weeks.		IMQ (twice per week for 16 weeks): n=20, mean age=68.30 years ±10.73, disease duration: 2.68±2.30 Basal TTS: 3.80±0.41 BC (twice daily for 12 weeks): n=20, mean age = 65.85 years ±9.57, disease duration_ 2.55±1.75 Basal TTS_ 3.85±0.37	Improvement Index=PGII from 0-6 Both outcomes assessed at 0, 4, 8, 12, 16, 20 and 24 weeks	of DFS group was higher than that of IMQ group at week 24 Significant difference between TTS for DFS and IMQ treatment at week 24 (p=0.034, mean difference 0.85, 95% CI = 0.36-1.66), PGII values not significantly different DFS: in 28%: mild degrees of erythema and scaling IMQ: In 75%: erythema, erosion, oedema, crusting and scaling cost-benefit analysis: IMQ more expensive than DFS	cessation of treatment	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					(3 boxes = € 163.8 vs € 54.60 for 4 boxes)		
Alberts et al 2000★	To determine whether topically administered DFMO (=2-Difluoromethyl-dl-ornithine) is associated with a significant reduction in the number of AKs on the forearm. Intervention: DFMO or placebo twice daily for 6 months.	Randomized, placebo-controlled, double-blinded, intraindividual phase 2b trial Randomization of DFMO to left or right arm, placebo cream on the contralateral arm, twice daily for 6 months Overall adherence to study protocol: >95% Washout period: 3 months for topical or systemic therapies for AK and 30 days for any other topical medications on the forearms 1 month run-in period with placebo ointment	n=48 participants with moderate-severe AKs in the forearms, 32 men Mean age: 69 years	Percentage reduction in the number of AKs Mean number of lesions at baseline and 6 months	Reduction in number of AKs after 6 months: 23.5% (p=0.001) from the baseline mean of 28.1 AKs. Decrease of 6.6 on the treated posterior forearm (compared with the placebo forearm) There was a 10.8 AK reduction on treated right arms (p<0.001) with no effect on treated left arms.	% reduction in lesion counts was given only for the DFMO-treated group (selective reporting bias) small sample size 6/48 participants did not complete the study protocol 7/48 (14.6%) participants: severe to moderate inflammatory reactions on their DFMO-treated arms → dosis modification This study was supported by USPHS Grant PO1 CA27502.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
						Statement regarding potential conflict of interest is missing.	
Alirezai et al 1994 ★	To evaluate the efficacy and tolerability of isotretinoin 0.1% cream in the treatment of AKs. Intervention: Isotretinoin 0.1% cream or vehicle twice daily for 24 weeks.	Randomized, multicentred, double-blind, placebo-controlled, parallel-group study Application of vehicle cream/placebo twice daily for 24 weeks to the face, scalp, upper extremities Washout period: Topical retinoids/steroids 2 weeks before treatment of the treatment areas Topical 5-fluorouracil, systemic retinoid or systemic steroids 4 weeks before	n=124 patients >21 years with at least 5 AKs on the face and/or scalp, 100 randomised, 93 analysed and 79 completed the 24-week study	mean reduction in lesions counts at the end of the treatment Global therapeutic response (investigators' evaluation)	On the face: Increased reduction in number of AKs for the isotretinoin group: mean =3.9±0.6, 65% of patients with a reduction > 30% vs placebo: mean=1.7±0.5, 45% of patients with a reduction > 30% p=0.001 at the end of the treatment No significant effect for lesions on the scalp/upper extremities Mean reduction in lesions counts at the end of the treatment: on the	Unclear risk of allocation bias At baseline, week 12 and week 24: two investigators counted the lesions independently, at the other time points: only one investigator → might bias the results/selection bias Treatment was applied to the face in fewer total days in the isotretinoin group than in placebo group (146±8.5 days vs 170±3.6 days) due	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					scalp: isotretinoin group: 4.1±1.5, placebo: 3.6±0.9; 44% of patients with a reduction > 30% vs 65 % placebo on the upper extremities: isotretinoin group: 2.9±0.9, placebo: 1.0±0.8, 53% of patients with a reduction > 30% vs 50 % placebo	to modification of treatment: chance of bias Statement regarding potential conflict of interest is missing.	
Alomar et al 2007★	To determine whether imiquimod is effective in clearing AK lesions when administered over a 4-week treatment period followed by a 4-week rest period (up to two courses of treatment).	Multicentre, randomized, vehicle-controlled, double-blind, parallel-group study Randomization: 1:1 to vehicle or imiquimod N=129 randomized to imiquimod 5% cream once daily 3 days per week, N=130 to vehicle	n= 259 white patients with 5-9 clinically diagnosed AK lesions within a contiguous 25 cm² treatment area on the head Median age=71 years, range 44-94 228 men, 31 women	Clearance rates at week 8 and at week 16 Odds ratio (OR) for complete clearance Partial clearance rates at week 16 Adverse events	Imiquimod group vs vehicle group: <u>Clearance rates:</u> 55.0% (71/129) vs 2.3% (3/130) (p<0.0001), difference: 52.7% (95% CI 43.8%-61.7%), week 16 Imiquimod CR: higher for treatment areas on the face (64.6%)	29 study centres Short follow-up Unclear risk of random sequence generation and allocation concealment Participant complete clearance for the face and scalp was reported for the imiquimod group but not the	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	Intervention: Imiquimod 5% cream or vehicle once daily, 3 days per week,				than for scalp (49.4%) OR complete clearance: 43.7% (95% C I 13.56-140.9) Partial clearance: 65.9% (85/129) vs 3.8% (5/130), p<0.0001 Adverse events: 53.5% (69/129) vs 30.8% (40/130)	vehicle group: high risk for selective reporting bias This study was supported by 3M Pharmaceuticals.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
Anderson et al 2009	To assess the efficacy and safety of ingenol mebutate gel at 3 dosing regimens (0.025% for 3 days, 0.05% for 3 days, 0.05% for 2 days) for the treatment of AKs.	Randomized, multicentre, double-blind, double-dummy, vehicle-controlled phase 2b trial	n=222 patients with non-facial AKs, 4-8 clinically typical, visible, and discrete AK lesions within a contiguous area of 25 cm² on the arms, shoulder, chest, back, or scalp Mean age: 67 years (range 43-85) 80.2% male, 68.5% of patients had FST I/II N=60: vehicle group N=50: 0.025% gel for 3 days N=55: 0.05% gel for 2 days N=57: 0.05% gel for 3 days EOT: after 57 days	Partial clearance rate Complete clearance rate Median percentage reduction Adverse events/local skin reactions	0.025% gel 3 days vs 0.05% gel 2 days vs 0.05% gel 3 days vs vehicle: All 3 active treatments: sign. more effective than vehicle <u>Partial clearance rate:</u> 65% (28/50, 95%CI: 42.4-69.76) vs 61.8% (34/55, 95%CI: 48.98-74.66) vs 75.4% (43/57 95%CI: 64.26-86.6) vs 21.7% (13/60, 95%CI 11.24-32.09) <u>Complete clearance rate:</u> 40.0% (20/50, 95%CI: 26.42-53.58) vs 43.6% (24/55, 95%CI: 30.53-56.74)	Limitation: Local skin responses may have suggested active treatment to investigators Funding sources: Peplin Ltd	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					vs 54.4% (31/57, 95%CI: 41.46-67.32) vs 11.7% (7/60, 95%CI: 3.54-19.79) <u>Median percentage reduction:</u> 75.0% vs 83.3% vs 100% vs 0% <u>LSRs for active treatment</u> (n=162) at day 3 (highest): Erythema (158/97.5%), flaking/scaling (124/76.5%), crusting (71/43.8%), swelling (72/44.4%), vesiculation/pustulation (63/38.9%), pigmentation, erosion/ulceration, and scarring <22% At day 8, erythema and flaking/scaling were the most freuqnetly reported LSRs (96.9% and		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					96.3%, resp.) 45 treatment-related AEs: 2 in the vehicle group, 11 in the ingenol mebutate gel, 0.025% group, 11 in the 0.05% for 2 days group and 21 in the 0.05% for 3 days group. 8 serious AEs in 4 patients in the vehicle group, 5 serious AEs in 5 patients in the ingenol mebutate gel, 0.025% group, 2 serious AEs in 2 patients in the ingenol mebutate gel, 0.05% for 2 days group, and 1 serious AE in 1 patient in the ingenol mebutate gel, 0.05% for 3		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					days group. No serious AE was reported as being treatment related.		
Apalla et al 2011	To describe the efficacy of PDT at different fluence rates for the treatment of AKs using 20% ALA-cream and red light (570-670 nm)	Randomized, open-label, intraindividual comparison study	n=50 Caucasian subjects (29 males) with 150 AKs Mean age: 58 years±11 Random allocation of each lesion to treatment groups	Participant complete response rate Pain according to visual analogue scale (VAS): mean VAS score (0-10, 0= no pain, 10 = maximal	25 mW/cm² vs 75 mW/cm² vs 50 mW/cm² <u>CR after 3 months:</u> 92.0% vs 90.0% vs 92.0% <u>CR after 12 months</u>: 88.0% vs 88.0% vs 90.0%	Clinical evaluation, counting and recording of lesions: same 'blinded' examiners (at baseline and at follow-up visits)	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
				pain)	All differences were not statistically significant Mean VAS Score: 6.9 (95%CI: 6.5-7.3) vs 8.2(95%CI: 8.0-8.4 vs 7.0 (95%CI: 6.6-7.3) <u>Conclusion:</u> a fluence rate between 25 and 50mW/cm² is effective and better tolerated by patients treated with topical 5-ALA PDT for AKs		
Assikar et al 2020	To assess the efficacy and the safety of DL-PDT vs. PDT in blue light in the treatment of AKs at 12 weeks. Intervention: Removal of scales and crusts with a curette	Randomized, controlled, single-centre, intra-individual, open-label study Conventional MAL PDT with blue light (n=26) vs. daylight PDT with MAL (n=26)	N=26 patients with AK on the face or scalp Men: 96,2% (25/26) Mean age; 75 years (range: 47.0–88.0). Mean number of AKs: 21.7 per patient (DL-PDT) vs. 21.4 per patient (cPDT)	mean number of cleared AK lesions ± sd (after 1, 3, and 6 months) lesion clearance rate Recurrence: Raw number of	DL-PDT vs. cPDT mean number of cleared AK lesions: after 3 months: 19.6 (±6.0) for DL-PDT and 20.0 (±6.9) after 6 months: 19.7 (±6.2) vs. (±7.3)	Small sample size, women are underrepresented No blinding of participants or personnel might lead to performance or detection bias Due to the intra-individual design,	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	Separate the 2 treatment areas with marker Application of MAL with 1-mm thick layer in AK surrounding 5 mm in normal skin DL-PDT: Daylight exposure 30 min after MAL application for 2 h. cPDT: Removal of occlusive dressing after 3 h of MAL application Blue light illumination (10 J/cm² within 10 min)		Total number of AKs treated: n=1119	new AK lesions at 1, 3 and 6 months after treatment Adverse events Pain measured on a numerical scale from 0 (no pain) to 10 (extreme pain) after exposure to the light	lesion clearance: after 3 months: 90.5% vs. 94.2% after 6 months: 90.0% vs. 94.6% Recurrence of lesions (difference DL-PDT-cPDT): After 3 months: 0.6±0.8 After 6 months: 1.3± 0.9 No treatment-related AEs were observed. Pain intensity 1.2 (±1.9) vs. 5.1 (±2.3)	patients act as their own controls and minimize the risk of confounding No drop-outs Efficacy results were statistically not significant; only differences in recurrence and safety were statistically significant	
Berman et al 2020	To evaluate efficacy and safety of ingenol disoxate gel versus vehicle Intervention: Application of Ingenol disoxate gel 0.018% for face/chest (FC)	Four identical phase 3 multicenter, randomized, double-blind controlled trials AK had to be on either the full chest (up to 250cm²) or the full balding scalp. Patients were randomized	N=616 randomized to FC (N= 410 received IngDsx) N=626 randomized to S (N= 420 received IngDsx) FC vs S Men:400 vs 622 AK count: 5-10AKs:267 vs 240	Participant complete and partial clearance at week 8 %reduction in AK count Safety	IngDsx vs. vehicle Participant complete clearance at week 8: Face/chest: 25.9% vs. 2.0% Scalp: 24.5% vs. 1.5% Participant partial	Large sample size Possible heterogeneity among different trials	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	or 0.037% for scalp (S) once daily for 3 consecutive days versus vehicle gel.	in a 2:1 ratio to receiver Ingenol Disoxate gel once daily for 3 consecutive days (0.018% for chest; 0.037% for scalp) or vehicle.	>10AKs: 344 vs 383	Cosmetic outcome improvement. Global satisfaction	clearance at week 8: Face/chest: 58.1% vs. 7.7% Scalp: 61.0% vs. 6.0% % reduction in AK count at week 8 Face/chest: 73.5% vs. 11,2% Scalp: 73.4% vs. 6% Safety: More cases of SCC, BCC and Bowen's disease in the IngDsx group: HR 2.38 95% CI 1.28-4.41 At 12 months: 4 SCC in IngDsx group, 1 Bowen's disease, 1 Melanoma, and 1 BCC vs. 0 in the vehicle group Treatment-related AEs at week 8 Face/chest: 63.9% vs. 7.4% Scalp: 73.3% vs. 13.2% Application site		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					pain: Face/chest: 57.2% vs. 2.9% Scalp:58.5% vs. 2.9% Application site pruritus: 32.9% vs. 2.5% Scalp:31.3% vs. 3.9% Cosmetic outcome improvement Much improved: Face/chest: 54.4% vs. 6.2% Scalp: 61.1% vs. 4.4% Global satisfaction Face/chest: 73.0±20.9 vs. 39.1±30.1 Scalp: 71.8±22.6 vs. 35.3±28.2		
Blauvelt et al 2021	To present the results of two identically designed phase 3 trials that evaluated the efficacy and	Two identically designed multicenter, randomized, controlled, double-blind trials Tirbanibulin 1% vs. placebo	Total sample size: n=702; 351 patients per trial <u>Trial 1:</u> Tirbanibulin (n=175) vs. vehicle (n=176) Age: 69.5±8.6 vs.	Participant complete clearance after 57 days Participant partial	Tirbanibulin vs. placebo Participant complete clearance: Trial 1: 44% (77/175) vs. 5%	No recurrence rates were reported for the vehicle groups Unblinding might be likely due to the	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	safety of tirbanibulin ointment, as compared with vehicle ointment, applied for 5 days in adults with actinic keratoses on the face or scalp. <u>Intervention:</u> Application of tibanibulin 1% ointment or vehicle to a 25-cm² contiguous area containing four to eight lesions once daily for 5 consecutive days.	Patients had to have four to eight clinically typical, visible, and discrete actinic keratosis lesions on the face or scalp within a contiguous area measuring 25 cm²	70.2±9.4 Male: 84% vs. 88% Median count of AK. 6 (IQR 5-7) vs, 6 (IQR 5-7) <u>Trial 2:</u> Tirbanibulin (n=178) vs. vehicle (n=173) Age: 69.1±8.7 vs. 70.2±8.9 Male: 89% vs. 87% Median count of AK. 6 (IQR 5-7) vs. 6 (IQR 5-7)	clearance at 57 days Mean percent reduction Patients with recurrent AK after 1 year Local skin reactions (4-point scale, ranging 0-3))	(8/176) Trial 2: 54% (97/178) vs. 13% (22/173) Participant partial clearance: Trial 1: 68% (119/175) vs. 16% (29/176) Trial 2: 76% (136/178) vs. 20% (34/173) Mean % reduction: 83% vs. 20% Trial 1: 86% ± 31 vs. 28%±36 Trial 2: 82%±29 vs. 34%±36 <u>Subgroup analysis</u> Complete clearance <u>Trial 1:</u> Face: 50% vs. 6% Scalp: 30% 2% <u>Trial 2:</u> Face: 61 vs. 14% Scalp: 41% vs. 11%	presence of local skin reactions	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Recurrence: At 1 year, the percentage of patients with recurrent lesions was 47% and the estimate of the percentage of those with recurrent or new lesions within the application area was 73%; the estimate of sustained complete clearance was 27%. <u>Safety</u> most common local reactions to tirbanibulin were erythema in 91% of the patients and flaking or scaling in 82% Pooled anaylsis: tirbanibulin vs. vehicle Any sAE: 1% vs. 2%		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Application-site pain: 10% vs. 3% Application-site pruritus: 9% vs. 6% Across the two trials, squamous-cell cancer developed in 10 patients outside the application area. One tirbanibulin-treated patient, who did not have complete clearance of lesions, had new onset squamous-cell cancer within the application area.		
Bourcier et al 2017	To assess the safety and efficacy of ingenol disoxate (LEO 43204) on full face or approximately 250 cm² on the chest in patients	Part 1: phase-I, open-label study Part 2: multicenter, randomized, double-blind, vehicle-controlled, parallel group trial	Part 2: 243 patients were randomized 1:1:1:1 to ingenol disoxate 0.018% (N=62), 0.012% (N=60), 0.006% gel (N=62) or vehicle (N=59), applied once daily for 2 consecutive days to the full face or to	Participant complete clearance Participant partial clearance (≥75%)	ingenol disoxate 0.018% vs 0.012% vs 0.006% gel vs vehicle <u>Complete clearance:</u> 24.2% vs 18.8% vs 9.9% vs 12.2%, ingenol disoxate	Results are obtained from part 2 of the study Unclear allocation concealment This study was funded by LEO	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	with AKs. Intervention:0.018%, 0.012%, 0.006% ingenol disoxate or vehicle once daily for 2 consecutive days to the full face or to approximately 250 cm² on the chest.		approximately 250 cm² on the chest. N=166 men Median age: 69 years, range: 42-91 Skin type: N=32:I, N=147: II, N=54: III, N=9: IV One patient in the vehicle group discontinued before first treatment application; the remaining 242 patients were included in the final analysis set.	Reduction in AK count from baseline at week 8 Local skin responses Adverse events Patients' treatment satisfaction (Treatment Satisfaction Questionnaire for Medication, TSQM) at week 8	0.018% vs 0.006% p<0.05 <u>Partial clearance:</u> 62.2% vs 54.5% vs 52.4% vs 29.9%, p<0.05 for all active treatment groups vs vehicle <u>Reduction in AK count:</u> 79.0% vs 73.4% vs 69.7% vs 42.3%, p<0.001 % reductions in AK and AK clearance were higher in vehicle-treated patients than in previous ingenol mebutate trials using the same vehicle as a control. <u>Local skin responses:</u> peak at day 3 for all doses, rapidly declined and	Pharma.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					reached mild levels at week 2 Mean composite scores on day 3: 8.6±3.8 vs 8.0±4.0 vs 6.0±3.5 vs 1.4±1.1 Erythema and flaking/scaling: most common LSRs in all groups <u>Adverse events:</u> at least 50% of patients in the active treatment groups had treatment-related AEs AEs were mild or moderate in intensity, most commonly application site pain/pruritus 4 patients: sAEs: 0.006% N=1, 0.012% N=3		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					TSQM: sign. higher in all active treatment groups than vehicle in pairwise analyses (p<0.001). Derived TSQM scores for side effects were significantly lower between the highest active treatment groups (0.012% and 0.018%) and vehicle (p <001), but not between the 0.006% group and vehicle. Furthermore, the 0.012% group had a significantly lower score than the 0.006% group (p=0.004).		
Brian Jiang et al 2019	To prove the safety and efficacy of ALA-PDT versus vehicle (VEH-PDT) in the spot treatment of multiple AKs on	Multicenter, randomized, Vehicle-Controlled, evaluator-blinded Phase 3 Study Patients had to have 4-15 grade 1 or 2 AKs on one upper extremity (dorsal	N=269 (262 patients completed the study) Men:188 Mean age: 68 (range 45-90)	AK lesion clearance rate at weeks 8 and 12: mean and median number of cleared AK lesions ± sd	ALA_PDT vs. vehicle PDT Participant complete clearance At week 12: 31.1% (42/135) vs. 12.7% (17/134)	Study was funded by Sun Pharmaceutical Industries, Inc.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	upper extremities at week 12. Intervention: Aminolevulinic acid or VEH was spot applied only to lesions on one upper extremity 3 hours before blue-light exposure. Treated extremity was covered with occlusive dressing during incubation. Identical treatment was repeated at Week 8 if AK lesions were present in the treated area. Blue light (BLU-U) delivered at a power density of 10 mW/cm² at the skin surface was administered to the treatment	hand/forearm). ALA-PDT (n=135) vs VEH-PDT (n=134)	FST: I [12%], II [52%], III [26%], IV [10%] Mean baseline AK count: 8.5 (sd:3.6) (range 4-15)	complete clearance rates at week 8 and 12 overall satisfaction (4-point scale 0=none/worse, 3=excellent) safety symptoms (Erythema, Edema, Stinging/Burning, Scaling and dryness, oozing, vesiculation, crust,	Mean AK clearance at week 12: 69.1±37.4% vs 29.9 ±51.5% Patient satisfaction 88% (118/134) vs. 42% (55/131) were very or moderately satisfied with treatment Adverse events: Stinging/burning: 93% vs 17% Erythema: 91% vs. 58% Edema: ~30/40% of ALA-PDT subjects Scaling: 76% No sAEs occurred Two ALA-PDT–treated subjects and one VEH-PDT–treated subject, all with a previous history of SCC, developed SCCson their treated extremities during		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	area for 16 minutes, 40 seconds for a total fluence of 10 J/cm².				the post-treatment period of this study.		
Chen et al 2003★	To evaluate the safety and efficacy of short courses of therapy with imiquimod 5% cream in clearing ≥75% of baseline SK (solar keratosis) within a field of treatment. Intervention: Application of study cream or vehicle three times a week.	Dual-centre, randomized, double-blind, vehicle-controlled, parallel-group study	Subjects with 5-15 baseline SK within one treatment area (scalp, forehead and temples, or both cheeks). N=29 in experimental group (imiquimod 5% cream), mean age: 64.9±10.2, 19male, 10 female N=10 in control group (vehicle cream only), mean age: 63.0±12.1, 4 male, 6 female Randomization ratio: 3:1 Application of study cream three times a week, followed by a treatment-free interval of 4 weeks	≥75% clearance of baseline lesions 100% clearance Type and severity of LSR Mean SK counts (baseline vs vehicle)	Imiquimod group vs vehicle group ≥75% clearance of baseline lesions: 72% (21/29), (1st course 45%, 13/29; 2nd course: 56%, 9/16) vs 30% (3/10), p=0.027 <u>100% clearance:</u> 28% (8/29) vs 10% (1/10), p=0.4 <u>LSR:</u> 93% (27/29) vs 40% (4/10) Mild to moderate severity most common LSR within imiquimod group:	Small sample size N=5 dropouts (intervention: 4 vs control:1) High risk for attrition bias Subgroup analysis: sex does not act as confounder Compliance of participants might differ: bias Randomization codes by 3M Pharmaceutical Services, codes not revealed to investigators until final assessment were complete: low risk of	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
			Subjects with <75% clearance of the baseline SK number were treated with a second course of study cream		erythema (26/29, 90%), erosions (17/29, 59%), scabbing/crusting (17/29, 59%), oedema (13/29, 45%) and flaking/scaling (11/29, 38%) <u>Mean SK counts:</u> Imiquimod: 10.5 to 18.1 Vehicle: 10.8 to 9.3, p=0.0017	selection and performance bias This study was supported by 3M Pharmaceuticals. Statement regarding potential conflict of interest is missing.	
Dirschka et al 2012	To evaluate the efficacy and safety of PDT of AKs with BF-200 ALA in comparison with a registered MAL cream and with placebo. Intervention: After application of the gel an	Multicentre, randomized, observer-blind, placebo-controlled phase III study Washout period: Topical treatments: 12 weeks Substances with phototoxic/allergic potential: 8 weeks Systemic treatments: 1-6 months	n=570 patients with 4-8 mild to moderate AK lesions on the face and/or bald scalp 84% male (479/570) Median age: 71.0 years, range: 39-87 BF-200 ALA: N=248, mean lesions per patient 6.1±1.6 MAL: N=247, mean	Patient Complete clearance rate Lesion complete clearance rate Adverse events Mean VAS score (0-11), after 1st treatment	<u>Patient Complete clearance rate (at 3 months):</u> BF-200 ALA vs placebo: 78.2% vs 17.1%, p<0.0001 BF-200 ALA vs MAL: 78.2% vs 64.2%, p<0.05 Better patient complete clearance rates of BF-200 ALA	Different light sources were used for PDT due to multicentric design of the study: stratification of results: patient complete clearance rates/lesion complete clearance rates: higher if irradiated with narrow-spectrum	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	occlusive, light-tight dressing was placed over the lesion and illumination was performed 3 h later. The light sources included in the study are frequently used for PDT of AK in Europe with a narrow emission spectrum around 630 nm and a recommended light dose of 37 J/cm² or an incoherent broad-spectrum light source emitting light between 580 and 1400 nm with a recommended light dose of 170 J/cm² or a light spectrum from	BF-200 ALA gel contains 7.8% or 78 mg/g ALA (corresponding to 10% ALA hydrochloride). MAL cream contains 160 mg/g of MAL. Randomization BF-200 ALA: MAL cream: placebo: 3:3:1	lesions per patient: 6.3±1.5 Placebo: N=76, mean lesions per patient. 6.4±1.4		and MAL at the face/forehead than on the scalp. BF-200 ALA vs MAL vs Placebo: <u>Total clearance after first PDT:</u> 48.4% vs 37% vs 3.9% BF-200 ALA vs placebo:p<0.0001 <u>Lesion complete clearance rate (at 3 months):</u> 90.4% (1359/1504 lesions) vs 83.2% (1295/1557 lesions) vs 37.1% (182/490 lesions) <u>Cosmetic outcome:</u> Very good/good: 43.1% vs 45.2% vs 36.4% Unsatisfactory: 7.9% vs 8.1% vs 18.2%	light sources This study was sponsored by Biofrontera Bioscience GmbH.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	600 to 750 nm, and the recommended light dose is 100 J/cm².				Occurrence of Adverse events: 96.4% vs 98.0% vs 72.4% Most common and most severe AEs: erythema, burning and pain Mean VAS score: 4.8±3.61 vs 4.0±3.58 vs 0.5±1.12		
Dirschka et al 2013 (follow up study to Szeimies 2010 and Dirschka et al 2012)	To evaluate long-term efficacy and safety of PDT for AK 6 and 12 months after the last PDT with BF-200 ALA, MAL or placebo. Intervention: See Dirschka 2012 and Szeimies 2010	6 and 12 months follow-up study of two randomized, placebo-controlled, multicentric phase III studies Both studies compared BF-200 ALA with placebo, one of the studies additionally with MAL.	N=663 patients, 630 completed the follow-up,104 women Age range: 39-87 years	Complete clearance Cosmetic outcome Incidence of new lesions	Complete clearance (12 months): 47% (both studies for BF-200 ALA) vs 36% (MAL) Subgroup: narrow wavelength LED lamps: 69% (BF-200 ALA) vs 53% (BF-200 ALA) vs 41% (MAL) Cosmetic outcome: at 6 months: very good/god: 39.7% and 43.1% for BF-	See Dirschka et al 2012	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					200 ALA groups, 42.6% MAL, 34.8% and 44.1% placebo At 12 months: very good/good: 38.9% and 45.0% for the BF-200 ALA groups, in 41.1% MAL, 32.8% and 46.9% placebo <u>Overall new lesions:</u> 41.7% and 41.8% in BF-200 ALA, 20.6% and 56.1% in placebo and 48.7% in MAL		
Dirschka et al 2019	To determine whether BF-200 ALA (a nanoemulsion gel containing 7.8% 5-aminolaevulinic acid) is non-inferior to MAL (a cream containing 16% methyl-aminolaevulinate) in the	Multicenter, randomized, intra-individual, non-inferiority, observer-blinded Phase III Study Randomization in a 1:1 ratio to daylight ALA-PDT (N= 52) or MAL-PDT (n=52) AK had to be localized on the face/scalp	N = 52 patients 96.2% male Age 72.2±7.2 years Fitzpatrick skin type: I-III: 48 IV-V: 4 Mean number of target lesions per side: 6.4 ±2.2 Nr of lesions: 316	Participant complete clearance rate total lesion clearance rate 12 wks after dPDT Recurrence rates Cosmetic outcome and	ALA-PDT vs MAL-PDT Participant complete clearance rate 42.9% vs. 38.8% Lesion specific clearance at 12 weeks: 79.8%± 23.6% vs 76.5% ± 26.5	Only per-protocol data were available; attrition bias might be likely The study was sponsored by Biofrontera Bioscience GmbH. Patients were not blinded, thus, performance bias	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	treatment of mild-to-moderate AK with daylight PDT (dPDT).			patient satisfaction Pain intensity during PDT (0-10)	Subgroup analysis: AKs in the face 85.2% vs. 84.2% mild AKs: 93.7vs. 91.2% Lesion specific recurrence rates 1 year after the treatment: 19.9% vs 31.6% Cosmetic outcome Very good or good: 40.7% vs. 37.5% Patient satisfaction: very good/good/satisfactory: 91.8% for both sides Adverse reactions including pain: mostly mild and transient and identical to those previously described for dPDT. Pain: 1.2±2.1 vs. 1.1±2.2	might be likely women are underrepresented	
Dragieva et al 2004★	To evaluate the efficacy and	Prospective, single-centre, randomized, double-	n=17 OTRs with 129 mild to moderate AKs	Complete response rate	Complete response rate vs partial	Small sample size	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	tolerability of topical photodynamic therapy with the new highly tumour-selective photosensitizer MAL vs. placebo in the treatment of AK in transplant recipients. Intervention: Two lesional areas within a patient were randomized for two consecutive treatment of topical PDT 1 week apart using either MAL or placebo cream. Sites were illuminated with 75 J/cm² of visible light	blind, placebo-controlled, intraindividual study	Mean age (range): 61 (44-76) years, 14 male, 3 female, transplantations: N=13 kidney, N=4 heart face or scalp (N=107), neck (N=1), extremities (N=21) (N=number of lesions)	at 16 weeks after 2nd treatment Partial response rate Overall lesion complete response rate Adverse events VAS score	response MAL:75.4% (13/17 patients, 95% CI: 9,16) vs 94.1% (16/17 patients) No reduction in number or size of AKs in the placebo group Overall lesion complete response rate: MAL vs placebo: 90.3% (56/62) vs 0% (0/67), p=0.0003 Adverse events: No quantification of AEs reported, discomofort higher for MAL than placebo Mild to moderate AEs such as erythema, oedema and crust formation reported	Population: OTRs with AK→results of this study are limited to this study population Lack of confidence intervals and p-values: selective reporting bias likely Each patient received 1 g paracetamol orally 1h before illumination; a fan was used to cool the treated area and to reduce discomfort during illumination → this may bias the pain reception and consequently the VAS-score (underestimation) Unclear risk of	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	delivered at 80 mW/cm² by a noncoherent light source.				<u>VAS score:</u> MAL: after 1st treatment: mild: N=11, moderate: N=6 After 2nd treatment: mild: N=6, moderate N=9, severe N=2 Placebo: mild in all cases	random sequence generation and allocation concealment VAS score only reported as mild/moderate/severe, lack of exact scores. Besides, quantity of adverse events is not reported: risk for selective reporting bias Study was double-blind, but because discomfort was higher with MAL, unblinding possible: detection bias and performance bias Statement regarding potential conflict of interest is missing.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
Evans et al 2014	To assess the effects of a 3-month application of a canola phenolic acid-based cream (CPA) on AK lesions. Intervention: Application of one sachet of cream of CPA or vehicle on the preselected skin area twice a day, after showering for 12 weeks.	Randomized, double-blind, placebo-controlled, single-center, clinical trial Study was conducted in the Dominican Republic.	n=45 subjects with 3-10 AKs within a 20 cm² treatment area (30 CPA, 15 placebo) Range 45-82 years Mean age CPA: 60.0±10.8, placebo: 55.7±9.1 years 4 male, 41 female Application of one sachet of cream on the preselected skin area twice a day, after showering for 12 weeks.	Complete lesion clearance Partial lesion clearance Mean change from baseline in the average lesion area Adverse events	No complete lesion clearance Significant reduction in the <u>mean change from baseline in the average lesion area</u> at weeks 3 (P=0.002), 6 (P<0.001), and 12 (P<0.001) in the CPA group, but only at weeks 6 and 12 in the placebo group (P=0.005 and P=0.002, respectively) <u>≥10% decrease in average lesion area:</u> Significantly higher in the CPA group than the placebo group at weeks 3 (P=0.05) and 6 (P=0.02), and showed a trend at week 12 (P=0.06)	Mainly p-values provided and not the exact results: selective reporting bias likely	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Adverse events: one severe AE in placebo group 56 AEs (45 CPA, 11 placebo) were reported in 30 (20 CPA, 10 placebo) participants.		
Foley et al 2011	To evaluate lesion clearance, safety, and skin quality through 12 months post-initial treatment of AKs in patients treated with cryotherapy or imiquimod 5% cream. Intervention: Cryotherapy: up to 10 lesions per session, up to 4 sessions every 3 months Imiquimod: 3-times-per-week	Prospective, single-centre, randomized, controlled study	n=71 patients with 700 baseline-lesions N=56 male (78.9%) Mean age: 71.5 years±1.23 Inclusion criteria: ≥10 AK lesions in one anatomical area N=36 patients randomized to cryotherapy, N=35 patients randomized to imiquimod 5% cream Randomization 1:1	Lesion Clearance Patient complete and partial response rate (PP) Skin Quality Safety (Adverse events)	Cryotherapy vs imiquimod: <u>ITT Lesion complete response rates:</u> 85.0% (306/360) vs 66.9% (234/350), p<0.0002 (5 cryotherapy and 10 imiquimod patients unable for evaluation) <u>PP Lesion complete response rates:</u> 98.7% (306/310) vs 93.6% (234/250), p=0.0420 Patient complete	Results are limited to this population (Australia), may not be representative In the imiquimod group: self-application of participants, which might bias the results (recall-bias/compliance) Open study: performance and detection bias likely Withdrawal rates:	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	for 3-4 weeks, up to two courses				response rate: 90.3% (28/31) vs 68-0% (17/25) Patient partial response rate: 9.7% (3/31) vs 28.0% (7/25) <u>Global skin quality</u> in completely cleared lesions: 82% (250/306) vs 100% (234/234), p<0.0001 <u>Adverse events:</u> Hypopigmentation: 54.8% vs 24.0%, p=0.0197 Mild intensity: Blister formation, redness/erythema, flaking/scaling/dryness, scabbing/crusting <u>Conclusion:</u> 12-month lesion	13.9% (5/36) for cryotherapy and 28.6% (10/35) for imiquimod: increases the risk for bias. The study was supported by an unrestricted educational grant and a gift of imiquimod 5% cream by 3M pharmaceuticals. P. Foley has been a clinical investigator and speaker for 3M Pharmaceuticals.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					complete clearance: higher with repeated cryotherapy, cosmetic outcome better with imiquimod		
Garbe et al 2016	To demonstrate the efficacy and safety of follow-up ingenol mebutate 0.015% field treatment of AK present at 8 weeks after initial treatment or emerging in a previously cleared field on the face or scalp. Intervention: IMB 0.015% for three consecutive days. If lesions were present in the field at 8	Randomized, stratified, double-blind, vehicle-controlled, parallel group, multicenter study	n=450 patients received initial treatment with ingenol mebutate 0.015% gel N=397 male (88.2%) Median age: 72 years (range: 36-92) If lesions were present in the field at 8 weeks, or emerged at weeks 26 or 44 (N=141), patients were randomized (2:1) to follow-up ingenol mebutate 0.015% (N=92) or vehicle gel (N=49) for three consecutive days.	Patient Complete clearance rates Incidence of AEs Change in local skin response score at day 4 between treatment cycles (mean composite LSR score)	<u>Complete clearance:</u> 61.6% (n=277/450) of initially treated patients with IngMeb at 8 weeks 8 weeks after randomization: IngMeb (N=134) vs vehicle (N=69): <u>Complete clearance of AKs present at week 8:</u> 46.7% vs 18.4%, p<0.01 Emergent AKs: 59.5% vs 25.0%, p=0.01 <u>After 12 months:</u> AKs present at 8	Risk of Recall bias/Compliance of participants when applying gel. Blinding of patients and investigators to the second treatment cycle: minimizes risk of bias This study was funded by LEO Pharma.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	weeks, or emerged at weeks 26 or 44, patients were randomized (2:1) to follow-up ingenol mebutate 0.015% or vehicle gel for three consecutive days.				weeks: 18.5% vs 4.1%, p=0.02 Emergent AKs: 31.0% vs 15.0%, p=0.10 <u>12-month clearance rate</u> (N=340): estimated at 50.0% (95%CI: 44.0-56.1) Mean composite LSR scores at day 4 after a second treatment course of IngMeb were significantly reduced vs. first treatment cycle: mean difference was -1.22 (95% CI -1.90 to -0.53; p < 001) Most common LSR: erythema and flaking/scaling AEs:		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Overall: 7.8% of patients (35/450) reported 49 AEs. 1st cycle: Pain (13.5%), pruritus (4.4%), headache (4.0%), eyelid oedema (3.8%) Follow-up: application site pruritus (5.2%) No significant difference in frequency of treatment-related AEs when comparing 1st and 2nd cycle (p=0.22)		
Gebauer et al 2003	To compare the efficacy and safety of 3% diclofenac in 2.5% hyaluronan gel with placebo (2.5% hyaluronan gel alone) in the treatment of	Randomized, double-blind, placebo-controlled, multicentred, parallel-group study	n=150 patients (89 men, 61 women) Mean age: 68 years (range: 27-87 years) Random allocation to active treatment (N=73) or placebo (N=77) Patients applied 0.25g of	Mean lesion-count reduction Complete lesion resolution >50% lesion reduction	Diclofenac group vs placebo At 16 weeks: highly significant decrease in number of lesions: 6.2±7.5 (56.1% reductions) vs 2.4±4.3 (23.6%	Study was conducted in Australia (higher prevalence rate of SKs: results are limited to this population, results have to be interpreted	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	patients with SK. Intervention: Application of 0.25g gel to 5cm² twice daily until lesions resolved or for 12 weeks.		gel to a designated 5cm² study area twice daily over 12 weeks.	Adverse events	reduction), p<0.001 <u>Complete lesion resolution:</u> At 16 weeks: 38% vs 10%, p=0.002 <u>>50% lesion reduction:</u> at 16 weeks: 65% vs 29%, p=0.002 <u>Adverse events:</u> Most common (majority mild to moderate): pruritus, erythema, oedema and scaling Severe: 19% of reported cases of pruritus, 18% of dry skin, 12% of rash. Patients were highly compliant	cautiously and might only apply to this certain population Drop-outs: N=35, more drop-outs in experimental group: increased risk for attrition bias Unclear random sequence generation and allocation concealment Patients were highly compliant: small chance for recall bias: Gel and placebo are nearly identical: small risk of allocation bias and unblinding	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
						This study was supported by Hyal Pharmaceutical Corporation. Statement regarding potential conflict of interest is missing.	
Gebauer et al 2009★	To evaluate dosing frequency response of imiquimod 5% cream for treatment of AK. Intervention: Application of imiquimod 5% cream or placebo once daily 2, 3, 5 or 7 times per week.	Phase II, multicentre, randomized, double-blind, placebo-controlled, parallel-group study	n=149 subjects (94 men, 54 women) Mean age: 71±10.2 years 42% FST II, 36% FST I Randomization to imiquimod 5% cream or placebo (4:1) to be applied once daily 2, 3, 5 or 7 times per week. Combined placebo = pooled result of all placebos (=placebos of 2,3,5 or 7 times per week)	Complete clearance rates at week 16 Partial clearance rates at week 16 Adverse events, local skin reaction	Combined placebo and in the imiquimod 2, 3, 5 or 7 times per week groups: <u>Complete clearance:</u> 0% vs 3.2% vs 6.9% vs 3.3% vs 6.7% of subjects (ITT) <u>≥75% lesion reduction:</u> 0% vs 22.6% vs 24.1% vs 20.0% vs 36.7% (p=0.002) <u>Median percentage lesion reductions:</u> 25.0%, 50.6%,	Drop-outs: N=28 (18.8%): Risk for attrition bias remains unclear Participant self-applied the drug: risk for recall bias Dosing compliance was assessed at each treatment visit via self-reporting (dosing diary): 80% of subjects were considered compliant Study was not	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					57.6%, 64.7% and 70.3% <u>Mean percentage lesion reduction:</u> 21.2% for placebo, 44.6-65.3% for imiquimod. <u>Adverse events:</u> Proportion of subjects with possibly related AEs: higher in the imiquimod groups (58.1–93.3%) than the combined placebo group (6.9%); most reported AE was application site reactions (application site itching (59.1%), pain (39.6%), burning (15.4%)) Author's <u>conclusion:</u>	blinded for the frequency of application: high risk of performance bias The known local pharmacological effect of imiquimod (e.g. erythema) may have biased subject and investigator assessments Unclear risk for allocation concealment This study was funded by 3M Pharmaceuticals. Statement regarding potential conflict of interest is unclear.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					application of immiquimod 5% cream more frequently than 3 times per week should be avoided		
Giehl et al 2014	To compare pain scores, short- and long-term efficacy rates of ALA-PDT of multiple AKs when employing different red light sources. Intervention: Randomization to ALA/PD750: n=44 with 151 lesions irradiation with a broadband VIS+wIRAlamp with a water cuvette and an orange filter BTE 595. The water-filtered spectrum	Randomized, single-centre, controlled trial	n=88 Caucasian patients with 310 AKs 67 male, 21 female Mean age: 73 years (range: 46-90)	Pain scores (VAS score, 0-10) Desire for pause, anaesthesia, cancellation of treatment Patient complete clearance rates Lesion complete clearance rates	<u>Pain scores</u> PD750: median=5±2.1, IQR=3-6 Wa1200L: median=7±2.1, IQR: 6-9, p<0.0001 <u>Desire for:</u> Pause: PD750 vs Wa1200L 4(9%) vs 9(20%) Anaesthesia: 2% vs 27% Cancellation: 2 (5%) vs 8 (18%) <u>Patient complete clearance rates:</u> PD750 vs Wa1200L: After 1 month: 85% vs 91%, p=0.51 After 3 months: 79%	Randomization: assignment of the patients to the different groups occurred depending on the daily availability of the two lamps and the location of the lesions to be treated Evaluation of therapy outcome was done by a different person than the PDT on the patient Additional cooling with cold air was offered during	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	was in the range 595-1400nm without distinct peaks. The absolute irradiance was 196 mW/cm2 VIS + wIRA and the application time was 30 min with a distance of 27 cm to the skin surface, resulting in an absolute irradiation dose of 350 J/cm2. ALA/Wa1200L: n=44 with 159 lesion: incoherent halogen light source with a spectrum in the range of 600-720 nm and without distinct peaks. The				vs 92%, p=0.19 After 6 months: 97% vs 92%, p=0.61 After 12 months: 69% vs 85%, p=0.15 <u>Lesion complete clearance rates:</u> PD750 vs Wa1200L: After 1 month: 94% vs 92% After 3 months: 88% vs 97%, p=0.027 After 6 months: 96% vs 95% After 12 months: 81% vs 89%, p=0.13 75% (66/88) of patients completed the 12 months follow-up	treatment. 17% did not need it (all from P750 group)	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	absolute irradiance was 150 mW/cm2, the application time 10-11 min and the absolute irradiation dose was 100 J/cm2 with the control of an individual interactive measuring system.						
Gollnick et al 2020	To compare IMIQ and DIC in the treatment of AK with respect to the risk of change to grade III AK or invasive SCC, after 3 years Intervention: IMQ: Application of IMQ 3 nights per weeks, for 4 weeks followed by a 4-week treatment pause. If lesions were still present,	Data were pooled from two randomized, active-controlled, open-label, multicentre, multinational, inter-individual, phase IV studies (NCT00777127/NCT01453179; LEIDA1/2) Immunocompetent patients with 5-10 visible AK on the face/scalp and grade I/II AK were included. IMIQ: n=242 DIC: n=237	N=479 patients majority of patients in both treatment groups were male (IMIQ 83.9%; DIC 90.3%) mean age: 70.8 and 71.1 years (IMQ vs. DIC)	Participant complete clearance rate at week 20 Participant specific recurrence rate Histological change to grade III AK or invasive SCC Adverse events	IMQ vs. DIC Participant complete clearance rate: 52.1% vs. 35.4% Participant specific recurrence rate: higher in the DIC group at all time points At month 12: 68.6% (166/242) vs. 82.3% (195/237)	N=162 (33.8% withdrew from the study during the 3-years study period (33.8%; IMQ vs. DIC: 28.9% vs. 38.8%) → attrition bias is likely This study and the writing/editorial support were funded by Meda Pharma S.p.A., a Mylan company. Both studies had an open-label	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	induction of a second course. DIC: Application twice daily for 12 weeks followed by an 8-week off-treatment phase.				Histological change to grade III AK or invasive SCC: 5.4% (13) vs. 11.0% (26) until month 36 Treatment emergent AEs: 86% vs. 82%, 21% and 18% were assessed as treatment-related Application site pruritus: 5.3% (13/243) vs. 6.7% (16/238)	design and thus, an increased risk for detection and performance bias. However, all professionals and all documentation at, and provided by, the central histopathological laboratory remained blinded to the study treatments administered throughout the study.	
Hanke et al 2010★	To evaluate imiquimod 2.5% and 3.75% creams for short-course treatment of the entire face and scalp. Intervention: Imiquimod 2.5%, 3.75% or placebo	Two multicentre placebo-controlled, multi-centre, double-blind, randomized studies, conducted in parallel	n=490 subjects 386 men, 104 women, 99% white, 27% treated the face, mean age: 65 years Randomization 1:1:1 to imiquimod 2.5% once daily, imiquimod 3.75% once daily, or placebo (applied as 3-week on/off/on regimen).	Complete clearance rates at week 17 Partial clearance rates at week 17 Median reduction from baseline in lesion count	Placebo vs imiquimod 2.5% vs imiquimod 3.75% (weeks posttreatment) <u>Complete clearance rates:</u> 5.5% vs 25.0% vs 34.0% <u>Partial clearance:</u> 12.8% vs 42.7% vs 53.7%	Drop-outs: N=27 Limitations: Local effects of imiquimod, including erythema, may have led to investigator and subject bias (performance and detection	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	once daily applied as a 3-week on/off/on regimen.			Investigator Global Integrated Photodamage (IGIP) score Safety (adverse events, LSR)	(p< 0.001, each imiquimod vs placebo; p = 0.034, 3.75% vs 2.5% for partial clearance) <u>Median reduction from baseline in lesion count:</u> 23.6% vs 66.7% vs 80.0% (p<0.001 each imiquimod vs placebo) <u>Mean IGIP score:</u> 0.7±1.1, 23.4% vs 2.0±1.1, 62.3% vs 1.8±1.1, 70.9%) <u>Adverse events:</u> Treatment related: 44 (26.8%) in imiquimod 2.5% group, 60 (37.0%) in imiquimod 3.75% group and 4 (2.4%) in placebo group	bias/Hawthorne effect) Investigator selected the treatment area for each subject (face or balding scalp)-> selection bias participants applied the cream once daily: recall bias/compliance might overestimate the results (96% of subjects were compliant with dosing per study protocol) unclear risk for random sequence generation and allocation concealment Data for safety	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					LSR: imiquimod 2.5% vs Imiquimod 3.75%: Erythema: n=46 (28.2%) vs n=72 (44.7%), Erosion/ulceration: n=39 (23.9%) vs n=49 (30.4%) and scabbing/crusting: n=37 (22.7%) vs n=56 (30.4%)	were reported differently in the published record and the protocol; besides, additional outcomes were presented in the paper (cosmetic outcome): selective reporting bias This study was supported by Graceway Pharamceuticals.	
Hanke et al 2020	To determine efficacy and safety of IMB 0.027% in areas of AK of up to 250 cm^2 during an 8-week initial assessment period and extended 12-month follow-up. Intervention: Application IMB (n=552) or vehicle (n=177)	Multicenter, randomized, parallel-group, double-blind, vehicle-controlled phase III study patients with 5 to 20 AK lesions on the face/scalp (25-250 cm^2) or chest (approximately 250 cm^2)	N = 729 (698 pts entered the extended 12-month follow-up) Ingenol mebutate 0.027%: n= 552 Age: 68 (38-91) Sex: 403 men, 149 women Skin type: I (110), II (265), III (149), IV (27), V(1) vehicle: n = 177	Participant complete AK clearance Participant partial clearance Reduction in AK lesion count Recurrence patient satisfaction	IMB vs vehicle: At week 8: complete AK clearance: 21.4% vs 3.4% Participant partial clearance : 59.4% vs 8.9% Reduction in AK lesion count 75.7% vs. 12.7% Probability of	Potential unblinding was possible due to localized skin responses The study was supported by LEO Pharma. Selective reporting for the outcome “treatment satisfaction” 65/549 (11.8%)	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	once-daily for 3 consecutive days on the full face, full balding scalp, or approximately 250 cm^2 on the chest		Age. 69 (45-91) Sex: 132 men, 45 women Skin type: I(28), II 894), III (51), IV (4)	cosmetic outcome safety	sustained clearance during the 12-month follow-up: 22.9% (IMB) Satisfaction: increased satisfaction were observed with IMB in comparison to vehicle Cosmetic outcome: improvements in overall feel and appearance were reported by 92.2% and 93.9% of patients receiving IMB and by 17.7% and 19.0% of those receiving vehicle, respectively Safety: No unexpected safety signals were identified. Occurrence of AEs: 79.8% vs. 34.7% sAEs: 1.5% vs. 1.1% Application site pain: 63.8% vs. 2.3% Pruritus: 37.0% vs. 4.0%	patients receiving IMB and 6/176 (3.4%) patients receiving vehicle did not apply the full dose on a given day or skipped a treatment day completely. Noncompliance was mostly due to reactions in the treatment area.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
Hauschild et al 2009	To investigate both the efficacy of different application times and the safety of a novel patch (PD P 506 A) containing aminolaevulinic acid in the PDT of mild to moderate AK. Intervention: Application duration of 0.5h, 1h, 2h or 4h of the ALA patch followed by PDT.	Multicentre, randomized, blinded-observer, parallel-group study	n=149 patients of which 140 patients with 520 lesions completed the study (PP) 0.5 h: N=34, median age: 73 years (range: 39-88), 9 females (26%) and 25 males (74%) 1 h: N=38, median age: 70.0 years (range: 55-91) 13 female (34%), 25 males (66%) 2 h: N=34, median age: 68.5 years (range: 57-84) 9 females (26%), 25 males (74%) 4 h: N=34, median age: 69.5 years (range 49-83) 6 females (18%), 28 males (82%)	Complete clearance (patient- and lesion-based) at 12 weeks post-treatment Adverse events	Complete clearance: 4 h vs 2 h vs 1 h vs 0.5 h group: 74% patients (86% of lesions, 95% CI: 0.75-0.95) vs 47% (73%) vs 50% (72%) vs 24% (51%) Statistically, the 4-h application was identified as “best treatment” In some patients, lesions that presented as ‘cleared’ at week 4 worsened and were apparent again at week 8 (in all but the 4h group) Patients with clearance seemed to experience local reactions to a greater extent than patients without	To ensure blinding, treatment was administered by a 2nd investigator The study was funded by Photonamic GmbH & Co. KG.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					clearance (e.g. redness in 74% of cleared lesions whereas only in 38% of not cleared lesions) Adverse events: 5/149 related to the study medication: headache (one severe in 0.5 h group, two moderate in 2h and 4h group), moderate epistaxis (4 h) and mild increase of alanine transaminase (0.5 h group)		
Holzer et al 2016	To investigate the efficacy and safety of 35% trichloroacetic acid peel versus 20% ALA-PDT in patients with extensive field cancerization	Randomized, observer-blinded, intrapatient, single-centre, comparison study Follow-up: 1, 3, 6 and 12 months after treatment .	n=28 patients with ≥5 AKs in two comparable anatomical areas on the head Mean age: 70.0 years±7.6 (range 56-88) N=4 female	Total lesion count reduction Complete clearance Treatment failure (number of AK	TCA vs ALA PDT: Total lesion count reduction (ITT): 31.9% vs 58.0% (p=0.006) Mean Complete clearance rate:	Drop-outs at 12-month follow-up: N=5: moderate risk for attrition bias Patients were instructed to regularly apply	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	and multiple AKs in the face or on the scalp. Intervention: PDT: Scales overlying AK were gently removed with a curette before ALA application. 20% ALA in an oil in water emulsion was evenly applied on the target area and occluded with a transparent film dressing. After four hours the dressing was removed, excess cream was wiped off and the area was illuminated with a filtered metal halide lamp (Waldmann			greater than 50% of the baseline count) Adverse events, treatment-related pain (mean VAS score 0-10) Cosmetic outcome (excellent, good, fair and poor)	48.8%±35.1 vs 73.7%±29.5 (p=0.011) <u>Treatment failure N</u> patients (%): 7 (25%) vs 2 (7.1%) <u>Mean VAS score:</u> 7.5±2.3 vs 5.1±2.6, p=0.04 Scarring was only seen in TCA group (n=6, 21.4%) <u>Cosmetic outcome</u> (excellent): N=11 (44.0%) vs N=19 (76.0%), p=0.202	sunscreen until completion of study.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	PDT 1200, 600 – 740 nm, using a dose of 75 J/cm² at an irradiance of 75 mW/cm²). TCA peeling: After topical anaesthesia for 30 minutes with a cream containing 5% lidocaine and 5% prilocaine the skin was cleaned with 95% isopropyl alcohol and degreased with acetone soaked sponges. 35% TCA was then applied						
Jansen et al 2019	To compare treatment success at 12 months of 5% fluorouracil cream, 5% imiquimod cream, methyl	multicenter, single-blind, randomized, controlled, inter-individual trial Patients 18 years of age or older with a clinical diagnosis of five or more actinic keratosis lesions in	N= 624 patient 89.4% male (558/624) Median age: 73 years (range 48-94) Skin type: I: 39.3% (245/624) II: 53.4% (333/624) III: 7.4% (46/624)	Proportion of patients who remained free from treatment failure during 12 months of follow-up after the last	cumulative probability of remaining free from treatment failure: 5-FU: 74.7%; 95% confidence interval [CI], 66.8 to 81.0) than among those	ITT analysis was performed Participant were not blinded, performance bias is likely; however, all investigator	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	aminolevulinate PDT (MAL-PDT), and 0.015% ingenol mebutate gel in patients with actinic keratosis lesions of any grade. Interventions: 5-FU: Application of 5-FU 5% cream twice daily for 4 weeks. (n=155) MAL-PDT: Application of MAL under occlusion for 3h, followed by illumination with red LED with an optimum wavelength of 635 ± 18 nm (fluence 37 J/cm² during 7.23 minutes). Directly after illumination the treatment area was covered up for 24 hours. (n=156)	one continuous area of skin measuring 25 to 100 cm² in the head and neck area were eligible for participation. Randomization in a 1:1:1:1 ratio	History of AK. 78.0% (487/624) History of NMSC: 56.6% (353/624) Median number of AK: 16 (range 5-48)s	treatment Participant partial clearance = initial treatment success at 3 months/12 months after the last treatment (defined as ≥75% reduction from baseline in the number of actinic keratosis lesions), Adverse events Patient satisfaction Cosmetic outcome	who received imiquimod (53.9%; 95% CI, 45.4 to 61.6), MAL-PDT (37.7%; 95% CI, 30.0 to 45.3), or ingenol mebutate (28.9%; 95% CI, 21.8 to 36.3) Treatment success: 3 months after EOT 5-FU: 90.6% (135/149) IMQ: 75.8% (113/149) MAL-PDT: 76.0% (117/154) IMB: 67-3% (101/150) Treatment success 12 months after EOT: 5-FU: 82.4% (108/131) IMQ: 71.0% (76/107) Mal-PDT: 49.6% (57/115) IMB: 42.9% (42/98) Adverse events: no treatment-related sAEs	assessments were blinded The percentage of patients with 100% adherence was higher in the ingenol mebutate group (98.7%) and the MAL-PDT group (96.8%) than in the fluorouracil group (88.7%) and the imiquimod group (88.2%). Grade III lesions are included in this study Approximately half the patients who were assessed for eligibility declined to participate in this trial, usually because of personal preference or disfavor regarding a specific therapy.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	IMB: Application of IMB 0.015% once daily for 3 consecutive days. (n=157) IMQ: Application of IMQ 5% cream 3 days a week for 4 consecutive weeks. (n=156)				Any AE: 5-FU: 92.6% (125/135) IMQ: 85.1% (103/121) MAL-PDT: 96.6% (113/117) IMB: 95.7% (134/140) Patient satisfaction: recommendation: 5-FU: 93.1% (135/145); IMQ: 81.0% (111/137); PDT: 70.3% (104/148); IMQ: 84.7% (122/144) Cosmetic outcome Good-to-excellent: MAL-PDT: 96.6%; IMB: 95.1%; 5-FU: 90.3%; IMQ:89.7%		
Jeffes et al 2001★	To examine the safety and efficacy of PDT using topical 20% ALA in a solution formulation and varying blue light doses (2, 5,	Multicentre, randomized, assessor-blinded, vehicle-controlled, intraindividual study	n=36 participants 30 men, 6 women Mean age: 68.8 years, range: 38-100 On each patient two AKs were treated with vehicle and 2 with 20% ALA.	Participant complete clearance Lesion complete response rates CR rate of AKs 8 weeks after a	ALA vs vehicle <u>Complete response rate:</u> -8 weeks: 46 (66%) vs 12 (17%), p<0.001 -16 weeks for ALA PDT: 56 (85%),	Hyperkeratotic, hypertrophic grade 3 AKs were excluded because of previous experience suggesting these did not respond well to PDT:	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	and 10 J/cm²) to treat multiple AKs on the face and scalp.			single PDT according to varying light doses Application site reactions during illumination and after treatment	increase in CR rate was significant (p=0.013) <u>Partial response:</u> 12 (17%) vs 12 (17%) 16 weeks for ALA PDT: 4 (6%) <u>Number of cleared lesions at week 8:</u> 0: 5 (14%) vs 25 (71%) 1: 14 (40%) vs 8 (23%) 2: 16 (46%) vs 2 (6%) <u>CR rate of AKs 8 weeks after a single PDT according to varying light doses:</u> 2 J/cm²: 16 (57%) vs 8 (29%), p=0.058 5 J/cm²: 16 (62%) vs 3 (12%), p<0.001 10 J/cm²: 14 (88%) vs 1 (6%), p<0.001	selection bias High risk of performance bias: non-blinded investigator performed the treatments Unclear risk of random sequence generation and allocation concealment. This study was supported by DUSA pharmaceuticals, Inc.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Subjective signs during/after ALA PDT: burning/stinging (most frequently reported), itching, pain Objective signs: erythema (most frequently reported), edema, wheal		
Jorizzo et al 2007★	To evaluate imiquimod 5% cream applied 3 days per week in one or two shorter courses of treatment for AKs on the head. Intervention: Imiquimod 5% or vehicle cream 3 days per week in one or two shorter courses.	Multicentre, randomized, double-blind, vehicle-controlled, parallel-group study Randomization imiquimod:vehicle 1:1	n=246 participants randomized Imiquimod group: N=123 Vehicle group: N=123	Recurrence at 1 year Participant complete and partial clearance rates Adverse events/Local skin reactions	Imiquimod vs vehicle Recurrence rate: 39% vs 57% Complete clearance rates: 26.8% (course 1) vs 4.1%and 53.7% (overall) vs 14.6% Partial clearance rates: 36.6% (course 1) vs 5.7% and 61.0% (overall) vs 25.2%	Blinded investigators may have been biased toward participants treated with imiquimod identified by treatment site reactions (detection bias) Lack of participants' clinical and demographic data:	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Adverse events: Itching = most frequently reported application site reaction LSR: Erythema and scabbing/crusting (16% of patients rated them as severe)	selective reporting bias likey Only statistically significant results were reported, results for AEs and LSRs are unclearly reported: selective reporting bias likely This study was supported by 3M Pharmaceuticals.	
Jorizzo et al 2002★	To compare the efficacy and safety of a new 0.5% fluorouracil topical cream once daily for 1, 2, or 4 weeks with vehicle control for the treatment of AK. Intervention: Application of 0.5% 5-FU or	Multicentre, randomized, double-blind, open (treatment duration), vehicle-controlled, parallel-group study	n=207 participants 166 men, 41 women N=69 patients received vehicle cream N=47 patients received 1 week of active treatment N=46 received 2 weeks of active treatment N=45 received 4 weeks of active treatment	% reduction of lesions (mean percentage of reduction in lesion counts) Absolute mean reduction in lesion counts Participant complete clearance rate	Mean % reduction: After 1 week: 69.5%, after 2 weeks: 86.1%, after 3 weeks: 91.7% For all: p<0.001 vs Vehicle control: 21.6% Proportion of patients with total lesion clearance: 1 week: 14.9% (p<0.001 vs vehicle)	Unclear risk of allocation concealment and random sequence generation. No placebo cream was used to conceal the treatment duration. Study was partly double-blinded	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	vehicle cream once daily for 1, 2 or 4 weeks.			Physician Global Assessment of Improvement Adverse events	2 weeks: 37.0% (p<0.001 vs vehicle, p=0.014 vs 1 week active treatment) 4 weeks: 57.8% (p<0.001 vs vehicle, p<0.001 vs 1 week active treatment, p=0.029 vs 2 weeks active treatment) Vehicle: 0% Physician Global Assessment of Improvement scores: improved significantly in the 1-, 2- and 4-week active treatment groups compared to vehicle group (p<0.001) AEs: facial irritation reported by most patients in the 1-week fluorouracil (89%), 2-week fluorouracil (98%),	and partly open. High risk for performance and detection bias. Unclear which type of analysis was used: High risk for attrition bias Several data were not reported (eg PGAI, sd on mean percentages etc): selective reporting bias likely This study was supported by Dermik Laboratories.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					4-week fluorouracil (96%), and vehicle (65%) study group		
Kang et al 2003★	To determine the safety and efficacy of adapalene gel 0.1% vs 0.3% vs placebo in the treatment of AK and solar lentigines. Intervention: Daily application of 0.1% or 0.3% adalpene gel or vehicle for 4 weeks, followed by twice-daily applications, if tolerated, for up to 9 months.	Multicentre, randomized, placebo-controlled, active-controlled, assessor-blinded, parallel-group study Randomization: 1:1:1	n=90 participants 69 men, 21 women Mean age: 63, range 43-83 79% white, with skin phototypes I and II	Mean reduction/changes of lesion count at 9 months Physician global assessment improvement Tolerability Adverse events	Adalpene gel 0.1% vs 0.3% vs vehicle <u>Mean reduction of lesion count</u> 0.5±0.9 vs 2.5±0.9 (decrease) vs 1.5±1.3 (increase) P<0.05 <u>Global improvement:</u> 0.3% significantly greater global improvement in AKs than vehicle at 3 (p<0.05), 6 (p<0.01) and 9 (p<0.01) motnhs of treatment 0.1% sign. improvement vs vehicle at 1 (p<0.05) and 6 months (p<0.05)	No follow-up Authors pooled together selected PGAI data, i.e. for clear, marked, moderate improvement to reach statistically significant difference: selective reporting bias likely This study was supported by Galderma Corporation, Texas, US.	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					62% (p<0.01) and 66% (p<0.01) of patients in 0.1% and 0.3% groups were considered to have clear, marked, or moderate improvements, compared with 34% in the vehicle group. After 9 months: proportion of subjects with lighter lesions: 57% vs 59% vs 36% (p<0.05) <u>Adverse events:</u> Higher levels of erythema, peeling, dryness, burning, and pruritus were observed in the adapalene 0.3% and 0.1% groups in comparison with the vehicle group No potentially sAEs		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					were considered related to adapalene gel 0.1% or 0.3% treatment.		
Kaufmann et al 2008★	To compare efficacy, safety, cosmetic outcomes and patient preference of MAL-PDT vs cryotherapy in patients with AK on the extremities. Intervention: Treatment with PDT using MAL 160 mg/g cream or conventional cryotherapy.	Multicentre, randomized, open, active-controlled, intraindividual, right-left comparison study At the baseline visit, eligible patients received treatment with PDT using MAL 160 mg/g cream and conventional cryotherapy, randomly allocated to alternate sides of the body.	n=121 participants with 1343 lesions 78 men, 43 women Mean age: 69 years, range: 39-89	Mean percentage of reduction in lesion counts Cosmetic outcome assessed by investigator and participants Participant preference Adverse events	MAL-PDT vs cryotherapy (PP) <u>Mean percentage reduction in lesion count:</u> 78% vs 88% (p=0.002) <u>Investigator's assessment of cosmetic outcome:</u> 79% vs 56%, (p<0.001) <u>Patients' assessment:</u> 50% vs 22% (p<0.001) <u>Patients' preference:</u> 59% vs 25% (p<0.001) Both treatment regimens: safe and well-tolerated	Sd of mean percentage reduction in lesion counts were not provided: selective reporting bias likely High risk for attrition bias: Sometimes not clear which analysis type was used No blinding: High risk for detection and performance bias Participant's assessment of cosmetic outcomes has negative value if cryotherapy is	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
						better and positive value if MAL-PDT is better. This could influence the participant perception. This study was supported by Galderma.	
Kohl et al 2016	To evaluate the efficacy of PDT with intense pulsed light (IPL λ≥600nm, 16.2 J/cm²) for treating AK of the dorsal hands, inducing neocollagenesis and improving photoaged skin. Intervention: Three treatments of MAL IPL (IPL λ≥600nm, 16.2 J/cm²) or	Prospective, randomized, placebo-controlled, monocentric, within-patient, intra-individual right–left, observer-blinded trial Random allocation of the right and left hand to two treatment groups: MAL and IPL or placebo and IPL Patients received three treatments at 6-week intervals; follow-up: 10 weeks after last treatment	N=37 patients Mean age: 68.84 years±9.28 (range 48-88) 15 men	Complete AK clearance per hand and per lesion at visit 4 (10 weeks after treatment 3) Pain (VAS score) Patient satisfaction with the appearance of the back of their hand (very satisfied – satisfied – moderately	MAL-IPL vs placebo IPL <u>Complete AK clearance per hand:</u> 54.5% vs 3.0%, p<0.0001 (after 10 weeks) <u>Complete AK clearance rates per lesion:</u> 69% vs 15%, p<0.001 Per hand: 55% vs 3%, p<0.001 <u>Mean VAS score</u> at treatment 3: 4.9±2.1 vs 4.3±2.1,	Small sample size Only observer-blinded: performance bias might bias the results	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	placebo IPL.			satisfied – not satisfied) at follow-up Investigator evaluation (0-4, 0= no improvement) 10 weeks after treatment 3 Adverse events	p<0.001 Patient satisfaction: 63.6% vs 21.2% Investigator evaluation: Overall appearance: 2.2±1.7 vs 1.8±1.7, p=0.042 Adverse events: Mild erythema were observed after MAL-IPL Both treatment modalities significantly improved photoaged skin and induced neocollagenesis		
Korman et al 2005★	To evaluate the efficacy and safety of 5% imiquimod cream once daily 3 times per week	Multicentre, randomized, double-blind, vehicle-controlled, parallel-group study	n=492 participants 431 men, 61 women Mean age: 66.3 years, range: 41-93 Imiquimod group: n=242	Participant complete clearance rates for all lesions at 8 weeks post-treatment	Imiquimod vs vehicle Complete clearance rates: 48.3% (117/242) vs	This study was supported by 3M Pharmaceuticals. Skin quality rating not reported for	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	for 16 weeks compared with vehicle in the treatment of AK. Intervention: Application of 5% imiquimod cream or vehicle once daily 3 times per week for 16 weeks.		Vehicle group: N=250	Partial clearance rates for all lesions at 8 weeks post-treatment Median percentage reduction of baseline lesion Adverse events Local skin reactions	7.2% (18/250), p<0.001 <u>Partial clearance rates:</u> 64.0% (155/242) vs 13.6% (24/250), p<0.001 <u>Median percentage reduction of baseline lesions:</u> 86.6% vs 14.3% <u>Adverse events:</u> Itching at target site: 70 (28.9%) vs 10 (4.0%), p<0.001 Burning at target site: 18 (7.4%) vs 2 (0.8%), p<0.001 <u>Local skin reactions:</u> common and occurred in both groups, most frequently reported: erythema, flaking/scaling/dryness and	placebo: selective reporting bias	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					scabbing/crusting		
Lee et al 2005: long-term follow-up of Korman et al and Lebwohl 2004	To obtain long-term safety follow-up data and estimate AK recurrence in patients who completely cleared their AK lesions in the treatment area at the 8-week post-treatment visit in the phase III studies. Intervention: application of 5% imiquimod 3 times per week or twice per week.	Multicentre, randomized, double-blind, vehicle-controlled, parallel-group study	n=146 patients with completely cleared AKs 131 imiquimod treated, 15 vehicle treated Median age: 69 years, range: 45-86 years All but one of the patients were white, and 15.8% (23 of 146) were female and 84.2% (123 of 146) were male. The majority of patients had a skin type classified as either Fitzpatrick II or III.	Recurrence rates Median number of lesions presen Safety Skin quality	Recurrence rate: Patients with imiquimod 3/week: 24.7% (19/77) vs patients with imiquimod 2/week: 42.6% (23/54) No long-term safety issues Skin quality was maintained ->long-term clinical benefit in a majority of patients who experienced complete clearance of their AK lesions.	The study was conducted with financial support from 3M Pharmaceuticals.	2
Kose et al 2008★	To compare the efficacy and safety of topical 3% diclofenac gel plus hyaluronic acid and 5%	Randomized, open-label, active-controlled, parallel-group study	n=49 participants 28 men, 21 women Mean age: 56 years, range: 41-82 N=24 patients: 3%	Investigator and participant global improvement indices at the end of	Diclofenac vs imiquimod group (no sign. differences between the two groups)	No blinding: high risk for performance and detection bias No data reported	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	imiquimod cream in the treatment of AK. Intervention: Application of Diclofenac 3% natrium in 2.5% HA gel once daily or 5% imiquimod cream three times a week for 12 weeks.		diclofenac gel once daily to their lesions N=25 patients: 5% imiquimod cream three times a week for 12 weeks	treatment (IGII and PGII) Local skin reactions and adverse events	IGII: Participant complete response: 12% vs 22% PGII: Participant complete response: 28% vs 23% Incidence of Local skin reactions (N): Erythema: 11 vs 10 Crusting: 7 vs 4 Scaling: 2 vs 3 Dryness: 8 vs 7 Adverse events: Most AEs related to skin, most common: erythema, pruritus, dry skin, and scaling (mild to moderate) 12 patients in diclofenac group an 15 patients in imiquimod group experience at least on AE related to the treatment	for participant partial clearance: high risk for selective reporting bias No information regarding participants' compliance: this might skew the data. Statement regarding potential conflict of interest is missing.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
Krawtchenko et al 2007★	To compare the initial and 12-month clinical clearance, histological clearance, and cosmetic outcomes of topically applied 5% imiquimod (IMIQ) cream, 5% 5-fluorouracil (5-FU) ointment and cryosurgery for the treatment of AK. Intervention: One or two courses of cryosurgery (20-40 seconds per lesion) or application of 5% 5-FU twice daily for 4 weeks or application of 5% imiquimod cream three	Single-centre, randomized, active-controlled, parallel-group study Randomization to one or two courses of cryosurgery (20–40 s per lesion), topical 5-FU (twice daily for 4 weeks), or one or two courses of topical imquimod (three times per week for 4 weeks each)	n=75 participants 61 men, 14 women Mean age: 73 years, range: 57-88 Imiquimod group: N=26 5-FU: N=24 Cryosurgery: N=25	Participant complete clearance rates at test of cure and 12 months after the end of treatment Recurrence at 12 months after the end of the treatment Adverse events Cosmetic outcome 12 months after EOT	Cryosurgery vs 5-FU vs IMIQ: <u>Initial clinical clearance:</u> 68% (17/25) vs 96% (23/24) vs 85% (22/26), p=0.03 <u>Histological total clearance rate:</u> 32% (8/25) vs 67% (16/24) vs 73% (19/26), p=0.02 <u>Recurrence rate:</u> 25% vs 24% vs 16%, p<0.01 <u>Sustained clearance rate of intitially cleared lesions:</u> 28% (7/25) vs 54% (13/24) vs 73% (19/26), p<0.01 <u>Sustained clearance of the total treatment field:</u> 4%	No information regarding blinding: risk for performance and detection and bias Lack of information regarding patients adherence to the treatment No detailed information regarding adverse events: selective reporting bias likely.	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	times a week for 4 weeks (up to two courses).				(19/26) vs 33% (8/24) vs 73% (19/26), p<0.01 Cosmetic outcome: excellent: 4% vs 4% vs 81% (patient and investirgator-assessed) p<0.0001for overall differences for both, investigator's and patients' assessments Adverse events: No sAEs occurred		
Lebwohl et al 2004★	To evaluate the efficacy of imiquimod 5% cream compared with vehicle in the treatment of AK lesions on the face and balding scalp. Intervention: Application of	Multicentre, randomized, double-blind, vehicle-controlled, parallel-group study	n=436 participants 380 men, 56 women Age: range=37-88 Randomization to either imiquimod 5% or vehicle cream. Application: once per day, 2 days per week for 16 weeks	Participant complete clearance rates at 8 weeks post-treatment Partial clearance rates at 8 weeks post-treatment Median percent	Imiquimod vs vehicle Complete clearance rate: 45.1% vs 3.2%; difference: 41.9% (95%CI: 34.9%-49%) Partial clearance rate: 59.1% vs 11.8%; difference: 47.3% (95%CI:	High risk for attrition bias (9 drop-outs in intervention, 11 in control group) Not all outcomes reported: selective reporting bias likely No information	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	imiquimod 5% cream once daily, 2 days per week for 16 weeks.			reduction in baseline lesions at 8 weeks post-treatment Adverse events Application site reactions Local skin reactions	39.5%-55.1%) <u>Median % reduction in AK lesions:</u> 83.3% vs 0% <u>Severe LSR:</u> erythema: 17.7% vs 2.3% scabbing/crusting: 8.4% vs 1.8% flaking/scaling/dryness: 7.4% vs 3.2% <u>At least one AE:</u> 6% (13 of 215) vs 6.3% (14 of 221) Most commonly reported: Itching at target site: 20.5% vs 6.8% Burning at target site: 5.6% vs 1.8% <u>Application site reactions:</u> 33% vs 14.5%	provided regarding patients' adherence This study was supported by 3M Pharmaceuticals.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Imiquimod was well tolerated		
Lebwohl et al 2012★	To investigate the efficacy and safety of a new topical field therapy for AK, ingenol mebutate gel (0.015% for face and scalp and 0.05% for trunk and extremities).	Multicenter, randomized, double-blind, parallel-group, placebo-controlled study Randomization: 1:1 Self-application of ingenol mebutate or placebo once daily for 3 consecutive days for lesions on the face or scalp or for 2 consecutive days for the trunk or extremities	N=547 patients in the face/scalp group (277 received ingenol mebutate gel 0.015%, 270 placebo) N=458 in the trunk/extremities group (N=226 received ingenol mebutate 0.05%, 232 placebo) Mean age: 65.1 years	Participant complete clearance at 57 days Participant partial clearance Median reduction of AKs Mean maximum composite score (0-24)	Ingenol mebutate vs placebo Face and scalp Complete clearance 42.2% vs 3.7%, p<0.001 Partial clearance: 63.9% vs 7.4%, p<0.001 Median reduction of AKs: 83% vs 0% Mean maximum composite score: 9.1±4.1 vs 1.8±1.6 application-site conditions: 19.0% vs 2.6% for ingenol mebutate treated patients: pain (13.9%), pruritus (8.0%), and irritation (1.8%)	Data were pooled Face/scalp group: 3 drop-outs in the ingenol mebutate group, 8 drop-outs in the placebo group Trunk/extremities group: 6 drop-outs in ingenol mebutate group, 5 drop-outs in the placebo group) Risk for attrition bias is low Overall, good adherence in all groups This study was funded by LEO Pharma.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Trunk and extremities Complete clearance 34.1% vs 4.7%, p<0.001 Partial clearance: 49.1% vs 6.9%, p<0.001 Median percentage reduction of AKs: 75% vs 0% Mean maximum composite score: 6.8±3.5 vs 1.6±1.5 application-site conditions: 12.0% vs 2.6% ingenol mebutate group: pruritus (8.4%), irritation (3.6%), pain (2.2%) Adverse events: mild to moderate		
Lebwohl et al. 2013:	To assess 12-month	Observational follow-up study of patients who had	Population: N=108 patients with	Recurrence rate Median time to	12-month recurrene rate:	The study was supported by LEO	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
long term follow up-study of Lebwohl et al 2012 and three other studies	recurrence rates and safety associated with ingenol mebutate gel treatment in patients who previously had achieved complete clearance of actinic keratoses. Intervention: Self-application of ingenol mebutate or placebo once daily for 3 consecutive days for lesions on the face or scalp or for 2 consecutive days for the trunk or extremities.	achieved complete clearance of AK in 4 studies, results are pooled from 4 studies Randomization 1:1	complete clearance of face or scalp lesions; N=76 patients with complete clearance of trunk or extremity lesions. To enroll in the follow-up studies, patients had to have achieved complete clearance in a prespecified 25-cm2 area on day 57 of their original trial.	recurrence Safety	87.2% (face/scalp) and 86.8% (trunk/extremities) Estimated median times to recurrence: 365 days (face/scSlp) and 274 days (trunk/extremities) No safety concerns during follow-up Conclusion: Ingenol mebutate gel applied as field therapy for 2 or 3 consecutive days to treat actinic keratoses produced clinically relevant sustained clearance and long-term lesion reduction.	Pharma.	
Loven et al.	To compare the	Randomized, multicenter,	n=24 patients	Reduction of	0.5% vs 5% FU	Study was only	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
2002	tolerability and efficacy of the 0.5% and 5% fluorouracil creams in the treatment of AKs. Intervention: Application of 0.5% 5-FU cream once daily and 5% 5-FU cream twice daily for 4 weeks.	single-blind, split-face study Patients with ≥6 AK lesions were treated for 4 weeks with 0.5% (once daily) and 5% (twice daily) fluorouracil creams applied to opposite sides of the face/balding scalp for 4 weeks. Application by trained personnel at the 2 study sites, on holidays, weekends, and evenings by the participants.	mean age: 70.4 years±8.5 17 male (81%) Mean number of 21.7 lesions at baseline (10.9 on the right side, 10.8 on the left side of the face) n=11 received 0.5% cream on the left side of the face an 5% cream on the right side of the face, the remaining 10 patients received the treatments in the reverse manner. Eighteen patients prematurely associated discontinued application of treatment: 4 due to irritation with 0.5% fluorouracil cream, 8 due to irritation associated with 5% fluorouracil cream, 4 due to irritation associated with both treatments, and 2 for other reasons. Of the 18 patients who	number of AK lesions (absolute and %) Adverse events Patients' treatment preference (questionnaire)	Reduction of mean lesion counts from baseline to week 8: 8.8 vs 6.1 (p=0.044 Mean absolute change of AKs by side: 0.5% FU: 8.2 on the left side, 9.5 on the right side 5% FU: 6.3 on the left side and 6.0 on the right side %change in the number of AK lesions: 67% vs 47%, not statistically significant but significant for each treatment versus baseline Adverse events: Erythema: 21 (100%) vs 21 (100%)	single-blind (evaluator-blinded): high risk for detection bias/patients compliance might bias the results Small sample size (n=24) Intra-patient design reduces the risk for confounding Study is underpowered: 24 patients were estimated, only 21 were enrolled 20 patients completed the study, one withdrawal due to clinical depression: risk for attrition bias very low.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
			discontinued treatment, 1 withdrew from the study entirely and 17 discontinued treatment applications before completing the trial but completed all required posttreatment visits Sunscreen/moisturizer was used by 86.0% (18/2 1) of patients during the study. Acetylsalicylic acid was used by 33.3% (7/21) of patients, bacitracin/neomycin/polymyxin was used by 28.6% (6/21), and hydrocortisone was used by 23.8% (5/21). These treatments were applied to both sides of the face.		Erosion: 17 (81%) vs 20 (95.2%) Dryness: 15 (71.4%) vs 18 (85.7%) Burning: 14 (66.7%) vs 18 (85.7%) Pruritus: 14 (66.7%) vs 18 (85.7%) Pain: 9 (42.9%) vs 12 (57.1%) Edema: 7 (33.3%) vs 10 (47.6%) Patient preference: 85% (17/20) vs 15% (3/20), p=0.003	Statement regarding potential conflict of interest is missing.	
McEwan et al 1997★	To study the efficacy and tolerability of topical 3% diclofenac in	Single-centre, randomized, double-blind, placebo-controlled, parallel-group study	n=130 participants 73 men, 57 women Age range: 48-87 Active treatment: N=65	Complete response rate Partial response rate	Active vs placebo <u>Complete response rate:</u> 29% (95%CI: 19-42) vs 17%	High risk for attrition bias: N=31 drop-outs in the intervention group and N=16 in	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	2.5% hyaluronic acid gel versus gel containing 2.5% hyaluronic acid alone in the treatment of SK. Intervention: Application of 3% diclofenac in 2.5% HA gel or vehicle twice daily as well as sunscreen once a day for 24 weeks.	Self-application twice/day and also sunscreen once/day for 24 weeks	Control group: N=65	Adverse events	(95%CI: 9-28), p=0.14 <u>Partial response rate:</u> 38% vs 45%, p=0.18 <u>Adverse reactions in treatment groups:</u> 29% (95%CI: 18-42) vs 5% (95%CI: 1-13), p=0.0002 Most common: rashes 3 severe AEs reported, none related to treatment	the control group Dose applied by the patients was variable, despite adherence to the requested frequency of application (size of lesions varied, which influenced the amount of gel needed) The study was supported by Hyal Pharamceutical Australia Ltd. Statement regarding potential conflict of interest is missing.	
Miola et al 2018	To evaluate the effectiveness and safety of 0.5% colchicine (COL) cream vs. methyl aminolaevulinate	Single-center, randomized, open, intra-individual controlled trial AK were located on the forearm	N = 36 participants 50% male (18/36) Age: mean: 70.9±8.6 years Skin types:	Participant complete clearance Participant partial clearance (-	COL vs MAL-PDT: Participant complete clearance: 17% vs 19%	No blinding was performed; thus detection and performance bias is likely Small sample size	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	photodynamic therapy (MAL-PDT) in the treatment of AK and field cancerization. Intervention: COL: Application of colchicine cream 0.5% twice daily for 10 days MAL-PDT: After curettage, application of MAL under occlusion for 3h, then illumination for 8 min using a 630-nm wavelength LED (single session).		I (11), II (21), III (4)	50%) Reduction in AK count Adverse events Patient preference	Participant partial clearance: 44% vs 67% Reductions in AK count: 45% vs. 40% Mild or moderate adverse effects were similar for both groups: 69% vs. 67%; no sAEs reported Most frequently: Erythema and crusts (2%), peeling (1%), oedema (MAL-PDT) Erythema (12%), crusts (5%), peeling (4%), oedema (4%) (COL) Patient preference 28% vs. 60%	Study was conducted in Brazil	
Misiewicz et al 1991★	To compare the efficacy and tolerability of arotinoid methyl sulfone (Ro 14-9706) cream with tretinoin cream in the	Randomized, double-blind, active-controlled, intraindividual study	n=26 participants ≥3 clinically typical AKs 17 men, 9 women Mean age: 75.1 years, range: 55-88 Application twice daily for 16 weeks, each as a 0.05%	Overall response at 16 weeks (Complete response, no response) Mean %	Ro 14-9706 vs tretinoin <u>Complete response:</u> 0 (0%) vs 2 (8%) <u>Partial response:</u> 12 (48%) vs 10 (40%)	1 drop out This study was supported by La Roche Ltd.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	treatment of AK. Intervention: Application of 0.05% Ro 14-9706 cream and tretinoin cream twice daily for 16 weeks.		cream to opposite sides of the face	decrease in the number of lesions at 16 weeks Tolerability scoring	No response: 13 (52%) vs 11 (44%) Worsening: 0 (0%) vs 2 (8%) Mean % decrease: 37.8%±6.5 vs 30.3%±9.9, for each: p<0.01 from baseline, but not sign. different from each other (p=0.58) Tolerability: Ro 14-9706: better tolerated, local inflammation was slight/absent in most patients Tretinoin: severe erythema in 50% and severe scaling in 23% of patients		
Moggio et al 2016	To compare treatment outcomes of DL-MAL-PDT and	Comparative, intra-patient, split-face, single-centre, investigator-blinded, randomized	n=22 patients with 311 AKs 18 men, 4 women	Complete remission rate at 90 days	IMB vs DL-MAL-PDT Complete remission rate: 75.8% vs	Small sample size Open study: performance and	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	ingenol mebutate 0.015% gel (IMB). Intervention: Application of 0.015% IBM overnight for 3 consecutive days and on the 4th day single session of DL-MAL PDT.	clinical trial Randomization of two symmetrical contralateral 25cm² areas to either 3 days IMB treatment cycle or to a single session of DL-MAL-PDT (1:1) Conducted always from 10 to 12 am in sunny days or with mild to moderate cloud coverage DlPDT was administered according to a standard technique: a broad spectrum UVA and UVB organic sun protection (Sun protection factor: 60; UVA protection factor: 20) containing only chemical filters was applied on sun-exposed areas (including treated areas) prior to skin preparation of the treated area with a mildly abrasive pad to remove scales and crusts and to	Median age: 74.6 years, range: 58-84 FST I: 2 (9.1%), FST II: 7 (31.8%), FST III: 12 (54.5%), FST IV: 1 (4.5%) Patients with an incomplete response of multiple lesions after 3 months from EOT were treated with cryotherapy, a second session of DL-PDT, or another treatment cycle with IMB according to the number of lesions and preferences of the patients.	Mean days necessary for wound closure Mean LSR score 1 day after treatment Patient complete clearance rate Patient's scored pain (VAS score) after treatment Cosmetic outcome at 90 days Patient preference	77.9% Mean days necessary for wound closure: 9.45±3.51 vs 4.36±1.18 (p<0.01) Mean LSR score: 9.91±4.24 vs 4.59±4.03, p<0.01 Patient complete clearance rate: 8 patients (36.4%) had all lesions cleared with IMB and 7 (31.8%) with DL-MAL-PDT Mean VAS score: 3.55±1.82 vs 2.05±0.72 (p<0.01) Cosmetic outcome: better with DL-MAL-PDT Preference: 5 vs 17	detection bias likely Self-application by patients might bias the results (compliance): results might be over/underestimate.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
		roughen the surface of the AKs. Soon after a 1 mm thick layer of a cream containing 160 mg MAL g^{-1} was applied and, after 30 min, the 2 h exposure to daylight began.					
Moloney et al 2010★	To assess the effect of topical 1% nicotinamide on AKs. Intervention: Application of 1% nicotinamide or vehicle twice daily.	Randomized, double-blind, placebo-controlled, parallel-group study	n=30 participants 26 men, 4 women Mean age: 74 years, range: 48-89 Randomization to apply 1% nicotinamide (N=13) or vehicle (N=17) twice daily	Mean % of reduction in lesion counts from baseline at 3 and 6 months	Nicotinamide vs vehicle: <u>Mean % of reduction:</u> At 3 months: 21.8±10.0%, p=0.04 vs 10.0±12.0%, p=0.3 At 6 months: 24.6±15.4%, p=0.1 vs 22.4±9.6%, p=0.06	This study was supported by cancer Council NSW, the Dermatology Research Foundation and Epiderm. Selective reporting: appearance of new/subclinical lesions was not reported, but included in the protocol Unclear for how long the verum or vehicle was applied: selective reporting bias	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
						likely.	
Moloney et al 2007★	To compare the efficacy and adverse effects of MAL-PDT with ALA-PDT in the treatment of scalp AK. Intervention: Treatment of two treatment fields two weeks apart and reception of either MAL-PDT or ALA-PDT as first or second treatment. Application of MAL cream for 3h, 20% ALA for 5h.	Single-centre, randomized, double-blind, active-controlled, intraindividual, split-scalp study	n=16 men Mean age: 71 years, range: 59-87 Randomization of treatment fields to receive either MAL or ALA as first or second treatment. MAL cream was applied for 3 h; 20% ALA cream was applied for 5 h.	Field complete clearance rates at 1-month post-treatment Mean reduction in lesion counts at 1-month post-treatment Adverse events Pain (VAS score at 3,6,12,16 minutes) Duration of discomfort Participant preference	ALA-PDT vs MAL-PDT <u>Field complete clearance rate:</u> 40% vs 46.7% = clearing of 87% of AKs treated with ALA-PDT vs 71% treated with MAL-PDT <u>Mean reduction from baseline in AK counts:</u> 6.2±1.9 vs 5.6±3.2 (p=0.588) → no sign. difference in efficacy <u>Adverse events:</u> no AEs apart from mild erythema in all treated sites and superficial erosions in two patients <u>Pain:</u> All patients experienced pain	Small sample size consisting of only men: Interpretation of the results is limited to this study 1 dropout: risk for attrition bias very unlikely Wood's light was used to look at PpIX fluorescence after cream incubation, results not reported: selective reporting bias likely	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					which was of greater intensity in the ALA-treated side at all time points Mean VAS score at 12 min: 38.6±24.4 vs 21.6±15.1 (p=0.012; result of 12 minutes was the most significant one) <u>Duration of discomfort:</u> longer following treatment with ALA when compared with MAL-PDT (p=0.044) <u>Patient preference:</u> 2 (13.3%) vs 10 (66.7%)		
Moriarty et al 1982★	To investigate the efficacy of etretinate (tigason) in the treatment of AK. Intervention:	Single centre, randomized, double-blind, placebo-controlled, cross-over study (2-part study)	n=50 participants 36 men, 14 women Mean age: 71, range: 50-85 Each treatment (etretinate 75 mg per os once daily	Participant complete clearance rates Partial remission rates (50% reduction	Etretinate vs placebo group <u>Participant complete clearance rate:</u> 22.7% (5/22) vs 0%	N=3 dropouts in the intervention group and N=2 dropouts in the control group: Risk for attrition bias unclear	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	75mg etretinate as first or second treatment and placebo consequently either as first or second treatment per os once daily for 2 months.		or placebo) given for two months, order of administration was randomized.	in size of 75% of lesions) Adverse events	Partial remission: 63.6% (14/22) vs 4.3% (1/23) After crossover: Complete or partial response: 84% (37/44) vs 5% (2/42) Adverse reactions: Etretinate group: Dryness of mouth/lips: 86.1%, skin desquamation: 70.4%, rash/itch: 15.9%, nausea: 4.5%, non-specific: 4.5%	Random sequence generation and allocation concealment unclear Unclear if second part of the study was also double-blind Complete or partial response is not separately reported after the crossover (only pooled results) Statement regarding potential conflict of interest is missing.	
Morton et al 2006★	To compare the lesion response and subject preference for topical MAL-PDT vs. cryotherapy	Multicentre, randomized, open-label, active-controlled, intraindividual, right-left comparison study	n=119 participants with 1501 lesions 108 men, 11 women Mean age: 75 years, range: 53-93	Mean % reduction in lesion counts from baseline at 12 and 24 weeks	MAL-PDT vs cryotherapy Mean % lesion reduction from baseline (PP): 86.9%	Study design was open since 2 physically distinct treatments were compared: risk for performance and	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	for the treatment of AK. Intervention: Subjects received both one treatment session of MAL-PDT (illumination with a narrowband red light (average wavelength approximately 630 nm, light dose 37 J/cm²) from a standard light-emitting diode (LED) light source) and a double freeze–thaw cryotherapy.	Lesions with a noncomplete response were retreated after 12 weeks		Lesion complete response rates of baseline lesions at 12 and 24 weeks Participant preference Cosmetic outcomes Investigator preference Mean VAS score (pain) Adverse events	vs 76.2%, p<0.001 (week 12); 89.1% vs 86.1%, p=0.20, week 24 <u>Lesion complete response rate:</u> 85.8% vs 82.5%, regardless of lesion location and severity (week 24) <u>Cosmetic outcome (investigator)</u> Rated as excellent: 70.8% vs 57.5% (week 12), 77.2% vs 49.7%, week 24 <u>Participant preference</u> (cosmetic outcome, efficacy, skin discomfort): 44.7% vs 9.9%, p<0.001 <u>Investigator preference:</u> 52.2% vs 15.9%, p<0.001	detection bias Standard deviations for the mean percentages of reduction in lesion counts were not reported: selective reporting bias likely This study was supported by Galderma France.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Mean VAS score: 5.2 vs 4.0, p=0.24 after 1st session Adverse events: Fewer skin-related AEs with MAL-PDT: 62.2% vs 72.3% Most adverse events were mild to moderate and transient in nature If patients had to be retreated, 70 (64.8%) preferred to receive MAL-PDT relative to 30 (31.5%) who preferred cryotherapy		
Neittaanmaki-Perttu et al 2016	To assess the cost-effectiveness of DL-PDT compared with LED-PDT.	Single-centre, randomized, prospective, controlled trial Washout period: 6 months	n=70 patients with 210 AKs 39 men, 31 women Mean age: 76 years, range: 59-93 years DL-PDT: N=35 LED-PDT: N=35	Patient complete response rate at 6 months Lesion complete response rate	DL-PDT vs LED-PDT Patient complete response rate: 42.9% (15/35) vs 68.6% (24/35), p=0.030	Random sequence generation and allocation concealment unclear Detailed information of the	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
				at 6 months Pain (mean VAS score during and after treatments, 0-10)	Lesion complete response rate: 89.2% vs 72.4%, p=0.0025 Mean VAS score: 1.53 (range: 0.1-6.0) vs 4.36 (range: 0.3-8.4), p<0.001 Conclusion: DL-PDT is less costly and less effective than LED-PDT	intervention is missing: selective reporting bias likely Study was open: performance and detection bias likely This study was supported by a research grant from Orion Pharmos Foundation and from Foundation for Clinical Chemistry Research.	
Ooi et al 2006	To determine the nature of cellular infiltrates induced by the application of imiquimod 5% cream to AK lesions and to	Randomized, double-blind, parallel-group, vehicle-controlled, phase I study	n=18 patients 15 men, 3 women Mean age: 68 years Randomization 2:1 to receive imiquimod 5% cream (N=12) or vehicle cream (N=6)	Patient complete clearance Patient partial clearance Percentage lesion	Imiquimod vs vehicle Patient complete clearance: 45% vs 0% Partial clearance (>50%): 82% vs 50%	Small sample size N=1 lost to follow-up: risk for attrition bias is low Self-application of the treatment by the participants:	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	study cells involved in the cutaneous immune response. Intervention: Application of imiquimod 5% cream or vehicle cream once daily, three days per week for up to 16 weeks.			reduction Local skin reactions Application site reactions Adverse events	<u>% lesion reduction:</u> 75% vs 37.5% <u>Local skin reactions:</u> Erythema: 100% (majority: moderate) vs 67% (majority: mild) Severe erythema: 17% vs 0% <u>Application site reactions:</u> Itching: 67% vs 17% hzeadache and influenza-like symptoms: 25% in imiquimod group No serious AEs reported No results were statistically significant	compliance might differ which might bias the results This study was supported by 3M Pharmaceuticals.	
Ortonne et al 2010	To compare cross polarized light	Randomized, double-blind, vehicle-controlled, parallel-group,	n=12 patients with at least 5 clinically visible AK lesions in a single	Mean reduction Adverse event	Mean reduction in lesion count: Imiquimod group:	Small sample size The study was	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	photography (CPL) and fluorescence diagnosis (FD) using methyl-levulinic acid and illumination with Wood's lamp for their ability to detect subclinical lesions when treated with imiquimod 5% cream. To compare these findings with biopsy results taken before and after treatment with imiquimod 5% cream or vehicle	exploratory pilot study Randomization 3:1 (imiquimod: vehicle) Application to a contiguous 20cm² treatment area on the head prior to the patient's sleeping hours. In the first course, application once daily, 3 days per week for 4 weeks. After a 4-week break, a second course followed.	contiguous 20 cm² area on the head mean age: 66 years±10 9 patients were treated with imiquimod 5% cream and three with vehicle cream		2.0±1.9 at week 4, 0.9±1.4 at week 8, 1.2±2.1 at week 12 and 0.3±1.0 at week 20 Adverse events: 10 AEs in 6 patients: mild n=7, moderate n=3 7AEs possibly/probably related to the study drug	funded by 3M Pharmaceuticals.	
Ostertag et al 2006★	To compare the recurrence rates and the improvement of actinic-damage	Single-centre, randomized, double-blind, active-controlled, parallel-group study	n=55 participants 50 men, 5 women Mean age: 72 years, range: 52-85	Recurrence rates at 3, 6, and 12 months post-treatment	FU group vs LA group <u>Recurrence rates:</u> <u>3 months:</u> 61.5%	Unclear allocation concealment. Self-application of the treatment: lack	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	in patients who were assigned to the topical 5-FU group (FU-group) and those who were assigned to the laser resurfacing group (LA-group). Intervention: Application of 5% 5-FU cream twice daily for 4 weeks or treatment with laser resurfacing (Derma-K laser, Er:YAG mode in combination with CO2 laser).	Follow-up=1 years	N=27 patients were treated with 5-FU 5% cream twice daily for 4 weeks and N=28 with laser resurfacing (Derma-K laser, Er:YAG mode in combination with CO2 laser).	RR of recurrence in FU group vs LA group Mean % lesion cleared Adverse events Additional outcome: Photoaging score (a simplified form of the Glogau score to classify photoaging)	(95% CI: 48.6-71.0) vs 21.7% (95%CI: 10.9-36.3), p=0.005 6 months: 57.7% (95%CI 44.8-67.3) vs 21.7% (95%CI: 10.9-36.3), p=0.011 12 months: 60.0% (95%CI: 46.1-71.3) vs 25.9% (95%CI: 15.4-38.8), p=0.013 RR (95% CI) of recurrence in FU group vs LA: 3 months vs 6 months vs 1 year: 2.83 (1.34-6.45) vs 2.65 (1.24-6.15) vs 2.31 (1.19-4.62) Photoaging score: improvement of 50% vs 65% after 3 months (p=0.39), 50% vs 78% after 6 months (p=0.07) and 43% vs 74% (p=0.07) at 12	of information regarding patients' compliance Standard deviations associated with mean values were not reported: high risk for selective reporting bias	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					months Mean % lesion cleared: 6 months: 79.2% vs 94.4%, p=0.022 12 months: 76.6% vs 91.1%, p=0.048 Side effects: more frequently in the laser group, esp. erythema and hypopigmentation		
Pariser et al 2016	To evaluate the effect of short-incubation time and application method on the safety and efficacy of ALA-PDT versus vehicle-PDT in the treatement of AKs of the face and scalp. Intervention: Aminolevulinic	Randomized, multicenter, vehicle-controlled, investigator-blinded study	n=234 participants ith 6-20 grade 1 or 2 AKs on the face or scalp (ITT) 211 male, 23 female Mean age: 68 years, range: 40-88 FST I: 6%, FST II: 44%, FST III: 43%, FST IV: 6%, and FST V: 0.4% Randomization to one of 5 treatment groups: -broad application of ALA 1,2, or 3 hours before	Median AK clearance rate for subjects at week 12 Complete clearance rate Partial clearance rate Participant complete clearance rate at week 12	Median AK lesion clearance rate: ALA-PDT vs vehicle PDT range: 68-79% vs 7% (p<0.0001) ALA-BA 1 vs ALA-BA2 vs ALA-BA3 vs ALA-SP2 vs VEH at week 8: 35.7 vs 52.2 vs 57.1 vs 57.1 vs 5.7, p<0.0001 Participant	Unclear randomization scheme More men than women among the included participants: this might bias the results, results are limited to this study population (males have a higher tendency toward the	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	acid or vehicle was applied to face/scalp for 1,2, or 3 hours(broad application) or 2 hours (spot application) before blue light activation (10 J/cm²). Re-treatment at week 8 if any AK lesion remained.		blue light (N= 47, N=48, N=47) -spot application of ALA 2 hours before blue light (N=46), Or vehicle before blue light (N=46) 98% (231/235) completed the study	Subject satisfaction and acceptability of treatment (4-point scale) at follow-up Safety	complete clearance rate: range: 17% (8/46) – 30% (14/47) versus 2% (1/46), p=0.0041 ALA-BA 1 vs ALA-BA2 vs ALA-BA3 vs ALA-SP2 vs VEH: Median lesion clearance rate: Week 8: 35.7%±42.0 vs 52.5%±37.2 vs 57.1%±37.0 vs 57.1%±43.8 vs 5.7%±33.5 Week 24: 66.7%±43.4 vs 64.9%±36.3 vs 75.0±46.3 vs 63.4%±44.3 vs 14.3%±44.0 Participant complete clearance (week 8): 6.4% (3/47) vs 14.6% (7/48) vs	development of AKs) Study was only investigator-blinded: Participants compliance might bias the results This study was supported by DUSA Pharmaceuticals.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					17.0% (8/47) vs 8.7% (4/46) vs 0%. ALA-BA2 and ALA-BA3: p<0.05 in comparison to vehicle Participant partial clearance (week 8): 21.3% (10/47) vs 27.1% (13/48) vs 31.9% (15/47) vs 28.3% (13/46) vs 2.2% (1/46), p<0.05 for all interventions in comparison to vehicle Subject satisfaction: 79% (147/185) of subjects treated with ALA-PDT: moderate/excellent improvement from baseline, 35% (16/46) of subjects treated with VEH-PDT		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Safety: For ALA-treated subjects, stinging/burning during light treatment was rated as moderate or severe for 63.8%, 79.2%, 78.7%, and 58.7% of subjects in ALA-BA1, ALA-BA2, ALA-BA3, and ALA-SP2, respectively. Incidence of erythema increased over baseline levels in all treatment groups immediately after light treatment, but appeared to be more severe in theALA groups than in the VEH group (38.3%, 58.3%, 61.7%, 41.3%, vs 6.5%)		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Incidence of edema was greatest for subjects treated with BA ALA for 2 or 3 hours. All ALA groups exhibited an increase in scaling and dryness at the 24- to 48-hour visit, compared to baseline. Additionally: A total of 7 skin cancers were diagnosed within the treated area during the study, including 2 basal cell carcinomas (BCCs), 1Bowen disease, and 1SCC in the 188 ALA-treated subjects, and 2 BCCs and 1 SCC in the 46 VEH-treated subjects.		
Pariser et al 2008	To evaluate the efficacy of MAL	Multicenter, double-blind, randomized, vehicle-	100 Caucasian patients with 4-10 previously	Complete lesion response	MAL-PDT vs vehicle-PDT	4 patients with 36 lesions were	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	PDT using red light-emitting diode light. Intervention: 16.8% MAL cream or vehicle cream was applied under occlusion for 3 hours, illumination with repeated treatment 1 week later (630 nm, light dose 37 J/cm²).	controlled study	untreated non-pigmented, nonhyperkeratotic grade 1 or grade 2 AK lesions on the face and scalp. n=96 patients were randomized n= 49 patients with 363 AK lesions: 16.8% MAL cream applied under occlusion for 3 hours 42 male Mean age: 66.1 years, range: 43-86 n=47 patients with 360 AK lesions: vehicle cream 37 male Mean age: 66.7 years, range: 48-89 illumination with repeated treatment 1 week later (630 nm, light dose 37 J/cm²)	rate 3 months after EOT Patient response rate at 3 months after EOT Adverse events	Lesion complete response rate:86.2% (313/363) 95% CI 82.2%-89.6% vs 52.2% (188/360), 95% CI 46.9% - 57.5% OR= 6.9 (95% CI = 4.7-10.3), p<0.0001 Patient complete response rate: 59.2% (29/49) 95% CI 44.2%-73.0% vs 14.9% (7/47), 95% CI 6.2%-28.3% OR= 13.2 (95% CI = 4.1-43.1), p<0.0001 Adverse events: Number of patients with AEs, including 4 training patients: 98% (52/53) vs 47% (22/47) Erythema: 77% (41/53) vs 15% (7/47)	treated with MAL-PDT during the training period. Study population may not be representative Data may be skewed by the inclusion of data from one center in which none of the 16 patients treated had a CR. The study was supported by PhotoCure ASA, Oslo, Norway.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Skin burning sensation: 72% (38/53) vs 11% (5/47) Pain of skin: 60% (32/53) vs 21% (10/47) Pruritus: 23% (12/53) vs 11% (5/47) Further AEs: Skin edema, scab, skin discomfort, blister, skin exfoliation (more frequent in the MAL-PDT group)		
Pariser et al 2003	To evaluate efficacy and tolerability for PDT with cream containing 160 mg/g MAL or placebo cream in the treatment of patients with multiple mild to moderate AKs.	Multicenter, randomized, double-blind, placebo-controlled study	n=80 patients with 4-10 previously untreated, mild to moderate non-pigmented AKs on the face and scalp 70 men, 10 women Mean age: 65 years, range 31-84 N=42 in the active group with 260 lesions 36 male Mean age: 64 years, range	Complete lesion response rate Patient complete response rate Cosmetic outcome, assessed by patient and investigator on	MAL PDT vs placebo PDT Complete lesion response rate: 89% (209/236) vs 38% (92/241), p=0.001 Patient complete response rate: 82% (32/39) 95% CI: 67%-93% vs 21% (8/38) 95% CI: 10%-	Only patients with previously untreated AKs were included but according to the baseline characteristic table, 76% of patients in the active treatment group and 84% in the placebo group had prior	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	Intervention: Application of the cream under occlusion for 3 hours, lesions were then illuminated by noncoherent red light (570-670 nm, light dose 75 J/cm²). Treatment was repeated after 1 week and response was assessed 3 months later.		31-84 N=38 in the placebo group with 242 lesions 34 male Mean age: 67 years, range 39-84	a 4-point rating scale Safety: Adverse events	37%, p=0.001 Cosmetic outcome: Good correlation between patient and investigator-assessed cosmetic outcome Investigator: MAL PDT: excellent/good: in 31/32 patients (97%) Patient: excellent/good: 29/32 (91%) Neither the investigator nor the patient-rated the outcome as poor. Patient satisfaction with MAL-PDT: 73% in comparison to previous treatments Safety: Any AE:)0% (38) vs	treatment of AKs. This study was supported by a grant from PhotoCure ASA, Oslo, Norway. 3 drop-outs in the active treatment group (withdrawal after first PDT. 1 due to AE, 2 lost to follow-up) Cosmetic outcome was only reported for the active treatment group and 95% CI was only reported for the outcome patient complete response: selective reporting bias likely	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					58% (22) Total number of AEs: 182 vs 49 Total number of locale AEs: 116 vs 28, mild: 61 vs 26, moderate: 49 vs 2, severe: 6 vs 0 Burning sensation of the skin: 27 vs 4 Erythema: 22 vs 8 Crusting: 16 vs 6 Pain on the skin: 10 vs 0 Blisters: 8 vs 2 Skin edema: 6 vs 1 Stinging skin: 6 vs 1 Skin ulceration: 5 vs 0		
Pellacani et al 2015	To investigate safety, efficacy and treatment satisfaction when treating separate areas simultaneously or sequentially	Multicentre, randomized, two-arm, parallel-group, open-label, intraindividual study Randomization (1:1) of two treatment areas to simultaneous or	n=199 patients 169 men, 31 women Mean age: 74.5 years Most patients had been treated previously for AK with cryosurgery on the face (simultaneous 55.1%,	Complete AK clearance at week 8 Percentage reduction in AKs at week 8	Simultaneous vs sequential group <u>Complete AK clearance rate:</u> 52.7% vs 46.9%, p=0.34 Face/scalp: 53.3%	Unclear random sequence generation and allocation concealment Drop-outs: N=9 in the simultaneous	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	with different concentrations of ingenol mebutate gel Intervention: Ingenol mebutate 0.015% gel was self-applied to the face/scalp once daily for 3 days and ingenol mebutate 0.05% gel to the trunk/extremities for 2 days. Patients in the simultaneous group were treated with ingenol mebutate gel in both areas from day 1. Patients in the sequential group treated one area with ingenol	sequential treatment with ingenol mebutate gel (0.015% and 0.05%): Simultaneous group: N=101 Sequential: N=98	sequential 43.6%)	Local skin response score after 3 days of first application Adverse events Patient satisfaction (mean TSQM score, 0-100)	vs 50.0% Trunk/extremities: 52.2% vs 43.6% <u>Percentage reduction:</u> 83.4% vs 79.1%, p=0.20 <u>LSR score:</u> 10.4 vs 9.7, p=0.13 Mean composite LSR score: Face/scalp: 11.8 vs 10.6 Trunk/extremities: 9.1 vs 8.8 <u>AEs:</u> 32 AEs reported by 22 patients in the simultaneous treatment group, 25 AEs by 22 patients in the sequential group comparable between the	group, N=22 in the sequential group: attrition bias likely Study was open: high chance for performance and detection bias Self-application of the treatment: adherence: simultaneous vs sequential: 94.1% vs 87.8% for face/scalp and 97.0% vs 92.2% for trunk/extemities The study was funded by LEO Pharma.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	mebutate gel from day 1 (Visit 1) and then treated the second area 8 weeks later.				groups, most common treatment-related AEs: pruritus and pain at application site <u>Patient satisfaction:</u> mean: 64.6 vs 67.4, p=0.3		
Pflugfelder et al 2015	To confirm the efficacy and tolerability/safety of betulin-based Oleogel-S10 in the treatment of AKs. Intervention: Application of Oleogel S10 or placebo gel either once or twice daily for three months.	Multicenter, placebo-controlled, double-blind, four-arm (A-D), parallel study	n=165 patients Median age: 72 years (A and D), 74 years (B), 69 years (C) 81.%: male Allocation to: Oleogel-S10 once daily (A, N=53) Oleogel-S10 twice daily (B, N=51) Placebo once daily (C, N=25) Placebo twice daily (D, N=28) for three months	Complete clearance rates 1 month after last treatment (week 18) Partial clearance rates 1 month after last treatment (week 18) Tolerability of Oleogel-S10 (assessed by investigator and patients) Adverse events	A vs B vs C vs D <u>Complete clearance rates:</u> 4% vs 7% vs 0 vs 0 <u>Partial clearance rates:</u> 15% vs 18% vs 13% (placebo) Differences not stat. sign. TLNS >75%: 15% vs 15% vs 13% vs 13% <u>Tolerability:</u> Investigator vs patient: very good: 78.8% vs 56.4%, good: 18.2%	Compliance/adherence not reported although bottles of treatment were weighed: selective reporting bias likely This study was funded by Birken AG, Germany.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					vs 34.5% Adverse events: 29 occurred (5 sAEs, unrelated to treatment): most common: pruritus (5 cases)		
Pflugfelder et al 2012	To investigate whether a prolonged treatment with 3% diclofenac in 2.5% HA of 6 versus 3 months adds to the efficacy in treatment for AK and if this will influence tolerability and quality of life (QoL). Intervention: Self-application of 3% diclofenac in 2.5% HA gel twice daily for 3	Multicentre, randomized open-label study Patients in group A were examined during treatment at week 6 and 12, patients in group B additionally at week 18 and 24	n=418 patients with mild to moderate AKs 329 men, 89 women Median age: 69 years, range: 45-90 Randomization to: diclofenac in HA for 3 months (N=204) or 6 months (N=214)	Clinical complete clearance Histopathological clearance Mean tolerability score DLQI score (max. 30 pts)	3 vs 6 month groups: Clinical complete clearance: 40% vs 45% (p=0.38) Histopathological clearance: 30% vs 40% (p=0.16) Mean tolerability score: 3.69 vs 4.22 QoL was significantly improved after treatment in both treatment groups	Open study: performance and detection bias likely No information regarding adherence/patient compliance: compliance might bias the results This study was funded by Shire GmbH, Germany and Almirall, S.A., Spain.	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	or 6 months.						
Piacquadio et al 2004★	To determine the safety and efficacy of PDT using 20% ALA or vehicle and visible blue light for the treatment of multiple AKs of the face and scalp. Intervention: 20% ALA or vehicle in combination with visible blue light PDT 14 to 18 hours later.	Multicentre, randomized, assessor-blinded, placebo-controlled, parallel-group study	n=243 participants 203 men, 40 women Age range: 34-89 ALA group: N=181 Vehicle group: N=62 Randomization to receive vehicle or ALA followed within 14 to 18 hours by PDT Follow-up visits: 24 hours, 1,4,8, and 12 weeks following PDT	Lesion complete response rate at week 8 Participant complete clearance at week 8 Participant partial clearance at week 8 Application site reactions LSR Adverse events	Active vs vehicle <u>Lesion complete response rate:</u> 83% vs 31%; Week 12: 91% vs 25% <u>Complete clearance</u>: 66% vs 11%; Week 12: 73% vs 8% <u>Participant partial clearance:</u> 77% vs 18%; Week 12: 89% vs 13% <u>Application site reactions:</u> Most experience: erythema and edema at treated sites; stinging and burning during light treatment Incidence of headache: 6.6% vs 3.2%, injury: 5.0% vs	Unblinded investigator for safety assessments: high risk for performance and detection bias Per protocol analysis was used: intervention: 7 drop-outs, control: 3 drop-out. Attrition bias likely High risk for selective reporting bias: not all data reported This study was supported by DUSA Pharmaceuticals.	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					1.6%, hypertension: 1.7% vs 0%, skin hypertrophy: 1.7% vs 0% Adverse events:113 AEs, 92%: mild/moderate, 7% severe LSRs: Local responses to ALA PDT: crusting, pruritus, scaling		
Pomerantz et al 2015	To evaluate the long-term efficacy of a single course of fluorouracil cream, 5% for AK treatment. Intervention: Self-application of 5% 5-FU cream or vehicle cream to the face and ears twice daily for	Multicentre, randomized, double-blinded, placebo-controlled trial	n=932 participants Participants applied either topical fluorouracil cream, 5% (N=468, mean age: 71 years±9, 457 men), or vehicle control cream (N=464, mean age: 71 years±9, 459 men) to the face and ears twice daily for up to 4weeks	Complete AK clearance rates AK lesion count reduction at 6 months Hazard ratio (fluoruracil group vs control group) Time to require the first spot AK treatment	5% FU cream vs vehicle Complete AK clearance rates: At 6 months: 38% vs 17%, p<0.01 AK lesion count reduction: 73% vs 24% HR: 0.69 (95% CI: 0.60-0.79)	High risk population was under investigation: might overestimate the results No adherence/compliance of participants reported The study was supported by the	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	up to 4 weeks.				Median time to require the first spot AK treatment: 6.2 months vs 6.0 months	Office of Research and Development Cooperative Studies Program, US Department of Veterans Affairs	
Räsänen et al 2019	To assess the clinical efficacy, tolerability and cost-effectiveness of 5-aminolaevulinic acid nanoemulsion (BF-200 ALA) compared with MAL in DL-PDT for grade I–II AKs Intervention: single DL-PDT treatment using BF-200 ALA on one face side and MAL on the other. After application of sunscreen, curettage of crusts and application of photosensitizer	Multicentre, randomized double-blind, intra-individual trial	N = 69 43 men, 26 women Age: mean 74.8±7.1 (range 49-92) FST: I: 12; II: 42; III: 16 N= 767 AK lesions AK on the face or scalp N=375 (BF-200 ALA), N=392 (MAL-PDT) Previous NMSC: AK: 58% Bowen's disease: 11.6% SCC: 5.8% BCC: 36.2%	Lesion specific clearance at 12 months Participant complete clearance (treatment field completely clear of AK) pain treatment reactions cosmetic outcome	BF-200 ALA vs MAL: Lesion specific clearance: 79.7% (299/375) vs 73.5% (288/392) Participant complete clearance 27.5% vs. 27.5% Pain: Mean: 1.51± 1.61 vs 1.35±1.45 Skin reaction: 26 vs 7 stronger skin reactions Cosmetic outcome: excellent or good in > 90% of cases with both photosensitizers	blinding of the patients with regard to the photosensitizer precursors was not absolute due to the different formulations (gel vs. cream) large sample size	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	for 30 min. Then 2h exposure on the hospital balcony to daylight.						
Reinhold et al 2016	To evaluate the efficacy, safety and cosmetic outcome of BF-200 ALA combined with the BF-RhodoLED lamp ((635 nm± 9 nm) until a total light dose of 37 J/cm² was achieved) for the field-directed treatment of mild to moderate AK with PDT. Intervention: BF-200 ALA or placebo combined with the BF-RhodoLED lamp ((635 nm±	Randomized, double-blind, phase III, multicentre, placebo-controlled, parallel-group study Randomization: 2:1 If residual lesions remained at 3 months after treatment, PDT was repeated.	n=94 patients were enrolled with 4-8 mild-to-moderate AKs in the face and/or on the scalp, 87 were randomized (55 patients: BF-200 ALA, 32 placebo) 79 men, 8 women Mean age: 71.6 years±6.4	Patient complete clearance rate Lesion complete clearance rate Histopathologically confirmed response rate Patient partial response % of treatment-emergent AEs in the two groups Local skin reactions Cosmetic	BF-200 ALA vs placebo after a maximum of 2 PDTs: Patient complete clearance rate: 91% vs 22%, p<0.0001 Lesion complete clearance rate: 94.3% vs 32.9%, p<0.0001 Histopathologically confirmed response rate: 78% vs 22%, p<0.0001 Patient partial response: 94% vs 25%, p<0.0001 Treatment-	5 drop-outs, 2 lost to follow-up: low risk for attrition bias	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	9 nm) until a total light dose of 37 J/cm² was achieved.			outcome at 12 weeks pain (VAS score) patient satisfaction	emergent AEs: 100% vs 69% most commonly reported: application site TEAEs: application site pain, erythema, pruritus, scab, exfoliation, oedema and vesicles LSRs: mild to moderate cosmetic outcome: improved in BF-200 ALA: very good or good: 59% vs 31%, p=0.0032 pain: mean VAS score: 5.5 (95% CI: 4.7-6.9) during the first and 5.8 (95% CI: 4.7-6.9) during the second PDT vs 0.9 (95% CI 0.3-1.6) and 0.3 (95% CI 0-0.6), no sign. difference		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					patient satisfaction: satisfied: very good orn good: 91% vs 45%		
Rivers et al 2002	To evaluate the efficacy and safety of 3.0% diclofenac in 2.5% hyaluronan gel as a treatment for AK. Intervention: Application of 3.0% diclofenac in 2.5% hyaluronan gel or placebo gel twice daily for 30 or 60 days.	Multicentre, double-blind, placebo-controlled, parallel-group study Randomization to 4 treatment groups: A30: 3.0% diclofenac in 2.5% hyaluronan gel 0.5 twice daily for 30 days (N=49) A60: 3.0% diclofenac in 2.5% hyaluronan gel 0.5 twice daily for 60 days (N=48) Placebo: V30 (N=49) and V60 (N=49): 2.5% hyaluronan gel 0.5 g twice daily for 30 or 60 days, respectively.	n=195 patients with ≥5 AKs 73% male	Target lesion number scores (TLNS) Cumulative lesion number scores (CLNS) Lesion total thickness score (TTS) Patient global improvement indices (IGII and PGII) Adverse events	Active treatment vs placebo (60-day groups) TLNS =0: 33% vs 10%, p<0.005 Improvement: 65% vs 34% CLNS=0: 31% vs 8%, p<0.05 Improvement: 54% vs 23% TTS=0: 25% vs 6%, p<0.05 Improvement: 59% vs 31% IGII=4 (complete improvement): 31% vs 10%, p<0.05 PGII=4: 29% vs 10%,	N=11 drop-outs: Risk for attrition bias rather low Unclear random sequence generation and allocation concealment. Results for A30 and V30 were not reported narratively, instead only graphically since they were not statistically significant: selective reporting bias likely Groups were comparable for compliance	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					p<0.05 Adverse events: 10 sAEs: 7 in the active treatment (pruritus, application site reaction, paraesthesia, rash, oedema, contact dermatitis), 6 probably related to treatment; 4 sAEs in placebo group	(measured by comparing expected and actual use of gel and records in the patient diaries) This study was supported by Hyal Pharmaceutical Corporation. Statement regarding potential conflict of interest is missing.	
Salehi Farid et al 2020	To compare the efficacy and safety of topical 5-fluorouracil cream (5-FU) and potassium hydroxide 5% (KOH) in the treatment of AK. Intervention: Application of KOH solution or 5-FU on each side of the	Single-center, randomized controlled, intra-individual, investigator blinded trial Patients had to have at least two AK on each side of the scalp/face	N = 13 patients with 118 lesions (1-month FU) N=10 patients with 83 lesions (3 month FU) Only men Mean age: 75±7.1years (range: 57-84) Mean number lesions: 8.2±3.1 (range 4-15) 68 lesions treated by KOH 50 treated by 5-FU	lesion response AK recurrence rate of the lesion safety (lesion based)	KOH vs 5-FU: Lesion response 81% (55/68) vs. 58% (29/50) (1 month 83% (38/46) vs.70% (26/37) (3 months) Recurrence rate: 8.0% (3/37) vs. 4% (1/24) at 3 months Safety:	Low number of patients short-term follow-up no women were included attrition bias likely due to loss to follow-up	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	scalp/face once a night for 4 weeks For the KOH group, patients were trained to completely cover normal skin with a thick layer of Zinc Oxide ointment to prevent its exposure to normal skin and to apply KOH with a cotton-tipped applicator precisely on the lesion.				Erythema: 19.1% vs. 48% Crust: 23.5% vs. 18% Scaling: 5.9% vs. 58% Swelling: 0 vs. 20% Erosion: 30.9% vs. 8% Ulcer: 98.5% vs. 8%		
Schmieder et al 2012	To determine and compare the safety and efficacy of blue light ALA-PDT vs blue light placebo vehicle in the treatment of AKs of the	Multicenter, randomized, vehicle-controlled, intraindividual, investigator-blinded phase 2 study application of ALA/VEH to both dorsal hands/forearms for 3-	n=70 patients 45 men, 25 women Mean age: 64 years, range: 44-83 years Randomization to receive either ALA or vehicle to both upper extremities. Each subject's left and	Median AK lesion clearance rate at week 12 Complete lesion clearance rate at week 12 Subject	ALA+OCC vs non-occluded ALA vs VEH+OCC vs non-occluded VEH <u>Median AK lesion clearance rate:</u> 88.7% vs 70.0% vs 16.7% vs 5.6%,	Participants were not blinded: performance bias likely Unclear random sequence generation and allocation	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	upper extremities and to evaluate the effect of occlusion after application of ALA versus vehicle. Intervention: Blue light ALA-PDT or blue light placebo PDT with application of ALA/vehicle 3 hours before blue light treatment to both dorsal hands/forearms.	hours before blue light treatment Treatment was repeated at week 8 if any AK lesion remained.	right extremity were randomized to be occluded or without occlusion during the incubation period.	complete clearance rate at week 12 Subject partialclearance rate at week 12 Subject satisfaction Tolerability/safety	p<0.001 <u>Complete lesion clearance rate</u> 88.7% vs 70% vs 16.7% vs 5.6% (stat. sign.) <u>Subject complete clearance:</u> 34.3% vs 20.0% vs 0 vs 2.9% <u>Subject Partial clearance rate:</u> 60% vs 42.9% vs 8.6% vs 5.7% <u>Subject satisfaction</u> (moderate or excellent improvement): 83% vs 60% vs 23% vs 17% <u>Tolerability/safety:</u> Incidence of erythema increased after blue light PDT,	concealment Tolerability/AEs were assessed on a 5/4-point scale. These results are not presented: selection bias likely Three ALA-treated subjects with prior history of multiple SCCs were diagnosed with SCC on the non-occluded arm during study. This study was supported by DUSA Pharmaceuticals.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					more frequent in ALA-treated subjects than VEH (100% vs 88.6%) Incidence of scaling/dryness increased, more frequent in ALA than VEH-treated subjects (91.4% and 85.7% vs 71.4% vs 68.6%) AEs: cellulitis (3%), myalgia (3%) in the ALA-treated subjects		
Segatto et al 2013	To assess and compare the effectiveness of 3% diclofenac sodium associated with 2.5% hyaluronic acid and of 5% 5-Fluorouracil cream for the treatment of actinic keratosis, as well as the	Randomized, parallel-group, comparative study Randomization to receive diclofenac sodium (twice daily for 12 weeks) or 5 %-FU (twice daily for 4 weeks)	n=31 patients, 28 patients completed the study Diclofenac group: N=15 6 men, mean age: 74.4 years±8.31 5-FU group: N=13, 7 men Mean age: 71.54 years±8.6	average number of lesions before and after treatment average reduction of lesions Investigator and Patient Global	Diclofenac vs 5-FU average number of lesions before and after treatment: diclofenac: 13.6 vs 6.6 (p<0.001) 5-FU: 17.4 vs 3.15 (p<0.001) Average reduction: 7 vs 14.25, p<0.001 Investigator	Small sample size 3 drop-outs in 5-FU group: Risk for attrition bias unclear Study is underpowered, estimated sample size was 52 patients.	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	patient's degree of satisfaction and tolerability. Intervention: Application of 3% diclofenac sodium in 2.5% HA gel twice daily or 5% 5-FU cream twice daily for 4 weeks.			Improvement Scores (modified versions) Adverse events	<u>assessment:</u> 66.6% vs 92.3% satisfactory response (improvement >50%) to treatment (p=0.09) <u>Patients satisfaction</u> (highly satisfied): 73% vs 77%, p=0.827 <u>Adverse events:</u> erythema, edema, crusts and itching: sign. Higher in 5-FU group	No information regarding patients' compliance/adherence provided. Compliance might bias the results Blinded investigator only evaluated photographic pictures Unclear random sequence generation and allocation concealment Study was open: performance and detection bias likely	
Serra-Guillen 2018	To compare methyl-5-aminolaevulinate (MAL) cream and 5-aminolaevulinic	prospective, randomized, intra-individual, investigator-blinded clinical trial Eligible patients had to have two	N=50 patients 96% men) Mean age: 72.2 years FST II: 56% mean number of AK lesions was similar in the MAL and BF-200 ALA	Lesion clearance Participant complete response	MAL-PDT vs. ALA-PDT Lesion clearance: 88.1% (600/681) vs. 89.6% (604/674) Pain:	Due to the letter format of the publication insufficient information regarding study characteristics	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	acid nanoemulsion (BF-200 ALA) in the treatment of actinic keratosis (AK) with photodynamic therapy (PDT). MAL PDT vs. ALA-PDT	symmetric, comparable areas of skin (left and right) containing at least eight non-hypertrophic AK lesions on the face or scalp.	areas (13.6 vs. 13.4).	Participant partial response Pain Local skin reaction Patient satisfaction	4.3±2.9 vs. 4.7±2.8 Participant complete response: 56% (28/50) vs. 62% (31/50) Participant partial response: 80% (40/50) vs. 88% (44/50) Local skin reaction 5.4±1.9 vs. 7±1.8 Patient satisfaction 9.0±2.0 vs. 8.8±2.1	available Patients were not blinded which might lead to performance bias	
Seubring et al 2016	The primary objective was to determine the number of new lesions at 9 months after MAL-PDT therapy. Secondary objectives were	Single-centre, randomized, split-face, investigator-blind pilot study Follow-up at 3, 6, and 9 months One side was treated with 1 session of “lesion-by-	n=20 participants with 5-10 AKs in the face or head, 2 symmetrical areas 50 cm² 19 men, 1 woman Mean age: 73.7 years±6.4 years Baseline: mean number of AKs was 8.6 ± 1.6 (LT	Participant complete and partial response at 3 and 9 months Mean lesion reduction at 3 and 9 months	LT vs FT Sign. reduction of lesions in both areas after 3, 6, and 9 months (p=0.009) <u>Participant complete response:</u> 35% vs 25% (3	Small sample size Performance bias likely since participants have not been blinded Split-face design reduces the risk for confounding	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	to determine the number of new lesions at 3 and 6 months after treatment and the percentage reduction of AKs from baseline at 3, 6, and 9 months after MAL-PDT. Intervention: "lesion-by-lesion" MAL-PDT or field-MAL-PDT.	lesion" MAL-PDT (LT side) and the other side with 1 session of field MAL-PDT (FT side).	side) versus 9 ± 1.2 (FT side)	Mean number of new AKs at 3 and 9 months Mean % lesion reduction at 3 and 9 months	months) 43.8% vs 12.5% (9 months) <u>Participant partial response:</u> 35% vs 45% (3 months) 25.0% vs 62.5% (9 months) <u>Mean lesion reduction:</u> 7.0±2.3 vs 7.2±1.8, p=0.981 (3 months) 7.0±1.9 vs 6.7±1.9, p=0.308 (9 months) <u>Mean number of new AKs</u> 0.8±1.4 vs 0.4±0.8, p=0.257 (3 months) 1.3±1.7 vs 0.6±0.9, p=0.016 (9 months) <u>Mean % lesion reduction:</u> 81.1±21.0 vs 80.8±17.5, p=0.669		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					(3 months) 84.3±19.5 vs 76.6±18.5, p=0.006 (9 months)		
Simon et al 2015	To evaluate the efficacy, tolerability and safety of low-dose 0.5% 5-FU and 10% salicylic acid (5-FU/SA) topical solution versus cryosurgery in patients with moderate/severe (grade II/III) hyperkeratotic AKs. Intervention: Application of 5% 5-FU/SA once daily for 6 weeks or up to 2 courses of cryosurgery (3 weeks apart).	Multicentre, exploratory, open, randomized, prospective, two-armed, observer-blinded phase 2 study Randomization to receive 6 weeks of once-daily topical 0.5% 5-FU/SA, or up to two cryosurgery treatments (3 weeks apart).	n=66 patients Mean age: 70.9 years 8 women 33 patients in each treatment arm	Mean change in lesion count from baseline to day 98 Histological AK clearance rate Recurrence rate (6 months posttreatment follow-up) AEs, local skin reactions Physicians global assessment Patients' assessment regarding clinical improvement,	5-FU/SA vs cryosurgery Mean change in lesion count: -5.2 vs -5.7 Histological AK clearance rate: 62.1% vs 41.9% Lesion recurrence rate: 39.4% vs 84.8% Adverse events: rated as severe by the investigator: 24.2% vs 6.1% All drug-related AEs were skin reactions Most common: erythema, scabbing/crusting, burning (more	Small patient population Open study: performance and detection bias likely This study was sponsored by Almirall, S.A.	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
				and cosmetic outcome	frequently in 5-FU/SA group) <u>Physicians global assessment:</u> very good/good outcome: 84.9% vs 83.9% <u>Patients' assessment:</u> clinical improvement =very good/good: 81.8% vs 78.2% cosmetic outcome =good/very good: 84.9% vs 81.3% (week 14); 87.8% vs 80.7% at 6-month follow-up		
Sinnya et al 2016	To compare the safety and preliminary efficacy of three doses of LEO 43204 gel with ingenol mebutate in AKs.	Single-centre, randomized, intrapatient, active-controlled, investigator-blinded Randomization to 0.025%, 0.05% and 0.075% LEO 43204 gel (ingenol	n=40 patients with ≥3 AKs on four separate selected treatment areas on the forearms (12 AKs) 31 men Mean age: 70.3 years, range: 48-91	LSR_{max} Score Mean LSR Score (range 0-24) Adverse events % change in the	LEO 0.025% vs 0.05% vs 0.075% vs ingenol mebutate Mean LSR Score peak at week 1, below baseline by week 8 (all	High-risk cohort (95% had previous history of skin cancer), results are limited to this study and population	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	Intervention: Application of 0.025%, 0.05%, 0.075% ingenol derivate (LEO 43204) or IMB once daily for 2 consecutive days.	derivate) and 0.05% ingenol mebutate gel, application once daily for 2 consecutive days	All patients had previously been treated for AKs, predominantly cryosurgery 95% had a previous history of skin cancer	number of visible AKs Clearance rate	treatments) Mean LSR_{max} score: 9.2 vs 10.1 vs 11.2 vs 10.0 Most frequent AEs (across all treatments), N=172 AEs: application site pruritus (82%), burning sensation (52%), tenderness (30%), and pain Mean % reduction in number of AKs: 73% vs 72% vs 82% vs 73% Clearance rates: 15% vs 28% vs 33% vs 22%	Intrapatient design reduces the risk for confounding Unclear random sequence generation and allocation concealment Performance bias likely since patients were not blinded In one patient the treatment areas were not assigned per-protocol, so that they received only two treatment types (LEO 43204 0.025% and ingenol mebutate) each on two treatment areas. This study was funded by LEO	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
						Pharma.	
Smith et al 2003★	To compare the efficacy and tolerability of PDT using short incubation time, broad area treatment with ALA plus activation with either blue light or laser light to topical 5-FU in the treatment of AK of the face and scalp. Intervention: Application of ALA for 1 hour followed by activation with blue light (Blue) or 595 nm pulsed dye laser (PDL-PDT) or topical 5-FU 0.5% cream once once or twice daily for	Randomized, active-controlled, parallel-group study. Randomization of face/scalp to receive either application of ALA for 1 hour followed by activation with blue light (Blue) or 595 nm pulsed dye laser (PDL-PDT) or topical 5-FU 0.5% cream (once or twice daily for 4 weeks).	n=36 participants 29 men, 7 women Mean age: 61 years	100% lesion clearance Partial clearance rate Global response Tolerability: local skin reaction	5-FU vs Blue-PDT vs PDL-PDT <u>Complete lesion clearance:</u> 50% vs 50% vs 8% <u>Partial clearance:</u> 75% vs 75% vs 42% <u>Global response:</u> complete/almost complete response: 8% vs 17% vs 8% Marked/moderate response: 58% vs 33% vs 42% Erythema was most common, subjects treated with 5-FU: greatest average increase in erythema, average scores for erythema peaked at visit 4	Small sample size Unclear risk of random sequence generation and allocation concealment Lost to follow-up: N=1 (intolerance and severe erythema after only 3 days of 5-FU treatment) Blinding was not stated, but 2 physically distinct treatments were compared: high risk for performance and detection bias Percentages of participants reporting adverse events were not	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	4 weeks.				average score for crusting and erosion peaked at visit 3 for 5-FU (2), other treatments below 0.3	given except for stinging: selective reporting bias very likely. This study was supported by DUSA laboratories. Statement regarding potential conflict of interest is missing..	
Sotiriou et al 2018	To compare short- and long-term efficacy, safety and tolerability of DLPDT with that of CPDT in face and scalp AKs. Intervention: cPDT: After removal of scales/crusts, application of MAL under occlusion for 3h, illumination with red light at a	Multicenter, randomized, intra-individual, assessor-blinded trial only mild-to moderate AK on the face/scalp were included Weather was recorded as sunny in 32 (69.5%) DLPDT sessions, partly sunny during nine (19.5%) and cloudy during five (10.8%) sessions. Mean outdoor temperature during DLPDT sessions was 26.04±1.712 ˚C	N=46 66.7% male Age: mean: 73.5 years (range: 59-84) Selected areas, n (%) Face 28 (61.1) Scalp 18 (38.9) Total lesions per subject: mean +- SD (range) DLPDT: 5.13 +- 1.258 (3–9) CPDT: 4.72 +- 0.935 (3–8) Total lesions (n): DLPDT:236	lesion complete response at 3 and 12 months PDT-associated pain during PDT session Safety/local skin reactions 3 days after treatment patients' preference 3 months after treatment	DL-PDT vs. cPDT lesion complete response rate: 78% (184/236) vs. 80.6% (175/217) (at 3 months) 71.8% (168/236) vs. 73.7% (160/217) (at 12 months) grade-I lesions were higher with DLPDT, while treatment with CPDT resulted to higher rates of cured grade-II lesions at both follow-up visits.	Results were not supported by statistical significance Patients were not blinded, thus, performance bias might be likely	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	peak of 630 nm at 37 J/cm² DL-PDT: Application of sunscreen, then removal of scales and crusts and application of MAL without occlusion. After 30 min, patients spent 2 h in the hospitals' garden.	(range 22–29).	CPDT: 217		Safety: Pain: 1.14 (SD 0.79) vs. 6.06 (SD 1.75) Erythema and edema: 71.64% vs. 100% Patient preference: 82.6% vs. 17.3%		
Stockfleth et al 2011	To compare 5-fluorouracil 0.5% with salicylic acid 10.0% [low-dose 5-FU/SA] with diclofenac 3% in hyaluronic acid and vehicle for the treatment of AKs. Intervention: 0.5% 5-FU/SA once daily, its vehicle or	Randomized, placebo-controlled, double-blind, parallel-group, multicentre trial	N=470 patients with 4-10 AK lesions on the face/forehead or bald scalp Mean age: 71.8 years Patients received topical low-dose 5-FU/SA (N=187) once daily, its vehicle (N=98) or diclofenac 3% HA (N=185) twice daily for a maximum of 12 weeks (randomization: 2:1:2)	Histological clearance rate Patient complete clinical clearance % of lesions cleared Physician's and subject's reported assessment	5-FU/SA vs diclofenac HA vs vehicle (PP) <u>Histological clearance rate:</u> 72% vs 59.1% vs 44.8% <u>Patient complete clinical clearance:</u> 55.4% vs 32% vs 15.1% (at week 20) <u>% of lesions cleared</u>	Drop-outs: N=35 (7.4%), 14 pts in the 5-FU/SA group, 16 pts in the diclofenac group and 5 pts in the vehicle group Patients had a good compliance. This study was funded by Almirall Hermal GmbH.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	diclofenac/HA twice daily for a maximum of 12 weeks.			Tolerability Safety/adverse events	at week 20:74.5% vs 54.6% vs 35.5% Physicians reported assessment: Very good/good: at week 20: 54.9% vs 92.0% vs 73.8% Subject's reported assessment: Very good/good: at week 20: 66.7% vs 93.2% vs 81.6% Treatment-related AEs: 95.2% vs 76.8% vs 84.7% Application-site disorders (mainly burning and inflammation): more frequent with 5-FU/SA, mainly mild to moderate Severe AEs: 1.1% vs 4.9% vs 4.1%, none		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					considered to be related to study drug		
Stockfleth et al 2012: Additional results from Stockfleth 2011	To evaluate the clinical benefit of 5-FU/SA versus 3% diclofenac/HA for the treatment of AK and report patients' assessments of efficacy, tolerability, and practicability. Intervention: 0.5% 5-FU/SA once daily, its vehicle or diclofenac/HA twice daily for a maximum of 12 weeks.	Randomized, placebo-controlled, double-blind, parallel-group, multicentre trial	N=470 patients with 4-10 AK lesions on the face/forehead or bald scalp Mean age: 71.8 years Patients received topical low-dose 5-FU/SA (N=187) once daily, its vehicle (N=98) or diclofenac 3% HA (N=185) twice daily for a maximum of 12 weeks (randomization: 2:1:2)	Lesion recurrence rate Clinical improvement Patients assessment Recommendation of the treatment Side effects	5-FU/SA group vs vehicle vs diclofenac/HA: Lesion recurrence rate: 85.8% vs 79.8% vs 81.0% (12 months) Clinical improvement: good/very good: 93.2% vs 66.7% vs 81.6% Patients' assessment: good/very good: 80.6% vs 91.0% vs 90.5% Recommendation of the treatment: 94.7% vs 79.5% vs 88.7%	See Stockfleth 2011	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Local side effects: more common in 5-FU/SA (inflammation, burning)		
Stockfleth et al 2002	To assess the efficacy and safety of 5% imiquimod cream for the treatment of AK. Intervention: Application of 5% imiquimod cream or vehicle to AK lesions 3 times per week for a maximum of 12 weeks or until lesions had resolved.	Randomized, double-blind, vehicle-controlled, parallel-group study	n=52 participants screened, 36 participants enrolled (N=25 in active group, N=11 in control group) 38 men, 14 women Mean age: 68 years, range: 45-8	Participant complete clearance rates at 14 weeks Participant partial clearance rates Local skin reactions Adverse events Recurrence Compliance	Imiquimod (PP analysis) Participants complete clearance rate: 84% (95% CI: 64-95%) Participant partial complete clearance rate: 8% Recurrence rate: 90% Adverse events (imiquimod group): erythema, oedema, induration, vesicles, erosion, ulceration, excoriation, and scabbing Compliance: high in	Drop-outs: N=16, 25 patients remained in the group treated with imiquimod and 11 in the control group: moderate risk for attrition bias Results are only presented for experimental group, not for the control group LSR and AEs were presented graphically Unclear random sequence generation	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					both group	This study was supported by 3M Pharmaceuticals. Statement regarding potential conflict of interest is missing.	
Stockfleth et al 2016	To evaluate the efficacy and safety of 5-fluorouracil (5-FU) 0.5%/salicylic acid 10% (5-FU/SA) as field-directed treatment of AK lesions. Intervention: Self-application of 5-FU/SA or verhicle once daily for 12 weeks.	Randomized, multicenter, double-blind, vehicle-controlled study Randomization 2:1 (5-FU:vehicle) Treatment was self-administered once daily for 12 weeks	n=166 patients Mean age: 72.2 years±7.1 87.7% male N=111 received 5-FU/SA, N=55 vehicle	Complete clinical clearance 8 weeks after EOT Partial clearance 8 weeks after EOT Proportional reduction from baseline in the total number of AK lesions per patient Safety Physician Global	5-FU/SA vs vehicle <u>Complete clinical clearance:</u> 49.5% vs 18.2% [OR: 3.9 (95% CI: 1.7-8.7), p=0.0006] <u>Partial clearance:</u> 69.5% vs 34.6% [OR: 4,9 (95% CI: 2.3-10.5), p<0.0001] <u>Proportional reduction from baseline in the total number of AK lesions per patient:</u> 78.0% vs 46.9%, p<0.0001	Self-application of the treatment: compliance might skew the results Higher incidence of local skin reactions in the 5-FU/SA group might have compromised the blinding of the study This study was funded by Almirall S.A.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
				Assessment mean scores in the DLQI questionnaire (week 12 and 8 weeks after last treatment) Patient satisfaction	Physician Global assessment: good or very good: 5-FU: week 2 vs follow-up: 45.2% vs 90.2% Vehicle: week 2 vs follow-up: 61.1% vs 75.5% Total scores in the DLQI: week 12: 0.53 vs -0.327, p=0.0052 8 weeks follow-up: -0.667 vs -0.133, p=0.0725 Inicidence of treatment-emergent adverse events: 99.1% vs 83.6% Erythema: 88.9% vs 52.7%, pain: 69.4% vs 41.8%, irritation: 59.3% vs 27.3%		
Stockfleth et al 2018	To compare the efficacy and safety of IMB 0015% gel with	Phase IV, multicentre, randomized, open-label, investigator-blinded, active-controlled, parallel-	N=502 patients Median age: 75 years, range 34-96 85.2% male (428/502)	Participant complete clearance of AK at the end of 1st	IMB vs. DIC Participant complete clearance	There was one case of SCC reported inside the treatment	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	DIC 3% gel. Intervention: IMB: Application of IMB 0.015% gel once daily for three consecutive days or DIC 3% gel twice daily for 90 days; if lesions persisted, another 3-day treatment course was possible (n=255) DIC: Application of DIC gel twice daily for 90 days. (n=247)	group trial (NCT02406014). Patients aged ≥18 years with 4–8 clinically typical, visible and discrete AK lesions within a contiguous 25 cm² treatment area on the face or scalp were eligible.	Median AK baseline count: 6 (range 4-9) IMB 0.015%: n=255 Median age: 75 years (range 49-95) Male: 84.7% (216/255) Median AK baseline count: 6 (range 4-8) DIC: n=248 Median age: 75 years (range 34-96) Male: 85.8% (212/247) Median AK baseline count: 6 (range 4-9)	treatment course (Week 8 or Week 17 for IMB; Week 17 for DIC) Participant partial clearance rate Treatment satisfaction, measured with the Treatment Satisfaction Questionnaire for Medication (TSQM v1.4) Safety	of AK at the end of 1st treatment course: 34.5% vs. 23.5% At last treatment course: 53.3% vs. 23.5% At week 17: 45.1% vs. 23.5% Participant partial clearance rate at the end of 1st treatment course: 57.6% vs. 43.3% At last treatment course: 72.2% vs. 43.3% At week 17: 69.0% vs. 43.3% Treatment satisfaction scores at week 17: greater in the IMB group Safety Incidence of AEs: 49% vs. 41% Incidence of sAEs; 7% vs. 5% Treatment-related AEs: 28% vs. 22% patients receiving	area in the IMB group and considered possibly related to treatment. Thirteen patients in the IMB group and five in the DS group reported skin cancers outside the treatment area: in the IMB group, seven patients had basal cell carcinoma (BCC), of which one reported two events; two patients had Bowen disease; four patients had SCC, of which one reported two events; and two patients reported malignant melanoma. In the DS group, three patients had BCC and two patients had Bowen disease. This study was	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					DS experienced more TRAEs leading to withdrawal from the trial (6% vs. 2% with IMB) Application site erythema: 19.0% (47/247) vs. 11.5% (27/234) Application site scab: 8.1% (20/247) vs. 2.6% (6/234) Application site pain: 6.5% (16/247) vs. 3.4% (8/234)	sponsored by LEO Pharma A/S. Study had an open-label design, however, investigator was blinded. Large sample size	
Stoddard et al 2017	To investigate the efficacy of a topical DNA repair enzyme lotion as field therapy for AKs in comparison to vehicle. Intervention: Self-application of DNA repair enzyme lotion or placebo twice daily for 8 consecutive weeks.	Single-center, randomized, controlled, double-blind stud	N=15 patients with AKs on the face or scalp 10 men, 5 women Mean AK number 16.2 range 5-52	Complete clearance at 8 weeks Local reactions	DNA repair enzyme vs. placebo % Decrease 46.6% vs. 32.7% Satisfaction 85% of patients reported being satisfied No side effects were reported	N=13 of 15 patients completed the trial; small sample size Subject compliance was determined by diary shee	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
Swanson et al 2010★	To evaluate imiquimod 2.5% and 3.75% cream for short-course treatment of the full face or balding scalp. Intervention: Application of imiquimod 2.5%, 3.75% or vehicle cream once daily for 2- week treatmen cycles, with a 2-week, no-treatment interval between cycles.	Two identical multicentre, randomized, double-blind, placebo-controlled studies Randomization to receive imiquimod 3.75%, 2.5% or vehicle cream (1:1:1) applied once daily for two 2- week treatmen cycles, with a 2-week, no-treatment interval between cycles.	n=479 participants 389 men, 90 women Mean age: 64 years	Participant complete clearance rates at week 14 Participant partial clearance rates at week 14 Median percentage of reduction from baseline in lesion counts Patient rest period rates Local skin reactions Adverse events	Placebo vs imiquimod 2.5% vs imiquimod 3.75% <u>Participant complete clearance:</u> 6.3% vs 30.6% vs 35.6% (p<0.001 vs placebo, each) <u>Partial clearance:</u> 22.6% vs 48.1% vs 59.4% (p=0.047, 3.75% vs 2.5%) <u>Median % reductions</u>: 25.0% vs 71.8% vs 81.8% (p<0.001, each active vs placebo; p=0.048 3.75% vs 2.5%) <u>Patient rest period rates:</u> 0% vs 6.9% vs 10.6% <u>Adverse events:</u>	Data from 2 studies were pooled together. Unclear random sequence generation. Study was double-blind, but AEs could be an issue for the concealment of the assigned treatment in some participants: detection and performance bias likely Data for safety were reported differently in the published record and protocol This study was supported by Graceway	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					15 sAEs reported in 12 pts (2 placebo, 5 imi 2.5%, 5 imi 3.75%) Only one of the severe AEs, severe diarrhea in a patient in the imiquimod 3.75% group, considered as treatment-related. Greater incidence of treatment-related AEs in the imiquimod groups (headache, application site pruritus, fatigue, and nausea) <u>Local skin reactions:</u> greater incidence of patients experiencing LSRs, and severe LSRs, with increasing imiquimod	Pharmaceuticals LLC	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					concentration (erythema and scabbing/crusting)		
Peris et al. 2015: Pooled results from Swanson et al. 2010 and Stockfleth et al 2014	To evaluate the efficacy of imiquimod 3.75% using the reduction in lesions from Lmax (the maximum lesion count during treatment) in subgroups of patients with low and high AK lesion counts. Intervention: Patients applied up to two sachets of study cream (250 mg cream/sachet) or placebo to the full face or balding scalp each day for 2 weeks. The first	Post-hoc analysis Patients from two 14-week, placebo-controlled, double-blind studies were subgrouped according to whether they had ≤10 or >10 AK lesions at baseline. Randomization to 4 groups: Imiquimod 3.75% and ≤10 baseline lesions: n=82 Placebo and ≤10 lesions: n=85 Imiquimod 3.75% and ≥10 baseline lesions: n=78 Placebo and ≥10 lesions: n=74	N=167 patients with ≤ 10 lesions and n=152 patients > 10 AK lesions Imiquimod 3.75% and ≤10 baseline lesions: mean age: 62.6 years (sd: 10.6), 75.6% male Placebo and ≤10 lesions: mean age: 62.5 years (sd: 7.9), 72.9% male Imiquimod 3.75% and ≥10 baseline lesions: mean age: 66.6 (sd: 10.2), 89.7% male Placebo and ≥10 lesions: mean age: 66.4 years (sd: 9.7), 91.9% male	Median % reduction in AK lesions from Lmax to end of study Median absolute reduction in AK lesions from Lmax to end of study Median % reductions from AK lesions from baseline to EOS Median absolute reduction in AK lesions from baseline to EOS	Patients ≤ vs > 10 lesions at baseline Median % reduction in AK lesions from Lmax to end of study: for imquimod: 91.5% vs 93.0% Median absolute reduction in AK lesions from Lmax to end of study: for imiquimod: 24.0 vs 10.0 Median % reductions from AK lesions from baseline to EOS: imiquimod: 78.9% vs 82.6% placebo: 25.0% vs 16.7%	The studies were funded by Graceway Pharmaceuticals, LLC; the analyses were funded by Meda Pharma GmbH & Co. KG.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	treatment period was followed by 2 weeks without treatment and then a compulsory second 2-week treatment period.				Median absolute reduction in AK lesions from baseline to EOS: imiquimod: 5 vs 12 placebo: 2 vs 2.5 (p<0.0001 active vs placebo)		
Hanke 2011: Follow-up study (including Lebwohl et al. 2004 and Swanson et al. 2010)	To assess long-term, sustained, complete clearance of actinic keratosis after treatment with imiquimod 3.75% or 2.5% cream using two two-week or three-week cycles of daily dosing. Intervention: Application of imiquimod 2.5%, 3.75% or vehicle cream once daily for 2- week	Follow-up study of two multicentre, randomized, double-blind, vehicle-controlled, parallel-group study	Adults with 5-20 baseline lesions who achieved complete clearance at the 8-week-post-treatment visit	Complete clearance Safety	Imiquimod 3.75% vs 2.5% Complete clearance was sustained for 12 months in 17/42 (40.5%) and 13/39 (33.3%) subjects from the 2-week cycle studies, and in 23/48 (47.9%) and 16/37 (43.2%) subjects from the 3-week cycle studies. No Safety concerns during the follow-up.	See lebwohl et al. 2004 and Swanson et al. 2010	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	treatmen cycles, with a 2-week, no-treatment interval between cycles.						
Szeimies et al 2008★	To evaluate the effect of resiquimod gel in different concentrations on AK lesion clearance. Intervention: Application of resiquimod 0.01%, 0.03%, 0.06% or 0.01% gel once daily three times a week for 4 weeks.	Multicentre, randomized, active-controlled, double-blind, parallel-group study. Randomization to resiquimod 0.01%, 0.03%, 0.06% or 0.1% gel applied once daily three times a week for 4 weeks.	n=132 participants 109 men, 23 women Mean age: 70 years	Participant complete clearance rates after 1 to 2 treatment courses (week 24) Participant partial clearance rates after 1 to 2 treatment courses Participant complete clearance rates after 1 course only (week 12) Discontinuation rate due to adverse events	Resiquimod 0.01% vs 0.03% vs 0.06% vs 0.1% <u>Overall complete clearance rates:</u> 77.1% vs 90.3% vs 78.1% vs 85.3% <u>Complete clearance rates PP:</u> 78% vs 95% vs 76% vs 92% <u>Complete clearance rates after course 1:</u> 40.0% vs 74.2% vs 56.3% vs 70.6% <u>Overall partial clearance rates:</u> 63% vs 81% vs 63% vs 76% <u>Discontinuation due</u>	Small sample size within the randomized groups Patients with persistent lesions received a second course after an 8-week treatment-free interval. PP analysis excluded 59 patients. Unclear allocation concealment suggestion that intensity of local skin reactions may have an association with	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
				or local skin reactions Incidence of severe adverse events and local skin reactions (possibly treatment-related)	to AEs/LSRs: 0% vs 13% vs 31% vs 38% Incidence of sAEs (possibly/probably related): 0% vs 35% vs 16% vs 38% Possibly or probably related non-application site sever AEs: 0% vs 3% vs 13% vs 12%	complete clearance (resiquimod 0.03% and 0.1% groups had higher complete clearance rates) This study was supported by 3M Pharmaceuticals.	
Szeimies et al 2004★	To evaluate the efficacy of imiquimod 5% cream compared with vehicle in the treatment of AK lesions on the face and balding scalp including pretreatment and posttreatment biopsy specimens.	Multicentre, randomized, double-blind, vehicle-controlled, parallel-group study Randomization to either imiquimod 5% cream (N=147) or vehicle cream (N=139).	n=286 participants 248 men, 38 women Age range: 44-94	Participant complete clearance rates at 8 weeks post-treatment Participant partial clearance rates at 8 weeks post-treatment Local skin reactions/ Adverse events	Imiquimod vs vehicle Participant complete clearance rate: 57.1% vs 2.2%, p<0.001 Partial clearance rate: 72.1% vs 4.3%, p<0.001 Adverse events and local skin reactions: 70.7% vs 48.2% of which 46.3% vs	ITT analysis was used, but some lost to follow-up participants were missing for the description 10 dropouts in the intervention group, 18 drop-outs in the control group: attrition bias likely Not all skin quality outcomes were	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	Intervention: Application of imiquimod 5% cream or vehicle cream once/day, 3 days per week for 16 weeks				11.5% were application site reactions Incidence of sever AEs: erythema 30.6% vs 0.7%, scabbing/crusting 29.9% vs 1.4%, erosion/ulceration 10.2% vs 0.7%, and flaking/scaling/dryness: 10.2% vs 1.4% For all: p<0.001	reported: selective reporting bias This study was supported by 3M Pharmaceuticals	
Szeimies et al 2009★	To evaluate the efficacy and tolerability of PDT using a red light-emitting diode (LED) and topical MAL for treatment of multiple AKs. Intervention: Application of MAL or placebo cream 3 hours before	Multicentre, randomized, double-blind, placebo-controlled, parallel-group study Randomization to MAL (N=57) or matching placebo cream (N=58), application to the lesions for 3 hours before illumination with noncoherent red light (LED); treatment was repeated 1 week later.	n=115 participants 91 men, 24 women Age range: 41-90	Participant complete response rates at 3 months after last treatment Lesion complete response rates at 3 months post-treatment Adverse events	MAL PDT vs placebo PDT Participant complete response rate: 68.4% vs 6.9%, OR=39.5, 95% CI: 10.5-149.2, p<0.001 Lesion complete response rates: 83.3% (95% CI: 79.3-86.7%) vs 28.7% (95% CI:	Unclear allocation concealment. This study was supported by Photocure ASA. Statement regarding potential conflict of interest is unclear.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	illumination with noncoherent red light (LED); treatment was repeated 1 week later.			Local skin reaction	24.4-33.4%), p<0.001 <u>Adverse events:</u> 85% vs 60% Most commonly reported treatment-related: pain of the skin: 55% vs 22%, erythema: 52% vs 5%, skin burning sensation: 36% vs 12% 19 pts of MAL PDT group: sAEs related to treatment: pain of the skin (N=13), erythema (N=6), skin burning (N=5), skin exfoliation (N=4), and scab, skin swelling, and swelling of the face (N=1 each)		
Szeimies et al 2010★	To evaluate the efficacy and safety of PDT of	Multicentre, randomized, double-blind, placebo-controlled, interindividual,	n=122 participants with 4-8 mild to moderate AK lesions	Participant complete clearance rate	PDT BF-200 ALA vs placebo PDT	Use of light source depends on the study centre:	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	AK with BF-200 ALA vs placebo. Intervention: Illumination was performed 3 h after the application of the gel with a narrow emission spectrum between 590 and 670 nm and a recommended light dose of 37 J/cm² or an incoherent broad-spectrum light source emitting light between 580 and 1400nm and a light dose of 170 J/cm².	two-armed study Randomization to BF-200 ALA (N=81) or placebo (N=41).	105 men, 17 women Mean age: 71 years, range: 57-85	Lesion complete clearance rate Local skin reactions Adverse events Cosmetic outcomes	<u>Participant complete clearance rate:</u> 64% vs 11%, p<0.0001 (PP) at 12 weeks 49% vs 11% after 1st treatment Lesion complete clearance rate: 81% vs 22% (PP), p<0.0001(1st and 2nd treatment) patient and lesion complete clearance rates after illumination with the Aktilite were higher than with PhotoDyn for BF-200 ALA: (96% and 99%, respectively, PhotoDyn: 53% vs 70%) <u>Cosmetic outcome</u> (investigator-	either Aktilite CL128 (Photocure, Oslo, Norway) or PhotoDyn 750 (Hydrosun Medizintechnik GmbH, Mühlheim, Germany) Unclear allocation concealment. This study was supported by Biofrontera Bioscience GmbH.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					assessed): very good/good: 49% vs 27% Unsatisfactory: 4% vs 22% <u>Adverse events</u>: No AEs due to application of the gel Improvement of skin quality in BF-200 ALA group, especially for 'roughness, dryness, scaling' and 'hyperpigmentation detectable' Less improvement in placebo group Incidence of pain, itching and burning was much higher in subjects irradiated with the Aktilite, severe symptoms		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					mainly observed during/after irradiation with Aktilite: severe burning in 8 subjects and severe pain in 4 subjects, severe burning and pain in 3 subjects 2 symptoms of severe intensity during irradiation with PhotoDyn: itching on the face/forehead and burning on the bald scalp		
Tanghetti et al 2007★	To compare the efficacy and tolerability of imiquimod with 5-FU. Intervention: Application of 5% 5-FU twice daily for 2-4 weeks or	Multicentre, randomized, assessor-blinded, active-controlled, parallel-group study Randomization to receive 5% 5-FU cream (N=19) twice daily for 2 to 4 weeks or 5% imiquimod cream (N=17) twice weekly for 16 weeks	n=36 patients with ≥4 AKs	Total AK count (baseline and week 24) Mean % reduction in lesion counts at week 24 Participant complete and	5% 5-FU vs imiquimod <u>Total AK count:</u> Baseline: 646 vs 490 At week 24: 40 vs 167, p<0.05 <u>Mean % reduction in lesion counts:</u> 94%	Lack of sociodemographic information of patients Unclear random sequence generation and allocation concealment	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	imiquimod 5% cream twice weekly for 16 weeks.			partial (<66%) clearance Physician's grading of erythema Local skin reactions Mean scores for patients discomfort (1-4, 1=very painful)	vs 66%, p<0.05 <u>Participant complete clearance:</u> 84% vs 24%, p<0.01 Participant partial clearance: 100% vs 53% <u>Local skin reactions: similar:</u> erythema, crusting, erosion, and edema erythema persisted longer in imiquimod group Mean levels were moderate in the 5% 5-FU group at week 4, then decreased. In the imiquimod group, mean levels remained mild the entire time of treatment (investigator assessment)	Performance bias likely: dosing schedules were not concealed with a double-dummy technique Values for participants' perception of efficacy were not presented: selective reporting bias likely This study was supported by Valeant Pharamceuticals International	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Mean scores patients' perception of discomfort: week 4: 3.1±1.02 vs 3.9±0.26 week 24: 3.7±0.81 vs 3.9±0.33		
Tarstedt et al 2005★	To compare the efficacy and safety of MAL-PDT given as a single treatment with two treatments of MAL-PDT 1 week apart. Intervention: single treatment with PDT using topical MAL or two treatments 1 week apart.	Multicentric, randomized, open, active-controlled, parallel-group study	n=211 participants with 413 lesions Mean age: 68 years single treatment: N=105, 2 treatments: N=106 82 men, 129 women Thirty-seven lesions (19%) with a non-complete response 3 months after a single treatment were re-treated.	Lesion complete response at 3 months post-treatment (overall, think and thick lesions) Participant complete clearance Patient satisfaction Adverse events Cosmetic outcome	Single vs double treatment Lesion complete response rate: 81% vs 87% *Thin* lesions: 93% (95% CI: 87-97%; repeated therapy: 97%) vs 89% (95% CI: 82-96%) *Thick* lesions: 70% (95% CI: 60-78%) vs 84% (95% CI: 82-94%) Participant complete clearance rate: 89% (95% CI: 81-94%) vs 80% (95% CI: 71-87%)	Unclear random sequence generation. Study was open: High risk for detection and performance bias. PP-Analysis was used: 0 dropouts in intervention, 6 dropouts in the control group. Attrition bias likely This study was supported by PhotoCure ASA. Statement regarding potential	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Patient satisfaction: 68% vs 55% In comparison to cryotherapy: 66% vs 58% Adverse events:42 patients vs 53 patients Treatment-related local AEs: burning sensation of the skin (15% vs 19%), skin pain (9% vs 18%), erythema (9% vs 10%) (mild to moderate, short duration) Cosmetic outcome: excellent in >75% of the lesions in each treatment group	conflict of interest is missing.	
Taub et al 2011	To compare the efficacy and tolerability of PDT using 20% 5-ALA and blue	Randomized, blinded, bilateral intraindividual, vehicle-controlled study	n=15 (11 women, 4 men) with ≥4 AK lesions on the dorsal sides of both hands and forearms Mean age: 55.8 years±9.4	Mean lesion count reductions 4 weeks after second	20% 5-ALA vs vehicle Mean lesion count reductions:	Small sample size Intrapatient design reduces the risk for confounding	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	light versus ALA vehicle and blue light for the treatment of AKs of the dorsal hand and forearm. Intervention: Treatment twice at an 8-week interval by ALA with blue light on one hand and forearm and with ALA vehicle and blue light on the contralateral hand and forearm.			treatment Partial reduction in lesion count (50%) Subject satisfaction Adverse events	58.4±22.2% vs 24.8±20.6%, p=0.0004 <u>50% reduction in lesion count:</u> 73% vs 13%, p=0.0143 <u>Subject satisfaction:</u> 86.7% moderate to satisfied <u>Adverse events:</u> Tolerance levels for ALA and vehicle-treated subjects differed sign. for erythema, edema, and stinging and burning, more frequent side effects on the treated site	Unclear random sequence generation and allocation concealment Only overall subject satisfaction reported, not stratified: selective reporting bias likely The study was funded by Dusa Pharmaceuticals.	
Thompson et al 1993★	To examine the effect of the regular use of sunscreen on the appearance of new solar	Single-centre, randomized, placebo-controlled, parallel-group study Study was conducted in	n=588 white participants randomized, 431 evaluable participants 180 men, 251 women Mean age: 63 years, range: 40-93	Mean reduction/increase in lesion counts at 7 months	Sunscreen group vs base group <u>Mean reduction/increase in lesion counts:</u>	Unclear allocation concealment, blinding of outcome assessment was not stated: unclear	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	keratosis and the disappearance of existing SKs during one summer in Australia. Intervention: Self-application of approximately 1.5ml of sunscreen or base cream to the head and neck or forearm and hand once every morning. Reapplication during the day, if necessary.	Australia	N=210 subjects in the base-cream group (vehicle), N=210 subjects in the sunscreen group	Mean % of lesions remitting throughout the study New lesions Participants' compliance	-0.6±0.3 vs +1.0±0.3 RR new lesions: 0.62 (95% CI: 0.54-0.71) OR remissions: 1.53 (95% CI: 1.29-1.80) Mean % of lesions remitting throughout the study: 25% vs 18% New lesions: 333 vs 508 (1.6 vs 2.3 mean lesions per subject) Compliance: 81% of pat. reported applying the cream daily for at least 80% of the study period; no difference in the amount of cream used by the two groups	risk of detection bias High risk for attrition bias since type of analysis was unclear. Initial number of participants randomized and the number of dropouts were given for the 2 groups together. Reasons for withdrawal were given in a table, which was unclear to interpret. This study was supported by grants from the Victorian Health promotion Foundation, Melbourne, the Skin and cancer Foundation,	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
						Sydney, the Skin and Psoriasis Foundation, Melbourne; the Uoyd William trust, Maryborough; the Sydney Melanoma Foundation; and the Australasian College of Dermatologists. Statement regarding potential conflict of interest is unclear.	
Togsverd-Bo et al 2018	To compare the efficacy and safety of field treatment with methyl aminolaevulinate photodynamic therapy (MAL-PDT) and imiquimod (IMIQ) for AKs in OTRs. Intervention IMQ: Application	Randomized, controlled, intra-individual, assessor-blinded trial All patients received one PDT and one IMIQ treatment at baseline and were seen at 1, 2 and 3 months after baseline. In cases of nonresponding AKs, IMIQ treatment was repeated 2 months after baseline and PDT was	N=35 OTRs with 572 AKs (grade I–III) in two similar areas on the face, scalp, dorsal hands or forearms 22 men, 13 women 33 patients completed all study visits median time since transplantation was 10 years (range 4–32) and graft organs included kidney transplants (n =	complete lesion response (CR) skin reactions treatment preference pain using a numerical rating scale ranging from 0 to 10 (0 = no pain, 10 = worst pain	PDT vs. IMIQ at 3 months Participant complete clearance: 7 vs. 4 CR: median 78% (range 50-100) vs. 61% (range 22-100) CR rates increased from 66% to 78% and 49% to 61% when patients received two	Only investigators had been blinded; performance bias is likely among participants Outcome allograft rejection was not considered in this study	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	of IMIQ 3/week for 4 weeks to the treatment area prior to sleep; leaving it for approx. 6-10 h on the AKs. PDT: After curettage, application of MAL under occlusion for 3h. Illumination with a red LED at 634 nm, 68 mW/cm^{-2} irradiance with a total light dose of 37 J/cm^{-2}.	repeated 3 months after baseline	28), lung transplants (n = 3) and liver transplants (n = 4) patients received immunosuppression with tacrolimus (n = 12), ciclosporin (n = 14), azathioprine (n = 12), mycophenolate mofetil (n = 15), mechanistic target of rapamycin inhibitor (n = 8) and low-dose steroids (n = 31) in a triple (n = 24) or double (n = 9) immunosuppressive regimen	imaginable) cosmesis (poor, acceptable, good, excellent)	treatment sessions/cycles of PDT and IMIQ, resp. According to AK grade, PDT was more effective than IMIQ for thin grade-I AKs (median CR 82% vs. 66%, P < 0.01) and for keratotic grade-II and grade-III AKs (median CR 33% vs. 25%). Skin reactions: median 2.8, range 1–4 vs. 1.7, range 0–4 Emergent AKs: 0.7 (range 0-3) vs. 1.5 (range 0-6) AKs Patient preference and cosmesis were similar for PDT and IMQ Pain: median 5.6 range 3-9 vs. no pain (0)		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					No patients developed hyperpigmentation, hypopigmentation or textural changes.		
Tong et al 1996★	To investigate the efficacy and skin tolerance of β-1,3-D-glucan gel versus placebo in the treatment of SK. Intervention: Application of glucan gel cream or placebo cream twice daily for seven days.	Randomized, double-blind, placebo-controlled, intraindividual study Randomization of one arm to glucan gel, the other to placebo.	n=20 participants 11 men, 0 women Mean age: 69 years, range: 52-93	Mean reduction of lesion counts Tolerability (local skin/adverse reactions)	<u>Mean number of SK:</u> Baseline vs final Glucan: 22.5 vs 16.8 (reduction: 5.7) Placebo: 23.9 vs 15.6 (reduction: 8.3) Not stat. sign. <u>Tolerability:</u> No skin reactions/AEs reported	Small sample size Unclear random sequence generation and allocation concealment An unclear type of analysis was used, unclear risk of attrition bias Lack of information regarding patients compliance Standard deviations associated with mean values were not provided: high risk of selective	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
						reporting bias Statement regarding potential conflict of interest is missing.	
Ulrich et al 2007★	To evaluate the safety and efficacy of imiquimod 5% cream for the treatments of AKs in kidney, heart, and liver transplant recipients. Intervention: Application of 500 mg of imiquimod 5% cream or vehicle cream to the treatment area on three consecutive days per week for 16 weeks.	Multicentre, randomized, double-blind, placebo-controlled, parallel-group study Randomization (2:1) to apply 500 mg of imiquimod 5% cream (N=29) or vehicle cream (N=14) to the treatment area on three consecutive days per week for 16 weeks.	n=43 OTRs (kidney: N=30, liver: N=4, heart: N=9) 29 men, 5 women Age range: 37-76 years	Participant complete or partial clearance rates Adverse events	Imiquimod vs vehicle <u>Complete clearance rates:</u> 62.1% vs 0% Liver: 100% vs 0% Kidney: 65% vs 0% Heart: 42.9% vs 0% <u>Partial clearance rates:</u> 79.3% vs 0% Liver: 100% vs 0% Kidney: 80% vs 0% Heart: 71.4% vs 0% <u>Possibly/probably related AEs:</u> Imiquimod: application site reaction (5/29), fatigue 81/29), headache (1/29), diarrhea (1/29),	Unclear random sequence generation and allocation concealment Little was reported on skin quality outcomes. Several outcomes were reported only for the imiquimod group. Selective reporting bias is likely. This study was supported by 3M Pharamceuticals.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					nausea (1/29), rash (1/29), skin disorder (1/29), and leucopenia (1/29) Erythema and erosion were mild to moderate		
Ulrich et al 2010★	To investigate the effect and graft-related safety of diclofenac 3% gel on clearance rates of multiple AK lesions in organ transplant patients. Intervention: Self-application diclofenac 3% in 2.5% HA or vehicle twice daily for 16 weeks to a defined are of 50 cm.	Randomized, double-blind, vehicle-controlled, parallel-group study Randomization to either active treatment (N=24) or vehicle (N=8), twice daily for 16 weeks	n=32 OTRs (liver: N=6, kidney: N=18, heart: N=8) 31 men and 3 women Age range: 49-77 years	Participant complete clearance at 20 weeks and 24 months Participant partial clearance at 20 weeks and 24 months Average % reduction of lesions at 20 weeks Recurrence rate Adverse events	Diclofenac vs placebo: Complete clearance: 41% vs 0% Kidney: 30.7% vs 0% Liver: 40% vs 0% Heart: 75% vs 0% Partial clearance: 59% vs 16.7% Kidney: 53.8% vs 33% Liver: 40% vs 0% Heart: 100% vs 0% Average % reduction in the individual lesion count: 53% vs 17% Recurrence rate: 55% after an	Unclear random sequence generation and allocation concealment PP was used. 2 drop-outs in intervention and control group: Attrition bias likely No information regarding patients' adherence or compliance to the study medication: over/underestimation of the results might be possible. Discrepancy in the	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					average of 9.3 months <u>Adverse events:</u> mild to moderate erythema, desquamation, itching, inflammation, edema	number of participants completely cleared between abstract and report: selective reporting bias likely This study was supported by Shire Pharmaceuticals.	
Veronese et al 2019	To evaluate the effectiveness of a new class I Medical Device (MD, DNA repair enzymes) for the prevention and treatment of AKs vs traditional sunscreen alone (SPF 100+). MD consists of physical and chemical UVA-UVB filters (corresponding to SPF 100+) and active ingredients with antioxidant and	Single-center, randomized, controlled, inter-individual trial Re-evaluation 3 and 6 months Patients with AK on the face or scalp were included OTRs group included patients with kidney transplants and immunosuppressive treatment for at least 5 years.	N=90 Caucasian patients (62 immunocompetent, 28 OTR) 72.22% were male (65/90) Mean age: 75.98 ± 7.52 median time of immunosuppression of 11.43 years (range 5-35)	Reduction of the mean number of AKs Appearance of NMSC	Medical device and sunscreen at the end of the study (6 months) Reduction of the mean number of AKs: Immunocompetent patients: 54.7% vs. 9.43% OTRs 36.7% vs. 14.3% Prevalence of NMSCs 11.8 vs. 17.18 Incidence of NMSCs 19.7 vs. 32.1	ITT analysis was used Compliance of patients might underestimate the results due to the long application period of 6 months Baseline characteristics were similar between immunocompetent and OTRs patients; except slight differences in gender and use of MD analogs. OTR	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	repairing action, among which the most important is DNA repair complex (a complex of amino acids, acetyl-tyrosine and proline, ATP and vegetable protein hydrolyzate). Intervention Application of the MD or sunscreen twice daily (morning and early afternoon) for 6 months.					patients were more frequently males and MD analogs users; used more frequently sunscreens Allograft rejection was not investigated as outcome Study was not blinded	
Von Felbert et al 2010★	To compare pain intensity, efficacy, safety and cosmetic outcome of MAL-PDT with two different light sources in an	Randomized, double-blind, active-controlled, parallel-group study Randomization: 1:1	n=80 participants 71 men, 9 women Median age: 70 years, range: 56-85	Participant complete and partial clearance at 3, 6, and 12 months Median	VIS + wIRA PDT (with spray cooling) vs VIS + wIRA PDT (without) vs LED PDT with spray cooling vs without spray cooling	Unclear random sequence generation and allocation concealment. Attrition bias likely: PP analysis	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	investigator-initiated, randomized, double-blind study. Intervention: Group 1: MAL-PDT with visible light and water-filtered infrared A (VIS+wIRA) Group 2: MAL-PDT with light from light-emitting diodes (LEDs), with a further division into two subgroups: A, no spray cooling; B, spray cooling on demand. MAL was applied 3 h before light treatment.			maximum pain (VAS score) Cosmetic outcome Adverse events and local skin reaction	<u>Complete clearance rate:</u> *3 months:* 50% vs 59% vs 64% vs 47% *6 months:* 62% vs 72% vs 80% vs 56% *12 months:* 36% vs 57% vs 49% vs 44% <u>Partial clearance rate:</u> *3 months:* 90% vs 97% vs 97% cs 91% *6 months:* 92% vs 97% vs 97% vs 93% *12 months:* 85% vs 92% vs 95% vs 83% <u>Median max pain (VAS score):</u> 50 vs 65 vs 80 vs 60 PDT had to be discontinued for a few seconds in 29% (5 of 17) of the VIS + wIRA PDTs and in 42% (8 of 19) of the LED PDTs	was used, 1 drop-out in the intervention group and 3 in the control group This study was supported by Erwin Braun Foundation.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Cosmetic outcome: after 2 weeks: improved after 3, 6, and 12 months: rated as excellent, no difference between the groups Adverse events: VIS + wIRA PDT and LED PDT: mild to moderate AEs erythema, crusting, skin scaling, blisters, pustules, pruritus, headaches, dizziness More blisters and pustules in the LED PDT group		
Weiss et al 2017	To investigate the efficacy and safety of ingenol disoxate gel (LEO 43204) optimized for the treatment of	Part 1: Phase I, open-label, multicenter, dose-escalation trial investigating up to 6 doses of ingenol disoxate to determine MTD	Part 2: n=197 patients with 5-20 clinically typical, visible and discrete AKs on the balding scalp n=163 were randomized	Percentage reduction in AK count from baseline Complete and partial	0.037% vs 0.05% vs vehicle: Reduction in AK count: 72.7% vs 78.5% vs 12.6%, p<0.001, no stat.	Only men participated: results of this study are only limited to this population and might not be	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	AK on the balding scalp (25cm²-250cm²). Intervention part 2: Application of Ingenol Disoxate 0.037%, 0.05% or vehicle once daily for 2 consecutive days.	Part 2: Phase II, multicenter, randomized, double-blind, parallel group, vehicle-controlled trial Randomization: 2:2:1 to receive ingenol disoxate 0.037%, 0.05% or vehicle gel once daily for two consecutive days	and included in the full analysis all patients were white males median age: 72 years, range 47-89 years 91% FST II-III, 9.2% FST I 90.2% (147 patients) have been previously treated 44.2% (72 patients) had a previous history of NMSC 25 persons did not meet the inclusion criteria, 7 withdrew voluntarily, one was lost to follow-up and one was excluded as randomization was closed.	clearance at week 8 Patients satisfaction (Treatment Satisfaction Questionnaire for Medication TSQM score at week 8, range 0-100) Local skin responses Adverse events	difference between the two doses of ingenol disoxate Lesion complete clearance rate: 21.9% (14/64) vs 29.9% (29/67) vs 3.1% (1/32), p≤0.007 for both active groups vs vehicle Lesion partial clearance rate: 54.7% (35/64) vs 59.7% (40/67) vs 6.3% (2/32), p≤0.001 for both active groups vs vehicle Patient satisfaction: 73.6-87.7 in the two active treatment groups Global treatment satisfaction and effectiveness scores	generalizable. High adherence was observed among the participants. This study was funded by LEO Pharma.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					for both doses of ingenol disoxate were high and superior to vehicle (p<0.001) Local skin responses peaked at day 3, declined rapidly Adverse events: Generally mild to moderate, most commonly: application site pain (48.4% vs 56.7% vs 6.3%), and pruritus (25% vs 26.9% vs 3.1%) 7 patients experienced 8 severe AEs of which 2 were considered to be treatment-related, 3 patients discontinued treatment following		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					moderate AEs within the treatment area that were considered possibly treatment-related		
Weiss et al 2002★	To evaluate the efficacy and safety of 1-, 2-, and 4-week treatments with 0.5% fluorouracil cream versus vehicle control for the treatment of AK. Intervention: Application of 0.5% 5-FU or vehicle cream once daily for 1, 2 or 4 weeks.	Multicentre, randomized, double-blind (treatment versus placebo), open (treatment duration), vehicle-controlled, parallel-group study Randomization to receive 0.5% fluorouracil cream or vehicle (n=58) once daily for 1 (n=38), 2 (n=41), or 4 weeks (n=40).	n=177 participants 152 men, 25 women Age range: 35-89 years	Participant complete clearance rate Physician Global Assessment of Improvement (PGAI) score Mean % reduction in lesion counts Tolerability	0.5% FU 1 week vs 2 weeks vs 4 weeks vs vehicle <u>Participant complete clearance rate:</u> 26.3% vs 19.5% vs 47.5% vs 3.4, stat. sign. vs vehicle <u>PGAI overall score:</u> 3.1 vs 3.2 vs 3.9 vs 0.9, stat. sign. vs vehicle <u>Mean % reduction in lesion counts:</u> 78.5% vs 83.6% vs 88.7% vs 24.4%, stat. sign. vs vehicle <u>Tolerability:</u> facial irritation=	Unclear random sequence generation and allocation concealment. Placebo cream was not used to conceal allocation to 1, 2, or 4 weeks: performance bias likely Different assessment time points were used for 1-, 2-, or 4-week groups: high risk for detection bias standard deviations were	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					most commonly reported AE, usually mild to moderate; dryness, burning and erythema were the most commonly reported clinical signs and symptoms of facial irritation in all groups.	not provided: selective reporting bias likely There was slight difference (p=0.048) in the women ratio (more in 4-week group and less in placebo group) at baseline. Statement regarding potential conflict of interest is missing.	
Wiegell et al 2011★	To compare the efficacy of MAL-PDT with 1.5 vs. 2.5 h of daylight exposure in a randomized multicentre study. Intervention: After gentle lesion preparation and	Multicentre, randomized, assessor-blinded, active-controlled, parallel-group study	n=120 participants 96 men, 24 women Mean age: 72 years, range: 47-95 1.5h treatment arm: N=58 2.5h treatment arm: N=62	Mean lesion response rate at 3 months post-treatment Mean reduction in lesion counts at 3 months post-treatment Mean pain scores (0-10)	1.5 h vs 2.5 h group: <u>Mean lesion response rate:</u> 77.2% vs 74.6%, p=0.57 <u>Mean decrease in the number of lesions:</u> Grade I: 9.8±8.8 vs 9.7±9.5	Blinding was not stated, participants were exposed to light for different periods: performance bias likely Additional outcomes were reported that were not described in	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	application of a sunscreen of sun protection factor 20, MAL was applied to the entire treatment area. Immediately after, patients left the clinic and exposed themselves to either 1.5 hours or 2.5 hours of daylight.			Local adverse reactions: erythema and pustular eruptions Participant's satisfaction	<u>Mean pain score during dPDT:</u> 1.3±1.5, decreased to 0.5±0.7 the day after treatment, no differences between 1.5h and 2.5h groups more intense pain sensation seen on sunny days ($p=0.002$, $r^2=0.12$) higher maximal pain score during daylight exposure ($p=0.030$, $r^2=0.04$) <u>Adverse reactions:</u> day 2: majority of patients erythema: 33% mild, 34% moderate, 7% severe; pustular eruption: 22% mild, 5% moderate and 2% severe; no differences between the 2 groups	the methodological part: unclear risk of selective reporting bias This study was supported by Department of dermatology, Bisebjerg Hospital, Copenhagen	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Increased severity of erythema was related to an increased light dose (p<0.001, r2=0.24) and more sunny weather conditions (p=0.002, r2=0.28) <u>Satisfaction:</u> after 2 days: 87% of patients were very satisfied, 12% moderately satisfied, 2 patients were unsatisfied after 3 months: 72% very satisfied, 24% moderately satisfied, 5 patients were slightly satisfied		
Wiegell et al 2012: Follow-Up study Wiegell 2012★	To compare the efficacy of MAL-PDT with 1.5 vs. 2.5 h of daylight exposure in a randomized	Multicentre, randomized, assessor-blinded, active-controlled, parallel-group study	n=120 participants 96 men, 24 women Mean age: 72 years, range: 47-95 1.5h treatment arm: N=58	Mean lesion response rate Complete response	Grade I vs grade II vs grade III: <u>Mean lesion response rate:</u>	This study was supported by Department of dermatology, Bisebjerg Hospital, Copenhagen	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	multicentre study. Intervention: After gentle lesion preparation and application of a sunscreen of sun protection factor 20, MAL was applied to the entire treatment area. Immediately after, patients left the clinic and exposed themselves to either 1.5 hours or 2.5 hours of daylight.		2.5h treatment arm: N=62		75.9% vs 61.2% vs 49.1% (p<0.0001) No difference between 1.5h and 2.5h groups Complete response: 73% vs 63% vs 55% Complete response rate: 75.9% vs 61.2% vs 49.1%	Blinding was not stated, participants were exposed to light for different periods of time: performance bias likely	
Wiegell et al 2009★	To compare response rates and adverse effects after PDT using conventional 16% and 8% MAL	Randomized, double-blind, active-controlled, intraindividual study	n=30 participants 26 men, 4 women Mean age: 71 years, range: 51-94	Mean reduction in lesion counts Absolute decrease in lesion count	16% MAL-dPDT vs 8% MAL-dPDT <u>Mean reduction in lesion count:</u> 75% vs 79%	Intrapatient design reduces the risk for confounding Number of participants and average time spent	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	with home-based daylight exposure in treatment of AK. Intervention: Treatment with 16% and 8% MAL-PDT in two symmetrical areas on the face or scalp after application of sunscreen. Immediately after, patients left the hospital with instructions to spend the remaining day outside at home in daylight.			Lesion complete response rate Mean complete response rate according to AK grade Pain scores Erythema scale Participant's preference	Absolute decrease: 429 vs 420 Lesion complete response rate: 76.9% vs 79.5%, p=0.37 Mean complete response rates: grade I: 80.2%, grade II: 63.8%, grade III: 39.3% Mean maximum pains score during daylight exposure: 3.7±2.4 vs 3.6±2.4, p=0.74 Pain intensity increased during daylight exposure Erythema: All patients developed erythema and crusting after treatment, no difference between	outside were different between the abstract and published report. Confusion regarding the type of efficacy outcome reported in the abstract. High risk for selective reporting bias Linear association was found between increasing light dose and increasing response rate ($p=0.005$, $r^2=0.27$)	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					the two groups Preference: 17 patients had previously been treated with conventional PDT, 12 (71%) preferred dPDT		
Wiegell et al 2008★	To compare response rates and adverse effects after MAL-PDT using conventional red light-emitting diode (LED) light vs. daylight. Intervention: Intervention: Treatment with MAL-PDT in two symmetrical areas. One area was illuminated by red LED light (37 J cm^{-2}) after 3h incubation	Single center, randomized, assessor-blind, active-controlled, intraindividual study	n=30 patients 23 men, 7 women Mean age: 78 years, age range: 63-90	Mean and absolute reduction in lesion counts at 3 months post-treatment Pain (scale: 0-10) Adverse events Participant's preference	Daylight vs LED Mean reduction of AK lesions: 79.0%±17.5% vs 71.1%±22.9%, p=0.13 Absolute decrease: 8.4±5.4 vs 8.0±5.6, p=0.50 Pain: 2.0±1.9 vs 6.7±2.2, p<0.0001 Adverse events: Both treatment areas developed erythema and crusting, most	The 2 treatments were physically different: performance bias likely N=1 drop-out: low risk for attrition bias No outcomes specified in the protocol: unclear risk of selective reporting bias This study was supported by The Eva and Henry Fraenkels	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	with MAL under occlusive dressing. The other area was treated with daylight for 2.5h after the MAL cream had been under occlusion for half an hour.				severe in the sun-exposed area in 10 patients (42%), in the LED area in 5 patients (21%) Preference: 62% daylight exposure, 14% LED	Memorial Foundation.	
Wolf et al 2001★	To explore the therapeutic potential of 3% diclofenac in 2.5% hyaluronan gel. Intervention: Application of 0.5 g diclofenac 3% in 2.5% HA or vehicle twice daily in each 5 cm² treatment area for 90 days.	Multicentre, randomized, double-blind, placebo-controlled, parallel-group study Patients received either active treatment (n=58, 3% diclofenac gel in 2.5% hyaluronan gel) or inactive gel vehicle (hyaluronan) as placebo (n=59).	N=120 patients were enrolled, 118 received treatment, 117 analyzede	TLSN (target lesion number score) CLNS (cumulative lesion number score) Investigator improvement indices (IGII) Patient improvement indices (PGII) Adverse events	Active treatment vs placebo TLSN=0: 50% vs 20%, p<0.001 CLNS=0: 47% vs 19%, p<0.001 IGII=4: 47% vs 41%, p<0.001 PGII=4: 41% vs 17%, p<0.001 Adverse events: At least 1 AE: 90% vs 81%, most related to skin	Unclear random sequence generation and allocation concealment. ITT analysis was used; 14 drop-outs in the intervention group, 8 drop-outs in the control group. Reasons were reported. Unclear risk of attrition bias. 96 patients were available at follow-up	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					(pruritus: 55% vs 49%, application site reaction: 34% vs 20%, dry skin: 36% vs 17%)	This study was supported by Hyal Pharmaceutical Co. Statement regarding potential conflict of interest is missing.	
Yang et al 2018	To evaluate the efficacy and safety of topical SR-T100 gel in treating AK. Intervention: Application of SR-T100 (n=76) vs. vehicle (n=37) to a continuous or non-continuous 25 cm² (approx. 0.3-0.5g study gel) under occlusion of at least 8h.	Multicenter, randomized, double-blinded phase III trial from Taiwan Patients with at least two clinically visible, non-hyperkeratotic and non-hypertrophic AK were enrolled with one of the lesions having a diameter greater than 4 mm. Location: arm, chest face, scalp Punch biopsy was performed on one of the AK to confirm the diagnosis	N=123 patients were recruited, n=113 were randomized SR-T100 vs. vehicle Total lesion count: 220 vs. 91 53.6% vs. 50.5% of lesions were larger than 1 cm Male: 67.1% (51/76) vs. 61.1% (22/36) Mean age: 76.6 years ± 8.8 vs. 76.7 years ± 9.2	Participant complete clearance at 8 weeks after EOT Participant partial clearance (75%) at 8 weeks after EOT geometric mean target lesion size changed Local skin reactions (ulceration, erythema, dryness, burning/ stinging,	SR-T100 vs. vehicle Participant complete clearance: 32.39% (23/71) vs. 17.14% (6/35); OR: 2.14 Participant partial clearance: 71.83% (51/71) vs. 37.1% (13/35); OR: 4.36 geometric mean target lesion size changed: 314.30 mm² to 1.95 mm² vs. 274.96 mm² to 15.50 mm² Adverse events: 55.3% (42) vs. 51.4% (19) reported	Taiwanese population 1 participant was excluded from the vehicle group analysis; however, in the safety analysis the results referred to 37 patients instead. Thus, the vehicle results may be over- or underestimated for the respective analysis. No information regarding random sequence generation or allocation concealment	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
				erosion, and edema) graded as 0 = absent, 1 = mild, 2 = moderate and 3 = severe Pain and itching were measured on a VAS ranging from 0-10	at least one AE sAEs: 13.2% (10/76) vs. 13.5% (5/37); not considered to be treatment-related Local skin reactions: Erythema: 43.4% vs.18.9%), burning/stinging: 36.8% vs. 8.1% erosion: 34.2% vs. 5.4% VAS pain and itching scores were rated as mild during the treatment period	reported. No statistically significant difference in the baseline characteristics of the intervention and control group.	
Zane et al 2016	To compare treatment outcomes of MAL-PDT and IMB. Intervention: Two symmetrical contralateral areas with a	Single-centre, randomized, open-label, intraindividual, split-face study Randomization of two symmetrical contralateral areas with a similar number of AKs to 3 days of an IMB treatment cycle	n=35 patients with 437 lesions Mean age: 68.0 years, range: 52-90 34 men, 1 woman	Complete lesion response at 3 months Mean % reduction at 3 months Participant complete	IMB vs MAL-PDT <u>Complete lesion response:</u> 62.9% vs 67.1%, n.s. <u>Mean % reduction:</u> 65.8±33.0 vs 67.6±31.2, n.s.	Clear description of the IMB intervention is not provided (e.g. dosage): selective reporting bias likely Small sample size	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	similar number of AKs were either treated with a single session of conventional MAL-PDT or 3 days of daily application of IMB.	or a single session of MAL-PDT.		response at 3 months Pain (mean VAS score) Local skin reaction (LSR) score Cosmetic outcome Patient preference Time to healing (days)	Participant complete response: 42.9% vs 31.4%, n.s. Pain: 3.74±2.28 vs 5.46±3.05, p<0.01 LSR score: 11.17±2.28 vs 5.46±3.06, p<0.01 Cosmetic outcome: Excellent: 31.4% vs 57.1% Good: 68.6% vs 42.9%, p<0.05 Patient preference: 40% vs 60% Time to healing: 12.91±4.86 vs 8.20±2.75, p<0.01	Intrapatient design reduces the risk for confounding Study was open: performance and detection bias likely MAL-PDT is approved for a 2nd treatment cycle, which might enhance the results	
Zane et al 2014a	To compare the treatment results and cost-effectiveness of MAL-PDT and 3% diclofenac plus	Single-centre, open-label, prospective, nonsponsored, randomized controlled clinical trial	n=200 patients with 1674 AKs 58 women Age range: 42-93	Overall lesion response rate Patient complete remission	MAL-PDT vs DHA Overall lesion response rates: 85.9% vs 51.8%, p<0.0001	Study was open: performance and detection bias likely 42 patients needed	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	hyaluronic acid gel (DHA) twice daily for 90 days for the treatment of multiple AKs of the face and scalp. Intervention: Self-application of 0.5g Diclofenac 3% in 2.5% HA twice daily for 90 days or conventional MAL-PDT.	Randomization 1:1 (MAL-PDT:DHA, N=100 in each arm)		rate/partial remission rate after 90 days Cosmetic outcome (patient- and investigator-assessed) Patients' overall satisfaction	<u>Patient complete remission rate:</u> 68% vs 27% <u>Patient partial remission rate:</u> 30% vs 48%, p<0.0001 <u>Cosmetic outcome:</u> Investigator-assessed: excellent: 64% vs 17% Good: 31% vs 75% Fair: 4% vs 8% p=0.0003 Patient-assessed: excellent: 70% vs 28% Good: 25% vs 68% Fair: 4% vs 4% N=2 missing data p=0.0007 <u>Patients' satisfaction:</u> Fair: 2% vs 53% Good: 38% vs 39% Excellent: 59% vs	retreatment with MAL-PDT because of remaining lesions 3 months after the first treatment N=2 lost to follow-up: low risk for attrition bias DHA group self-applied the gel twice daily: compliance/adherence might bias the results; compliance is not reported	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					6%, p<0.0001 N=3 missing data		
Zane et al 2014b	To compare CO_2 laser ablation with cryotherapy in the treatment of isolated AKs of the face and scalp. Intervention: Cryotherapy or laser: Cryotherapy: a cotton tip soaked with liquid nitrogen was applied on the lesion surface for 10–20 s until a 1–2-mm perilesional frozen rim was achieved. Laser: A single session of CO^2 laser ablation	Single-centre, open-label, prospective, non-sponsored, randomized, controlled clinical trial Randomization to receive CO^2 laser ablation or cryotherapy (1:1) CO2 laser ablation arm: N=102 Cryotherapy arm: N=98	n=200 patients with ≤4 AKs of the face and scalp (543 AKs total) 72 women Age range: 39-9	Lesion complete remission (after 90 days) Participant complete and partial remission (after 90 days) Recurrence rate Cosmetic outcome (patient- and investigator-assessed) Patient satisfaction Safety	Cryotherapy vs CO_2 laser ablation <u>Lesion complete remission rates:</u> 78.2% vs 72.4% Thicker lesions were more responsive to cryotherapy (p=0.034) <u>Participant partial remission:</u> 19.6% vs 21.4% <u>Participant complete remission:</u> 71.6% (73) vs 65.3% (64) At 12 months: 53 vs 14 <u>Recurrence rate:</u> 27.4% vs 78.1%, p<0.0001	Study was open: performance and detection bias likely	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	was delivered. Two to three laser passes resulted in epidermal ablation. The laser was applied in char-free mode, using 500- µs pulses at a power of 2.3 W with a 50-Hz repetition rate. CO^2 laser treatment was done under local anaesthesia with lidocaine 2%. Following either treatment gentamicin 0.1% cream was applied twice daily until the defect was completely re-epithelized.				Cosmetic outcome: *Investigator:* Excellent: 50.7% vs 48.4% Good: 35.6% vs 43.8% Fair: 13.7% vs 7.8% p=0.430 *Patient:* Excellent: 58.9% vs 50.0% Good: 34.2% vs 45.3% Fair: 6.8% vs 4.7% p=0.401 Patient satisfaction: fair: 0% vs 18.4% Good: 40.2% vs 57.1% Excellent: 59.8% vs 24.5%, p<0.0001 Safety: cryotherapy: erythema, edema, hemorrhagic vesicles and blisters, erosions, crusts		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					CO2 laser: erosions and crusts		

Remarks and notes:

Overview excluded records (n=88), publications may be excluded due to several reasons, those publications are labelled with a †

Unclear regarding study design or randomization (n=14)	Defined efficacy outcomes not reported, outcomes unclear (n=45)	Combination therapies assessed (n=34)	No original data reported, doublettes (n=3)	Small sample size (n=1)
• Berlin 2008† • Campione 2010 • Dragieva 2004† • Galitzer 2011 • Grimaître 2000 • Jenni 2016† • Lawrence 1995 • Nguyen 2016 • Perras 2004† • Puviani 2017 • Scarpa 1970 • Serra-Guillen 2009 • Thai 2004 • Weiss 2013	• Babilas 2007 • Babilas 2008 • Braathen 2009 • Buinauskaite 2014 • Buinauskaite 2013 • Calzavara-Pinton 2016 • Carducci 2015 • Choi 2015† • Choi 2017† • Deonizio 2011 • Di Nuzzo 2015 • Edwards 1990 • Edwards 1986 • Ericson 2004 • Faghihi 2016 • Falagas 2006	• Alexiades 2017 • Bercovitch 1987 • Berlin 2008† • Berman 2014a • Berman 2014b • Choi 2015† • Choi 2017† • Dragieva 2004† • Eibenschutz 2016 • Goldenberg 2013 • Hashim 2016 • Helsing 2013 • Hoover 2014 • Huyke 2009 • Jenni 2016† • Jorizzo 2004	• Gupta 2015 • Swanson 2013† • Perras 2004†	• Seckin 2009

Unclear regarding study design or randomization (n=14)	Defined efficacy outcomes not reported, outcomes unclear (n=45)	Combination therapies assessed (n=34)	No original data reported, doublettes (n=3)	Small sample size (n=1)
	• Fariba 2006 • Freeman 2003 • Haddad 2011 • Hadley 2012 • Jury 2005 • Klein 2015 • Kurwa 1999 • Lacour 2015 • Langan 2006† • Levy 2001 • Nashan 2013 • Neittaanmaki-Perttu 2016 • Neittaanmaki-Perttu 2014 • O'Gorman 2016 • Patel 2014 • Pirard 2005 • Radakovic-Fijan 2005 • Rubel 2014 • Samorano 2015 • Scola 2012 • Serra-Guillen 2011 • Siller 2009 • Sotiriou 2012 • Sotiriou 2009 • Surjana 2012 • Szeimies 2002 • Touma 2004† • Watson 1986	• Jorizzo 2006 • Jorizzo 2010 • Ko 2014 • Langan 2006† • Lev-Tov 2016 • Nissen 2016 • Nissen 2017 • Serra-Guillen 2012 • Shaffelburg 2009 • Song 2015 • Spencer 2016 • Swanson 2013† • Tan 2007 • Tanghetti 2015 • Togsverd-Bo 2012 • Togsverd-Bo 2015 • Touma 2004† • Van der Geer 2009 • Zhu 2018		

Unclear regarding study design or randomization (n=14)	Defined efficacy outcomes not reported, outcomes unclear (n=45)	Combination therapies assessed (n=34)	No original data reported, doublettes (n=3)	Small sample size (n=1)
	• Zeichner 2009			

4.1.5. Literature

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4.2. Question III.2. Which combination treatments are recommended for AK?

(Frage III.2. Welche Kombinationstherapien sind für AK geeignet)

4.2.1. PICO

PICO scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Patients with actinic keratosis	Any intervention such as: • Cryotherapy • Curettage or shave-excision	placebo, vehicle only, active control therapy	At least one of the following **efficacy** outcomes: • Mean reduction in lesion counts from baseline to assessment (indicated as

PICO scheme			
	• Laser • Diclofenac Natrium 3% in 2.5% Hyaluronic Acid • 5-FU, 5-FU and 10% SA • Ingenolmebutate • Ingenoldisoxat • Imiquimod • Resiquimod • MAL-PDT, ALA-PDT • Retinoids		absolute values or percentages) • Participant complete clearance (rate of participants with a complete clearance of all lesions within a predefined field) • Participant partial clearance (rate of participants with 75% reduction in the AK lesions within a predefined field) **Optional:** safety, tolerability, cosmesis optional

4.2.2. Databases, search strategy, number of results

Databases	Searching strategy	Date	Number of results
1. Search			
Medline	(keratos*[Title] AND (actinic[Title] OR solar[Title] OR senil*[Title] OR hyperkeratos*[Title])) AND (randomized controlled trial[Title/Abstract] OR controlled clinical trial[Title/Abstract] OR random* [Title/Abstract] OR clinical trial [Title/Abstract] OR placebo[Title/Abstract] OR trial[Title/Abstract]) NOT case report AND (German[language] OR English[language]) filter article types to “systematic review” or “meta-analysis”	05 January 2021	29

Databases	Searching strategy	Date	Number of results
Remarks and notes: -			

4.2.3. Selection criteria

Literature selection	
Total number of results	29
Inclusion criteria	Systematic reviews, meta-analysis
Exclusion criteria	Case reports, small sample size (n<10), studies without relevant outcomes
Number of results after title and abstract screening	10
Number of full texts included	4

4.2.4. Evidence table

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
Heppt et al 2019a	To investigate if PDT combined with a topical intervention is superior to monotherapy in terms of efficacy and tolerability.	Systematic review and meta-analysis	Systematic literature search in Medline, Embase, and CENTRAL and trial registers for RCTs until 20 August 2018 Results were pooled	Participant complete clearance rate Participant partial clearance rate Lesion-specific clearance rate	Combination treatment vs. monotherapy Participant complete clearance rate: RR 1.63; 95% CI 1.15-2.33; P = 0.007	The studies were estimated at high risk for performance and detection bias. Quality of evidence was rated as low by the authors.	1

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	PDT + IMQ: n=4 studies PDT + 5-FU: n=3 studies PDT + IMB: n=1 study PDT* tazarotene gel: n=1 study PDT + calcipotriol ointment: n=1 study		using a random-effects model N=10 RCTs with a total sample size of n = 277 were included		Participant partial clearance rate: RR 1.19; 95% CI 0.84–1.67; P = 0.33 Lesion-specific clearance rate: RR 1.48; 95% CI 1.04–2.11; P = 0.03		
Heppt et al 2019b	To investigate whether an upfront combination of cryosurgery with a topical intervention is superior to cryosurgery alone for treatment of AK. Systematic review and meta-analysis	Systematic literature search in MEDLINE, Embase, and CENTRAL and trial register until 17 July 2018 Results from individual studies were pooled using a random-effects model. The risk of bias was estimated with the Cochrane Risk of Bias Tool and the quality of evidence of the outcomes with the GRADE approach.	N=9 RCTs with a total sample size of 1644 patients were included Four of the nine studies investigated cryosurgery followed by imiquimod (3.75% cream, n = 2; 5% cream, n = 2) and two studies investigated cryosurgery followed by ingenol mebutate (0.015% gel, n = 1; 0.05% gel, n = 1). The remaining three studies assessed diclofenac 3% in 2.5% hyaluronic	Participant complete clearance rate Participant partial clearance rate Safety: number of patients who completed the study protocol and did not withdraw due to adverse events	Combination vs. monotherapy Participant complete clearance rate: RR 1.74, 95% CI 1.25–2.43, I^2 = 73%, eight studies Participant partial clearance rate: RR 1.64, 95% CI 0.88–3.03, I^2 = 77%, three studies number of patients who completed the study protocol and did not withdraw due to adverse events: RR 0.98, 95% CI 0.95–1.01, I^2=75%, seven	The studies were estimated to have a high risk for selective reporting bias. Besides, the quality of evidence was rated mainly as low due to heterogeneity and imprecision.	1

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
			acid, 5-fluorouracil 0.5% cream, and photodynamic therapy with aminolaevulinic acid after cryosurgery		studies <u>Comparator-specific stratified analyses:</u> Cryosurgery + IMB vs. monotherapy: participant complete clearance rate (RR 3.51, 95% CI 0.22–56.5, I^2 = 77, two studies) partial clearance rate (RR 2.97, 95% CI 0.28–31.0, I^2 = 83%, two studies safety: RR 0.99, 95% CI 0.97– 1.01, I^2 = 0%, two studies Cryosurgery + IMQ vs. Monotherapy: participant complete clearance: RR 2.46, 95% CI 0.63– 9.57, I^2 = 87%, three studies Safety: RR 0.99, 95% CI 0.97–1.01, I^2 = 0%		
Steeb et al 2020	To systematically review and synthesize the current knowledge on chemically	systematic literature research in Medline, Embase, and CENTRAL and trial register were	N=8 studies were included in the qualitative synthesis and n=4 studies in the meta-	Participant complete clearance Lesion clearance rate	COMBINATION APPROACHES TCA + Jessner's solution v.s 5-FU 5% cream	All studies had a high risk of bias: neither the participants were blinded in the trials	1

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	exfoliative peelings as interventions for AK.	searched until 5 August 2019. Results from individual studies were pooled using a random-effects model or described in a qualitative synthesis. The risk of bias was estimated with the tools provided by the Cochrane Collaboration (randomized and non-randomized trials) and the Evidence Project (single-arm trials).	analysis. Two studies investigated a combination of TCA 35% peeling in combination with Jessner's solution in comparison with 5-fluorouracil (5-FU) 5% cream for AKs located on the face. One study assessed glycolic acid 70% in combination with 5-FU 5% solution compared to glycolic acid monotherapy for AKs on the face. Another study investigated 5-FU 5% followed by chemical peeling with glycolic acid 70% in patients with AK in the head and neck area.	Pain	participant complete clearance: RR 0.36, 95% CI: 0.14–0.90, two studies, I^2 = 0%, P = 0.03 Lesion clearance rate: RR 0.92, 95% CI: 0.85–0.99, one study, P = 0.03 5-FU plus glycolic acid vs. GA monotherapy: Participant complete clearance: RR 9.00 (95% CI 0.52–155.86) Lesion clearance rate: RR 5.87 (95% CI 4.39–7.85) 5-FU + GA (single-arm trial): Participant complete clearance: 30% (6/20) Lesion complete clearance: 92% (322/350)	nor were sham interventions performed in any of the controlled studies High heterogeneity among included trials. RCTs as well as single-arm trials were included.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					MONOTHERAPY TCA monotherapy vs. PDT: Participant complete clearance: RR 0.75, 95% CI: 0.69–0.82, two studies, I^2 = 7%, P < 0.001 Pain cPDT vs. TCA: MD -1.71 95% CI: -3.02 to -0.41, two studies, I^2 = 55%, P = 0.01 Phenol peeling: participant complete clearance: 90.6%		
Steeb et al 2019	To summarize the current evidence on the efficacy and safety of laser-assisted PDT.	Systematic literature research in Medline, Embase, and the Cochrane Central Register of Controlled Trials; pertinent trial registers were hand-searched for RCTs. Results from individual studies were pooled by	N=7 RCTs were included in the qualitative analysis and 4 were included in the meta-analysis	lesion-specific complete clearance rate pain	Laser-assisted PDT vs. monotherapy 1.33; 95% CI 1.24-1.42; I^2 = 25% Pain intensity: MD 0.31; 95% CI 0.12 to 0.74; I^2 = 0%; P=0.16	Limitations included the clinical heterogeneity of included studies and high risk of bias. Further outcomes were specified, however, they were inconsistently reported in the included studies and thus no	1

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
		using a random-effects model. The risk of bias was estimated with the Cochrane Risk of Bias Tool, and the quality of evidence of the outcomes was assessed with the Grading of Recommendations, Assessment, Development, and Evaluation approach.				quantitative analysis was feasible.	

4.2.5. Full texts not included with reason

Author, year	Reason for exclusion (n=6)
Ezzedine et al 2021	no combination included
Fu et al 2019	no combination included
Mei et al 2019	no combination included
Nashan et al 2013	combination included, but no statement
Wu et al 2019	no combination allowed
Zhao et al 2019	no combination included

4.2.6. Literature

Heppt MV, Steeb T, Leiter U, et al. Efficacy of photodynamic therapy combined with topical interventions for the treatment of actinic keratosis: a meta-analysis. J Eur Acad Dermatol Venereol 2019;33(5):863-73. doi: 10.1111/jdv.15459 [published Online First: 2019/02/03]
Heppt MV, Steeb T, Ruzicka T, et al. Cryosurgery combined with topical interventions for actinic keratosis: a systematic review and meta-analysis. Br J Dermatol 2019;180(4):740-48. doi: 10.1111/bjd.17435 [published Online First: 2018/11/18]
Steeb T, Koch EAT, Wessely A, et al. Chemical peelings for the treatment of actinic keratosis: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2020 doi: 10.1111/jdv.16844 [published Online First: 2020/08/04]
Steeb T, Schlager JG, Kohl C, et al. Laser-assisted photodynamic therapy for actinic keratosis: A systematic review and meta-analysis. J Am Acad Dermatol 2019;80(4):947-56. doi: 10.1016/j.jaad.2018.09.021 [published Online First: 2018/09/30]

4.3. Question III.3. For which patients should preventive measures be recomended?

(Frage III.3. Für welche Patienten sind welche präventiven Therapiemaßnahmen geeignet?) Verweis auf Präventionsleitlinie

See S3-guideline for the prevention of skin cancer.

5. Interventions for actinic cheilitis

(Therapie der Cheilitis actinica)

5.1. Question IV.1. Which treatment is recommended for actinic cheilitis?

(Frage IV.1. Wie soll die Cheilitis actinica therapiert werden?)

De-novo-Recherche

5.1.1. PICO

PICO – Scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Patients with cheilitis actinica/ actinic cheilitis	Any intervention	placebo, vehicle only, active control therapy	At least one of the following **efficacy** outcomes: • Participant complete clearance (rate of participants with a complete clearance) • Participant partial clearance (rate of participants with 75% reduction) **Optional:** safety, tolerability, cosmesis optional

5.1.2. Database, search strategy, number of results

Database	Search strategy	Date	Number of results
1. Search			
Medline	((cheilitis*[Title] AND (actinic[Title] OR solar[Title] OR senil*[Title] OR hyperkeratos*[Title])) AND treatment ((cheilitis*[Title] AND (actinic[Title] OR solar[Title] OR senil*[Title] OR hyperkeratos*[Title])) AND (randomized controlled trial[Title/Abstract] OR controlled clinical trial[Title/Abstract] OR random* [Title/Abstract] OR clinical trial [Title/Abstract] OR placebo[Title/Abstract] OR trial[Title/Abstract]) NOT case report AND (German[language] OR English[language])	03.09.2020	11
Remarks and notes: -			

5.1.3. Selection criteria

Literature selection	
Number of total results	112
Inclusion criteria	Comparative trials (randomized, non-randomized), observational trials, cross-sectional trials, sample size of investigated patients n>10, quantitative outcomes measures **Study design**: RCTs, systematic reviews or meta-analyses of RCTs, total sample size N≥10, inter- and intra-individual design

Literature selection	
Exclusion criteria	Case reports, case series, narrative reviews, sample size n<10, qualitative reports without quantified accuracy measures, experimental studies
Number of results after abstract searching	35
Number of full texts reviewed	33

5.1.4. Evidence table

5.1.4.1. Evidence from systematic reviews and meta-analysis

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Brignardello-Petersen R et al 2019	To assess the effects of the treatments for AC	Systematic review	Patients with actinic cheilitis	Efficacy	29 studies that evaluated several types of treatments were found. Laser therapy was evaluated in 19 studies in which researchers enrolled 503 patients. The studies assessing low-power lasers showed that 43% through 100% of the patients improved clinically	The authors did not provide a description of the degree of severity of the AC, which would have facilitated proper use of this evidence. In addition, they did not describe separately the results from the controlled studies to provide a less biased comparison between options.	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					but that there was a high frequency of adverse events. The studies assessing high-power lasers showed that 60% through 100% of patients improved clinically, but the adverse events were more severe. The 7 studies assessing chemotherapeutic agents included a total of 105 patients. The proportion of patients who improved clinically ranged from 80% through 100%. Adverse effects ranged from 10% through 100%. Researchers assessed surgery in 6 studies in which 104 patients were included.	In summary, the results of this SR show that the rate of clinical improvement in patients with AC is high for most treatment options when patients are seen as good candidates for each treatment	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Clinical improvement was seen in 100% of the patients, and adverse effects ranged from 10% through 100%. Anti-inflammatory drugs were assessed in 2 studies in which researchers included 33 patients. Clinical improvement was seen in 44% through 67%. Rates of histologic improvement were lower for all treatment options.		
Carvalho MV et al 2018	The aim of this systematic review was to compare outcomes between surgical and non-surgical treatment of actinic cheilitis (AC).	A systematic review and meta-analysis based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses guideline	Search of PubMed/MEDLINE, Web of Science, and Cochrane Library databases Articles were selected based on the inclusion criteria: randomized clinical trials, prospective/retrospective	Remission rate and recurrence rate	A total of 283 ACs in 10 studies were included. About 2.5% surgically treated cases underwent malignant transformation. The weighted	In this systematic review, the surgical treatment was more favorable than non-surgical for AC. Meanwhile, further studies are needed that should	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			studies, and case series with at least 10 patients, with a minimum follow-up period of 6 months. A weighted remission rate (RER) and recurrence rate (RR) with a 95% confidence interval was performed. Data analysis was performed using a comprehensive meta-analysis software		remission rate was higher for surgical (92.8%) compared to non-surgical treatment (65.9%). The recurrence rate was lower for surgical (8.4%) compared to non-surgical treatment (19.2%).	maxi- mize methodological standardization and have greater rigor of the data collection process.	
Lai M et al 2019	Systematic review in order to define the best therapies of actinic cheilitis in terms of clinical response and recurrences.	Systematic review	Patients diagnosed with actinic cheilitis		444 papers and 49 were finally considered, including 789 patients and 843 treated areas. The following therapies were recorded in order of frequency: laser-therapy, photodynamic therapy (PDT), 3% diclofenac in 2.5% hyaluronic acid, PDT+5% imiquimod, ALA- or MAL- laser, 5% imiquimod,	Laser therapy appears as the best option among non-surgical approaches for actinic cheilitis, while PDT showed higher efficacy when sequentially combined with 5% imiquimod. Larger studies are needed to confirm these data.	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					fluorouracil, partial surgery, 0.015% ingenol mebutate, 50% trichloroacetic acid and laser+PDT. Concerning the primary outcome 85.9% of patients underwent 13 complete clinical response and 11.0% had clinical recurrences. Partial surgery and laser therapy showed the highest complete response rates (14/14 [100%] and 244/260 [93.8%], respectively) with low recurrences. Only a limited number of patients were treated with other therapies, with the exception of PDT with 68.9% complete responses and		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					12.6% of recurrences. Interestingly, when combined with 5% imiquimod efficacy of PDT was significantly enhanced. Limitations: Heterogeneity across studies.		
Salgueiro AP et al 2019	To identify the best therapies for actinic cheilitis using a computer-based systematic search conducted on electronic databases	Computer-based systematic search	29 journal articles	Efficacy	Results were divided according to the type of treatment employed: laser therapy, chemotherapy agents, surgical treatment, and application of anti-inflammatory agents. Clinically, photodynamic therapy showed positive results, with improvement in up to 100% of the patients; however,	The scientific evidence available on the treatment of AC is scarce and heterogeneous, photodynamic therapy, and imiquimod application are promising. The study of the treatments for AC in the form of a systematic review allows us to evaluate the results against the different treatments. Being	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					histopathological improvement varied greatly, from 16 to 100%. Among the chemotherapeutic agents assessed, imiquimod showed the best results: clinical improvement in 80 to 100% of the patients, and histopathological improvement in 73 to 100%. Regarding studies describing surgical approaches, the main focus was the search for the best technique, rather than the cure of AC. Finally, studies employing anti-inflammatory agents are sparse and have small samples, thus providing limited results.	a potentially malignant lesion, it is important to seek evidence about the best results found.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Yazdani Abyaneh MA et al 2015	To systematically review the safety and efficacy of PDT for AC	Systematic review	The terms “photodynamic,” “actinic,” “solar,” “cheilitis,” and “cheilosis” were used in combinations to search the PubMed database	Safety and efficacy	The authors identified 15 eligible case series encompassing a total of 242 treated subjects. Among studies that evaluated subjects for complete clinical response, 139 of 223 subjects (62%) showed complete response at final follow-ups ranging from 3 to 30 months. Among studies that evaluated subjects for histological outcome, 57 of 121 subjects (47%) demonstrated histological cure at final follow-ups ranging from 1.5 to 18 months. Cosmetic outcomes were good to excellent in the majority of	Photodynamic therapy is safe and has the potential to clinically and histologically treat AC, with a need for future randomized controlled trials.	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					subjects, and adverse events were well tolerated.		

5.1.4.2. Evidence from individual studies

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Alamillos-Granados, et al 1993	To propose a quick, outpatient procedure that yields good cos-metic, clinical and, functional results and allows histologic examination of the ablated vermilion	Prospective study; n=19	Patients diagnosed with actinic cheilitis and referred for therapy in one center	Cosmetic, clinical and, functional results after vermilionectomy using CO2 laser	Seven patients experienced pain the first 2 or 3 days after the operation. Two of them required an analgesic. Five patients had slight swelling that disappeared by the fifth postoperative day. In two patients, bleeding developed the second postoperative day and required electrocoagulation or ligation of a small vessel Complete epi-thelization was	CO2 laser vermilionectomy has the advantages of both scalpel vermilionectomy and CO2laser vaporization of the vermilion. It is a quick, definitive, esthetic form of treatment. As with vaporization, there is little postoperative pain or edema. The technique is done under local anesthesia in an	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					achieved in 4 weeks in 14 patients, 5 weeks in 2, 6 weeks in two, and 7 weeks in one patient. The cosmetic result was good in all cases and the procedure had excellent patient acceptance. After epithelization, three patients developed a fibrous band in the lower lip that softened after 6 months and did not interfere with normal lip function.	outpatient setting, and is well tolerated by the patients. Epithelization occurs within 4 to 7 weeks (4 weeks for most patients) and no special care is necessary. The excised vermilion may be sent for histologic examination, thus allowing for further treatment if malignancy is present.	
Andreadis D et al 2020	To assess long-term efficacy of photodynamic therapy with the use of the day light (DLPDT) in actinic cheilitis as well as safety and tolerance.	Prospective study; n=22	Patients histologically diagnosed with AC (grade I dysplasia—affecting no more than one-third of the total epithelium, and grade II	Long-term efficacy, safety and tolerance	Ages ranged from 48–83 years (mean ± SD, 67.5 ± 9.43). Clinical changes at baseline consisted of crusting, scaling, fissuring, and superficial erosions. Dermoscopic changes	DLPDT seems to be of significant benefit for grade I AC. As the treatment procedure is well tolerated and associated with only mild and transient side	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			dysplasia—affecting no more than two-thirds of the total epithelium)		mainly included alternations of white and pink structureless areas, scales, erosions, and whitish peripheral projections. Seventeen patients had not received any previous treatment, while three patients had been treated previously with cryotherapy. The study was completed by 20 patients (17 males and 3 females). Two patients were lost to follow-up and were thus not included in the analysis. Baseline histological examination revealed grade I AC in 12 patients and grade II AC in 8 patients. Mean outdoor temperature during DLPDT sessions was 20.83 ± 4.68°C (range 15–28 °C).	effects, it could be used as a first-line treatment for AC with grade I dysplasia. Combination with other treatment modalities and more treatment sessions may be necessary to improve efficacy in grade II AC.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					At 3 months, 18 of the 20 (18/20, 90%) patients achieved complete CR. Two patients achieved only partial response, were biopsied, and histopathological examination confirmed alterations indicative of AC. At the 6-month follow-up visit, one patient showed the signs of clinical recurrence that was histologically confirmed. At the last follow-up visit, 12 months after treatment, clinical recurrence confirmed by histology was recorded in one more patient. Sixteen out of the twenty (16/20) patients included in the analysis remained both		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					clinically and dermoscopically disease free. Thus, according to our results, the overall complete clinical cure rate achieved 12 months after treatment was 80%. Of note is that partial response at the 3-month follow-up and recurrences at the 6- and 12-month follow-up visits were observed only in patients with the initial grade II dysplasia. According to this observation complete clinical cure rate in grade I AC was achieved in 100% (12/12) of the patients, while complete cure rate of grade II AC decreased from 75% (6/8) 3 months after treatment to 50% (4/8)		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					12 months after treatment. An association between treatment response 12 months post-treatment and grade of dysplasia was observed [$\chi 2(2)$ = 7.500, p = 0.024, Monte Carlo method's result p = 0.016, 99% CI 0.013–0.019, Cramer's V = 0.612], while no statistically significant association between treatment response 3 months (Fisher's exact test, p = 0.147) and 6 months [$\chi 2(2)$ = 5.294, p = 0.071, Monte Carlo method's result p = 0.050, 99% CI 0.045–0.056] post-treatment and grade of dysplasia was observed. There were no unexpected safety issues during treatment and follow-		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					up period.		
Berking C et al 2007	The objective was to assess the efficacy of photodynamic therapy (PDT) in the treatment of actinic cheilitis of the lower lip	Prospective, uncontrolled study; n=15	Patients with actinic cheilitis	Efficacy	Complete clinical cure was observed in 47% (7/15) and partial cure in another 47% (7/15) of the patients. By histopathologic analysis, residual disease was found in 62% (8/13). Cosmetic results and patients' satisfaction were good to excellent in most cases. Local pain was sufficiently controlled by local anesthesia.	PDT can be an effective noninvasive method to treat actinic cheilitis of the lower lip	3
Castiñeiras I et al 2010	To evaluate the results obtained after treatment of AC by CO2 laser vaporization in comparison with other treatment modalities and the evolution rate of AC to SCC after CO2 laser treatment.	Retrospective review; n= 43	Patients with AC treated with CO2 laser vaporization at one center from 2002 to 2006	Results obtained in patients who had been treated by CO2 laser vaporization for AC, comparison with other treatment modalities and, in particular, to evaluate the evolution rate of	After a mean follow-up period of 29.4 months, 3/43 treated AC showed local recurrence. Another two patients developed SCC in the treated field. A residual scar was clinically evident in two patients.	CO2 laser vaporization with an adequate postoperative follow-up is an effective treatment for chronic AC. Nevertheless, some patients (4,6%) went on to develop lip SCC.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				AC to SCC after CO2 treatment.		The follow-up of these patients is mandatory.	
Chaves YN et al 2017	To conduct clinical and laboratory evaluation by histopathology and immunohistochemistry of the efficacy of actinic cheilitis treatment using photodynamic therapy (PDT) with methyl aminolevulinate (MAL) and noncoherent red light.	Prospective uncontrolled study; n=23	Patients with actinic cheilitis detected by histopathological examination submitted to two sessions of photodynamic therapy with a two-week interval between them	Efficacy	Of the 23 patients who underwent biopsy, 16 completed two photodynamic therapy sessions and the material of one patient was insufficient for immunohistochemistry. Complete clinical response was achieved in 62.5% (10 of 16 patients) and 37.5% still remained with clinical evidence of AC. In spite of this, no case of cure by histopathological analysis was found. There was no significant statistical change among the values of Ki-67, survivin, and p53 observed before and after treatment.	Photodynamic therapy, as carried out in this trial, was not an efficacious therapeutic option for treating patients with actinic cheilitis included in this sample.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Choi SH et al 2015	The aim of our study was to compare efficacy, recurrence rate, cosmetic outcome and safety between erbium:yttrium–aluminium–garnet ablative fractional laser-assisted methyl aminolaevulinate–PDT (Er:YAG AFL MAL-PDT) and standard MAL-PDT.	Randomized study; n=33	Patients with histologically confirmed AC	Efficacy, recurrence rate, cosmetic outcome and safety	In the per-protocol (PP) population, Er:YAG AFL MAL-PDT was significantly more effective (92% complete response rate) than MAL-PDT (59%; P = 0040) at the 3-month follow-up, and differences in efficacy remained significant at the 12-month follow-up (85% in Er:YAG AFL MAL-PDT and 29% in MAL-PDT). The recurrence rate was significantly lower for Er:YAG AFL MAL-PDT (8%) than for MAL-PDT (50%) group at 12 months (P = 0029). No significant difference in cosmetic outcome or safety was observed between Er:YAG AFL MAL-PDT and MAL-PDT.	Ablative fractional laser pretreatment has significant benefit for the treatment of AC with PDT.	2
de Oliveira Bezerra HI et al 2019	The objective of the study is to assess, by clinical follow-up, the	Prospective uncontrolled study; n=33	Patients diagnosed with AC	Efficacy	In the group treated with Fludroxycortide (n = 15), five patients	Conventional treatment with LS was effective in	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	efficacy of the dermatological cream fludroxycortide 0.125 mg/g (Drenison®) in the treatment of actinic cheilitis (AC)				showed total improvement, seven presented partial improvement, and three showed no clinical change. Concerning the patients treated with LS (n = 8), one presented total remission of the clinical lesion characteristics, four exhibited partial improvement, and three exhibited no clinical lip alteration. No case presented symptom worsening. Of the 15 patients undergoing corticotherapy, 12 were satisfied and reported that the product was not irritating and contributed to lesion improvement.	the remission of some AC lesions, but treatment responses were improved when associated with Fludroxycortide, especially in the more severe cases.	
Dufresne RG et al 1998	To evaluate the results with CO2 laser	Prospective, uncontrolled	Patients with chronic actinic	Efficacy	The procedure was well tolerated. All patients	CO2 laser vaporization	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	treatment in both conventional and super pulsed modes for vermilion ablation	study; n=13	cheilitis of the lower lip		were able to take fluids immediately, and several patients had no interruption in their routine dietary habits. None had pain that required narcotics. Two patients with minor pain at 4 and 7 days were treated successfully with viscous lidocaine. Re-epithelialization usually occurred by 3 weeks and was completed in all patients by 4 weeks. Focal scarring, none of which was functionally restrictive, developed in three patients. No scar was detected in the three patients who h a d prior lip excisions; their previous surgical scars were undetectable. Only one patient reported dysesthesia. There were no	offers a well-tolerated treatment modality for chronic actinic cheilitis.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					recurrences in any of the patients, with an average follow-up of over 11 months.		
Gonzaga AKG et al 2018	The aim of this research was to analyze the efficacy of diclofenac sodium 3% gel in the treatment of this condition, through clinical follow-up	Prospective uncontrolled study; n=31	Patients diagnosed with AC	Efficacy	Twelve cases abandoned the treatment for reasons unrelated to the study. Ten participants showed total remission of all clinical features of the lesion and three had partial improvement of the characteristics. One participant presented worsening of clinical condition, and in five cases, treatment was discontinued due to development of mild adverse effects at the site of gel application. Regarding satisfaction analyses and tolerability to the drug, from 14 patients who completed treatment without adverse effects	Topical application of the drug has provided a convenient and well-tolerated in most cases. Diclofenac sodium gel (3%) may be a promising alternative for treatment of actinic cheilitis	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					or complications, most agreed fully that they were satisfied with the therapy (n=11) and that the drug was not irritating to the mouth (n=9). Patients are being monitored without clinical signs of recurrence and/or progression of the lesions.		
Husein-ElAhmed H et al 2018	To compare the clinical efficacy of imiquimod (IMI), ingenol mebutate (IMB) and diclofenac (DIC) in AC	Randomized study; n=30	Patients diagnosed with AC and treated in one center	Efficacy	Ten patients were assigned to each drug. Complete clearance of AC was achieved in 5 (50%) of the 10 patients treated with IMI, 4 (40%) of the 10 patients treated with IMB and 2 (20%) of the 10 patients treated with DIC (Figs 1, 2). The clearance with IMI was statistically similar to that of IMB (P = 0.22), but significantly greater than with DIC (P = 0.03). Persistence	both IMI and IM produced a better response than DIC, but the latter has characteristics that may make it more useful for certain types of AC. Therefore, this novel study suggests that each drug may have specific clinical types of AC for which it is better suited.	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					of both leucoplasia and keratotic plaques was significantly more common in patients treated with DIC compared with either IMI ($P < 0.05$) or IMB ($P = 0.05$). Unstructured vermillion border persisted in 1 patient (10%) treated with IMI, 2 patients (20%) treated with IMB and 4 patients (40%) treated with DIC, but these differences were not statistically significant ($P > 0.05$). Similar outcomes were observed for dyschromic and/or atrophic areas. Exfoliative areas cleared up completely in all patients regardless of the therapy used. Table 2 provides further details on the results		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					In this study, we found that IMI was the most clinically effective therapy compared with IM or DIC. However, IM was not inferior to IMI, and as it has the shortest posology, it is the best choice for patients who have difficulties in adherence to therapy, e.g. patients with neurological disorders such as dementia. In patients with leucoplakia, keratotic plaques or involvement of the vermilion border, both IMI and IMB were acceptable, but DIC should be avoided as it had the lowest rate of response for all three of these conditions. DIC is more suitable for AC with exfoliative areas and erosions, and in absence of deeper		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					signs of AC such as atrophic areas. Furthermore, owing to its low inflammatory reaction, DIC is an acceptable option for subjects with low pain threshold.		
Laws RA et al 2000	To compare two treatment modalities (CO2 laser resurfacing and electrodessication) for the treatment of biopsy-confirmed actinic cheilitis.	Randomized bi-lateral study; n=14	Patients with biopsy-proven actinic cheilitis	Histologic cure, cosmetic outcome, and complication rate	The CO2 laser-treated side was reepithelialized after an average of 14.4 days (range 7–23 days). The side treated with electrodessication was reepithelialized after an average of 23.1 days (range 11–37 days), which was significantly longer than the side treated with CO2 laser (paired t-test, P <.001). In the 10 patients treated with the scroll-shaped electrode, comparison of the CO2 laser with electrodessication still demonstrated a	Electrodessication is an attractive, practical alternative to CO2 laser ablation when used to treat actinic cheilitis.	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					significant difference in healing time (14.3 days versus 22.5 days, P = .004). All patients described minimal to no pain at the first follow-up visit, 18 hours after the procedure. The most common scenario, described by 12 of the 14 patients, was a moderate burning discomfort beginning 3–6 hours after the procedure, and lasting 12 hours. Twelve patients required only plain acetaminophen for pain. Patient 14 received several hours of sun exposure during the first 10 days of healing, and complained of a new onset of burning which lasted for 1–2 days. Of interest, he also had the longest healing time of all the patients.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					With respect to all patients, there was no difference in perceived pain between the two treatment sides (repeated measures analysis of variance, P = .817). At the 3-month follow-up visit, the appearance of the lip was improved in all patients, and both sides of the lip appeared identical in all 14 patients. Five of the 14 patients agreed to undergo a 3-month follow-up biopsy.		
Levi A et al 2019	To determine the safety and efficacy of daylight photodynamic therapy (PDT) in a series of patients with actinic cheilitis	Prospective uncontrolled study; n=11	Patients with actinic cheilitis	Safety and efficacy	Cure rate was 91% (10 of 11 patients, three females/eight males; mean age 59.2 ± 14.4 years). Mean number of treatments to attain cure was 2.7. Patients experienced mild erythema and minimal to no pain during	Daylight PDT is a promising modality for the treatment of AC, with impressive cosmetic results and few side effects. Actinic cheilitis is	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					treatment.	a common premalignant condition of the lower lip that requires treatment to prevent its progression to squamous cell carcinoma. We describe our therapeutic experience using daylight photodynamic therapy. Treatment sessions continued until achieving clinical and histological remission. Symptoms were resolved in 10 of 11 patients (91%) after a median of two (range 1-6) treatments, with only few adverse effects. Daylight		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						photodynamic therapy is a promising modality for the treatment of actinic cheilitis.	
Lima Gda S et al 2010	To evaluate the effect of 3% diclofenac in 2.5% hyaluronic acid gel in the treatment of actinic cheilitis	Prospective uncontrolled study; n=34	Patients with actinic cheilitis	Efficacy	Of the 27 patients that completed the study, 12 (44%) showed complete remission of the whitish plaques and exfoliative areas, and 15 (56%) had partial remission of the clinical picture of cheilitis. The latter group was submitted to excision of the leukoplakic areas which diagnosis varied from mild to moderate epithelial dysplasia.	The results suggest a promising role for diclofenac in hyaluronic acid gel in the treatment of AC. This treatment has the advantages of not being invasive and showing few side effects.	3
Orenstein A et al 2007	To evaluate the efficacy and outcome of a new modality in the treatment of actinic cheilitis with	Prospective uncontrolled study; n=12	Patients with actinic cheilitis were treated at one center institute with the	Efficacy	Patients were men and women aged between 37 and 71 years. The healing duration varied from 7 to 30 days	Using the Er:YAG laser provides accurate tissue ablation, giving a very satisfactory	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	the Er:YAG laser		Er:YAG laser between 2002 and 2005		(mean 22.33-6.91 days) and the follow-up ranged from 8 months to 3 years (mean 23.16-9.48 months). No recurrences were detected in our study.	cosmetic result, with a short healing period, no lip deformity and no sensation loss.	
Paolino G et al 2020	To assess the efficacy and tolerability of imiquimod 3.75% in treating actinic keratosis, pigmented basal cell carcinomas, and actinic cheilitis	Case series report; n=11	Patients with actinic keratosis, pigmented basal cell carcinomas, and actinic cheilitis	Efficacy and tolerability	All patients experienced local skin reactions (LRS), with erythema that was the most common LRS followed by, edema, scaling, crusting, and erosions. Each LSR did resolve, without causing aesthetic alterations. Compared to topical imiquimod 5%, topical imiquimod 3.75% cream has an acceptable tolerability profile, with a short and simple treatment regimen. Besides, despite the lower percentage compared to topical imiquimod	In conclusion, imiquimod 3.75% cream is characterized by an acceptable tolerability profile and has the advantage of being self-applied by the patients,4 showing an efficacy not only at the level of AKs but also in nodulocystic pigmented BCCs and actinic cheilitis.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					5% cream, imiquimod 3.75% cream shows also effectiveness in the case of pigmented BCCs and actinic cheilitis, as reported in our patients.		
Radakovic S et al 2020	To evaluate the efficacy, tolerability, safety and cosmetic outcome of Alacare patch PDT for AC	Prospective uncontrolled study; n=21	Patients with actinic cheilitis	Efficacy, tolerability, safety and cosmetic outcome	Nineteen patients completed the study. Three months after PDT, 17 patients (89.5%) had achieved complete remission. Of these, one patient presented with recurrence of AC at the 6-month follow-up, whereas all other patients remained in remission until the end of the observation period. The complete clinical cure rate at 1 year after a single Ala-care patch PDT thus was 84.2%. Pain during illumination and the phototoxic skin reaction were in	The present prospective study on Alacare patch PDT for AC confirms its high clinical efficacy, good tolerability and favourable cosmetic effects. Alacare patch PDT should be considered as a valid treatment option for patients with AC.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					general mild to moderate. The cosmetic outcome was excellent.		
Radakovic S et al 2017	To assess the efficacy, tolerability and cosmetic outcome of Alacare patch-PDT in eleven patients with AC	Retrospective analysis; n=11	Patients with actinic cheilitis	Efficacy and safety	Complete clinical response at the 3-month follow-up was achieved in eight of 11 patients (72,7%) and 12 of 15 AC lesions (80,0%), respectively. Up to the final 12-month follow-up, a recurrence was observed in two lesions. The complete clinical cure rate at 1 year after Alacare patch-PDT, thus, was 66,6% (10/15 lesions). The cosmetic outcome of the treatment was excellent in all cases.	Alacare patch-PDT was found to have substantial efficacy in the treatment of mild to moderate AC. Given its ease of use, absence of long-term side effects and the excellent cosmetic results Alacare patch-PDT might be considered as a promising new treatment option for the management of AC.	4
Ribeiro CF et al 2012	To assess the efficacy of single photodynamic therapy (PDT) session using	Prospective uncontrolled study; n=19	Patients with actinic cheilitis of the lower lip	Efficacy	The sample was composed of 19 patients (10 males and 9 females), phototypes	PDT is effective in the treatment of actinic cheilitis, but it is	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	16% methyl-aminolevulinate and its cosmetic results.				I to III, with average age of 62 years. Main adverse effects were: sudden pain, scabs, herpes flare-up, and edema. The average score of pain during the procedure was 5,8+2,9. At the final assessment, the patients reported improvement of 80% and satisfaction of 85% ($p<0.01$). Pathological analysis showed a significant decrease of dysplasia ($p=0.03$) in spite of its presence in 84% of cases. There was no significant correlation between the level of dysplasia with either the subjective impression of clinical improvement ($p=0.82$) or with the patients' final satisfaction ($p=0.96$).	associated with a significant level of pain. Due to the persistence of dysplasia, more research needs to be done in order to define the ideal number of sessions for the effective treatment of these lesions.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Robinson JK 1989	To compare treatment with fluorouracil, chemical peeling, lip shave, or carbon dioxide laser treatment of actinic cheilitis	Prospective study; n=40	Patients diagnosed with actinic cheilitis and patients who had either a basal cell or squamous cell carcinoma of the face, but not of the lip, that was resected by the Mohs' micro-graphic surgery method.	Efficacy	Forty patients with actinic cheilitis were treated with one of four modalities: topical fluorouracil, chemical peel with trichloroacetic acid, lip shave, or carbon dioxide laser ablation of the vermilion. Patients treated with lip shave or carbon dioxide laser ablation had no recurrence of the problem during 4 years.	While the lip shave procedure offers the advantage of histologic examination of the specimen, the patients treated with the laser ablation had fewer postoperative complications.	3
Rossini RC et al 2020	To evaluate local skin reactions (LSR) in patients with actinic cheilitis receiving ingenol mebutate (IM) gel 0.015% for self-application	Interventional, prospective uncontrolled study; n=14	Patients with actinic cheilitis of the lower lip	Tolerability	All LSR had a complete resolution for up to 2weeks. The most common adverse events were burning sensation, angular cheilitis, and pain. There was an improvement of more than 80% in patients' subjective evaluation. There was no statistically significant	Despite being a safe therapeutic method, the absence of histopathological or immuno-histochemical response suggests that clinical improvement may not be accompanied by	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					histopathological response since all patients remained with mild dysplasia. No reduction in the P53 expression was observed in the current study.	histopathological cure for AC treated with IM.	
Smith KJ et al 2002	To review the results in patients who had been treated for actinic cheilitis with imiquimod cream.	Retrospective study; n=15	Patients with biopsy-proven actinic cheilitis who had been treated with topical imiquimod 3 times weekly for 4 to 6 weeks	Efficacy and tolerability	All 15 patients showed clinical clearing of their actinic cheilitis at 4 weeks after discontinuation of the topical imiquimod. Sixty percent of the patients experienced a moderate to marked increased local reaction consisting of increased erythema, induration, and erosions or ulcerations, which in some cases continued through the period of therapy.	Imiquimod appears to have a role in the treatment of actinic cheilitis. However, the dose and duration of therapy, as well as the long-term efficacy, need to be established; and local reactions are to be expected and may not improve during therapy.	3
Sotiriou E et al 2010	To assess the clinical and histological long-term outcome in AC	Prospective uncontrolled study; n=40	Patients with histologically proven grade 1	Cosmetic outcome	Of the 40 patients enrolled, 38 completed the study. Complete	PDT represents a moderately effective	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	after two ALA-PDT sessions.		and 2 AC		clinical response at 3 months was achieved in 26 patients. At 6 months, clinical and histological recurrence occurred in three patients and at 12 months, one more patient showed clinical and histological recurrence. At 18 months, overall clinical recurrence rate was 15.38% (4/26), while overall histological recurrence rate was 34.61% (9/26). Cosmetic outcome was rated as excellent in more than 80% of evaluated cases.	treatment modality in AC. Optimization of treatment procedure and protocols is still needed for higher response rates to be achieved. Moreover, the high treatment cost should be given consideration. Further long-term follow-up studies are needed for assessment of clinical and histological very late recurrences that could be expected after PDT.	
Sotiriou E et al 2008	To evaluate the therapeutic efficacy of photodynamic therapy (PDT) for the treatment of actinic	Prospective uncontrolled study; n=10	Patients with biopsy-proven AC	Efficacy, safety and cosmetic outcome	Treatment was well tolerated. All patients reported a burning sensation during irradiation, but none of	In conclusion, we believe that PDT using ALA is an effective and safe treatment option	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	cheilitis				them asked to interrupt the procedure. The CR rate was 90% (nine of 10) while the non-CR rate was 10% (one of 10). Lesions with CR were biopsied for histological examination to verify the response. A single punch biopsy was taken of the site with the severest clinical signs pretreatment. The CR rate dropped to 80% (eight of 10) when taking into account the results of histological examination. Patients with clinical or histological non-CR received another treatment cycle. These patients showed, before treatment, diffuse, poorly demarcated lesions, while their pretreatment	for AC, with the added advantage of excellent cosmesis, but with still unknown long-term cure rates. Further studies are needed to standardize optimal treatment protocols, to determine whether multiple treatment cycles can lead to complete clinical and histological cure and to compare the efficacy with conventional treatment modalities. Long-term follow-up is advised for assessment of recurrence.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					histological changes comprised mod- erate (grade 2) dysplasia. Significant reduction and relief of symptoms was reported by all patients. Cosmetic outcome was judged by the investigators as excellent in 60% of the patients and as good in 40%. The patients judged the outcome to be excellent in 80% and good in 20% All patients (100%) rated PDT as better than all previously received treatments.		
Sotiriou E et al 2011	To assess the clinical and histological long-term outcome as well as the safety and tolerability of sequential use of photodynamic therapy (PDT) and imiquimod in AC.	Prospective uncontrolled study; n=34	Patients with histologically confirmed grade 1 and 2 AC	Efficacy	Of the 34 enrolled patients, 30 completed the study. Complete clinical response was achieved by 27 patients in 3 months. At 6 months, clinical and histological recurrence occurred in	Sequential use of PDT and imiquimod cream is of significant benefit for the treatment of AC. Further studies are needed to confirm the	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					two patients, while at 12 months the complete clinical cure rate obtained was 80% and the histological complete cure rate was 73%. Treatment was well tolerated and adverse events were as expected and transient.	improved outcome using the combination treatment, to clarify the involved mechanisms and to optimize the therapeutic protocol.	
Vega-Memije ME et al 2002	To describe the clinicopathologic features and therapeutic results of 116 patients with actinic prurigo cheilitis seen over 11 years	Retrospective study; n=116	Patients with actinic prurigo cheilitis treated in one center admitted consecutively from 1990 through 2000	Patients characterization and efficacy	The study consisted of 42 male (36.2%) and 74 female (63.8%) patients, with a male to female ratio of 1:1.7. Age ranged from 9 to 82 years (mean, 27.9 years; standard deviation, 14.2). Thirty-two cases (27.6%) were found in which cheilitis was the only manifestation of this condition. Pruritus, tingling, and pain of the vermilion were recorded in 96 cases (82.7%). Typical	Our findings confirm that lip lesions may appear as the only manifestations of this photodermatosis and that it has typical clinical and microscopic features and should therefore be considered a specific form of cheilitis.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					histopathologic findings included in most cases the presence of acanthosis, spongiosis, basal cell vacuolation, ulceration with serohematic crust formation, edema of the lamina propria, lymphocytic inflammatory infiltrate with well-defined lymphoid follicles, and variable numbers of eosinophils and melanophages. Improvement of the symptoms was obtained in 112 cases (96.5%) with sun-protective measures and diverse anti-inflammatory agents. However, complete resolution of the labial lesions were more frequently achieved with the combination of topical steroids, thalidomide, and sun-		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					protective measures (42.2%) as compared with topical steroid therapy plus sun-protection measures (16.3%; $P < .005$).		

5.1.5. Literature

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6. Interventions for cSCC *in situ* (Bowen's disease, Morbus Bowen, BD)

(AG Therapie des Morbus Bowen)

6.1. Question V.1. Which treatment is recommended for cSCC in situ (Morbus Bowen)?

(Frage V.1. Wie soll der M. Bowen therapiert werden?)

De-novo-Recherche, adaption from Cochrane review on Bowen's disease published 2012

6.1.1. PICO

PICO scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Patients with Bowen's disease (any clinical or histologic type)	Any intervention such as: • Cryotherapy/ cryosurgery • Surgical treatments (e.g. curettage, shave excision complete excision) • Laser treatments • Topical drug-mediated treatments • PDT sequential or combination therapies were allowed	placebo, vehicle-controlled, active control	At least one of the following efficacy outcomes: • Lesion clearance rate • Lesion recurrence rate • Participant clearance rate (multiple lesions) • Participant recurrence rate (multiple lesions) Optional one of the following outcomes: • Lesional area reduction • Local adverse events

PICO scheme			
			• Pain on VAS (PDT trials) • Cosmesis • Patient satisfaction

6.1.2. Database, search strategy, number of results

Database	Search strategy	Date	Number of results
1. Search			
Medline	1. Bowen$ disease.mp. or exp Bowen's Disease/ 2. bowenoid papulosis.mp. 3. morbus bowen.mp. 4. exp Carcinoma, Squamous Cell/ or in situ squamous cell carcinoma.mp. 5. intraepidermal squamous cell carcinoma.mp. 6. in situ squamous cell carcinoma.mp. 7. exp Skin/ 8. 4 and 7 9. 1 or 2 or 3 or 5 or 6 or 8 10. randomized controlled trial.pt.	24.06.2020	123

Database	Search strategy	Date	Number of results
	11. controlled clinical trial.pt. 12. randomized.ab. 13. placebo.ab. 14. clinical trials as topic.sh. 15. randomly.ab. 16. trial.ti. 17. 10 or 11 or 12 or 13 or 14 or 15 or 16 18. exp animals/ not humans.sh. 19. 17 not 18 20. 9 and 19		
	Cross-references	20.08.2020	1

Remarks and notes:

Some of the studies were already thoroughly analyzed and included in a Cochrane Review by Bath-Hextall et al.. The review served as a supporting document for the evidence tables displayed here. Articles which were included in the review are highlighted with an asterisk (★).

6.1.3. Selection criteria

Literature selection	
Number of total results	124

Literature selection		
Inclusion criteria	**Study design**: RCTs, systematic reviews or meta-analyses of RCTs, total sample size N≥10, inter- and intra-individual design **Outcomes:** At least one of the following efficacy outcomes reported; • Lesion clearance rate • Lesion recurrence rate • Participant clearance rate (multiple lesions) • Participant recurrence rate (multiple lesions) Optional other outcomes: • Lesional area reduction • Local adverse events • Pain on VAS (PDT trials) • Cosmesis • Patient satisfaction	
Exclusion criteria	**Study design**: Observational studies (retrospective and prospective), controlled studies without randomization, case series, case reports, experimental studies, RCTs with a total sample size N<10	
Number of results after title and abstract screening		19

Literature selection	
Records excluded after full text review	7
Records included	12

6.1.4. Evidence table

6.1.4.1. Evidence from systematic reviews and meta-analysis

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
Bath-Hexall et al. 2013	To assess the effects of therapeutic interventions for cutaneous Bowen's disease.	Systematic review of RCTs Databases were searched up to September 2012 and included the Cochrane Skin Group Specialised Register, CENTRAL in The Cochrane Library (2012, Issue 9), MEDLINE (from 1946), EMBASE (from 1974), PsycINFO (from 1806), and LILACS (from 1982); besides	9 studies with a total of 363 participants (132 men, 231 women, mean age: 71 years, range 22-99 years) PDT (n=4 studies) Cryotherapy (n=2 studies) 5-FU (n=2 studies) Imiquimod (n=1 studies)	complete clearance of lesions recurrence rate at 12 months	One study demonstrated statistically significantly greater clearance of lesions of Bowen's disease with MAL-PDT when compared with placebo-PDT (RR 1.68, 95% CI 1.12 to 2.52; n=148) or cryotherapy (RR 1.17, 95% CI 1.01 to 1.37; n=215), but there was no significant difference when	According to the risk of bias evaluation, most studies had an unclear risk of bias. Dose ranging studies were included in this review.	1

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
		trial registers were searched.			MAL-PDT was compared to 5-FU). One study demonstrated statistically significantly greater clearance of lesions with ALA-PDT versus 5-FU (RR 1.83, 95% CI 1.10 to 3.06; n=66), but no statistically significant difference in recurrence rates at 12 months (RR 0.33, 95% CI 0.07 to 1.53). Cryotherapy showed no statistically significant difference in clearance rates (RR 0.99, 95% CI 0.78 to 1.26) or		

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					recurrences at 1 year (RR 1.48, 95% CI 0.53 to 4.17) when compared to 5-FU in 1 study of 127 participants. One study compared imiquimod to placebo and demonstrated statistically significantly greater clearance rates in the imiquimod group (9/15 lesions) compared to placebo (0/16) (Fisher's Exact P value < 0.001). The imiquimod group did not report any recurrences at 12 months, but at 18 months, 2/16 participants in the placebo group had		

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					developed early invasive cSCC		

6.1.4.2. Evidence from individual studies

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
Cai et al. 2015	To the therapeutic effects of ALA-PDT plus CO_2 laser and compare ALA-PDT plus CO_2 laser and CO_2 laser treatment alone in terms of control of BD recurrence. Group 1: ALA PDT (180 J/cm² at 100 mW/cm², occlusion for 5h) + CO_2 laser at a power ranging between 2 and 3 W for one to three sessions. Group 2: CO_2 laser alone at a power ranging between 2 and 3 W	Single-centre, inter-individual, randomized, controlled, double-blind trial	22 lesions from 18 patients (8 males, 10 females) were randomized mean age 52±10 years BD lesion diameter: on average 2.6±0.9 cm	Lesion complete response Overall clearance (no recurrence 6 months after the treatment) Recurrence rate Side effects Patient satisfaction	Lesion complete response: ALA-PDT + CO_2 laser vs CO_2 Laser: 72.72% (8/11) vs. 63.63% (7/11) Overall clearance: ALA-PDT + CO_2 laser vs CO_2 laser: 90.91% (10/11) vs. 54.55% (6/11) Recurrence rate ALA-PDT + CO_2 laser vs CO_2 laser: 9% (1/11) vs. 45.45% (5/11) Side effects: ALA-PDT + CO_2 laser: mild	BD lesions were sampled for biopsy before ALA-PDT. Cosmetic outcome was not reported for the laser monotherapy group: reporting bias	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					erythema, edema, erosion, and burning and/or stinging sensation CO_2 laser: mild to moderate edema, erosion, ulceration, delayed healing, prolonged pain, and scarring <u>Cosmetic outcome:</u> very good for combination group <u>Patient satisfaction</u> ALA-PDT + CO_2 laser vs CO_2 laser: 80% (8/10) vs. 62.5% (5/8)		
Genouw et al. 2018	To compare a continuous (CL) and a fractional (FL) ablative CO_2 laser-assisted MAL-PDT in the management of sBCC and BD. Treatment areas received CL (Group	Single-centre, intra-individual, randomized, controlled, evaluator-	30 treatment areas in 15 patients with inoperable, histologically verified sBCC	Participant complete clearance	<u>Participant complete clearance</u> CL+PDT vs. FL+PDT: 80.0% (4/5) vs.	Small sample size of included BD (n=6) Outcomes other than participant complete clearance are not	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	1) or FL (Group 2). Laser treatment was followed by MAL application and illumination occurred 3 h later. This treatment was repeated after 2 weeks.	blinded trial	(n=9) or BD (n=6) Median age (n=15) 73 years, range 46-87 7 male, 8 female Localization: Head and neck: n=4 Thorax: n=5 Arms: n=2 Legs: n=4		80.0% (4/5) (After 12 months)	reported for the subgroups (selective reporting bias)	
Kim et al. 2018	To compare the 5-year efficacy and recurrence rates of AFL-MAL-PDT with those of conventional MAL-PDT for the treatment of lower extremity BD. <u>Intervention:</u> single session of AFL-MAL-PDT or 2 sessions of MAL-PDT with a 1-week interval between sessions. The AFL treatment was performed	Single-center, inter-individual, randomized controlled, evaluator-blinded trial	60 patients with 84 BD lesions on the lower extremities AFL-MAL-PDT: 13 men, 17 women; mean age: 71.83±12.59 Skin type: III: 2	Lesion response Lesion recurrence Side effects Pain (VAS)	AFL-MAL-PDT vs. MAL-PDT: <u>Lesion response</u> 93.48% (43/46)vs. 76.3% (29/38) (3 months) 84.78% (39/46) vs. 44.74% (17/38) (5 years)	Small sample size Further result: Diameters larger than 20 mm and lesions with a history of previous treatment were independent factors for treatment failure. Results only apply to	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	with a 2940-nm erbium:yttrium-argon-garnet ablative fractional laser at a 550- to 600-µm ablation depth with level 1 coagulation, 22% treatment density, and a single pulse. After the AFL treatment, a 1-mm-thick layer of MAL 16% was applied to the lesion and to 5 mm of the surrounding normal tissue. After incubation for 3 h, the dressings and cream were removed. The area was irradiated with an Aktilite CL 128 red light-emitting diode lamp with a peak emission of 632 nm that was placed 5 cm above the skin for a total light dose of 37 J/cm²		(6.67%), IV: 21 (70%), V: 7 (23.33%) N=46 lesions MAL-PDT: 11 men, 19 women; mean age: 69.93±13.11 Skin type: III: 3 (10%), IV: 22 (73.33%), V: 5 (16.67%) N=38 lesions		<u>Recurrence rate:</u> 6.98% vs. 27.59% (12 months) 9.3% vs. 41.38% (5 years) <u>Side effects:</u> erythema (93% vs 90%), crusting (80% vs. 80%), hyperpigmentation (76% vs. 70%), pruritus (70% vs. 67%), and burning sensations (73% vs 67%) Occurrence of AEs was slightly higher in the AFL-MAL-PDT group Pain: 6.1±1.0 vs. 5.6±1.3	this sample (predominantly skin type III-V), Korean population, lower extremities, limited generalizability for other populations	
Ko et al. 2014	To compare the efficacy, recurrence rate, cosmetic outcomes and safety between Er:YAG AFL-assisted MAL-	Single-centre, randomized, intra-	N=21 Korean patients with 58 biopsy-	Lesion clearance rate	Er:YAG AFL-PDT vs. MAL-PDT	Patients might have been unblinded due to differences in	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	PDT (Er:YAG AFL-PDT) and standard MAL-PDT. Intervention: Er:YAG AFL therapy was performed with 550–600 nm ablation depth, level 1 coagulation, 22% treatment density and a single pulse. MAL cream was then applied under occlusion for 3 h and illuminated with a red light-emitting diode lamp at 37 J/cm^2. A second session of MAL-PDT was administered 7 days later.	individual, controlled, double-blinded trial	confirmed BD lesions on the lower extremity lesions Per-protocol population: N=18 patients were treated with Er:YAG AFL-PDT (32 lesions) or MAL-PDT (26 lesions) Patient age ranged from 35 to 88 years; 47.6% (10 of 21) were male and 52.4% (11 of 21) female. All were dark-skinned with the following Fitzpatrick scale distribution:	Recurrence Rate Cosmetic outcome Safety/Adverse events Pain (VAS)	Lesion clearance rate 93.8% (30/32) vs. 73.1% (19/26) (3 months) 87.5 (28/32) vs. 50% (13/26) (12 months) Recurrence rate 6.7% vs. 31.6% (12 months) No differences in terms of cosmetic outcome and safety Cosmetic outcome: Excellent or good: 90.6% vs. 92.3% Fair or poor: 9.4% vs. 7.7% Pain: 4.857±2.035 vs. 4.300±1.767 during	treatment protocol and side effects. Small sample size Results only apply to this sample (predominantly skin type III-V), Korean population, lower extremities	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
			III, 9.5% (n = 2); IV, 71.4% (n = 15); and V, 19.1% (n = 4).		illumination Adverse events: crust (100% vs. 100%), erythema (94.4% vs. 88.9%), burning sensation (83.3% vs. 72.2%), hyperpigmentation (66.7% vs. 55.6%), itching (27.8% vs. 22.2%), furthermore: scale, bullae, oozing, bleeding, ulceration, scarring, infection		
Morton et al. 2006★	To compare the efficacy, tolerability, and cosmetic outcome of PDT using topical MAL with cryotherapy or topical fluorouracil <u>Interventions:</u> MAL or placebo cream was applied for 3 hours before illumination with broadband red light (75 J/cm², 570-670 nm). Treatment was repeated 1 week later. Cryotherapy was	randomised placebo-controlled, multicentric, double-blind study Randomisation to MAL-PDT or placebo PDT or standard	N=225 patients with histologically confirmed BD (lesion size, 6-40 mm) Treatment with MAL-PDT: n=96 (124 lesions), mean	Lesion complete response rate Lesion recurrence rates Cosmetic outcome	MAL-PDT vs. placebo PDT vs. cryotherapy vs. 5-FU <u>Lesion complete respone rate</u> 93% (103/111) vs. 21% (4/19) vs. 86% (73/85) vs. 83% (24/29) (3	Participants and lesion characteristics of the four intervention groups were similar at baseline Unclear risk for detection/performance bias. Outcome assessor for the cosmetic outcome	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	performed with liquid nitrogen spray. Fluorouracil was applied for 4 weeks. Lesions with a partial response at 3 months were re-treated.	therapy (chosen by investigator, either cryotherapy or 5-FU)	age: 71.9 years (43-89), 36 male, 60 female, localization: 29 on face/scalp, 15 neck/trunk, 80 on extremities Placebo-PDT: n=17 (24 lesions), mean age: 42.4 years (53-88), 6 male, 11 female, localization: face, scalp: n=6, neck/trunk: n=2, extremities: n=16 Cryotherapy: n=82 (91 lesions), mean age: 74 years	Adverse events	months) <u>Lesion recurrence rates at 12 months</u> 15% (15/103) vs. 50% (2/4) vs. 21% (15/73) vs. 17% (4/24) <u>Adverse events</u> Pain: 20% vs. 24% vs. 24% vs. 33%, Erythema: 8% vs. 12% vs. 10% vs. 33%, Burning sensation: 17% vs. 18% vs. 7% vs. 7% Crusting: 8% vs. 6% vs. 4% vs. 13% Stinging: 9% vs. 6% vs. 1% vs. 7% <u>Cosmetic outcome: MAL-PDT vs. cryotherapy vs. 5-FU</u> Good or excellent:	assessment was blinded. Unclear risk for selection bias. Women were overrepresented in this sample. Cosmetic outcome was not reported for placebo PDT: Selective reporting bias	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
			(45-99), 34 male, 48 female; localization: face, scalp: n=26, neck/trunk: n=13, extremities: n=52 5-FU: n=30 (36 lesions), mean age: 72.5 years (39-86), 11 male, 19 female, localization: face, scalp: n=7, neck/trunk: n=4, extremities: n=25		94% (77/82) vs. 66% (43/65) vs. 76% (16/21) (at 3 and 12 months)		
Morton et al. 2000★	To determine the optimal wavelength (red or green light) for the treatment of BD.	single-centre, randomised comparison study	16 participants (61 lesions), mean age: 73 years (50-87)	Lesion clearance rate Recurrence	Red light vs. green light Lesion clearance	Risk of bias was unclear: There was no evidence of any blinding, risk for	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	Application of ALA under occlusion for 4h, then illumination with green light (62.5 J/cm², 540±15 nm, fluence rate: 86 mW/cm²) Application of ALA under occlusion for 4h, then illumination ALA-PDT with red filtered light (125 J/cm², 630±15 nm, fluence rate: 86 mW/cm²)		number of lesions per patient varied between 1 and 6 (median 3) The study randomised 70 lesions, all of the included lesions were on the lower limbs ALA-PDT with green light, n=29 lesions, median treated lesion area=125 mm² (range 16-441 mm²) ALA-PDT with red filtered light, n=32 lesions, median treated	rate Safety	rate 94% (30/32) vs. 72% (21/29) Recurrence rate 88% (2) vs. 48% (7) The frequency and severity of pain experienced were similar between the two treatment groups.	attrition bias and selection bias was unclear.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
			lesion area=100 mm² (range 25 to 400 mm²)				
Morton et al. 1996★	To compare clearance and recurrence rates, adverse reaction profiles and scarring potential of ALA-PDT vs. cryotherapy Lesions were randomized to receive either cryotherapy with liquid nitrogen (single freeze-thaw cycle with a 2-3 mm rim for 20 s), or PDT using a portable desktop lamp incorporating a 300 W xenon short arc discharge source. ALA was applied topically 4 h before irradiation in the PDT group. Each lesion received 125 J/cm² at a fluence rate of 70mW/cm².	single-centre, randomised, comparative study ALA-PDT (125 J/cm²), applied topically 4 hours before irradiation in the PDT group (50 mg/cm² to cover the irradiation field including a clinically disease-free margin). Each lesion received 125 J/cm² at a fluence rate of 70 mW/cm² (n=20)	19 participants (40 lesions of BD in 3 men and 16 women) Lesions were randomised to receive ALA-PDT (n=20) or cryotherapy (n=20) The 20 lesions treated by cryotherapy were located on the legs in n=16), face (n=3) and hand (n=11). Lesions treated by FDT were also	Lesion clearance rate Recurrence Pain Adverse effects	ALA-PDT vs cryotherapy <u>Lesion clearance rate</u> 75% (15/20) vs. 50% (10/20) after 1 treatment 100% (after 2 treatments) vs. 100% (after 3 treatments) <u>Recurrence rate</u> 2 areas of BD recurred in the cryotherapy group after 6 and 8 months; re-treatment achieved response No recurrence in the PDT group	Baseline characteristics: The lesions treated by PDT were overall larger (median size 150 mm², range 25 to 441 mm²) compared with those treated with cryotherapy (median size 82 mm², range 30 to 360 mm²) Lesions treated by PDT were overall larger (median 150 mm², range 25-441 mm²) than those treated by cryotherapy (median 82 mm², range 30-360 mm²). The larger lesions in each group also appeared to be the most likely to require more than one	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
		cryotherapy (1 freeze-thaw cycle: 20 seconds). The freeze was maintained for 20 s. A single freeze-thaw cycle was used with a 2 to 3 mm rim of clinically healthy tissue in the treatment field (n=20)	located on the legs (n=7), face (n=2) and hand (n=1). Mean age 76 years (62 to 88 years)		<u>Overall complete response</u> after 1 year: 90% (cryotherapy) vs. 100% (PDT) <u>Pain</u> Cryotherapy: present in 19 lesions and described as mild in 12 and moderate in seven lesions. PDT: present in only 11 lesions and was mild in six and moderate in five lesions. <u>Adverse events:</u> Cryotherapy was associated with ulceration (5/20). infection (2/20) and recurrent disease (2/20): no such	treatment. Unclear risk of bias; there was no evidence of blinding of the assessors or patients	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					complications occurred following PDT.		
Patel et al. 2006★	To evaluate the preliminary efficacy and safety of imiquimod 5% cream Intervention: Application of imiquimod 5% cream daily at night for 16 weeks (n=15) Control: Application of placebo cream at night for 16 weeks (n=16)	single-centre, randomised, double-blind, placebo-controlled study	31 participants (31 lesions in 11 men and 20 women) with biopsy-proven BD placebo group: 2 men, 14 women Mean age: 74 years±8 Imiquimod group: 9 men, 6 women; mean age: 74 years±8	Participant complete clearance rate Recurrence rate Adverse events	Imiquimod vs. vehicle <u>Participant complete clearance rate</u> 73% (11/15) vs. 0% (ITT analysis) <u>Mean change in lesion area</u> between weeks 0 and 28 was greater in the imiquimod group (mean -322 mm^2, SD 519 mm^2) compared with the placebo group (mean -37 mm^2, SD 114 mm^2) <u>Recurrence rate</u> 0% (at 9 months)	Imbalances in the baseline characteristics of the 2 groups: The 2 groups were similar at baseline, but mean duration and size of lesion was greater in the imiquimod group (23 mm^2 to 1176 mm^2 compared with 84 mm^2 to 555 mm^2 in the placebo group) Low risk for bias, however, adverse events were not reported separately for the intervention and control group (selective reporting bias)	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Adverse events: 19 patients experienced signs and symptoms ranging in severity from mild transient itching only to edema with erosion and weeping.		
Perrett et al. 2007★	To compare MAL-PDT with topical 5% fluorouracil (5-FU) cream in the treatment of post-transplant epidermal dysplasia. 5-FU cream, massaged into lesional areas twice daily for 3 weeks MAL-PDT (dose 75 J/cm²) twice at a 1-week interval (cream was applied 1 mm thick to area and covered with a semipermeable adhesive dressing; 3 h later cream was washed off with normal saline before illumination with non-coherent red light)	open-label, single-centre randomised intra-patient comparative study	n=8 post-transplant participants (6 men, 2 women) with a history of epidermal dysplasia (8 AK, 10 BD) lesional size treated ranged from 39 mm² to 5010 mm² mean age of 59 years (range 46–71).	Complete clearance Reduction in lesional area Cosmetic outcome Patient preference Adverse events	MAL-PDT vs. 5-FU Complete clearance rate 89% (8/9) vs. 11% (1/9) Mean reduction in lesional area: 100% vs. 79% Cosmetic outcome. PDT achieved a superior cosmetic result and was rated as excellent in 100%	No deterioration in renal function was noted in any patient during the study. Small sample size The study had an unclear risk of bias due to insufficient information regarding randomization, and blinding of participants and investigators. For the outcome “cosmetic outcome” no	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
			n=7 renal transplant recipients, n=1 combined renal and liver transplant recipient mean duration of transplantation was 20 years (11–30 years) All eight patients were Fitzpatrick skin phototype 1 or 2.		<u>Patient preference:</u> All patients preferred PDT to 5-FU <u>Adverse events</u> All patients experienced moderate to severe pain at treatment sites during the illumination phase of PDT, by day 3 all PDT-treated lesions were pain free, while the mean pain score for 5-FU increased. The mean pain scores for 5-FU-treated lesions subsequently varied from 0.22 to 0.44, values considerably lower than those experienced	absolute data are provided → selective reporting bias	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					during the illumination phase of PDT. Other AEs: 5-FU: superficial erosions, crusting and pruritus PDT: crusting, pruritus, hyperpigmentation		
Salim et al. 2003★	To compare the efficacy and tolerability of PDT and topical 5-fluorouracil (5-FU) in BD. ALA-PDT: Application of ALA 4 h before illumination with 300-W Xenon lamp (100 J/cm² at 50 to 90 mW/cm²) 5-FU: Application of 5-FU 5% cream daily for 1 week then twice daily for 2 to 4 weeks	randomised comparative study	40 participants (8 men, 32 women) with 1 to 3 lesions All patients had skin type I-III Mean age 76 years (65 to 88 years) Localisation: PDT: all lesions located on legs	Complete clearance of lesions Recurrence rate Adverse events Pain	PDT vs. 5-FU <u>Lesion clearance</u> 88% (29/33) vs. 67% (22/33) <u>Recurrence rate</u> 2 lesions vs. 6 lesions (12 months) <u>Complete clinical clearance:</u> 82% (27/33) vs. 48% (16/33)(12 months)	The study had an unclear risk of bias. Women were overrepresented (ratio: 32:8)	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
			5-FU: legs n=25, arms n=4, face n=4		Adverse events: In the 5-FU group, severe eczematous reactions developed around seven lesions, ulceration in three and erosions in two. No such reactions occurred following PDT. Pain: There was no difference in overall pain experienced during each therapy.		
Wu et al. 2018	To evaluate the effects of and adverse reactions to plum-blossing needling therapy administered before ALA-PDT in Asian patients. PBN-ALA-PDT: vertical skin tapping with PBN before applying 10% ALA cream for 3 h under occlusion and narrowband light-emitting diode	Single-center, randomized controlled prospective, international study	n=24 Asian patients with 43 lesions 12 men and 12 women, mean age 55.5 years ± 10.1	Lesion complete clearance Recurrence rate Pain (score from 0-10	PBN-ALA-PDT vs. ALA-PDT monotherapy Lesion complete clearance: 27.78% (5/18) vs 10% (2/20) after 4 weeks and 2	Small sample size Results only apply to this sample and are not generalizable (Asian population) Adverse events are not reported separately for	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	irradiation (λ = 633±10 nm; 100–200 J/cm²). (n=21 lesions) ALA-PDT monotherapy: applying 10% ALA cream for 3 h under occlusion and narrowband light-emitting diode irradiation (λ = 633±10 nm; 100–200 J/cm²). (n=22 lesions)			scale) Adverse events	treatment session 77.78% (14/18) vs. 40% (7”0) at 6 weeks after 2/3 treatment sessions <u>Recurrence rate</u> 0% vs. 11.76% (2/17) <u>Pain</u> Mean value: 4.5 for both groups <u>Adverse events</u> All the lesions experienced slight erythema and swelling, and 6 lesions developed erosions, which healed in 2 weeks. Ulcerations were found in 2 lesions.	the subgroups: Selective reporting bias is likely. No information regarding the blinding of the patients or investigators.	

6.1.5. Full texts not included with reason

Author, year	Reason for exclusion (n=7)
De Haas 2007	Dose-finding study
Lui 2004	Dose-finding study
Mizutani 2012	No randomization
Morton 2005	Duplicate
Fayter 2010	Unclear outcomes
Puizina-Ivic 2008	Unclear outcomes
Brown 2005	No results reported for BD subgroup

6.1.6. Literature

Bath-Hextall FJ, Matin RN, Wilkinson D, et al. Interventions for cutaneous Bowen's disease. Cochrane Database of Systematic Reviews 2013(6):CD007281.
Cai H, Wang YX, Zheng JC, et al. Photodynamic therapy in combination with CO2 laser for the treatment of Bowen's disease. Lasers in Medical Science 2015;30(5):1505-10.
Genouw E, Verheire B, Ongenae K, et al. Laser-assisted photodynamic therapy for superficial basal cell carcinoma and Bowen's disease: a randomized intrapatient comparison between a continuous and a fractional ablative CO₂ laser mode. Journal of the European Academy of Dermatology & Venereology 2018;32(11):1897-905.
Kim HJ, Song KH. Ablative fractional laser-assisted photodynamic therapy provides superior long-term efficacy compared with standard methyl aminolevulinate photodynamic therapy for lower extremity Bowen disease. Journal of the American Academy of Dermatology 2018;79(5):860-68.
Ko DY, Kim KH, Song KH. A randomized trial comparing methyl aminolaevulinate photodynamic therapy with and without Er:YAG ablative fractional laser treatment in Asian patients with lower extremity Bowen disease: results from a 12-month follow-up. British Journal of Dermatology 2014;170(1):165-72.
Morton C, Horn M, Leman J, et al. Comparison of topical methyl aminolevulinate photodynamic therapy with cryotherapy or Fluorouracil for treatment of squamous cell carcinoma in situ: Results of a multicenter randomized trial. Arch Dermatol 2006;142(6):729-35. doi: 10.1001/archderm.142.6.729 [published Online First: 2006/06/21]
Morton CA, Whitehurst C, Moore JV, et al. Comparison of red and green light in the treatment of Bowen's disease by photodynamic therapy. British Journal of Dermatology 2000;143(4):767-72.
Morton CA, Whitehurst C, Moseley H, et al. Comparison of photodynamic therapy with cryotherapy in the treatment of Bowen's disease. British Journal of Dermatology 1996;135(5):766-71.
Patel GK, Goodwin R, Chawla M, et al. Imiquimod 5% cream monotherapy for cutaneous squamous cell carcinoma in situ (Bowen's disease): a randomized, double-blind, placebo-controlled trial. Journal of the American Academy of Dermatology 2006;54(6):1025-32.
Perrett CM, McGregor JM, Warwick J, et al. Treatment of post-transplant premalignant skin disease: a randomized intrapatient comparative study of 5-fluorouracil cream and topical photodynamic therapy. British Journal of Dermatology 2007;156(2):320-8.
Salim A, Leman JA, McColl JH, et al. Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease. British Journal of Dermatology 2003;148(3):539-43.
Wu Y, Wang P, Zhang L, et al. Enhancement of Photodynamic Therapy for Bowen's Disease Using Plum-Blossom Needling to Augment Drug Delivery. Dermatologic Surgery 2018;44(12):1516-24.

7. Squamous cell carcinoma treatment

(Therapie des PEK)

7.1. Question VI.1. Which treatment is recommended for the primary tumor?

(Frage VI.1. Welche Therapie des Primärtumors wird empfohlen?)

Expert consensus

7.2. Question VI.2. Which safety margin is recommended for the excision of the primary tumor?

(Frage VI.2. Welcher Sicherheitsabstand wird bei der Exzision des Primärtumors empfohlen?

Expert consensus

7.3. Question VI.3. When is re-excision recommended ?

(Frage VI.3. Wann wird eine Nachexzision empfohlen?)

Expert consensus

7.4. Question VI.4. When should a microscopic control of the excision margin be performed?

(Frage VI.4. Wann soll eine mikroskopische Randschnittkontrolle durchgeführt werden?)

Expert consensus

7.5. Question VI.5. Should sentinel lymph node biopsy be recommended? If yes, in which cases?

(Frage VI.5. Ist die Entfernung des Wächterlymphknotens indiziert? In welchen Fällen?)

De-novo-Recherche

7.5.1. PICO

PICO – Scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Patients with SCC	Sentinel lymph node biopsy	Prospective or retrospective trials vs. Observation	Efficacy (diagnostic accuracy)

7.5.2. Databases, searche strategy, number of results

Database	Search strategy	Date	Number of results
1. Search			
Medline	(squamous[Title] AND (skin[Title] OR cutaneous[Title])) AND (sentinel[Title/Abstract] OR "lymph node"[Title/Abstract]) NOT "case report" AND (English[Language] OR German[Language])	15th December 2016 (initial search)	122
		Update 30th May 2017	127

Database	Search strategy	Date	Number of results
		Update September 2020	187
Remarks and notes:-			

7.5.3. Selection criteria

Literature selection	
Number of total results	187
Inclusion criteria	Clinical trials (randomized and non-randomized), prospective and retrospective studies, systematic reviews, case series with ≥10 patients involved.
Exclusion criteria	Studies that do not report indication of SLN biopsy in cutaneous SCC but detection methods or expression patterns of genes or prognostic variables or technical procedures were excluded.
Number of results after abstract searching	37
Number of full texts reviewed	26

7.5.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Ahmed et al 2014	Analyze the feasibility and	Systematic review; n= 221 articles;	MEDLINE, PubMed, Cochrane, and	Analyze the feasibility and	Studies ranged from 1 to 15 patients		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	reliability sentinel lymph node biopsy (SLNB) for cutaneous head and neck SCC (HNSCC). Identify risk factors associated with a positive SLN.	were screened of these 11 publications with 73 patients were selected; 3 case series; 8 prospective cohorts.	ASCO databases searches conducted (1946-2013).	reliability SLNB for HNSCC. Identify risk factors associated with a positive SLN.	(median 5). Median age was 74 years. Median follow-up was 21.5 months. Average tumor size was 3.09 cm. At least 1 SLN was identified in 100% of patients (median 2). Ten (13.5%) had a positive SLN; no additional metastatic nodes were identified in 9 patients receiving completion lymphadenectomy. Three of 63 (4.76%) failed regionally following a negative SLNB. HNSCC SLNB is feasible and reliable for staging, with a false omission rate of 4.7% mirroring melanoma. Tumor diameter was not associated with SLN status (P = .09;		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					95% CI, -.27 to 3.02). Risk factors (tumor depth, perineural invasion, location, differentiation) were not consistently recorded. Prospective studies documenting high-risk features are required to further define its role.		
Allen et al 2015	To define the predictive value and role of SLNB combined with the different high-risk factors to determine which patients could benefit from SLNB.	Retrospective review; n=173	Patients with cutaneous SCC (cSCC) in whom SLNB was performed, published in the year 2000 until May 2012.	Sensitivity, specificity and negative predictive value (NPV) for the cumulative results for each risk factor.	Sensitivity for the total cohort was 79%, specificity was 100% and negative predictive value was 96%. The sensitivity, specificity and NPV were 78.26%, 100% and 95.14%, respectively, for tumor size >2 cm. Sensitivity, specificity and NPV for a tumor localized at a high-risk area were 72.63%, 100% and 96.74%,		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					respectively. Specificity was 100% as was NPV for immunosuppression. SLNB has a high NPV and low false-negative rate and carries a low risk of complications. SLNB proves to enhance prognostic information of high-risk cSCC. Longer follow-up times are needed to evaluate the efficacy on OS and DFS.		
Bobin et al 2018	To identify factors for survival in PM from CSCC of the head and neck	Retrospective study; n= 35	Cutaneous SCC of the head and neck with parotid metastases diagnosed between 2005 and 2015	Overall and specific survival; prognostic factors for parotid metastases.	Thirty-five patients were included. Mean time to onset of PM was 13 months. Overall 1-, 2- and 5-year survival was respectively 70, 66 and 59%. Independent prognostic factors comprised immunodepression, age at treatment,		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					positive CSCC margins, macroscopic facial nerve involvement, and metastatic cervical adenopathies.		
Chabrillac et al 2019	To identify prognostic factors associated with sentinel lymph node positivity	Retrospective study; n= 74	Patients with high-risk cSCC undergoing sentinel lymph node biopsy	Risk factors statistically associated with sentinel lymph node positivity	Seventy-four patients were included. Five (6.8%) procedures failed. Of the 69 patients assessed, the positive sentinel lymph node biopsy rate was 11.6% (n=8) with a false negative rate of 5.7% (n=4). The positivity of sentinel lymph node biopsy was associated with tumour size (p=0.0194).	Sentinel lymph node biopsy is an effective staging procedure for clinically N0 high-risk cutaneous squamous cell carcinoma, with acceptable morbidity. To date, 2 risk factors of sentinel lymph node positivity have been identified with statistical significance: tumour size and poor tumour differentiation.	3
Daniels et al 2020	To investigate the effect of the treatment package time (TPT) defined as the interval between date of	Retrospective study; n= 152	Node-positive cHNSCC patients involving either the parotid or cervical nodes treated with curative intent	OS, cHNSCC specific survival (CSS), PFS, and freedom from locoregional failure (FFLRF).	152 patients met the inclusion criteria. The 5-year OS, CSS, PFS, and FFLRF were 62% (95% confidence interval [CI], 54-71),	Prolongation of TPT to 14 weeks or longer may confer a lower probability of locoregional control and survival in	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	surgery and completion of postoperative radiation therapy (PORT) on tumor control and survival outcomes in node-positive cHNSCC treated with curative surgery and PORT		surgery with macroscopic tumor clearance followed by standard fractionation PORT from 2001 to 2014.		78% (95% CI, 71-87), 54% (95% CI, 46-64), and 76% (95% CI ,68-85), respectively. In a multivariable model, TPT ≥14 weeks was associated with worse outcomes in all endpoints (OS [hazard ratio (HR) 4.93; 95% CI, 2.54-9.56, P < .001], CSS [HR 6.09; 95% CI, 2.33-15.92; P Z .001], PFS [HR 4.29; 95% CI, 2.21-8.34; P < .001], and FFLRF [HR 4.63; 95% CI, 1.71-12.51; P=0.007]). Immunosuppression and the presence of ≥ 2 pathologically involved lymph nodes were also significant adverse factors for both OS and FFLRF, although extracapsular extension was also	patients with lymph node-positive cHNSCC treated with surgery and PORT. Timely referral and commencement of PORT is necessary to maximize long-term disease outcomes.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					associated with lower FFRLF. Delays to commencing PORT rather than treatment breaks accounted for the majority of cases with prolonged TPT.		
Demir et al 2011	To evaluate and identify the role of lymphoscintigraphy and sentinel lymph node biopsy in patients with high-risk cutaneous SCC (cSCC). Tumor size greater than 2 cm, depth of invasion greater than 4 mm grade 2 differentiation or greater, perineural invasion and recurrent tumors were also regarded as high-risk characteristics	Prospective study; n= 19	Patients with high-risk cSCC treated in one center	To evaluate and identify the role of lymphoscintigraphy and sentinel lymph node biopsy in patients with high-risk cSCC.	A total of 26 SLNs and 32 secondary lymph nodes were imaged on LS and were marked. During surgery, 29 SLNs, 21 secondary lymph nodes and three non-active lymph nodes were excised. In total, 53 lymph nodes were removed surgically. A histopathological study revealed that all lymph nodes were negative for metastasis. Patients were followed up for an average of 41.1 ± 22.2 months (7–80		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					months). Until the time of data collection, 14 patients were alive and had no regional lymph node or distant metastasis. Local recurrence was seen in only one patient, operated upon 38 months ago. The feasibility of determining SLNs using LS and an intraoperative gamma probe in patients with cSCC was shown. Unnecessary elective lymph node dissection and possible complications could be avoided in 19 patients.		
Durham et al 2016	To evaluate a single institution's experience with use	Retrospective review; n=53	Patients with HNSCC, at high risk for nodal metastasis	Sentinel node (SN) identification rate	In 53 patients with 54 tumors the SN identification rate	Rigorous study of SLNB for cutaneous SCC incorporating	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of SLNB for regional staging of SCC on the head and neck (HNSCC).		based on National Comprehensive Cancer Network (NCCN) risk factors, and treated with wide local excision (WLE) and SLNB from December 1, 2010, through January 30, 2015 in one institution.	SLNB positivity rate Local recurrence Regional nodal recurrence Distant recurrence.	was 94%. The SLNB positivity rate was 11.3%. On more thorough tissue processing and IHC, metastatic SCC was identified in 2 of 5 (40%) cases previously deemed negative. After reclassification of these cases, the adjusted SLNB positivity rate was 15.1%. The adjusted rate of false omission was 7.1% (95% CI, 2%-19%). Nodal disease developed in 20.8% overall. Angiolymphatic invasion (Cohen d, 3.52; 95% CI, 1.83-5.21), perineural invasion (Cohen d, 0.81; 95% CI, 0.09-1.52), and clinical size (Cohen d, 0.83; 95% CI, 0.05-1.63) were associated with	prospectively-collected comprehensive data sets based on standardized treatment algorithms is justified with potential to modify clinical practice. Our study demonstrates the critical importance of serial sectioning and IHC of the SLNB specimen for accurate diagnosis. Use of the NCCN guidelines may facilitate identification of patients with SCC at high risk for nodal metastasis.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					the presence of nodal disease.		
Feinsten et al 2019	To characterize the risk factors for and clinical course of cutaneous SCC with nodal metastasis	Retrospective study; n= 53	Patients with cSCC and nodal metastasis	Disease-free survival rate after treatment of nodal disease	Most patients were men (84.6%, 44/52), and almost all primary tumors were on the head and neck (96.2%, 51/53). Most primary tumors were characterized by known “high-risk features” including perineural invasion (56.6%, 30/53), diameter ≥2 cm (54.7%, 29/53), invasion beyond subcutaneous fat (43.4%, 23/53), and poor differentiation (32.1%, 17/53). In addition, many tumors were recurrent (52.8%, 28/53), and many patients were immunosuppressed (30.8%, 16/52). Disease-free survival after treatment of		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					nodal disease was 7.5% (4/53) at 5 years.		
Fukushima et al 2014	To evaluate the efficacy of sentinel node biopsy for cutaneous SCC (cSCC)	Retrospective study; n= 54 patients	Patients with SCC who underwent SLNB in the Kumamoto University Hospital between 2006 and 2012	To evaluate the efficacy of sentinel node biopsy for cSCC	The positive rate of SLNB in SCC was 7.4%. If the cases were limited to more than T2, the positive rate was 12.9%. Three of 41 patients who was estimated negative LN metastasis by the preoperative tests had micrometastases (7.3%). Among 13 patients who were suggested to have metastasis in the preoperative tests, only one patient had histological metastasis. One patient with SCC located in the lower lip showed negative SLNB and subsequently developed node		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					recurrence. In conclusion, the efficacy of SLNB in SCC is comparable to that of melanoma in the positive rate. There are two kinds of benefit, avoidance of unnecessary complete lymph node dissection and early detection of metastasis.		
Gore et al 2016	To determine the rate of sentinel lymph node metastasis in cutaneous SCC with 1) tumor size>2 cm; (2) invasion into subcutaneous fat or tumor thickness >5 mm; (3) poorly differentiated tumor; (4) perineural invasion (PNI); (5) lymphovascular invasion (LVI); (6)	Prospective study; n=57 patients	Patients from one center with high-risk cutaneous SCC were assessed with sentinel node biopsy (SNB) either at the time of primary cutaneous tumor resection or at secondary wide local excision between 2010 and 2013.	Rate of nodal metastasis in “high-risk” cutaneous SCC. To examine whether the accepted clinicopathological factors should be considered “high-risk”	Of 57 patients, 8 (14%) had nodal metastasis. During a mean of 19.4 months, 9 patients developed recurrence and 6 died of cutaneous SCC. Significant predictors of metastasis are the number of high-risk factors (p5.008), perineural invasion		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	local recurrence in the setting of adequate prior resection margins; (7) ear or lip location; (8)Immuno-compromise (post-organ transplant, chemotherapy); and(9) carcinoma in a preexisting scar. to examine whether the accepted clinicopathological factors should be considered “high-risk,” and to decide whether a randomized controlled trial is feasible.				(PNI; p5.05), and lymphovascular invasion (LVI; p5.05). Lymph node metastasis occurs in 14% of patients with high-risk cutaneous SCC. A clinical trial with over 1300 patients would be required for a randomized controlled trial with 80% power to detect a significant difference in DFS.		
Haisma et al 2016	To identify independent risk factors for lymph node metastasis in patients with cHNSCC and to evaluate the impact of lymph node	Retrospective study; n= 36 patients with 545 primary cHNSCC	Patients with primary cHNSCC treated between 2000 and 2012 at a tertiary care center (University Medical Center Groningen, the Netherlands).	Disease-specific survival and OS	Three hundred thirty-six patients with 545 primary cHNSCCs were included. The median follow-up period was 43 months (range, 1-	Lymph node metastases from cHNSCC are common with diminished survival rates. This study confirmed some well-known risk factors, but also	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	metastasis on prognosis.				176 months). lymph node metastasis occurred in 55 patients (16.4%). The following independent risk factors of cHNSCC for the development of lymph node metastasis were identified: location on the ear, tumor diameter [50 mm, moderate and poor differentiation, and tumor thickness [2 mm. There was a significant decline in disease-specific survival and overall survival in patients with lymph node metastasis compared to patients without lymph node metastasis.	found moderate differentiation as an independent risk factor for lymph node metastasis.	
Hirshoren et al 2017	To describe the clinical outcomes and prognostic	Retrospective single-center study; n=149	Patients with node-positive cHNSCC treated surgically at	OS Locoregional	The median number of positive lymph nodes from 149		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	factors for patients with node-positive cutaneous head and neck SCC (cHNSCC) who underwent lymphadenectomy.	lymphadenectomies	a single tertiary center between June 1, 2001, and December 31, 2014.	control rates Prognostic factors	lymphadenectomies was 2 in the neck and 1 in the parotid gland. The 5-year OS and locoregional control rates were 50% and 77%, respectively. OS was worse among older patients (hazard ratio [HR], 1.04; p = .015), immunosuppressed patients (HR, 2.06; p = .034), and patients with a high total lymph node ratio (calculated from the number of positive lymph nodes divided by the total number of nodes; multivariate analysis [MVA]; HR, 1.13; p = .019).		
Kofler et al 2020	To analyze the role of the SLNB in lymph node status and survival	Retrospective study; n= 720	Patients with high-risk SCC (tumor thickness > 5 mm)	Proportion of distant metastasis and tumor-specific survival	A total of 11.11% of the patients showed lymph node metastasis in the course of their		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					treatment, with no difference in the proportion of patients in the SLNB group (11.9%) and the observation group (11.4%) (p = 0.873). The proportion of distant metastasis also did not differ between the groups (p = 0.898). In 3.96% of the patients in the SLNB group, metastasis was found in the sentinel lymph node. Tumor-specific death was observed in 7.14% of the patients in the SLNB group and 4.74% in the observation group (p = 0.269).		
Krediet et al 2015	To evaluate risk factors for metastasis in patients with cutaneous SCC	Retrospective review; n=143	Patients who underwent excision of cSCC between January 2005 and August 2009 at a	To evaluate risk factors for metastasis in patients with cSCC in a large cohort	The risk for metastases from a cSCC is associated with tumor thickness > 4 mm and tumor		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(cSCC) in a large cohort study with long-term follow-up and to determine the value of SLNB.		tertiary referral center	study with long-term follow-up. To determine the value of SLNB.	recurrence. All metastases occurred within 2 years after excision. SLNB seems to have a low sensitivity for metastases of cSCC. Despite a negative SLNB, some patients developed metastatic disease, underlining the necessity of close follow-up of high-risk patients in the first 2 years after excision, regardless of SLNB status. Based on our data SLNB does not provide diagnostic value for patients with cSCC.		
Maruyama et al 2016	Effects of SLNB on the further course of cSCC	Prospective study; n= 169	Patients who underwent treatment for cSCC between 2004 and 2015 in the Department of	Efficacy of sentinel lymph node biopsy for cSCC. Compared the outcomes with	Patients who were followed up for at least 6 months or developed metastases within the follow-up period		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			Dermatology, Tsukuba University Hospital.	those in cSCC patients who did not undergo concurrent SLNB.	were included. Forty-nine patients underwent sentinel lymph node biopsy, whereas 120 patients did not, including 13 who exhibited clinical lymph node metastases before treatment. Of these 49 patients, nine (18.4%) presented with sentinel lymph node metastasis, which occurred after treatment in three (6.1%) of them (false-negative). Among the 107 patients who did not undergo lymph node biopsy, 12 (11.2%) developed post-treatment metastases. The metastasis-free and DSS rates were not significantly		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					different in those who did or did not undergo sentinel lymph node biopsy. Patients with clinical lymph node metastases had a higher risk compared with those without. Patients with T2–T4 tumors had a higher risk compared with those with T1 tumors. When selecting for those with T2 tumors or greater, the same lack of relationship was observed. In this small retrospective cohort, in patients with cutaneous squamous cell carcinoma, there were no significant differences in metastasis-free and DSS rates between those who did or did not undergo sentinel		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					lymph node biopsy, regardless of T staging.		
McLaughlin et al 2017	To determine the rate of regional lymph node involvement in patients with cutaneous head and neck squamous cell carcinoma (cHNSCC)	Retrospective chart review; n= 30 solid organ transplant patients; 383 cHNSCC resections	All solid organ transplant recipients who underwent surgery between 2005 and 2015 for a cHNSCC at the Hospital of the University of Pennsylvania Department of Dermatology and/or Otorhinolaryngology	Rate of regional lymph node involvement; Time from first diagnosis to regional lymphatic disease	The average age of the patient was 63. Seven patients (5%) developed regional lymph node metastases (3 parotid, 4 cervical lymph nodes). The mean time from primary tumor resection to diagnosis of regional lymphatic disease was 6.7months. Six of these patients underwent definitive surgical resection followed by adjuvant radiation; one patient underwent definitive chemoradiation. 6 of the 7 patients died of disease progression with a mean survival of 15months. The	This is the largest study to date of cutaneous SCC in solid organ transplant patients. In addition, all of these lesions were limited to the head and neck. Despite the low rate of regional lymph node involvement demonstrated in these patients, their extremely poor prognosis makes managing a N0 neck in an immunocompromised patient a difficult clinical dilemma.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					average follow-up time was 3years (minimum 6months). Solid organ transplant recipients with cutaneous squamous cell carcinoma of the head and neck develop regional lymph node metastasis at a rate of 5%. Regional lymph node metastasis in this population has a poor prognosis and requires aggressive management and surveillance.		
Navarrete-Dechent et al 2015	To perform a review of the currently available evidence, in the form of systematic reviews, meta-analysis, trials, and case series and analyzed the features that	Retrospective review; n= 156 articles found; 16 articles included all types of studies (systematic reviews, meta-analysis, trials, and case series) published to date in English	Patients included in publications in the MEDLINE database published through November 25, 2014 found using the key words: ''squamous'' or ''non-melanoma'' or ''non-melanoma''	To perform a review of the currently available evidence, analyzed the features that define a group of cSCC patients who are at risk of developing nodal	This systematic review identified an overall positive rate for SLNB of 13.9% (32 of 231 patients) and a false-negative rate of 4.6% (10 of 215 patients) in cSCC. The authors		1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	define a high-risk cutaneous SCC (HRcSCC) and the feasibility of performing sentinel lymph node biopsy in this group of patients	and Spanish	or ''squamous cell carcinoma'' AND ''cutaneous'' or ''skin'' AND ''sentinel lymph node.''	metastasis and might benefit from SLNB	usually stated that patients had high-risk factors for lymph node involvement. However, these high-risk factors were not homogeneous and not always adequately detailed. Takahashi et al documented survival in 26 patients with HRcSCC with 23.1% (6 of 26) having a positive SLNB. This study included patients with external genital squamous cell carcinoma (SCC). The authors reported a 3-year survival 100% for SLN-negative SCC cases but only 20.8% for SLN-positive cases. Four patients died during the follow-up, all having a positive SLNB, 3 of		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					3 external genital SCC, and 1 of 3 cSCC. Patients with cSCC are at risk of developing nodal metastasis, death, or both, especially if risk factors are present. SLNB may identify occult nodal metastases in patients at risk. Its utility in cSCC is still to be confirmed because it is considered to be more precise than imaging procedures and less invasive than lymph node dissection and may ultimately emerge as the gold standard for HRcSCC staging.		
Quinn et al 2019	To analyze costs and survival in patients with cHNSCC based on their tumor and nodal metastasis			To determine the most cost-effective strategy for the treatment of patients with cHNSCC using one-	Not performing an SLNB results in 12.26 QALYs and a cost of $3712.98. Performing an SLNB resulted in a 0.59		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	staging and whether or not they received an SLNB			way, two-way, and probabilistic sensitivity analyses were performed to validate the results.	decrease in QALYs and an increase in cost of $1379.58 for an incremental cost-effectiveness ratio of -2338.27. This trend remained the same across all tumor stages and remained consistent within most sensitivity analyses.		
Ross et al 2006	To review reported SCC in which sentinel lymph node biopsy (SLNB) whether SLNB proofs as a staging tool for patients with high-risk SCC.	Retrospective review; n= 692	Patient's results of SLNB in patients with cutaneous SCC reported in the English medical literature. A total of 607 patients with anogenital SCC and 85 patients with non-anogenital SCC were included in the analysis.	The percentage of cases with a positive sentinel lymph node (SLN) was calculated. False-negative and no detection rates were tabulated. Rates of local recurrence, nodal and distant metastasis, and disease-specific death were reported.	A SLN could not be identified in 3% of anogenital and 4% of non-anogenital cases. SLNB was positive in 24% of anogenital and 21% of non-anogenital patients. False-negative rates as determined by completion lymphadenectomy were 4% (8/213) and 5% (1/20), respectively. Most false-negative results were		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					reported in studies from 2000 or earlier in which the combination of radioisotope and blue dye was not used in the SLN localization process. Complications were reported rarely and were limited to hematoma, seroma, cutaneous lymphatic fistula, wound infection, and dehiscence.		
Samsanavicius et al 2018	To determine cSCC micrometastases when non-invasive examination methods do not detect them	Retrospectve study; n= 88	Patients with cSCC and no distant or regional lymph node metastases detected during instrumental tests, grouped into low- and high-risk CSCC groups, who underwent one-stage surgery – radical tumour excision and sentinel lymph	Detection rate of cSCC micrometastases.	153 SLN were detected and excised in 88 patients. Micrometastases were found in five SLNs of three patients with high-risk CSCC. The rate of micrometastases was 3.4%; however, in the high-risk group it was 6.5%. The mean diameter	In patients with cSCC the rate of micrometastases directly correlates with the depth and diameter of the tumour. In patients with high-risk cSCC the rate of micrometastases is 6.5%.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			node/nodes biopsy (SLNB)		of CSCC with micrometastases in SLN was 5.6 ± 3.5 cm, and that without micrometastases was 1.5 ± 1.1 cm (p = 0.003). The depth of CSCC according to Breslow in the patients with detected micrometastases in SLN was 3.5 ± 1.2 mm, and that without detected micrometastases was 2.2 ± 1.4 mm (p = 0.047). Patients with micrometastases in sentinel lymphatic nodes under- went radical lymphadenectomy. There was neither recurrence of CSCC metastases in regional lymph nodes nor distant metastases during the research period		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					detected.		
Schmitt et al 2014	To define factors closely associated with positive SLNB findings in non-anogenital cSCC.	Retrospective review; n= 130 patients for AJCC staging; n= 117 for the alternative system	Patients with non-anogenital cSCC and SLNB.	To evaluate the positive SLNB findings by cSCC stage, quantified as the number and percentage of positive nodes. To analyze which stages in the American Joint Committee on Cancer (AJCC) criteria and a recently proposed alternative staging system are most closely associated with positive SLNB findings in non-anogenital cSCC.	A positive SLN was identified in 12.3%of all patients. All cSCCs with positive SLNs were greater than 2 cm diameter. The AJCC criteria identified positive SLNB findings in 0 of 9 T1 lesions (0%), 13 of 116 T2 lesions (11.2%), and 3 of 5 T4 lesions (60.0%). No T3 lesions were identified. The alternative staging systems identified positive SNLB findings in 0 of 9 T1 lesions (0%), 6 of 85 T2a lesions (7.1%), 5 of 17 T2b lesions (29.4%), and 3 of 6 T3 lesions (50.0%). Rates of positive SLNB findings in patients with T2b lesions were statistically higher		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					than those with T2a lesions (P = .02, Fisher exact test) in the alternative staging system. Our findings suggest that most cSCCs associated with positive SLNB findings occur in T2 lesions (in both staging systems) that are greater than 2 cm in diameter. The alternative staging system appears to more precisely delineate high-risk lesions in the T2b category that may warrant consideration of SLNB. Future prospective studies are necessary to validate the relationship between tumor stage and positive SLNB findings and to		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					identify the optimal staging system.		
Skulsky et al 2017	To evaluate surgical procedures as SLNB for high-risk cSCC defined as ((>2 cm), a deeply invasive lesion (>2 mm), incomplete excision, high-grade/desmoplastic lesions, perineural invasion (PNI), lymphovascular invasion, immunosuppression	Embase, CENTRAL, and MEDLINE were searched for published studies, clinical trials, and guidelines on high-risk cutaneous SCC of the head and neck. Reference lists from the relevant articles acquired were also searched. The search date range used January 2016 as the end date; no start date was specified. The following terms are examples of terms that were combined in the database searches: "high-risk cutaneous squamous cell carcinoma, guidelines, excision	Patients with high-risk cSCC	To compare two different guidelines (NCCN and AJCC) in what concerns SCC high-risk features discrepancies and omissions. The following aspects were evaluated: Tumor size Depth of invasion Recurrent setting Poorly differentiated lesions Histopathological subtype Perineural invasions Lymphovascular invasion High-risk anatomical location Immunosuppressed sate	The AJCC TNM staging system considers the following high-risk features when determining the primary tumor (T) classification: depth (>2mm thickness or Clark level ≥IV), anatomic location, poor histological differentiation, and perineural invasion (PNI). Tumors are classified as T2 in 2 ways: (1) tumors > 2 cm in greatest dimension, or (2) any size tumor with ≥2 high-risk features. NCCN has also identified several high-risk features of cSCC. High-risk cSCC, as per NCCN Guidelines refers to	Future studies are required to evaluate the extent to which the inclusion of these additional high-risk features would improve tumor staging and prognostic outcomes. Ultimately, a consensus on the definition of high-risk features of cSCC needs to be reached in order to produce accurate and practical treatment guidelines that will enhance patient care.	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		margins, organ transplant, immuno-suppression, depth, recurrence, sirolimus, cyclosporine, azathioprine, sentinel lymph node biopsy, superficial parotidectomy, elective neck dissection, and Mohs micrographic surgery." All records obtained from our searches were screened by title and abstract for selection.		Incomplete excision	a greater propensity for local recurrence and/or metastasis. NCCN classifies cSCC as high-risk if≥1 feature is present. Currently, there is no unanimous consensus on the high-risk features of cSCC. Although NCCN Guidelines and the AJCC TNM classification system share some overlapping high-risk features of cSCC, significant discrepancies exist. In comparison with NCCN Guidelines, the AJCC omits several high-risk features associated with poor clinical outcomes, including immunosuppression, lymphovascular invasion, recurrent tumors, and certain		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					prominent high-risk anatomic locations. Notably, neither NCCN nor the AJCC include incomplete excision as a feature warranting a tumor's treatment as high-risk cSCC. As a compounding factor, there are no guidelines for managing the deep tumor margin.		
Takahashi et al 2014	To investigate the usefulness of and indication criteria for SNB for cutaneous SCC (cSCC)	Retrospective review; n= 26	Patients who were diagnosed with high-risk cSCC and underwent SNB at our hospital from July 2005 to April 2012	To investigate the usefulness of and indication criteria for SNB for cSCC	Of the 26 patients, recurrence or metastasis was observed in 5 cases (19.2%). Six cases (23.1%) were sentinel node (SN) metastasis-positive. All cases that were SN metastasis-negative survived, and 4 of 6 SN metastasis-positive (66.7%) cases died of the original disease. The 3-year survival		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					rates of all cases, SN metastasis-negative cases, and SN metastasis-positive cases were 82.2%, 100%, and 20.8%, respectively. Tumor thickness was a significant risk factor for SN metastasis (p=0.049). Recurrence occurred in 4 of 7 cases involving external genitalia, 3 of which died. The 3-year survival rates of external genitalia and non-genital cases were 47.6% and 94.1%, respectively (p= 0.016). SNB aided the early discovery and treatment of latent lymph node metastasis and helped predict whether SN metastasis had		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					occurred, and therefore helped predict patient prognosis. These results suggest that thickness of the primary lesion is an indication criterion for the use of SNB in cases of cSCC. SNB should be considered in cases where tumor thickness is ≥ 2 mm and actively performed in cases ≥ 5 mm.		
Tejera-Vaquerizo et al 2019	To analyze the frequency of SLN metastasis in published series of cSCC in the context of the eighth edition of the American Joint Committee on Cancer (AJCC-8) and the Brigham and Women's Hospital (BWH) staging	Retrospective analysis; n= 153	Studies included in the analysis were those evaluating patients with cSCC who underwent SLN biopsy and that described biopsy results.	Rate of SLN metastases	In total, 153 patients with 24 positive SLN biopsies (15.7%) were included. Based on the AJCC-8 criteria positivity rates in the T2 and T3 categories were 8.3% (1/12 patients) and 25% (8/32), respectively. Using the BWH system there were, 2/33 in	It would seem reasonable to recommend SLN biopsy for patients with AJCC-8 Stage T3+ disease or BWH Stage T2b/T3 disease. Both the AJCC-8 and the BWH systems would appear to be useful for staging cSCC of the trunk and	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	criteria				category T2a (6.5%), and 5/17 in category T2b (29.8%). On applying the same criteria to tumors of the trunk and extremities the results were similar.	extremities.	
Tseros et al 2016	To analyze the correlation between lymph node ratio (LNR) and outcome - time to disease progression (TTDP) and OS - in patients who have undergone surgery for metastatic cutaneous nodal HNSCC.	Retrospective study; n= 238	Patients with metastatic cutaneous nodal HNSCC.	TTDP and OS.	In total, 193 males and 45 females with a median of age 68 years were identified, with a mean recorded LNR of 0.15. On multivariate analysis, an LNR cutpoint of 0.21 was a significant predictor of decreased TTDP (HR 2.34, 95 % CI: 4.40–0.49; p = 0.009] and OS (HR 2.75, 95 % CI 1.57–4.82; p< 0.001). Forty-nine of 238 patients (2 %) developed recurrence, with most recurrences	LNR is potentially an independent predictor of outcome in patients with metastatic cutaneous nodal SCC. The clinical relevance of this finding requires further validation.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					being regional (29 of 49; 59 %). A total of 17 % of patients with an LNR ≤0.21 recurred compared with 40 % for patients with an LNR >0.21.		
Vasan et al 2018	To validate the prognostic significance of the lymph node ratio in metastatic cHNSCC	Retrospective study; n= 326	Patients with cHNSCC with parotid and/or cervical nodal metastases was performed.	OS and disease-free survival	Data reported included 77 recurrences and 101 deaths. A lymph node ratio of 6% was a significant predictor of shorter DFS (HR 1.62; 95% CI: 1.11-2.38; P=0.01) and OS (HR 1.63; 95% CI 1.03-2.58; P=0.04) on multivariable analysis.	The lymph node ratio is an independent prognosticator of survival out- comes in patients presenting with metastatic head and neck cutaneous SCC. A lymph node ratio >6% is a significant threshold to categorize patients into low and high risk.	3

7.5.5. Literature

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7.6. Question VI.6. For which patients should lymph node dissection be recommended?

(Frage VI.6. Für welche Patienten ist eine Lymphknotendissektion zu empfehlen?)

Systematic search

7.6.1. PICO

PICO – Scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Patients with SCC	Lymph node dissection	Observation; other local therapies	Local/lymph node recurrence, local recurrence free survival, DFS, time to metastatic disease, OS

7.6.2. Databases, search strategy, number of results

Database	Search strategy	Date	Number of results
1. Search			
Medline	(squamous[Title] AND (skin[Title] OR cutaneous[Title] OR head[Title] OR neck[title])) AND (lymph node dissection[Title/Abstract] OR lymph adenectomy[title/abstract]) NOT “case report” AND (English[Language] OR German[Language]) ("lymph node excision"[MeSH Terms] OR ("lymph"[All Fields] AND "node"[All Fields] AND "excision"[All Fields]) OR "lymph node excision"[All Fields] OR ("lymph"[All Fields] AND "node"[All Fields] AND "dissection"[All Fields]) OR "lymph node	15th December 2016 (initial search)	

Database	Search strategy	Date	Number of results
	dissection"[All Fields]) AND cutaneous[All Fields] AND ("carcinoma, squamous cell"[MeSH Terms] OR ("carcinoma"[All Fields] AND "squamous"[All Fields] AND "cell"[All Fields]) OR "squamous cell carcinoma"[All Fields] OR ("squamous"[All Fields] AND "cell"[All Fields] AND "carcinoma"[All Fields]))	Update 30th May 2017	30
		Update September 2020	30
Remarks and notes:			

7.6.3. Selection criteria

Literature selection	
Number of total results	30
Inclusion criteria	Clinical trials (randomized and non-randomized), retrospective and prospective reviews, systematic reviews, case series ≥10 patients included
Exclusion criteria	Studies that include oral/esophageal SCC or SLN biopsy, which were already addressed in question IV. 2 were excluded.
Number of results after abstract searching	18
Number of full texts reviewed	18 (updated)

7.6.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Amoils et al 2019	To describe outcomes in one	Retrospective review; n=80	Patients treated for regionally	OS, failure rates, results by	On multivariate regression,	Regionally metastatic	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	institution, including patterns of metastasis, clinicopathologic factors related to survival, and failure rates. To stratify results by treatment modality.		metastatic cutaneous HNSCC	treatment modality	cutaneous primary >2 cm (p = .03) and extracapsular spread (ECS; p = .01) were significantly associated with decreased OS. Location of regional metastasis (neck vs parotid vs both) did not affect OS (p = .2), nor did the presence of a cutaneous primary at the time of presentation (p = .9). The 3-year survival was 43%, 52%, and 49% for surgery alone, adjuvant radiation, and adjuvant chemoradiation, respectively. Fifty-one percent of patients had a recurrence of their disease.	cutaneous HNSCC is an aggressive disease associated with high recurrence rates. Patients with tumors >2 cm and ECS have poorer OS despite adjuvant therapy.	
Bergstrom et al 2008	To review the available information on the	Review	n.a.	n.a.	Staging systems, which account only for the horizontal	New data from SCC studies help to predict high-risk	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	high-risk SCC patients treatment To define patients which may benefit from lymph node dissection				diameter and invasion of subcutaneous structures of cSCC may not be adequate to stratify risk and predict metastasis. Selective neck dissection or sentinel lymph node biopsy: elective neck dissection remains the standard of care for invasive SCC of the head and neck.	SCCs and, as in malignant, how to take advantage of SLNB to diagnose metastatic disease. The current tumor node metastasis classification could be refined to better predict which are “bad actors”. The role of HPV in SCC carcinogenesis continues to be elucidated and represents a potential approach to targeted therapy and prevention.	
Cannon 2016	To investigate the factors associated with elective neck dissection (END) in this population and the survival difference with END com- pared with observation for patients with a cN0 neck.	Retrospective; n= 59. Case series with chart review	Patients were treated surgically for head and neck cSCC with skull base invasion via perineural spread with a cN0 neck from 2004 to 2014.	Primary outcomes were disease-free survival (DFS) and overall survival (OS).	Fifty-nine patients met inclusion criteria: 28 underwent an END and 31 underwent neck observation. Free tissue transfer reconstruction was significantly associated with END (P <.001). Patients	END was more commonly used in cases requir- ing free tissue transfer. The use of END for head and neck cSCCs that have invaded the skull base is not routinely per- formed but was found to be	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					treated with an END had significantly improved 5-year DFS (57% and 32%, P = .042) and OS (60% and 37%, P = .036) compared with those who were observed and a significantly reduced rate of regional recurrence (9% and 37%, P = .024). The rate of occult nodal metastasis identified with END was 36% and is approxi-mately equal to the regional failure rate of the neck obser-vation group (37%).	associated with a survival advantage and reduced regional recurrence rate.	
Ebrahimi et al 2010	To analyze the distribution of regional nodal metastases according to the primary tumor location in patients with cutaneous squamous cell	Retrospective study; n= 295 neck dissections	Patients with clinically evident regional metastases from cSCCHN between 1987 and 2009 from one institution	To analyze the distribution of regional nodal metastases according to primary tumor location in patients with cSCCHN	Level I involvement in the absence of level II or III only occurred in patients with facial primaries. In patients with clear nodes in level II–III, the risk of level IV–V involvement was		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	carcinoma of the head and neck (cSCCHN).				0.0% for external ear primaries, 2.7% for face and anterior scalp, and 15.8% for posterior scalp and neck. In patients undergoing parotidectomy for metastatic cSCCHN with a clinically negative neck, the results of this study support selective neck dissection including level I–III for facial primaries, level II–III for anterior scalp and external ear primaries, and levels II–V for posterior scalp and neck primaries.		
Forest et al 2010	Review of clinical and pathological information of patients treated for metastatic cutaneous SCC (cSCC) to the parotid and/or	Retrospective study; n=215 patients	Patients with treated with curative intent between 1987 and 2007 for metastatic HN cSCC to the parotid and/or neck were	To identify potential prognostic factors using univariate and multivariate analyses. To elaborate a	All patients had surgery as their primary treatment; 148 had parotidectomy with neck dissection, 50 parotidectomy alone, and 18 neck		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	neck was conducted. Potential prognostic factors were analyzed using univariate and multivariate analyses. A staging system was elaborated and externally validated.		identified.	staging system and validated it externally.	dissection alone. One hundred seventy-five patients received postoperative radiotherapy. On univariate analysis, the number of involved lymph nodes (P < .001), maximal size (P=.01), and extracapsular spread (P=.003) were found to be significant predictors of survival. On Cox regression, the number of involved lymph nodes as single or multiple (P=.006) was significant. The N1S3 staging system incorporates involved lymph nodes from the parotid and neck (single or multiple) and the size (< or >3 cm). This system demonstrates a significant predictive		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					capacity for locoregional control (P < .001), DSS (P<.0001), and OS (P<.0001). N1S3 was tested on a different cohort of 250 patients, and the results confirmed those obtained from our primary analyses. The N1S3 system stages patients according to the number of involved lymph nodes and size, and incorporates parotid as 1 of the regional levels. These 2 predictors are easily applied to both clinical and pathological data.		
Girardi et al 2019	To evaluate the prognostic features among patients with head and neck cutaneous	Retrospective study; n=38	Patients with head and neck cutaneous squamous cell carcinoma with parotid and/or	Disease recurrence and death due to the disease	Thirty-eight cases of head and neck cutaneous squamous cell carcinoma with parotid and/or neck	Head and neck cutaneous squamous cell carcinoma with parotid lymph node	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	squamous cell carcinoma exhibiting regional metastasis.		neck metastasis		metastasis were identified. Overall, 18 (47.3 %) patients showed parotid metas- tasis alone, 12 (31.5 %) exhibited neck metastasis alone and 8 (21.0 %) had both. A primary tumor in the parotid zone (Hazard Ratio - HR = 5.53; p = 0.02) was associated with improved disease-specific survival. Poorer disease-specific survival was observed in patients with higher primary tumor diameter (HR = 1.54; p = 0.002), higher depth of invasion (HR = 2.89; p = 0.02), invasion beyond the subcutaneous fat (HR = 5.05; p = 0.002), neck metastasis at first presenta- tion (HR = 8.74; p < 0.001), number of	metas- tasis demonstrated better outcomes than cases with neck metastasis.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					positive lymph nodes (HR = 1.25; p = 0.004), and higher TNM stages (HR=7.13; p = 0.009). Patients presenting with isolated parotid metastasis dur- ing all follow-ups had better disease-specific survival than those with neck metastasis or both (HR = 3.12; p = 0.02).		
Kovatch et al 2019	To report one institutional experience, management, and outcomes of cutaneous periauricular squamous cell carcinoma (SCC).	Retrospective chart review; n=112	Patients undergoing treatment of cutaneous peri-auricular SCC from 2000 to 2016	Overall survival, disease-specific survival, and disease-free survival at 3 years	A total of 112 patients had a median follow-up of 24.5 months, a mean 6 SD age of 75.7 6 10.6 years, and a strong male predominance (93.8%). Site distribution shows 87 (77.7%) auricular, 26 (23.2%) preauricular, and 10 (8.8%) post- auricular lesions. Of auricular lesions, tumors	Among cutaneous SCC, periauricular subsites pose treatment challenges related to surrounding anatomy and represent a unique tumor population. The reported propensity toward recurrence and patterns of metastasis may better guide the treatment of	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					involved the tragus (n = 3, 3.4%), helix/antihelix (n = 47, 54.0%), conchal bowl (n = 31, 35.6%), external auditory canal (n = 18, 16.1%), and lobule (n = 3, 3.4%). Most patients presented at stage I (52.7%) versus stages II (28.6%), III (6.3%), and IV (12.5%). Patients were largely treated surgically with primary tumor resection ranging from wide local excision to lateral temporal bone resection (6 parotidectomy and neck dissection), with 17.0% and 5.4% receiving adjuvant radiation and chemoradia- tion, respectively. Metastatic spread was seen to the parotid (25.9%) and	aggressive tumors to include regional nodal dissection.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					neck (26.8%), with most common cervical spread to level II. Overall survival, disease-specific survival, and disease-free survival at 3 years were 62%, 89%, and 56%, respectively. Nodal disease was associated with worse disease-specific survival (P < .001) and disease-free survival (P = .042). Pre- and postauricular sites were associated with worse overall survival (P = .007) relative to auricular sites.		
Martinez et al 2007	To review the available literature regarding the use of elective node dissection (END) in the management of both cutaneous SCC (cSCC) and	Review article	Patients with cSCC and HNSCC that underwent END	To review the available literature regarding the use of elective node dissection (END) in the management of both cSCC and HNSCC.	Many surgical specialists recommend that END be routinely performed in patients with N0 HNSCC when the risk of occult metastases		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	head and neck SCC (HNSCC).				is estimated to exceed 20%; however, patients who undergo END have no proven survival benefit over those who are initially staged as N0 and undergo therapeutic neck dissection (TND) after the development of the apparent regional disease. There is a lack of data regarding the proper management of regional nodal basins in patients with N0 CSCC. In the absence of evidence-based data, the cutaneous surgeon must rely on clinical judgment to guide the management of patients with N0 high-risk CSCC of the head and neck.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Appropriate workup for occult nodal disease may occasionally be warranted in patients with high-risk cSCC. END may play a role in only a very limited number of patients with high-risk cSCC.		
Oddone et al 2009	To propose a prognostic score model using a prospective study of patients with regional metastatic cutaneous squamous cell carcinoma of the head and neck.	Prospective study; n=250 patients	Patients between 1980 to 2005 who had metastatic cSCC to lymph nodes of the HN (parotid and/or cervical) and who were treated with curative intent were eligible for inclusion in this study from one center.	To propose a prognostic score model using a prospective study of patients with regional metastatic cutaneous squamous cell carcinoma of the head and neck.	At a median follow-up of 54 months (range, 1.3-212 months) 70 of 250 patients (28%) developed recurrent disease: Most were regional recurrences (51 of 70 patients; 73%) in the treated lymph node basin. After regional recurrence, a majority (73%) died of disease. The following 4 variables were associated significantly with survival: immunosuppression		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(hazard ratio [HR], 3.13; 95% confidence interval [CI], 1.39-7.05), treatment (HR, 0.32; 95% CI, 0.16-0.66), extranodal spread (HR, 9.92; 95% CI, 1.28-77.09), and margin status (HR, 1.85; 95% CI, 1.85-3.369); and those 4 variables (immunosuppression, treatment, extranodal spread, and margin status) were used to calculate the ITEM score. The 5-year risk of dying from disease for patients with high-risk (>3.0), moderate-risk (>2.6-3.0), and low-risk (≤2.6) ITEM scores were 56%, 24%, and 6%, respectively. Fifty-six of 250 patients (22%) died from another cause.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Silberstein et al 2015	To find the rate of cervical lymph node metastasis in the series of patients with cutaneous SCC of the head and neck (cHNSCC) and to identify those who may need SLNB.	Retrospective review; n= 572 patients; 725 cHNSCC	Patients treated at the Soroka University Medical Center with a diagnosis of cHNSCC during the years 1998 to 2005.	To find the rate of cervical lymph node metastasis in the series of patients with cHNSCC and to identify those who may need SLNB.	A total of 572 patients with 725 cHNSCC were included in the study group. During the follow-up period, 10 (1.3%) patients developed lymph node metastases and no patients developed distant metastases. The probability of lymph node metastasis within 6 years for T1 and T2 tumors was 1.09% and 5.46%, respectively (p = .0387). Because of the relatively low incidence of cervical lymph node metastases in patients with cHNSCC, SLNB for clinically N0 patients is not justified.		3
Sood et al 2019	To determine if the number of metastatic lymph	Retrospective analysis; n=101	Patients undergoing curative-intent	Disease-free survival and risk of distant metastases	The mean number of nodal metastases was 2.5 (range 1–12).	Increasing number of nodal metastases is associated with	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	nodes is an independent prognostic factor in metastatic cSCCHN and whether it provides additional prognostic information to the American Joint Committee on Cancer (AJCC) staging.		treatment for metastatic cSCCHN to parotid and/or neck nodes by surgery +/− radiotherapy at Liver- pool Hospital, Sydney, Australia.		On multivariate analysis, an increasing number of nodal metastases significantly predicted reduced DFS (hazard ratio 1.17; 95% confidence interval 1.05–1.30; P = 0.004), with a 17% increased risk of recurrence or death for each additional node. This remained significant in multivariate models adjusted for AJCC 8th edition nodal and TNM stages. Number of nodal metastases was also associated with risk of distant metastatic failure (hazard ratio 1.21; 95% confidence interval 1.05–1.39; P = 0.009).	decreased DFS and increased risk of distant metastases in metastatic cSCCHN, with a cumulative risk increase with each additional node. It provides additional prognostic information to the AJCC stag- ing, which may be improved by incorporating information on the number of nodal metasta- ses beyond the current single versus multiple distinctions.	
Takeda et al 2013	To compare pre-surgical aspects	Retrospective review; n=164	Patients with cSCC from one center	Detection rate from lymph node	The following factors were compared		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	data between two groups: patients with lymph node metastasis and patients without lymph node metastasis	patients		metastasis of the SLNB	between the patients with lymph node metastasis group and the group with no lymph node metastasis: age, sex, tumour size, symptom period, lesions, and local recurrence. Detection rate from sentinel lymph biopsy node metastasis using the blue dye technique was evaluated. Among all subjects, lymph node metastasis was observed in 17 cases (10.4%). Lower lip SCC was observed only in the higher metastasis rate. Significant local recurrence occurred more frequently in the lymph node metastasis group. For other factors, no significant difference was observed		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					between the lymph node metastasis group and the no lymph node metastasis group. A sentinel lymph node biopsy was performed in 21 cases, two false-negative cases were observed, and local recurrence and lymph node metastasis were observed postoperatively. Operation should be given to the lower lip SCC and local recurrence cases considering lymph node metastasis. It is hard to say that the sentinel lymph node biopsy of cSCC using the blue dye technique has sufficient detection rates.		
Wang et al 2018	To compare	Retrospective	Patients with	Development of	Of the 303 study	The risk of nodal.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	differences in risks of recurrence, metastasis, and death from cSCCs on the vermilion vs cutaneous lip.	cohort study; n= 303	primary cSCCs of the lip (138 cutaneous, 172 vermilion) diagnosed between 2000 and 2015 at 2 academic tertiary care centers in Boston, Massachusetts.	local recurrence, nodal metastasis, distant metastasis, disease-specific death, and all-cause death	participants with 310 SCCs. Of the lip, 153 (50.5%) were men,and 150 (49.5%) were women; median age at diagnosis, 68 years (range, 27-93 years). Outcomes were as follows for vermilion vs cutaneous locations: local recurrence, 6.4% (11 of 172) vs 2.9% (4 of 138); nodal metastasis, 7.6% (13 of 172) vs 1.5% (2 of 138); distant metastasis, 0.6% (1 of 172) vs 0.7% (1 of 138); disease-specific death, 3.5% (6 of 172) vs 2.9% (4 of 138); and all-cause death, 26.7% (46 of 172) vs 29.0% (40 of 138). The difference was statistically significant for nodal metastasis (P = .01). In multivariable	Metastasis is 5-fold greater for cSCCs on the vermilion lip compared with those on the cutaneous lip. Squamous cell carcinomas of the cutaneous lip have a nodal metastasis risk similar to cSCCs in general (1.5%). Thus, vermilion involvement appears responsible for the increased risk associated with cSCC of the lip. Vermilion involvement may merit radiologic nodal staging and inclusion in future tumor staging since it was independently associated with higher-risk cSCC of the lip region.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					analysis, nodal metastasis was associated with vermilion lip location (subhazard ratio, 5.0; 95% CI, 1.1-23.8) and invasion beyond fat (fascia or beyond for vermilion lip) (subhazard ratio, 4.4; 95% CI, 1.3-14.9).		
Wang et al 2013	To compare recurrence and survival in patients undergoing either selective neck dissection or modified radical neck dissection to treat metastatic cutaneous head and neck squamous cell carcinoma (cHNSCC) to the cervical lymph nodes (levels I–V) only.	Retrospective review; n=122 patients	Patients undergoing neck dissection for metastatic cHNSCC between 1980 and 2008 from one center.	To compare recurrence and survival in patients undergoing either selective neck dissection or modified radical neck dissection to treat metastatic cHNSCC to the cervical lymph nodes (levels I–V) only.	There were 122 eligible patients: 96 males (79%) and 26 (21%) females (median age, 66 years). Sixty-six patients (54%) underwent selective neck dissection and 56 (46%) modified radical neck dissection. The former patients had a lower rate of regional recurrence compared with the latter (17 vs 23%, respectively). There was no significant difference		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					in five-year OS (61% vs 57%, respectively) or five-year DFS (74% vs 60%, respectively), comparing the two groups. OS and DFS were significantly improved by the addition of adjuvant radiotherapy .No difference was found in outcome in patients undergoing selective versus modified radical neck dissection. Adjuvant radiotherapy significantly improved outcome.		
Wermker K et al 2015	To identify predictive factors for lymph node metastasis (LNM) in SCC of the lip and to establish a prediction model identifying patients at high LNM risk.	Retrospective analysis; n=326	Patients with malignancies of the lip (ICD10-codes C00.1eC00.8) and histologically secured SCC, treated surgically between 2001 and 2011 from one institutional database.	To formulate a prediction model for LNM using binary logistic and Cox regression analysis	Lymph node metastasis occurred in 26 (8%) patients. Regression analysis revealed tumor extent, tumor depth and grading as the most important factors in the correct classification of LNM in 94.2% of patients.	This new prediction model was able to identify patients with lip cancer who had a high risk of LNM with a good level of accuracy. This algorithm is easy to apply as part of the decision	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					A prediction model taking tumor depth and grading into account allowed for stratification of patients into high and low-risk groups (sensitivity 92.3%, specificity 78.3%, negative predictive value 99.2%).	process for elective and selective lymph node dissection in SCC of the lip.	
Wong et al 2014	To examine the tradeoffs and benefits of different management approaches in the stage N0 patient.	Retrospective analysis; n=30 patients	Patients with stage N0 cutaneous squamous cell carcinoma of the head and neck (cSCCHN) from one center	To compare different management approaches in the stage N0 patient: surveillance, elective node irradiation, and elective node dissection.	Sensitivity analysis was performed and the effect on the expected utility was examined. When the probability of occult metastasis was[19 %, elective nodal irradiation resulted in a higher expected utility than observation. When the probability of occult metastasis exceeds 25 %, elective node dissection has a higher expected utility compared to		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					observation. Given the currently available evidence, a wait-and-see approach is justified in patients with a probability of occult metastases < 19 %.		
Wu et al 2020	To describe outcomes of a single institution experience with sentinel lymph node biopsy (SLNB) for high-risk cutaneous squamous cell carcinoma of the head and neck.	Retrospective analysis; n=83	Patients who presented with clinically node-negative cutaneous squamous cell carcinoma of the head and neck between December 2007 and May 2018	The main outcomes were SLNB result, lymph node spread, recurrence-free survival, disease-specific survival, and overall survival.	Eighty-three patients underwent successful SLNB, and one patient underwent selective neck dissection for intraoperatively identified occult lymph node metastasis. Five patients (6%) had a sentinel node-positive for tumor, of whom 4/5 received further treatment (neck dissection, radiation, and/or systemic therapy) with no further recurrence at the time of last follow-up. SLNB had a	SLNB can be used to identify regional lymph node metastases in cutaneous squamous cell carcinoma of the head and neck with a high negative predictive value (95%–100%). Factors associated with recurrence were tumor being locally recurrent at presentation, arising from an area of chronic inflammation, and immunosuppression.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					negative predictive value of 95% to 100%. Recurrent tumor at presentation, tumor arising from an area of chronic inflammation, and immunosuppression were significantly associated with increased risk of subsequent recurrence, with a mean follow-up of 19.9 months.		
Xiao et al 2018	To analyze the superiority of wait-and-see policy and elective neck dissection in treating cN0 patients with facial cutaneous cell carcinoma (cSCC).	Prospective study; n=111	Patients with cSCC and clinically negative parotid and neck metastasis disease from one center	Regional control and disease-specific survival rates between 3 groups: 1) wait and see; 2) superficial parotidectomy and 3) superficial parotidectomy and elective neck dissection	The occult parotid and neck metastasis rate was 20% and 16%, respectively. There was neck node metastasis without parotid metastasis in only 1 patient. All the node metastasis occurred in level II. Regional recurrence was noted in 16 (16%) patients, and 6 patients died of the	Superficial parotidectomy and elective neck dissection are suggested for patients with T3–4 facial cutaneous squamous cell carcinoma	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					disease. In the group undergoing superficial parotidectomy and elective neck dissection, 2 patients had neck node metastasis, and there was no disease-related death, further survival analysis indicated it had better regional control and disease-specific survival rates compared with the other 2 groups.		

7.6.5. Literature

Amoils M, Lee CS, Sunwoo J, et al. Node-positive cutaneous squamous cell carcinoma of the head and neck: Survival, high-risk features, and adjuvant chemoradiotherapy outcomes. Head & neck 2017;39(5):881-85. doi: 10.1002/hed.24692 [published Online First: 2017/03/03]
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7.7. Question VI.7. For which patients should adjuvant or postoperative radiation therapy (R1;R2) be recommended?

(Frage VI.7. Für welche Patienten wird eine adjuvante Strahlentherapie bzw. eine postoperative Radiatio (R1;R2) zu empfohlen?)

Guideline adaption

7.7.1. PICO

PICO – Scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Patients with SCC surgically treated	Radiation therapy	Observation, other local interventions	Local/lymph node recurrence, local recurrence-free survival, DFS, time to metastasis, OS

7.7.2. Database, search strategy, number of results

Database	Search strategy	Date	Number of results
1. Search			
Medline	(squamous[Title] AND (skin[Title] OR cutaneous[Title])) AND (radiother* AND (adjuvant OR surgery)) NOT case report AND (German[language] OR English[language])	15th December 2016 (Initial search)	116
		Update 30th May 2017	120
		Update January 2021	177
Remarks and notes:-			

7.7.3. Selection criteria

Literature selection	
Number of total results	177
Inclusion criteria	Clinical trials (randomized and non-randomized), prospective and retrospective reviews, systematic reviews and case series with ≥10 patients included
Exclusion criteria	Reports that do not address radiotherapy as therapy in this setting
Number of results after abstract searching	45
Number of full texts reviewed	36

7.7.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Amaral et al 2019	To describe and analyze patients and primary tumour characteristics, local and systemic treatments, as well as survival outcomes.	Retrospective analysis; n= 195	Patients with advanced cSCC diagnosed between 01/2011 and 06/2018 in one center	Survival rates	The median follow-up was 21 months [IQR = (10.0; 21.0)]. The median age at time of advanced disease diagnosis was 78 years [IQR = (72; 84)], with 40.5% of the patients in stage III and 59.5% in stage IV. One hundred and forty-five patients had resectable tumours. In this group the median overall survival (mOS) was 59 months (95%	Surgical complete resection should be the first therapeutic option for patients with acSCC. For patients with inoperable tumour, first-line immunotherapy should be preferably considered.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					CI: 28.2–89.8), significantly higher than the mOS in patients with inoperable tumour [n = 50; mOS: 19 months (96% CI: 7–31, P <0.0001)]. Patients receiving immunotherapy (n = 20) showed a statistically significant better survival compared to those treated with other systemic therapies (n = 37; mOS not reached vs. mOS: 22 months (95% CI: 6.5–43.5), P = 0.034). For patients without systemic therapy, a combination of surgery and radiotherapy provided better outcomes compared to radiotherapy alone or best supportive care (P<0.001).		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Amoils et al 2019	To describe outcomes in one institution, including patterns of metastasis, clinicopathologic factors related to survival, and failure rates. To stratify results by treatment modality.	Retrospective review; n= 80	Patients treated for regionally metastatic cutaneous HNSCC	OS, failure rates, results by treatment modality	On multivariate regression, cutaneous primary >2 cm (p = .03) and extracapsular spread (ECS; p = .01) were significantly associated with decreased OS. Location of regional metastasis (neck vs parotid vs both) did not affect OS (p = .2), nor did the presence of a cutaneous primary at the time of presentation (p = .9). The 3-year survival was 43%, 52%, and 49% for surgery alone, adjuvant radiation, and adjuvant chemoradiation, respectively. Fifty-one percent of patients had a recurrence of their disease.	Regionally metastatic cutaneous HNSCC is an aggressive disease associated with high recurrence rates. Patients with tumors >2 cm and ECS have poorer OS despite adjuvant therapy.	4
Arbab et al 2019	To evaluate outcomes and patterns of recurrence	Retrospective analysis; n= 111	Patients with head and neck cSCC patients treated with RT	Recurrence rate	With a median follow-up of 7 months, there were 29 (26%) recurrences, 73% of	In a cohort of cSCC treated with radiotherapy, there was an association	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	following radiation therapy (RT) for cutaneous squamous cell carcinoma (cSCC) of the head and neck				which were nodal (n = 21). Immunosuppression (IS) was the only factor associated with recurrence (47% in IS, 22% in non-IS, P = .04), and also with time to recurrence in multivariate analysis (HR 5.5; P = .03). No factors were associated with recurrence among patients who received definitive RT. The majority of patients who recurred were salvaged with surgery (n = 20, 69%).	between IS and increased failure risk. The majority of failures were salvaged surgically.	
Canueto et al 2020	To evaluate the usefulness of postoperative radiotherapy (PORT) in the treatment of CSCC with perineural invasion (PNI) to determine which patients would best	Retrospective multicenter cohort; n= 110	Patients with CSCCs and with PNI	Types of PNI associated with poor outcome and the effectiveness of PORT on different groups of CSCC with PNI. Assessed for the usefulness of PORT depending on the surgical	Postoperative radiotherapy showed clear benefit over observation in CSCC with PNI and positive margins after surgery, where the management by observation increased the risk of poor	The use of PORT on patients with CSCC with PNI and positive margins after surgery, especially in PNI ≥0.1 mm, significantly improves long-term outcome. The	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	benefit from this type of treatment.			margin status (either clear or positive).	outcome events 2.43 times (P = 0.025), and especially in those with positive margins and PNI ≥0.1 mm, where the risk of poor prognosis is eight times greater following management by observation (P = 0.0065). Multivariate competing risk analysis preserved statistical significance.	benefit of PORT in cases with clear margins is not as evident, especially in those with PNI of small-calibre nerves.	
Chen et al 2007	To report the clinical outcome of patients treated with radiation therapy for parotid-area metastases from cutaneous squamous cell carcinoma of the head and neck (cHNSCC).	Retrospective study; n= 36 patients	Patients treated with radiation therapy for parotid-area metastasis from primary skin cancer of the head and neck from 1970 to 2003	Clinical outcomes	Thirty patients (83%) were treated postoperatively after gross total tumor resection. Median dose to the parotid area was 60 Gy (range, 50–72 Gy). Treatment of clinically N0 necks consisted of surgical dissection (7 patients), irradiation (15 patients), and observation (14		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients). The 5-year estimate of local (parotid) control was 86% in patients treated using surgery with postoperative therapy and 47% in patients treated using radiation therapy alone. Three of 4 patients with tumors that relapsed locally after surgery and postoperative radiation received a dose of less than 60 Gy. Elective neck irradiation decreased the incidence of subsequent nodal failures from 50% to 0% and significantly improved neck control ($p < 0.001$). The 5-year OS rate was 63%. Surgery followed by radiation therapy to doses of at least 60 Gy results in effective local control for		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients with parotid area metastasis from cutaneous squamous cell carcinoma. Routine irradiation of the clinically N0 neck is recommended.		
Chua et al 2002	To report on the patterns of recurrence, outcome and predictors for locoregional recurrence following treatment at our institution. Locoregional recurrence was defined as disease relapse above the clavicles.	Retrospective review; n=52	Patients with head and neck SCC (HNSCC) treated within the department of Radiation Oncology, Westmead Hospital, Sydney between 1980–1997.	Patterns of recurrence, predictors for local recurrence.	Only extranodal spread (P = 0.02) was identified as an independent predictor for locoregional recurrence on multivariate analysis. The cumulative locoregional recurrence rates were 28 and 45% at 2 and 5 years, respectively. The 5-year cause-specific survival rate in this study was 65%. We conclude that parotid lymph-node metastases from cHNSCC are associated with a high rate of locoregional recurrence and cause-		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					specific mortality despite surgery and adjuvant radiotherapy. The role of altered fractionation after surgery as a means to further enhance locoregional control warrants further investigation.		
Dona et al 2003	To report on the patterns of recurrence, outcome and predictors for locoregional recurrence of cutaneous SCC metastatic to the parotid and neck lymph nodes, following surgery and high dose adjuvant radiotherapy	Retrospective review; n=74	Patients treated for metastatic cutaneous squamous cell carcinoma to the parotid with surgery and adjuvant radiotherapy at Westmead Hospital, Sydney, between 1983 and 2000.	Patterns of recurrence, outcome and predictors for locoregional recurrence.	24% developed locoregional recurrence, with a median time to relapse of 7.5 months. The most common site for recurrence was the treated parotid region and upper neck. Most relapsed patients died. No variable independently predicted for locoregional recurrence on multivariate analysis. The 5-year absolute and cause-specific		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					survival rates were 58% and 72%, respectively.		
Erkan et al 2017	To analyze the outcomes of multimodal treatment entailing the en bloc surgical resection and postoperative radiotherapy for previously untreated patients as well as the outcomes of the salvage treatment for previously treated patients with clinical perineural invasion (PNI) of the trigeminal and facial nerves from cutaneous squamous cell carcinoma of the head and neck (cHNSCC) at a single institution	Retrospective review; n= 21	Patients with clinical PNI from cHNSCC between the years 2006 and 2012 in one center.	DFS OS Correlation of OS and DFS with surgical factors, such as margin status, previous treatment, zone involvement, and trigeminal involvement (branch-specific), as well as the pretreatment and post-treatment pain scores	Of 21 patients with clinical PNI from cHNSCC, 7 patients (33%) were previously treated for their disease with primary radiotherapy. Negative tumor margins were achieved in 18 patients (86%). Three of the 7 patients (43%) undergoing salvage surgery had positive margins. One-year and 3-year DFS for previously untreated patients was 91% and 67%, respectively, whereas 1-year and 3-year DFS was 72% and 28%, respectively, for the previously treated patients. Previous radiotherapy, ophthalmic nerve involvement, and	The retrospective study of this rare clinical entity demonstrates that multimodal treatment can achieve favorable survival outcomes.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					positive margins portended poorer survival outcomes in this study.		
Goyal et al 2017	To evaluate the role of concurrent systemic therapy to postoperative radiation therapy (RT) for locally advanced cutaneous head and neck squamous cell carcinoma (LA-cHNSCC).	Retrospective study; n=32	Patients with LA-cHNSCC after surgical resection with one or more high-risk features.	Local regional control (LRC), distant control (DC), and acute and late toxicities; progression-free survival (PFS) and overall survival (OS).	While comparing patients receiving RT with systemic therapy (n = 14) vs RT alone (n = 18), LRC was 92.9% vs 72.2% (p = 0.20), DC 92.9% vs 94.4% (p = 1.0), median PFS 17.7 months vs 34.4 months (p = 0.48), and median OS 20.9 months vs 34.4 months (p = 0.03), respectively. On univariate analyses, use of concurrent systemic therapy was associated with an increased risk of death with an HR of 3.5 [95% confidence interval (CI): 1.04 - 11.6] (p = 0.04), while patients treated for recurrent disease who	Patients receiving postoperative RT alone for LA-cHNSCC had better OS than patients receiving concurrent systemic therapy. There were no differences in any other endpoints evaluated.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					had previously treated superficial primaries had improved OS with an HR of 0.10 [95% CI: 0.01-0.80] (p = 0.03). There were no significant differences in acute or chronic toxicities between groups.		
Han et al 2007	To evaluate the effectiveness of adjuvant RT in treating SCC with perineural invasion (PNI).	Literature review; n=554; n= 10 articles	Patients with SCC and PNI described in 10 published articles	Effectiveness	For SCC with PNI, the local control rate after MMS with or without RT was from 92% to 100% compared with a control rate from 38% to 100% after standard excision with or without RT. A better prognosis was associated with negative pretreatment MRI or CT findings than with positive radiographic evidence of PNI. Primary SCC with PNI was associated with better local control than recurrent SCC with	Few studies addressed the effectiveness of adjuvant RT in patients who have SCC with PNI. Although RT has been established as an adjuvant treatment for selected patients, the extent of nerve involvement by tumor, particularly in the setting of other high-risk features, may be helpful in defining its role.	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					PNI. When treatment outcomes were stratified by PNI type, SCC with microscopic PNI and SCC with extensive PNI had local control rates from 78% to 87% and from 50% mto 55%, respectively. Adjuvant RT was associated in selected patients with 100% local control.		
Harris et al 2019	To assess indications for adjuvant radiation therapy in patients with CSCC	Retrospective analysis; n=349	Patients with head and neck CSCC treated with primary resection with or without adjuvant radiation therapy at 2 tertiary referral centers from January 1, 2008, to June 30, 2016.	Disease-free survival (DFS) and overall survival (OS)	A total of 349 patients had tumors that met the inclusion criteria (mean [SD] age, 70 [12] years; age range, 32-94 years; 302 [86.5%] male), and 191 (54.7%) received adjuvant radiation therapy. The 5-year Kaplan-Meier estimates were 59.4% for DFS and 47.4% for OS. Patients with larger, regionally metastatic, poorly	Among patients with advanced CSCC, receipt of adjuvant radiation therapy was associated with improved survival in those with PNI and regional disease.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					differentiated tumors with perineural invasion (PNI) and younger immunosuppressed patients were more likely to receive adjuvant radiation therapy. On Cox proportional hazards multivariate regression, patients with periorbital tumors (hazard ratio [HR], 2.48; 95% CI, 1.00-6.16), PNI (HR, 1.90; 95% CI, 1.12-3.19), or N2 or greater nodal disease (HR, 2.16; 95% CI, 1.13-4.16) had lower DFS. Immunosuppressed patients (HR, 2.17; 95% CI, 1.12-4.17) and those with N2 or greater nodal disease (HR, 2.43; 95% CI, 1.42-4.17) had lower OS. Adjuvant radiation therapy was		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					associated with an improved OS for the entire cohort (HR, 0.59; 95% CI, 0.38-0.90). In a subset analysis of tumors with PNI, adjuvant radiation therapy was associated with improved DFS (HR, 0.47; 95% CI, 0.23-0.93) and OS (HR, 0.44; 95% CI, 0.24-0.86). Adjuvant radiation therapy was also associated with improved DFS (HR, 0.36; 95% CI, 0.15-0.84) and OS (HR, 0.30; 95% CI, 0.15-0.61) in patients with regional disease.		
Hirshoren et al 2018	To identify the patterns of recurrence, with attention paid to the incidence of parotid bed recurrence following protocols	A retrospective cohort study of parotidectomy with or without neck dissection for metastatic cSCC.	Patients with metastatic cSCC involving the parotid gland who underwent a curative-intent parotidectomy (superficial or	Overall survival and regional recurrence associated with surgical extent and adjuvant treatment.	Of 78 patients, 65 underwent superficial parotidectomy. Median follow-up was 6.5 years. Sixty-four patients (82%) patients received adjuvant	This study supports surgery plus adjuvant radiotherapy as a standard of care for metastatic cSCC. The low incidence of parotid bed	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	used at one institution.		total), with or without neck dissection, between 2003 and 2014.		radiotherapy. Cervical lymph nodes were involved in 6 (24%) elective neck dissections. Involved preauricular, facial, external jugular, and occipital nodes occurred in 36.9%. Adjuvant radiotherapy was associated with improved 5-year survival—50% (95% CI, 36%-69%) versus 20% (95% CI, 6%-70%)—and improved 2- year regional control: 89% (95% CI, 67%-100%) versus 40% (95% CI, 14%-100%). The ipsilateral parotid bed recurrence rate was 3.7% for those who received adjuvant radiotherapy and 27% for those who did not receive radiotherapy.	recurrence with this approach suggests that routine elective deep lobe resection may not be required.	
Jambusaria-Pahlajani et al 2009	To compare reported outcomes of high-risk SCC	Systematic review; n= 2,449	Medline reports of high-risk SCC treated with SM or	Local recurrence, regional	There were no controlled trials. Of the 2,449 cases of	High cure rates are achieved in high-risk cutaneous SCC	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	treated with surgical monotherapy (SM) with those of surgery plus adjuvant radiotherapy (S+ART).		S+ART that reported outcomes of interest: local recurrence, regional or distant metastasis, or disease-specific death, between January 1, 1980, and June 30, 2006. Case reports containing less than 5 cases were excluded	Distant metastasis Disease-specific death.	high-risk SCC included, 91 were treated with S+ART. Tumor stage and surgical margin status before ART were unreported. In 74 cases of perineural invasion (PNI), outcomes were statistically similar between SM and S+ART. In 943 SCC cases in which clear surgical margins were explicitly documented. Risk of local recurrence in cases with documented clear margins versus unreported margins was 5% versus 8% (p=.005), regional metastasis 5% versus 14% (p=.001), distant metastasis 1% versus 7%(p=.001), and disease-specific death 1% versus 7% (p=.001).	when clear surgical margins are obtained. Current data are insufficient to identify high-risk features in which ART may be beneficial. In cases of PNI, the extent of nerve involvement appears to affect outcomes, with the involvement of larger nerves imparting a worse prognosis.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Lansbury et al 2013	To assess the effects of treatments for non-metastatic invasive SCC of the skin using evidence from observational studies, given the paucity of evidence from randomized controlled trials.	Systematic review of observational studies; n=118 papers;	Patients with non-metastatic invasive SCC of the skin reported in observational studies in Medline or Embase, to December 2012.	Effects of treatments for non-metastatic invasive SCC of the skin Recurrence	Pooled estimates of recurrence of SCCs were lowest after cryotherapy (0.8% (95% confidence interval 0.1% to 2%)) and curettage and electrodesiccation (1.7% (0.5% to 3.4%)), but most treated SCCs were small, low-risk lesions. After Mohs micrographic surgery, the pooled estimate of local recurrence during variable follow-up periods from 10 studies were 3.0% (2.2% to 3.9%), which was non-significantly lower than the pooled average local recurrence of 5.4% (2.5% to 9.1%) after standard surgical excision (12 studies), and 6.4% (3.0% to 11.0%) after external radiotherapy (7 studies). After an apparently successful		1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					initial response of SCCs to photodynamic therapy, pooled average recurrence of 26.4% (12.3% to 43.7%; 8 studies) was significantly higher than other treatments. Evidence was limited for laser treatment (1 study) and for topical and systemic treatments (mostly single case reports or small non-comparative series with limited follow-up).		
Manyam et al 2018	To report survival outcomes of immunosuppressed and immunocompetent stage I-IV cSCC-HN patients treated with surgery and postoperative RT	Retrospective study; n=205	Immunosuppressed and immunocompetent patients from 3 institutions who underwent surgery and also received postoperative RT for primary or recurrent, stage I through IV cSCC-HN	Overall survival, locoregional recurrence-free survival, and progression-free survival	Of 205 patients, 138 (67.3%) were immunocompetent, and 67 (32.7%) were immuno- suppressed. Locoregional recurrence-free survival (47.3% vs 86.1%; P < .0001) and progression-free survival (38.7% vs	Immunosuppressed patients with cSCC-HN had dramatically lower outcomes compared with immunocompetent patients, despite receiving bimodality therapy. Immune status is a strong prognostic factor	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			between 1995 and 2015		71.6%; P = .002) were significantly lower in immunosuppressed patients at 2 years. The 2-year OS rate in immunosuppressed patients demonstrated a similar trend (60.9% vs 78.1%; P = .135) but did not meet significance. On multivariate analysis, immunosuppressed status (hazard ratio [HR], 3.79; P < .0001), recurrent disease (HR, 2.67; P = .001), poor differentiation (HR, 2.08; P = .006), and perineural invasion (HR, 2.05; P = .009) were significantly associated with locoregional recurrence.	that should be accounted for in prognostic systems, treatment algorithms, and clinical trial design.	
McDowell et al 2016	To review outcomes of current management in a tertiary center to	Retrospective study; n=132	Patients with metastatic cHNSCC involving the parotid gland, undergoing radical	Overall survival (OS), cancer-specific survival (CSS) and progression-free	One hundred and thirty-two patients met the inclusion criteria. Median follow-up was 5.0	Despite multimodality treatment metastatic cHNSCC involving the	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	target future strategies		surgery and adjuvant radiotherapy during 2000–2014	survival (PFS)	years. Five-year overall (OS), cancer-specific (CSS) and progression free survival (PFS) were 44% (95% Confidence Interval (CI) 34– 53%), 64% (95% CI 52–74%) and 37% (95% CI 28–47%) respectively. Locoregional control (LRC) was 68% (95% CI 55–77%) at 5 years. Immunosuppressed patients fared worse (compared with immunecompetent) with five-year OS, CSS, and PFS of 14% versus 53% (HR = 3.19; 95% CI 1.91– 5.34), 40% versus 71% (Hazard Ratio (HR) = 2.92; 95% CI 1.38–6.19) and 10% versus 46% (HR = 2.51; 95% CI 1.52–4.14) respectively. On multivariate analysis, immune status strongly predicted OS (P < 0.001), CSS (P =	parotid shows moderate rates of recurrence. Immunosuppressed patients with this disease have a particularly poor prognosis, demonstrating lower rates of CSS with similar rates of LRC compared to their immunocompetent counterparts.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					0.003), DMFS (P < 0.001) and PFS (P < 0.001), but not LRC. Largest lymph node size was the only significant factor predictive for LRC on multivariate analysis (P = 0.02).		
Mendenhall et al 2009	To discuss the role of radiotherapy (RT) in the treatment of cutaneous SCC and BCC of the head and neck.	Literature review	Patients with BCC and SCC treated with RT	Radiotherapy outcomes – cosmetic, local control, cure rate	The likelihood of cure with a good cosmetic outcome is high for patients with early-stage cancers treated with definitive RT. The probability of local control is higher for previously untreated cancers and is inversely related to tumor size. The likelihood of cure for patients with perineural invasion (PNI) is related to the presence of symptoms and to the radiographic extent of disease. It decreases as the tumor extends	Definitive RT is useful for treating early-stage skin cancers where resection would result in a significant cosmetic and/or functional deficit. Postoperative RT is indicated in situations where the probability of residual disease after surgery is high and the chance of successful salvage is modest. Patients with parotid-area node	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					centrally towards the central nervous system. Patients with incidental PNI have a local control rate of 80% to 90% compared with about 50% to 55% for those with clinical PNI. The optimal treatment for patients with clinically positive nodes is surgery and postoperative RT. The likelihood of cure for those with positive parotid nodes is approximately 70% to 80%.	metastases are optimally treated with surgery and postoperative RT.	
Miller et al 2019	To examine the clinical outcomes in a cohort of patients with cSCC who completed adjuvant radiotherapy (ART) after Mohs micrographic surgery or wide local excision with negative margins.	Retrospective study; n=32	Patients with cSCC treated in the Mayo Clinic Department of Radiation Oncology from March 10, 1998, through April 26, 2013. Inclusion criteria were age >18 years, resection with	Rates of local recurrence (LR), lymph node metastasis (NM), and disease-specific death (DSD)	Thirty-two patients met the inclusion criteria: 15 patients died, 12 without evidence of disease related to cSCC. Three patients developed recurrent disease, all with poorly differentiated cSCC, >2 cm in clinical	These data suggest that the combination of surgical resection and ART is a reasonable option for Brigham and Women's T2b/T3 tumors.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			negative histologic surgical margins, and completion of ART		diameter, perineural invasion, and Brigham and Women's (BWH) stage T2b/T3; 2 of 3 patients were immunosuppressed; and 2 of 3 patients died of cSCC-related causes.		
Nottage et al 2016	To present one group evaluation of the outcomes of concurrent chemoradiotherapy (CRT) in patients with locally advanced cutaneous squamous cell carcinoma (cSCC).	Prospective phase II study; n=21	Patients with locally or regionally advanced SCC of the skin unsuitable for surgery, who received definitive radiotherapy (RT; 70 Gy in 35fractions) and concurrent weekly platinum-based chemotherapy (cisplatin 40 mg/m2 or carboplatin area under the curve 2).	Primary endpoint was complete response (CR)	Twenty-one patients were enrolled in this study. Eighteen patients had a locally advanced primary or nodal disease in the head and neck region with 66% having stage IV non-metastatic disease. Of 19 evaluable patients, 10 achieved a CR to definitive CRT with 2 further patients rendered disease-free by salvage surgery for an overall CR of 63%.	This is the only prospective series of CRT for cSCC. A high CR rate was documented in patients with locoregional advanced disease who were unable to undergo surgery.	3
Palmer et al 2018	To investigate the safety, tolerability and preliminary efficacy of	Retrospective study; n= 68	Patients with high-risk CSCC diagnosed between 2006 and 2013	Safety, tolerability, PFS and OS rates	Median follow-up for living patients was 30 months. Patients in the cetuximab group	Although limited by small numbers, the combination of cetuximab and	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	radiotherapy plus cetuximab in high-risk CSCC patients.				were more likely to have advanced N stage, positive margins and recurrent disease. After propensity score matching the groups were well balanced. Six patients experienced ≥ grade 3 acute toxicity in the cetuximab group. The 1-year, 2-year and 5-year progression-free survival (PFS) for patients in the cetuximab group were 86%, 72% and 66%, respectively. The 1-year, 2-year and 5-year overall survival (OS) for patients in the cetuximab group was 98%, 80% and 80%, respectively.	radiotherapy in CSCC appears well-tolerated there were more long-term survivors and less distant metastasis in the cetuximab group. These promising findings warrant further studies.	
Porceddu et al 2018	To determine whether the addition of concurrent chemotherapy to	This was a multicenter, open-label, randomized, phase III clinical trial; n= 321	Patients with high-risk cutaneous squamous cell carcinoma of the head and neck.	The primary objective was to determine whether there was a difference in	Three hundred twenty-one patients were randomly assigned, with 310 patients commencing	Although surgery and postoperative RT provided excellent FFLRR, there was no	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	postoperative radiotherapy (CRT) improved locoregional control in patients with high-risk cutaneous squamous cell carcinoma of the head and neck.			freedom from locoregional relapse (FFLRR) between 60 or 66 Gy (6 to 6.5 weeks) with or without weekly carboplatin (area under the curve 2) after resection of gross disease. Secondary efficacy objectives were to compare disease-free survival and overall survival.	al- located treatment (radiotherapy [RT] alone, n = 157; CRT, n = 153). Two hundred thirty-eight patients (77%) had high-risk nodal disease, 59 (19%) had a high-risk primary or in-transit disease, and 13 (4%) had both. Median follow-up was 60 months. Median RT dose was 60 Gy, with 84% of patients randomly assigned to CRT completing six cycles of carboplatin. The 2- and 5-year FFLRR rates were 88% (95% CI, 83% to 93%) and 83% (95% CI, 77% to 90%), respectively, for RT and 89% (95% CI, 84% to 94%) and 87% (95% CI, 81% to 93%; hazard ratio, 0.84; 95% CI, 0.46 to 1.55; P = .58), respectively, for CRT. There were no	observed benefit with the addition of weekly carboplatin.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					significant differences in disease-free or overall survival. Locoregional failure was the most common site of first treatment failure, with isolated distant metastases as the first site of failure seen in 7% of both arms. Treatment was well tolerated in both arms, with no observed enhancement of RT toxicity with carboplatin. Grade 3 or 4 late toxicities were infrequent.		
Ruiz et al 2020	To compare surgery plus adjuvant radiation therapy (S1ART) to surgical monotherapy (SM) for primary cSCCs with LCNI and other risk factors	Retrospective study; n= 62	Patients with cSCC diagnosed at Brigham and Women's Hospital (BWH) during January 1, 2000-December 31, 2017	LR, NM, distant metastasis, and disease-specific death	In total, 62 cSCCs were included in matched analysis (31 S1ART and 31 SM) and 33 cSCCs in the LCNI analysis (16 S1ART and 17 SM). There were no significant differences in local recurrence,	Adjuvant radiation did not improve outcomes compared with SM due to a low baseline risk of recurrence, although adjuvant radiation for named nerve invasion and LCNI of ≥3 nerves	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					metastasis, or death from disease in either analysis. Risk of local recurrence was low (8%, 7/89), with 3 of the local recurrences being effectively treated upon recurrence.	has been shown to improve outcomes in a prior study. Randomized studies are needed to define the subset of cSCC for whom adjuvant radiation has utility.	
Strassen et al 2017	To determine whether surgical concepts are warranted in the collective of old patients with cutaneous (cSCC)	Retrospective study; n=67	Patients with cutaneous HNSCC treated in one department between January 2008 and December 2013	OS Recurrence-free interval (RFI)	The cohort was divided into patients with/without adjuvant therapeutic regimens. The median recurrent free interval and the median OS after recurrent disease therapy were 27 and 59 months (data not shown), respectively. There was a significant difference between patients who underwent surgery with adjuvant radiotherapy and patients without adjuvant treatment.	While the benefit of elective parotidectomy and/or neck dissection—particularly in high-risk patients (pN+, G3/ G4, tumour thickness >6 mm)—in the long-term preservation of neuronal structures, RFI and, OS has to be analyzed in a prospective randomized trial, our study demonstrated a favorable RFI/OS in patients with cSCC recurrent disease	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Patients with adjuvant treatment demonstrated a 5y-RFI and OS rate of 78 and 79 %, respectively, while patients without adjuvant therapy showed a 5y-RFI and OS rate of 30 and 46 % (p = 0.02; p<0.05). The distribution of T and N stages differed significantly between the groups. Patients who underwent adjuvant radiotherapy presented with limited T stages (T0-1), but advanced N stages (N2a-2b). Patients without adjuvant treatment concepts showed higher T stages (T1-2) and limited N stages (N0-1) (p=0.001; p<0.0001). There were no differences in patient' age (patients receiving adjuvant therapy: 76	who underwent surgical concepts and adjuvant radiotherapy. Locoregional metastases in the lymphatic basin might be more frequent than previously expected. Sonographic staging and follow-up screening of the cervical lymphatic basin might, therefore, be beneficial even in patients presenting with small primary tumors.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					years vs patients not receiving adjuvant therapy: 80 years; p = 0.07) and comorbidities (p=0.9).		
Stratigos et al 2020	To make recommendations on treatment, supportive care, education and follow-up of patients with invasive cutaneous squamous cell carcinoma (cSCC)	Recommendations were based on evidence-based literature review, guidelines and expert consensus. Treatment recommendations are presented for common primary cSCC (low risk, high risk), locally advanced cSCC, regional metastatic cSCC (operable or inoperable) and distant metastatic cSCC.	EDF-EADO-EORTC guideline	Treatment	Lymph node dissection is recommended for cSCC with cytologically or histologically confirmed regional nodal involvement. Radiotherapy should be considered as curative treatment for inoperable cSCC, or for non-surgical candidates.		1
Tang et al 2013	To report outcomes, failure patterns, and toxicity after stereotactic radiosurgery (SRS) for recurrent head	Retrospective study; n=10	Patients from one center, who received SRS as part of retreatment for recurrent head and neck cutaneous squamous cell	PFS rate OS rate Failure patterns Toxicity	At a median 22-month follow-up, the 2-year PFS and OS rates were 20% and 50%, respectively. Seven patients exhibited local failures, all of	Although there is excellent in-field control with this approach, the rate of out-of-field failures remains unacceptably high.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	and neck cutaneous squamous cell carcinoma with gross perineural invasion (GPNI).		carcinoma with GPNI, between December 2003 and September 2009.		which occurred outside both SRS and EBRT fields. Five local failures occurred in previously clinically uninvolved cranial nerves (CNs). CN disease spreads through 3 distinct patterns: among different branches of CN V; between CNs V and VII; and between V1 and CNs III, IV, and/or VI. Five patients experienced side effects potentially attributable to radiation.	We found that the majority of failures occurred in previously clinically uninvolved CNs often just outside treatment fields. Novel treatment strategies targeting this mode of perineural spread are needed.	
Tanvetyanon et al 2015	To report the efficacy of postoperative concurrent chemotherapy and radiotherapy for high-risk cutaneous squamous cell carcinoma of the head and neck	Retrospective cohort study; n=61	Patients with cSCCHN who underwent adjuvant radiation or concurrent chemoradiation. Patients must have had stage III/IV with high-risk features, including	RFS Risk of recurrence OR	27 (44%) received adjuvant radiation and 34 (56%) received adjuvant chemoradiation. The median recurrence-free survivals were 15.4 and 40.3 months, respectively. Adjuvant	For high-risk cSCCHN, adjuvant chemoradiation was associated with better recurrence-free survival than adjuvant radiation alone.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(cSCCHN).		metastatic involvement of >=2 lymph nodes, positive margins, or extracapsular invasion.		chemoradiation significantly decreased the risk of recurrence or death in a multivariable analysis: hazard ratio (HR) 0.31 (p= .01). However, a difference in OS was not found.		
Terra et al 2017	First to determine the local control rate (LC) of HNcSCC after radiotherapy, both as primary modality or when complete surgery is not possible. Secondly, to determine which specific patient, tumour or treatment characteristics are prognostic for local recurrence (LR).	Retrospective analysis	Patients who had primary HNcSCC or recurrent HNcSCC (after surgery with curative intent) over the period 2000– 2014 were selected from the database of the Department of Radiation Oncology. The patients were analyzed in two groups: I) primary RT (RT as primary modality) and II) postoperative RT (RT when radical surgery cannot be performed or when	Local control rate and local recurrence rate	Primary RT. A total of 52 tumours in 48 patients were included. The male-to-female ratio was 3:1, and the median age was 81 years (range 50–100). Median follow-up duration was 23 months (95% CI: 20.9–29.9). A clinical target volume margin of 1 cm was generally applied. All patients were treated five times per week. Postoperative RT. A total of 99 tumours in 90 patients were	Radiotherapy is an effective treatment modality for HNcSCC patients for whom surgery would impair functional or cosmetic outcomes and may be the preferred choice of treatment for elderly patients when surgery is expected to cause major side-effects. HNcSCCs larger than 2 cm in diameter (T2), with extradermal invasion (T3) or a poor differentiation	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			perineural invasion is present). Primary RT is defined as RT for primary HNcSCC or recurrent HNcSCC, after surgery (52 tumours in 48 patients), and postoperative RT as RT after incomplete resection or when perineural invasion was present (99 tumours in 90 patients).		included. There were more males (70.7%), and the median age was 76 years (range 39–106). The median follow-up was 24 months (95% CI: 24.9–35.8). A relatively large number of tumours had unfavourable characteristics such as poor differentiation (23.2%) and perineural growth (31.3%). A margin of 1 cm was generally applied. All patients were treated five times per week. LC and LR Primary RT. Two- and five-year LCs were both 82.5%. LR was 15.4% (8 of 52 tumours recurred). The median time to recurrence was five months (range 2–15).	grade, have a higher chance of recurrence after postoperative RT.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Postoperative RT. The two- and five-year LCs were 81.4% and 75.4%, respectively. LR was 18.2% (18 of 99 tumours recurred). The median time to recurrence was five months (range 0–50). Prognostic factors Primary RT. Kaplan–Meier estimates did not show statistically significant prognostic factors for local recurrence. The extension (T3) and poor differentiation grade were significantly associated with a higher risk of local recurrence. Multivariable analyses identified these three factors as independent		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					predictors of higher LR after RT (hazard ratios of 4.3, 3.9 and 3.5, respectively),		
Trosman et al 2020	To review the oncologic outcomes of patients with high-risk HNcSCC treated with surgery and to identify risk factors for treatment failure.	Retrospective cohort analysis; n=104	Patients treated for HNcSCC with definitive surgery involving at least parotidectomy and neck dissection at a tertiary care academic center from 2011 to 2017	The primary outcome was disease-free survival (DFS)	One-hundred four patients with a median age of 68 years (range = 42–91 years) were reviewed. Twenty-one patients were treated with surgery alone, 45 patients underwent adjuvant radiotherapy (RT), and 38 patients underwent adjuvant chemoradiotherapy (CRT). The 2-year DFS for patients treated with surgery, surgery + RT, and surgery + CRT were 71%, 65%, and 58%, respectively, with no significant difference between the groups (P = .70). On multivariate analyses, tumor size (P = .006) and perineural invasion	Advanced HNcSCC has a high recurrence rate despite adjuvant treatment. Tumor size >2 cm was a strong independent risk factor for recurrence. Out of the traditional mucosal HNcSCC risk factors, PNI was most strongly associated with worse DFS. There was no observed survival benefit to the addition of chemotherapy.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(PNI, P = .04) independently predicted recurrence. The addition of chemotherapy did not appear to improve DFS, neither for those patients with extranodal extension and/or positive margins (P = .93) nor for the entire cohort (P = .43).		
Varra et al 2018	To identify factors associated with disease recurrence and report failure patterns and survival outcomes in patients with nodal metastases from cutaneous squamous cell cancer of the head and neck (cSCC-HN) treated with surgery and postoperative radiotherapy (RT).	Retrospective analysis; n= 76	Patients with cSCC-HN with metastasis to cervical and/or parotid lymph nodes, treated with surgery and postoperative RT between 2002 and 2017.	Overall survival, disease-free survival and disease recurrence	This study included 76 patients (57 immunocompetent and 18 immunosuppressed) with a median follow-up of 18 months. Overall survival, disease-free survival (DFS), and disease recurrence (DR) at 2 years were 60%, 49%, and 40%, respectively. Immunosuppressed patients had significantly lower 2-year DFS (28% vs.	Patients with nodal metastases from cSCC-HN have suboptimal outcomes. ECE and immunosuppression were significantly associated with DR.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					55%; p=0.003) and higher DR (61% vs. 34%; p=0.04) compared to immunocompetent patients. Analysis of immunocompetent patients demonstrated extracapsular extension (ECE) as the only factor associated with DR (p<0.0001).		
Veness 2005	To discuss the treatment of patients with high-risk cutaneous SCC (cSCC) and, where applicable, also present the current role of radiotherapy in the management of these patients	Review article	n.a.	n.a.	ELECTIVE TREATMENT OF LYMPH NODES: The majority of patients with cSCC will not develop nodal metastases. The elective treatment of lymph nodes in all patients is inappropriate. Patients with adequately excised and previously untreated lesions are usually not candidates for further treatment. Patients with more		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					than one high-risk factor (deeply invasive >4–5 mm, >2 cm in diameter), especially in the recurrent setting, should be considered at risk of developing nodal metastases. In such cases, elective treatment to first echelon nodes may be of benefit. At a minimum, patients should be followed closely (2–3 months) for at least 2–3 years. If radiotherapy is used to treat a primary high-risk lesion (definitive or adjuvant), consideration should be given to encompassing first echelon nodes in the treatment field. METASTATIC SCC TO LYMPH NODES: Patients with		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					metastases to parotid lymph nodes should undergo a parotidectomy and neck dissection. The extent of both the parotidectomy and neck dissection depends on the extent of clinical disease. Essentially, all patients should also be recommended adjuvant RT (60 Gy) to the parotid bed, and in many cases, to the lower neck. Similarly, patients with operable metastases to cervical lymph nodes should undergo a comprehensive neck dissection followed by adjuvant RT. Single modality treatment alone, either surgery or RT, is associated with a worse outcome. Close follow-up for at least 3–4 years is		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					imperative if early loco-regional recurrence is to be potentially salvaged. The benefits from the addition of chemotherapy, altered fractionation or routine radical parotidectomy are currently unproven and not recommended. INCOMPLETELY EXCISED SCC: Ideally, 4–5 mm excision margins are desirable. Margins <2 mm should be considered inadequate and warrant further treatment. It is not recommended to wait and watch 'expectantly' as a minority of patients will recur and increase a patient's risk of developing nodal metastases. If		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					function is not compromised, re-excision should be considered. If re-excision is not appropriate, a course of adjuvant RT (55–60 Gy) is likely to provide excellent local control without compromising function. All patients should be followed up regularly for at least 4–5 years to monitor for recurrence. PERINEURAL INVASION: Patients with established palsies and/or involvement of the cavernous sinus or skull base are incurable. However, radiotherapy may palliate debilitating neuropathic-type symptoms. Following the reporting of perineural invasion of		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					a cranial nerve, or branch of a cranial nerve, patients should be considered candidates for wide-field radiotherapy to encompass the potential neural pathway which often extends back to the brainstem. IMMUNOSUPPRESSION: The basic tenets of obtaining adequate surgical margins and examining for perineural invasion are especially applicable to this group of patients. Although routine prophylactic treatment to regional lymph nodes cannot be recommended, adjuvant RT to incompletely excised SCC, or those with perineural invasion, should be strongly		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					considered. Close liaison with a transplant physician is important.		
Veness et al 2005	To present further supportive evidence on the addition of adjuvant RT for treatment of patients with cutaneous SCC (cSCC)	Retrospective review; n=167	Patients with metastatic cSCC to the parotid and/or cervical lymph nodes (levels I–V) were identified, treated with surgery alone or surgery and adjuvant RT with curative intent, between 1980 and 2002 in one Australian center	Relapse DFS rates OS rates	Median age was 67 years (range, 34–95) in 143 men and 24 women with a minimum follow-up of 24 months. Patients underwent surgery (21/167; 13%), or surgery and adjuvant RT (146/167; 87%). The majority (98/167; 59%) of metastatic nodes were located in the parotid and/or cervical nodes. The remaining 69 (41%) had metastatic cervical nodes (levels I–V). Forty-seven patients (28%) had recurrences, with the majority (35/47; 74%) as locoregional failures. On multivariate analysis, spread to multiple	In patients with metastatic cutaneous head and neck SCC, surgery and adjuvant RT provide the best chance of achieving locoregional control and should be considered best practice.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					nodes and single-modality treatment significantly predicted worse survival. Patients undergoing combined treatment had a lower rate of locoregional recurrence (20% vs. 43%) and a significantly better 5-year DFS rate (73% vs. 54%; P =.004) compared to surgery alone.		
Veness et al 2003	To present the experience of one Australian center on treating cutaneous SCC (cSCC) metastatic to cervical non-parotid lymph nodes.	Retrospective review; n=74	Patients diagnosed with previously untreated metastatic cSCC to cervical lymph nodes (level I-V)	Recurrence Time to relapse and recurrence rate.	34% of patients developed recurrent disease, predominantly locoregional (22 of 25). Median time to recurrence was 5.2 months (2 - 34.3). Increasing nodal size (>=3cm; p=0.01), metastatic spread to multiple nodes (p=0.5) and the presence of extranodal spread (p=		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					0.01) all predicted for worse survival. Patients undergoing combined modality treatment had a lower relapse rate (15%) and a significantly better DFS (p=0.01) when compared to single modality treatment.		
Wang et al 2012	To compare the outcome of surgery against surgery plus radiotherapy in patients with metastatic cutaneous head and neck squamous cell carcinoma (HNSCC) to cervical nodes.	Retrospective analysis; n=122	Patients who were treated for metastatic cutaneous HNSCC involving the cervical nodes (levels I–V), between 1980 and 2008 in one center	Recurrence DFS 5y-DFS 5y-OS	After surgery alone, 11 patients (55%) developed recurrence compared with 23 patients (23%) after surgery plus RT. On multivariate analysis, the following variables were significantly associated with DFS: immunosuppression (p= .002), treatment modality (p< .001), extracapsular spread (p=.009), and pathological nodal stage (p=.04). Patients undergoing surgery plus RT had a		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					significantly better 5-year DFS (74% vs 34%; p= .001) and 5-year OS (OS; 66% vs 27%; p =.003) compared with surgery alone.		
Warren et al 2016	To report the outcomes after surgery and postoperative RT for perineural spread of head and neck cutaneous SCC (cHNSCC)	Retrospective review; n=50	Patients with clinical PNI from cSCCHN treated with surgery and postoperative radiotherapy (PORT) between 2000 and 2011 and a minimum of 24 months follow-up, from one Australian center.	Recurrence-free survival (RFS) 5y disease-specific free survival (DSFS) OS	Fifty patients (mean age, 60 years) with median follow-up of 50 months were included in this study. A total of 54.8% of known primary tumors had incidental PNI. Ten percent had nodal disease at presentation. MRI neurogram was positive in 95.8%. RFS at 5-years was 62%. Five-year DSFS and OS were 75% and 64%, respectively. There were no perioperative deaths.	This report demonstrates that long-term survival is achievable in patients with clinical PNI from cSCCHN after surgery and postoperative RT	3
Waxweiler et al 2011	To review the current relevant evidence for the use of adjuvant RT (ART) in patients	Retrospective review	PubMed publications obtained using the search terms ‘‘squamous cell	n.a.	There is no strong evidence for or against the use of surgical excision (SE) with ART versus SE		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	with cutaneous SCC (cSCC), specifically, as it relates to those cSCCs that undergo perineural invasion (PNI).		carcinoma,'' ''cutaneous squamous cell carcinoma,'' ''radiotherapy,'' and ''perineural invasion'' for reports dealing with cSCC with PNI.		alone in the treatment of cSCC with PNI. Certain researchers suggest treating all cSCC with PNI, even microscopic, with ART, while others would disagree. Even the subject experts who write the National Comprehensive Cancer Network (NCCN) guidelines on cSCC have had difficulty agreeing upon exactly when ART should be utilized. Emerging ART technologies such as hyperfractionation, MRI fusion, and intensity-modulated radiotherapy, while offering hope for the future, will only further complicate this issue.		
Wray et al 2015	To report the	Retrospective	Consecutively	Acute and late	Median follow-up was	Elective nodal	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	efficacy of elective nodal radiotherapy to the regional nodes as an alternative to parotid or neck surgery	study; n=71	treated adults patients with SCC of the face, ears, or scalp from one institution	toxicity and regional control	4.5 years for all patients. The actuarial regional control rate at 5 years was 96 %. There were no (0 %) grade 3 or higher complications from elective nodal irradiation.	irradiation in patients with high-risk SCC of the face, ears, and scalp was safe and effective.	
Zaorsky et al 2017	To characterize the cosmetic outcomes and local recurrence (LR) rates of various hypofractionated radiation therapy (RT) regimens for skin basal and squamous cell cancers (BCCs/SCCs).	Systematic review: A PICOS /PRISMA/MOOSE selection protocol was performed to identify 344 articles published between 1985–2016 evaluating patients with T1–2 N0 SCCs/BCCs treated with definitive RT. Biologically equivalent doses with a/b = 3 (BED3s) were calculated. The primary endpoint was post- treatment cosmesis. Mixed-effects regression	Patients with skin basal and squamous cell cancers (BCCs/SCCs) treated with hypofractionated radiation therapy (RT) regimens	Cosmetic outcomes and local recurrence	A total of 21 studies were identified detailing the treatment of 9729 skin BCC/SCC patients, across seven countries, with external beam RT (n = 9255) or brachytherapy (n = 474). Median follow-up was 36 months (range: 12–77). Median dose was 45 Gy/11 fractions (interquartile range: 37.5 Gy/6–55 Gy/18) at 4 Gy/fraction (interquartile range: 2.5–6 Gy); most hypofractionated	Hypofractionated RT has favorable cosmesis for patients with skin BCCs/SCCs. We recommend clinicians consider these commonly-used regimens, which all have BED3 of $100 Gy: 50 Gy/15 fractions, 36.75 Gy/7 fractions, or 35 Gy/5 fractions, as they result in ‘‘good” cosmesis in 80% of patient	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		models were used to estimate weighted linear relationships between BED3 and cosmetic outcomes.			18.75 Gy/1. There was a trend to decreased ‘‘good” cosmesis with higher total dose: -3.4% ‘‘good” cosmesis/10 Gy BED3, p=0.01. Similarly, there was a trend to increased ‘‘fair” cosmesis with higher dose: +3.8% ‘‘fair” cosmesis/10 Gy BED3, p = 0.006. At a BED3 of 100 Gy, the expected rate of ‘‘good” cosmesis is 79% (95% confidence interval: 70%, 88%). Hypofractionated schedules produced similar cosmesis to conventionally fractionated schedules, at the same BED3. Fewer than 8% of patients experienced ‘‘poor” cosmesis, independent of dose or fractionation regimen.		

7.7.5. Literature

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7.8. Question VI.8. Which treatment is recommended for local or local-regional recurrence?

(Frage VI.8. Welche Therapie des lokalen bzw. loko-regionären Rezidivs wird empfohlen?)

Guideline adaption, orientierende Recherche

7.8.1. PICO

PICO – Scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Patients with SCC	Surgery, electochemotherapy systemic treatment radiotherapy	Prospective or retrospective trials vs. control or surgery or systemic treatment	Response

7.8.2. Database, search strategy, number of results

Database	Search strategy	Date	Number of results
1. Search			
Medline	((squamous[Title] OR SCC[Title]) AND (cutaneous[Title] OR skin[Title])) AND (local*[Title/Abstract] OR region*[Title/Abstract] OR loco*[Title/Abstract]) AND (relaps*[Title/Abstract] OR recur*[Title/Abstract]) NOT case report[Title/Abstract] AND (German[language] OR English[language])	15th December 2016 (Initial search)	171
		Update 30th May 2017	177
		Update January 2021	261
Remarks and notes:			

7.8.3. Selection criteria

Literatur selection	
Number of total results	261
Inclusion criteria	Clinical trials (randomized and non-randomized), prospective and retrospective reviews, systematic reviews and case series with ≥10 patients included
Exclusion criteria	Case reports, studies not approaching therapy in this setting
Number of results after abstract searching	38
Number of full texts reviewed	25

7.8.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Amoils et al 2017	To describe outcomes at one institution, including patterns of metastasis, clinicopathologic factors related to survival, and failure rates for patients treated for regionally metastatic cutaneous head and neck SCC (cHNSCC)	Retrospective study; n=80	Patients surgically treated for regionally metastatic cHNSCC between 2009 and 2014, available in Stanford Cancer Institute Research Database	The effect of various clinicopathologic variables on OS Outcomes by treatment modality	On multivariate regression, cutaneous primary >2 cm (p = .03) and extracapsular spread (ECS; p = .01) were significantly associated with decreased OS. Location of regional metastasis (neck vs. parotid vs. both) had no effect on OS (p = .2), nor did the presence of a cutaneous primary	Regionally metastatic cHNSCC is an aggressive disease associated with high recurrence rates. Adjuvant therapy may provide clinical benefit but patients with tumors >2 cm and ECS have poorer OS despite adjuvant treatment.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	To stratify results by treatment modality. To evaluate the following hypothesis in this population: 1) use of adjuvant therapy would be important; 2) radiotherapy and chemotherapy have a survival benefit				at the time of presentation (p = .9). The 3-year survival was 43%, 52%, and 49% for surgery alone, adjuvant radiation, and adjuvant chemoradiation, respectively. Fifty-one percent of patients had a recurrence of their disease.		
Canon et al 2017	To investigate the factors associated with elective neck dissection (END) in this patients with skull base invasion from cSCC via perineural spread To identify the survival difference with END compared with observation for patients with a cN0 neck	Retrospective study; n=59	Patients treated surgically for cHNSCC with skull base invasion via perineural spread with a cN0 neck from 2004 to 2014 in one center	DFS OS	Fifty-nine patients met inclusion criteria: 28 underwent an END and 31 underwent neck observation. Free tissue transfer reconstruction was significantly associated with END (P < .001). Patients treated with an END had significantly improved 5-year DFS (57% and 32%, P = .042) and OS (60%	END was more commonly used in cases requiring free tissue transfer. The use of END for head and neck cSCCs that have invaded the skull base is not routinely performed but was found to be associated with a survival advantage and reduced regional recurrence rate.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					and 37%, P = .036) compared with those who were observed and a significantly reduced rate of regional recurrence (9% and 37%, P = .024). The rate of occult nodal metastasis identified with END was 36% and is approximately equal to the regional failure rate of the neck observation group (37%).		
Chen et al 2007	To analyze the management of parotid-area metastasis from cutaneous squamous cell carcinoma with radiation therapy	Retrospective study; n=36	Patients treated with radiation therapy for cutaneous squamous cell carcinoma involving the parotid-area lymph nodes	Local (parotid) control OS	After treatment, 7 patients experienced a subsequent parotid resulting in a 5-year local (parotid) control rate of 76%. Of 30 patients treated using surgery and post-operative radiation therapy, 4 patients experienced local recurrence, resulting in a 5-year local	The present study shows that surgery and postoperative radiation therapy result in excellent rates of local-regional control for patients with parotid-area metastasis. Based on this analysis, a dose of 60 Gy or greater to the parotid region, as well as routine inclusion of the	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(parotid) control rate of 86%. OS rate for the entire patient population at 5 years was 63%	draining lymphatics of the ipsilateral neck in the radiation field, is recommended.	
Foote et al 2014	This study evaluated the Efficacy and safety of single-agent panitumumab in the treatment of patients with cutaneous SCC (cSCC) not suitable for local therapy	Single center prospective phase II study; n=16	Patients who received single-agent panitumumab at the Princess Alexandra Hospital, Brisbane, Australia	Best overall response rate (ORR) Evaluation of safety Toxicity PFS	The best overall response rate (ORR; PR or CR) was 31% with a further 6 of 16 patients achieving stable disease. The duration of overall response was a median 6 months. The 6-week disease control rate (DCR) was 69%. With a median follow-up of 24 months, 10 patients died due to progressive disease, 6 were alive, 1 patient with no evidence of disease at the time of analysis. The median OS was 11 months and median PFS was 8 months	This study reports that some patients were slow to respond to therapy. In this study of panitumumab, most of the patients had been pre-treated; 12 patients had previous surgery, 14 of 16 patients receiving previous radiotherapy and 7 of 16 patients having prior chemotherapy. The best ORR was 31%, with a DCR at 6 weeks of 69% and duration of response being 6 months.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Fujimura et al 2017	To determine the effective and safe dose of PEP and the curative rate of intra-arterial administration of peplomycin (IA-PEP)	Retrospective study; N=24	Patients with cutaneous SCC (cSCC) on the lips who were treated with IA-PEP in one dermatology department	Efficacy Safety	IA-PEP reduced the tumor mass in all 24 cases (100%). A complete response occurred in 17 patients (70.8%), and a partial response occurred in seven (29.2%). Moreover, 17 patients (70.8%) were cured, three patients developed cervical lymph node metastasis (12.5%), and four developed local recurrence (16.7%). Three out of the 24 patients developed interstitial pneumonia (12.5%).	Low-dose IA-PEP administered through a superficial temporal artery was a highly effective treatment that achieved a curative response for 70.8% of patients with cSCC on the lips. Nevertheless interstitial pneumonia can occur, even with low doses of PEP	3
Goh et al 2010	The aim of this retrospective study was to look at the treatment and outcome of patients with metastatic cutaneous SCC (cSCC) to the axilla and groin	Retrospective study; n=26	Patients treated between 1980 and 2007	Recurrence and survival	Seven patients (27%) developed a recurrence with a median time to recurrence of 2.2 months. The lungs were the most common site of first recurrence (four patients). The	In this study, patients were treated with radical intent with all patients proceeding to surgery and half also receiving adjuvant nodal radiotherapy. Although not well reported, the	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	nodes treated at Westmead Hospital, Sydney				median survival of patients was 18.5 months	decision not to offer combined treatment may have been related to the concern of the surgeon in regards to limb edema.	
Gonzalez et al 2017	To compare the AJCC-7 and BWH staging systems for cutaneous SCC (cSCC) in immunosuppressed patients	A single-institution retrospective cohort study; n=106	cSCC in immunosuppressed patients	Risks of local recurrence nodal metastasis in-transit metastasis To report poor outcomes	One hundred six patients had 412 primary invasive cSCC. Eighty-five percent were AJCC-7 T1, and 15% T2. Risks of NM and PO for AJCC-7 T1 versus T2 were 0.9% versus 5% and 12.8% versus 23.3%, respectively, $p < .05$. Eighty-one percent of tumors were BWH T1, 18% T2a, 1% T2b, and 0.2% T3. Risk of LR for BWH T1 versus T2a was 11.4% versus 20.3%, $p < .01$. Risk of NM increased from 0.3% for T1 to 4.1%, 25%, and 100% for T2a,	Low T-stage cSCC accounts for most poor outcomes. Brigham and Women's Hospital staging criteria better risk stratifies cSCC in immunosuppressed patients for risk of nodal metastasis and local recurrences. Additional studies are needed to quantify the increase in the risk of poor outcomes for the same T-stage cSCC in immunocompetent versus immunocompromised patients. Better risk stratification of low	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					T2b, and T3, p < .05. Ninety percent of PO occurred in low-stage BWH T1/T2a.	T-stage cSCC in immunosuppressed patients is needed. Alternatively, immune status can potentially be included as part of the staging criteria to reflect the inherently higher risk of poor outcomes associated with immuno-suppression. In the meantime, vigilant detection and definitive treatment of even low T-stage cSCC in immunosuppressed patients are recommended.	
Han et al 2007	To evaluate the effectiveness of adjuvant XRT in treating SCC with PNI	Literature review, focused on large studies in major dermatologic journals	Patients treated for SCC with PNI from the 1960s to 2005	Local control rates 5-year survival rate	Patients who underwent standard excision with or without receiving XRT had local control rates that ranged from 38% to 87%. The 5-year cause-specific and absolute survival	Although most studies reviewed here included between 9 and 135 patients, only 1 report was a meta-analysis of 70 studies. The disparate methodologies of these cited articles	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					rates ranged from 50% to 61% in imaging-positive patients and from 86% to 100% in imaging-negative patients	render their results and conclusions difficult to validate or compare	
Harris et al 2017	To evaluate which factors are predictive of recurrence and nodal spread and survival in patients with cutaneous head and neck SCC (cHNSCC) treated surgically	Retrospective review; n=212	Patients with cHNSCC treated between January 1998 and June 2014. All patients undergoing primary surgery, with or without adjuvant therapy, with curative intent for cSCC were included. Patients were excluded if they had distant metastases at presentation, were treated with palliative intent, and had <3 months of follow-up.	5-years DFS DSS OS Associations of patient and tumor characteristics with recurrence and survival Factors independently associated with the presence of nodal metastasis at presentation	A total of 212 patients met inclusion criteria, with a mean age of 70.4 years; 87.3% were men. Mean tumor diameter was 3.65 cm, with an average depth of invasion of 1.38 cm. The mean follow-up time was 35 months (median, 21.5), and over that period 67 recurrences were recorded, 49 of which were local. The 5-year Kaplan-Meier estimate of DFS for the cohort was 53.2%. On Cox multivariate analysis, recurrent	For advanced cHNSCC, patients with recurrent disease, PNI, and poorly differentiated tumors are at the highest risk for local recurrence. Patients with tumors or the ear, cheek, temple, or lip, as well as those with PNI, are at increased risk of harboring nodal disease.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					disease, perineural invasion (PNI), and poorly differentiated histology were independent predictors of recurrence. On multinomial logistic regression, patients with primary tumors on the ear, cheek, temple, or lip, as well as those with PNI, were more likely to present with nodal metastasis. Analysis of OS and DSS was limited given incomplete cause of death data and the advanced age of the patient cohort.		
Hong et al 2005	To present diagnostic methods, the interval between index lesion and metastasis,	Retrospective review; n=20	Patients confirmed to have parotid bed metastases of squamous cell carcinoma treated in the University of	Treatment Recurrence Survival	After the diagnosis of parotid bed metastases, 14 (70%) of 20 patients underwent primary surgery with	Most patients in this series underwent superficial parotidectomy, with total parotidectomy reserved for the 20%	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	treatment methods, and outcome		Wisconsin Tumor Registry and Head and Neck Oncology Tumor Board, during a period of 10y from 1989 to 1999		postoperative radiotherapy to the parotid bed and ipsilateral neck. Three patients (15%) manifested local recurrence in the parotid bed during their follow-up period. The minimum follow-up time for patients in this series was 24 months. Cumulative OS was 12 of 20, or 60%.	of patients with partially fixed lesions or preoperative facial nerve involvement. This rationale is based on several studies, which have demonstrated that most intraparotid lymph nodes lie lateral to the facial nerve.	
Khan et al 2018	To assess LR and LN metastasis in the same cohort of patients at 5 years in an attempt to examine time to recurrence and to identify risk factors that could predict recurrence.	Retrospective analysis; n= 598 SCCs; 633 cutaneous squamous cell cancer (SCC) excisions	Surgically excised cutaneous SCC from 4 centers	Rates of local recurrence (LR) and lymph node (LN) metastasis	We report 5-year outcomes from 598 SCCs (95% follow-up rate). The total recurrence rate (LR and LN metastasis) was 6.7% (n = 40) at 5 years, with 96% of these occurring within 2 years. Median time to LR was 9 months (1–57), with 76.9% (n = 20) undergoing	This study is one of the largest studies to date following up 598 SCC excisions at 5 years with total recurrence rates comparable to those in current published literature. We report perineural invasion as a significant predictor of recurrence and that 96% of total	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					further wide local excision. Median time to LN metastasis was 5.5 months (1–18 months). There were two cases of disease-related death. Only 15% (n = 6) of incomplete excisions recurred. Interestingly, 19.1% (n = 9) of 47 SCCs with perineural invasion on original histopathology recurred versus only 5.6% (n = 31) of the 551 SCCs without perineural invasion (p = 0.005).	recurrence occurred within 2 years. This is in contrast to current UK guidelines (75% at 2 years, 95% at 5 years), thus suggesting that a shorter length of hospital follow-up may be reasonable.	
Korhonen et al 2020	To determine the rate of local recurrences and metastases of cutaneous squamous cell carcinomas in a previously defined patient cohort in	Retrospective analysis; n= 774 patients with 1,131 cutaneous SCC	All patients in the Pirkanmaa region of Finland diagnosed with cSCC in 2006–2015	Rate of local recurrence and metastases in cSCC	Overall, 4.2% (48/1,131) of the tumours were metastatic and 2.2% (25/1,131) had a local recurrence. Three of the metastatic tumours and 8 of the	The study demonstrated recurrences and metastases even in the case of thin cutaneous squamous cell carcinomas and in high-risk cases close monitoring	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	Finland.				recurrent tumours had an invasion depth of ≤2 mm. The majority of metastases (28/48; 58%) were found within 3 months of the diagnosis of cutaneous squamous cell carcinoma.	should be organized during the first years after diagnosis.	
Jol et al 2002	To investigate the results of our treatment policy, we present our institutional experience in the management of regional neck node metastases of cutaneous head and neck squamous cell carcinoma (cHNSCC)	Retrospective study; n=41	Patients with cHNSCC diagnosis, treated between 1977 and 1997	OS	Seventy-six percent of the regional metastases occurred within the first 2 years, but a delay of more than 5 years was also observed. Parotid gland (56%), neck levels II (39%) and V (22%) were most frequently involved. Twenty-four percent of patients treated with curative intent failed at the regional site. Five years OS was 46%, with a median survival of	Although the present study was not set up to analyze prognostic parameters, it seems that the correlation between T-stage and the risk for regional metastases was not so outspoken in our material	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					49 months. No survival differences emerged between patients treated by surgery alone and patients receiving adjuvant radiotherapy		
Lu et al 2015	Presentation of institutional experience with radiation and concurrent systemic therapy consisting of either Pt-based chemotherapy or Cx in patients with high-risk cutaneous head and neck SCC (cHNSCC)	Single-institution retrospective review, n= 23	Patients from the Kaiser Permanente Los Angeles Medical Center Between 2005 to 2014	PSF OS	The majority (87%) of patients had stage III/IV disease and 9 (39%) patients had unresectable disease. All patients were being treated for recurrent disease. Aside from median age (59 Pt vs. 71 Cx, P = 0.04), there were no significant differences in patient and tumor characteristics between those receiving Pt versus Cx therapy. At mean follow-up of 24 months, locoregional	To our knowledge, this study is the first to report on the use of Cx with concurrent radiotherapy for this patient population. To date, only a handful of retrospective reports have been published describing the use of concurrent radiation and systemic therapy for locally advanced cHNSCC	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					recurrence and distant failure were observed in 52% and 17% of all patients, respectively. Estimated 2-year DFS and OS in the Cx versus Pt groups were: 50% versus 30% (P = 0.25), and 73% versus 40% (P = 0.32), respectively		
Oh et al 2020	To determine risk factors for recurrence including various patient factors in Asian patients with cSCC treated with Mohs micrographic surgery (MMS)	Retrospective study; n= 237	cSCC patients treated with MMS at a single tertiary referral center from 2000 to 2017	Rate of recurrence of cSCC after MMS	Two hundred and thirty-seven patients were included and 36 showed recurrence (20 with local recurrence, 16 with distant metastasis). History of organ transplantation, diabetes, other malignancies and poorly differentiated histology correlated with cSCC recurrence.	History of organ transplantation and cryotherapy at the cSCC site were related to higher local recurrence rates, and poor differentiation related to higher distant metastasis in Asian cSCC patients treated with MMS.	3
Manyam et al 2017	The current study is an effort to	Multi-institutional study; n=205	Patients from 3 institutions who	Locoregional RFS and PFS	RFS (47.7% vs 86.1%) and PFS (38.7% vs	Immunosuppressed status is strongly	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	validate preliminary findings in a large cohort from 3 institutions and to further elucidate the association between immune status and disease-related outcomes in patients with cutaneous HNSCC (cHNSCC)		underwent surgery and also received postoperative RT for primary or recurrent, stage I through IV cHNSCC between 1995 and 2015. 138 patients were immunocompetent and 67 were immunosuppressed	OS	71.6%) were significantly lower in immunosuppressed patients at 2 years. OS rate in immunosuppressed patients demonstrated a similar trend but did not meet significance. Immunosuppressed patients with cHNSCC had dramatically lower outcomes	associated with inferior locoregional control and PFS in patients with high-risk cHNSCC who undergo surgery and receive postoperative RT. These findings underscore the need for improved prognostic systems, increased multidisciplinary management and clinical trials investigating methods of intensified therapies for these patients.	
Palme et al 2003	To test ta new clinical staging system in patients with metastatic cutaneous squamous cell carcinoma (cSCC)	Retrospective analysis; n=126	Patients treated for metastatic cSCC involving the parotid and/ or neck between 1987 and 1999 with a minimum of 2 years follow-up	Locoregional recurrence DSS	Of the 126 patients, disease involved the parotid gland in 81 patients, of whom 14 also had clinical neck disease, while 45 patients had neck involvement only. The 5-year local control rate was 80% and this varied		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					statistically significantly with P stage. The 5-year DSS rate was 68%.		
Popovtzer et al 2020	To report the feasibility and safety of diffusing alpha-emitter radiation therapy (DaRT), which entails the interstitial implantation of a novel alpha-emitting brachytherapy source, for the treatment of locally advanced and recurrent squamous cancers of the skin and head and neck	Prospective first-in-human, multicenter clinical study; n=28 patients; 31 lesions	All patients with biopsy-proven squamous cancers of the skin and head and neck with either primary tumors or recurrent/previously treated disease by either surgery or prior external beam radiation therapy	The primary objective was to determine the feasibility and safety of this approach, and the secondary objectives were to evaluate the initial tumor response and local progression-free survival.	Acute toxicity included mostly local pain and erythema at the implantation site followed by swelling and mild skin ulceration. For pain and grade 2 skin ulcerations, 90% of patients had resolution within 3 to 5 weeks. Complete response to the Ra-224 DaRT treatment was observed in 22 lesions (22/28; 78.6%); 6 lesions (6/28, 21.4%) manifested a partial response (>30% tumor reduction). Among the 22 lesions with a complete response,	Alpha-emitter brachytherapy using DaRT achieved significant tumor responses without grade 3 or higher toxicities observed. Longer follow-up observations and larger studies are underway to validate these findings.	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					5 (22%) developed a subsequent local relapse at the site of DaRT implantation at a median time of 4.9 months (range, 2.43-5.52 months). The 1-year local progression-free survival probability at the implanted site was 44% overall (confidence interval [CI], 20.3%-64.3%) and 60% (95% CI, 28.61%-81.35%) for complete responders. Overall survival rates at 12 months post-DaRT implantation were 75% (95% CI, 46.14%-89.99%) among all patients and 93% (95% CI, 59.08%-98.96%) among complete responders.		
Ruiz et al 2017	To review utilization of	Retrospective study; n=98 patients; 108	Patients diagnosed with cutaneous SCC	Disease-related outcomes (DRO):	Imaging (mostly computed	Limitations: Single institution	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	radiologic imaging of high-stage cutaneous SCC (cSCC) to evaluate whether imaging impacted management and outcomes.	high-stage cSCC	from January 1, 2000, through May 30, 2013 treated in the Brigham and Women's Hospital.	local recurrence, nodal metastasis, death from disease	tomography, 79%) was utilized in 45 (46%) patients and management was altered in 16 (33%) patients who underwent imaging. Patients that received no imaging were at higher risk of developing nodal metastases (nonimaging, 30%; imaging, 13%; P = .041) and any DRO (nonimaging, 42%; imaging, 20%; P = .028) compared to the imaging group. Imaging was associated with a lower risk for DRO (subhazard ratio, 0.5; 95% CI 0.2-0.9; P = .046) adjusted for BWH T stage, sex, and location.	retrospective design and changes in technology over time. Radiologic imaging of high-stage cSCC may influence management and appears to positively impact outcomes. Further prospective studies are needed to establish which patients benefit from imaging.	
Skulsky et al 2017	To review the high-risk features included in NCCN	Embase, CENTRAL, and MEDLINE were searched for	Patients with high-risk cSCC	To compare two different guidelines (NCCN and AJCC) in	The AJCC TNM staging system considers the	Future studies are required to evaluate the extent to which	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	and AJCC guidelines, as well as their notable discrepancies and omissions. To provide a brief overview of current prophylactic measures, surgical options, and adjuvant therapies for high-risk cutaneous SCC (cSCC).	published studies, clinical trials, and guidelines on high-risk cutaneous SCC of the head and neck. Reference lists from the relevant articles acquired were also searched. The search date range used January 2016 as the end date; no start date was specified. The following terms are examples of terms that were combined in the database searches: "high-risk cutaneous squamous cell carcinoma, guidelines, excision margins, organ transplant, immunosuppression, depth, recurrence, sirolimus, cyclosporine, azathioprine, sentinel lymph node		what concerns SCC high-risk features discrepancies and omissions. The following aspects were evaluated: Tumor size Depth of invasion Recurrent setting Poorly differentiated lesions Histopathological subtype Perineural invasions Lymphovascular invasion High-risk anatomical location Immunosuppressed sate Incomplete excision	following high-risk features when determining the primary tumor (T) classification: depth (>2mm thickness or Clark level ≥IV), anatomic location, poor histological differentiation, and perineural invasion (PNI). Tumors are classified as T2 in 2 ways: (1) tumors > 2 cm in greatest dimension, or (2) any size tumor with ≥2 high-risk features. NCCN has also identified several high-risk features of cSCC. High-risk cSCC, as per NCCN Guidelines refers to a greater propensity for local recurrence and/or metastasis. NCCN classifies cSCC as high-risk if≥1 feature is	the inclusion of these additional high-risk features would improve tumor staging and prognostic outcomes. Ultimately, a consensus on the definition of high-risk features of cSCC needs to be reached to produce accurate and practical treatment guidelines that will enhance patient care.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		biopsy, superficial parotidectomy, elective neck dissection, and Mohs micrographic surgery." All records obtained from our searches were screened by title and abstract for selection.			present. Currently, there is no unanimous consensus on the high-risk features of cSCC. Although NCCN Guidelines and the AJCC TNM classification system share some overlapping high-risk features of cSCC, significant discrepancies exist. In comparison with NCCN Guidelines, the AJCC omits several high-risk features associated with poor clinical outcomes, including immunosuppression, lymphovascular invasion, recurrent tumors, and certain prominent high-risk anatomic locations. Notably, neither NCCN nor the AJCC includes incomplete excision as a feature		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					warranting a tumor's treatment as high-risk cSCC. As a compounding factor, there are no guidelines for managing the deep tumor margin.		
Strassen et al 2017	To determine whether surgical concepts are warranted in the collective of old patients with cutaneous head and neck SCC (cHNSCC)	Retrospective study; n=67	Patients who underwent surgical procedure due to recurrent disease of cHNSCC in one department between January 2008 and December 2013	OS Recurrence-free interval (RFI)	The cohort was divided into patients with/without adjuvant therapeutic regimens. The median recurrent free interval and the median OS after recurrent disease therapy were 27 and 59 months (data not shown), respectively. There was a significant difference between patients who underwent surgery with adjuvant radiotherapy and patients without	While the benefit of elective parotidectomy and/or neck dissection—particularly in high-risk patients (pN+, G3/ G4, tumor thickness >6 mm)—in the long-term preservation of neuronal structures, RFI and, OS has to be analyzed in a prospective randomized trial, our study demonstrated a favorable RFI/OS in patients with cSCC recurrent disease who underwent surgical concepts and	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					adjuvant treatment. Patients with adjuvant treatment demonstrated a 5y-RFI and OS rate of 78 and 79 %, respectively, while patients without adjuvant therapy showed a 5y-RFI and OS rate of 30 and 46 % (p = 0.02; p<0.05). The distribution of T and N stages differed significantly between the groups. Patients who underwent adjuvant radiotherapy presented with limited T stages (T0–1), but advanced N stages (N2a–2b). Patients without adjuvant treatment concepts showed higher T stages (T1–2) and limited N stages (N0–1) (p = 0.001; p<0.0001).	adjuvant radiotherapy. Locoregional metastases in the lymphatic basin might be more frequent than previously expected. Sonographic staging and follow-up screening of the cervical lymphatic basin might, therefore, be beneficial even in patients presenting with small primary tumors.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					There were no differences in patient' age (patients receiving adjuvant therapy: 76 years vs patients not receiving adjuvant therapy: 80 years; p = 0.07) and comorbidities (p = 0.9).		
Stratigos et 2020	to make recommendations on cutaneous SCC (cSCC) diagnosis and management	Retrospective review; search with terms 'cutaneous squamous cell carcinoma' using the PubMed, EMBASE and Cochrane Library was conducted. Articles included systematic reviews, pooled analyses and meta-analyses	EDF-EADO-EORTC guideline	Risk factor Clinical presentation and diagnosis Overall prognosis	The most prominent risk factors for cSCC include sun exposure, advanced age, and UVR-sensitive skin. The most common clinical appearance of invasive cSCC is an actinic keratosis that becomes hyperkeratotic or its base becomes infiltrated, or else becomes tender or ulcerated. The overall prognosis for the majority of patients with	The present EDF-EADO-EORTC guidelines represent a European consensus-based interdisciplinary set of recommendations (S2 level) addressing all aspects of management of invasive cSCC, from the diagnosis of primary tumor to the systemic treatment of locally advanced or metastatic disease. The recommendations	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					cSCC is excellent, with an overall five-year cure rate of greater than 90%, which is much better than other SCCs of the head and neck area	are based on current standards of care, existing guidelines and the expert panel opinion	
Sun et al 2019	To report survival outcomes in patients with cSCC-HN after disease recurrence after surgery and postoperative radiotherapy and to investigate the association of immune status with disease-related outcomes.	Retrospective study; n=205	Patients who underwent surgical resection and postoperative radiotherapy for primary or recurrent stage I to IV (nonmetastatic) cSCC-HN between January 1, 1995, and December 31, 2014	Overall survival	Of the 205 patients in the original cohort, 72 patients (63 men and 9 women; median age, 71 years [range, 43-91 years]) developed disease recurrence after surgery and postoperative radiotherapy. Forty patients (55.6%) were immunosuppressed, and 32 patients (44.4%) were immunocompetent. Locoregional recurrence was the most common first pattern of failure for both groups (31	Results of this study suggest that patients with cSCC-HN who experience disease recurrence after definitive treatment with surgery and postoperative radiotherapy have poor survival, irrespective of immune status. Survival rates are low for patients with recurrent disease that is not amenable to surgical salvage. The low rate of successful salvage underscores the importance of intensifying upfront treatment to prevent	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					immunosuppressed patients [77.5%]; 21 immunocompetent patients [65.6%]). After any recurrence, 1-year overall survival was 43.2% (95% CI, 30.9%-55.4%), and median survival was 8.4 months. For patients for whom information on salvage treatment was available (n = 45), those not amenable to surgical salvage had a significantly poorer median cumulative incidence of survival compared with those who were amenable to surgical salvage (4.7 months; 95% CI, 3.7-7.0 months vs 26.1 months; 95% CI, 6.6 months to not reached; P = .01), regardless of their immune status.	recurrence.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Tang et al 2013	To report outcomes, failure patterns, and toxicity after stereotactic radiosurgery (SRS) for recurrent head and neck cutaneous squamous cell carcinoma (cHNSCC) with gross perineural invasion (GPNI).	Retrospective study; n=10	Patients who received SRS as part of retreatment for recurrent head and neck cHNSCC with GPNI, between December 2003 and September 2009 were included	Median follow-up PFS	At a median 22-month follow-up, the 2-year progression-free and OS rates were 20% and 50%, respectively. At last follow-up, 7 patients had died and patients 1, 3, and 8 were alive at 23, 69, and 22 months, respectively	The drawbacks of our study include its retrospective nature and heterogeneity in treatment and patient characteristics. In addition, we only scored CN involvement when both imaging and associated symptomatic manifestations were present. Some study patients exhibited clinical findings interpretable as CN involvement outside of those listed. However, as these symptoms lacked the corresponding imaging findings, we did not score such instances as GPNI.	3
Xu et al 2018	To assess changes resulting from the American Joint Committee on Cancer (AJCC)	Retrospective analysis; n=101	Patients receiving surgery and postoperative radiotherapy (PORT) with or without	Locoregional recurrence, overall survival (OS), and cause-specific mortality rates	The 2-year locoregional recurrence, overall survival (OS), and cause-specific	In-transit metastasis was significantly associated with locoregional recurrence, OS, and	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	eighth edition for cutaneous squamous cell carcinoma (SCC) and evaluate pertinent excluded factors		concurrent systemic therapy for cutaneous SCC from 2007-2016		mortality rates were 25%, 72%, and 13%, respectively. The AJCC eighth edition upstaged T classification in 50% of patients and overall stage in 39%. In multivariate analysis, immunosuppression and in-transit metastasis were associated with locoregional recurrence. Older age and in-transit metastasis were associated with worse OS. In univariate analysis (limited by the number of events), cause-specific mortality was associated with a positive margin, in-transit metastasis, and the seventh edition dichotomized T	cause-specific mortality. Efforts should be made to define in-transit metastasis in the staging system.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					classification and overall stage.		

7.8.5. Literature

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7.9. Question VI.9. Which treatment is recommended for patients with metastatic disease in the first and second line?

(Frage VI.9. Welche Therapie wird für Patienten im fernmetastasierten Stadium (First- und Second-Line) empfohlen?)

De novo Recherche

7.9.1. PICO

PICO – Scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Cutaneous squamous cell carcinoma, or skin, alternatively HNSCC locally advanced or metastatic	Systemic treatment	Different systemic therapies	PFS, OS, response rate, quality of life, safety

7.9.2. Database, search strategy, number of results

Database	Search strategy	Date	Number of results
1. Search			
Medline	(squamous cell carcinoma[Title]or carcinoma squamous cell [title]) AND (clinical trial.pt.[Title/Abstract] OR Clinical Trial, Phase II[Title/Abstract] OR Clinical Trial, Phase III[Title/Abstract] OR Clinical Trial, Phase IV[Title/Abstract]) AND (randomized[Title/Abstract] OR random*[Title/Abstract]) NOT "case report" AND (English[Language] OR German[Language])	15th December 2016 (initial search)	114
		Update 30th May 2017	120
		Update January 2021	157

Database	Search strategy	Date	Number of results
Remarks and notes:-			

7.9.3. Selection criteria

Literature selection		
Number of total results		157
Inclusion criteria	Trials evaluating therapy in locally advanced cSCC or metastatic cSCC PD1 inhibitors in SCC treatment	
Exclusion criteria	Studies evaluating SCC with the following localizations: esophageal, mucosal and oral Reviews, exclusively QoL studies, studies not addressing therapy, studies with adjuvant therapies,	
Number of results after abstract searching		50
Number of full texts reviewed		34

7.9.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Adelstein et al 2000	To report the mature results from a phase III randomized trial comparing radiation therapy and concurrent chemoradiotherapy in patients with stage III and IV squamous cell carcinoma of the	Randomized, phase III study; n=100	Patients with stage III or IV disease, included between March 1990 and June 1995	Median follow-up DFS	After completing all therapy including surgery, 82% of the patients in Arm A and 98% of the patients in Arm B had been rendered disease-free (P= 0.02). At a median follow-up of 5 years (range, 3–8 years), the 5-	These results demonstrate the importance of assessing multiple endpoints in any evaluation of the role of chemotherapy for patients with this tumor. It also must	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	head and neck				year Kaplan-Meier projections for OS for Arm A versus Arm B were 48% versus 50% (P =0.55)	be pointed out that this study did not address the role of primary surgical resection in the management of these patients.	
Amaral et al 2019	To describe and analyze patients and primary tumour characteristics, local and systemic treatments, as well as survival outcomes.	Retrospective analysis; n=195	Patients with advanced cSCC diagnosed between 01/2011 and 06/2018 in one center	Survival rates	The median follow-up was 21 months [IQR = (10.0; 21.0)]. The median age at time of advanced disease diagnosis was 78 years [IQR = (72; 84)], with 40.5% of the patients in stage III and 59.5% in stage IV. One hundred and forty-five patients had resectable tumours. In this group the median overall survival (mOS) was 59 months (95% CI: 28.2-89.8), significantly higher than the mOS in patients with inoperable tumour [n = 50; mOS: 19 months (96% CI: 7-31, P <0.0001)]. Patients receiving immunotherapy (n = 20)	Surgical complete resection should be the first therapeutic option for patients with acSCC. For patients with an inoperable tumour, first-line immunotherapy should be preferably considered.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					showed a statistically significant better survival compared to those treated with other systemic therapies (n = 37; mOS not reached vs. mOS: 22 months (95% CI: 6.5–43.5), P = 0.034). For patients without systemic therapy, a combination of surgery and radiotherapy provided better outcomes compared to radiotherapy alone or best supportive care (P <0.001).		
Brewster et al 2007	To conduct a phase III trial of adjuvant 13-cis-retinoic acid (13cRA) plus interferon alfa (IFN-alfa) for preventing tumor recurrence and second primary tumors (SPTs) of SCC among patients with aggressive skin SCC.	Randomized controlled clinical trial; n=66	Patients who were recruited consecutively and observed prospectively at The University of TexasM.D.Anderson Cancer Center (Houston, TX) from 1996 to 2002	Median follow-up	At 21.5 months median follow-up, treatment did not improve the time to tumor recurrence and SPT versus control (hazard ratio, 1.13; 95% CI, 0.53 to 2.41), time to tumor recurrence (HR, 1.08; 95% CI, 0.43 to 2.72), or time to SPT (HR, 0.89; 95% CI, 0.27 to 2.93). Adjuvant 13cRA and IFN-alfa was	When we designed the trial in 1996, we projected that the event (recurrence or SPT) -free rate at 2 years would be 34% based on the available retrospective data from M.D. Anderson Cancer Center	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					moderately tolerable; 29% of patients in the treatment arm required dose reductions for grade 3 or 4 toxicities	(subsequent prospective data showed a disease-specific survival of 70% in similar patients observed for a median of 22 months). Therefore, our study was underpowered to detect an HR of 0.32 for the study endpoint or to detect a significant difference between arms in either recurrence or SPT alone, limiting the interpretation of our results	
Caponigro et al 2002	To evaluate response data for Cisplatin, Raltitrexed, Levofolinic Acid and 5-FU treatment	Phase II randomized study	Patients receive either CDDP 60 mg/m2 and raltitrexed 2.5 mg/m2 on day 1 and LFA 250mg/m2 and 5-FU 900mg/m2 on day 2 (arm A) or CDDP	Response data	An interim analysis was performed when 36 patients were evaluable in each arm. In arm A, 10 CR (28%) and 19 partial responses (PR) (53%) were observed, for an overall response rate of 81%. In arm B, 3 CR	Although response data for our experimental arm look encouraging, the hypothesis of a 35% activity, expressed as the capability to induce a CR,	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			65 mg/m2 and methotrexate 500 mg/m2 on day 1, and LFA 250 mg/m2 and 5-FU 800 mg/m2 on day 2 (arm B)		(8%) and 12 PR (34%) were observed, for an overall response rate of 42%. The difference in both CR and overall response rate between the two arms was statistically significant (p = 0.03 and 0.001, respectively).	cannot be accepted according to our statistical methods. The achievement of a CR following primary chemo-therapy is an important prognostic factor for these patients, and, if a survival advantage is to be expected with induction chemotherapy followed by locoregional treatment, the achievement of an CR after primary chemotherapy is an important step.	
Cavalieri et al 2018	To investigate the role of oral pan-HER inhibitor dacomitinib in In recurrent or metastatic (R/M) skin squamous cell cancer	Open-label, multicentric, uncontrolled phase II trial	Patients with diagnosis of R/M sSCC; n=42	Primary endpoint was the best response rate (RR) to dacomitinib, defined as the sum of partial	Forty-two patients (33 men; median age 77 years) were treated. Most (86%) received previous treatments consisting in surgery	In sSCC, dacomitinib showed activity similar to what was observed with anti-epidermal growth	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(sSCC) not amenable to radiotherapy (RT) or surgery, chemotherapy (CT)			response (PR) and complete response (CR) frequencies.	(86%), RT (50%) and CT (14%). RR was 28% (2% complete response; 26% partial response), disease control rate was 86%. Median progression-free survival and overall survival were 6 and 11 months, respectively. Most patients (93%) experienced at least one adverse event (AE): diarrhea, skin rash (71% each), fatigue (36%) and mucositis (31%); AEs grade 3e4 occurred in 36% of pts. In 16% of cases, treatment was discontinued because of drug-related toxicity. TP53, NOTCH1/2, KMT2C/D, FAT1 and HER4 were the most frequently mutated genes. BRAF, NRAS and HRAS mutations were more frequent in non-responders, and KMT2C and CASP8 mutations were restricted to this	factor receptor agents, and durable clinical benefit was observed. The safety pro- file was comparable to previous experiences in other cancers. Molecular pt selection could improve the therapeutic ratio.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					subgroup		
Cavalieri et al 2019	To explore the possible role of PD-L1 expression in predicting response to anti-EGFR agents.	Retrospective analysis; n=28	Patients with unresectable R/M sSCC treated with EGFR pathway inhibitors from 2010 to 2016.		Twenty-eight R/M sSCCs were analyzed (19 treated with dacomitinib, 9 with CT-cet). TC and IC were negative in 82 and 45% of cases, respectively; 15% sSCCs were both TC and IC positive. Progression-free survival (PFS) was longer in IC-positive cases (median 7.5 months vs. 2.1 in IC0, p = 0.02). No statistically significant differences were observed be- tween PD-L1 expression and both overall survival and response rates.	PD-L1 expression in microenvironment predicted better PFS. The combination of EGFR inhibitors and ICB could help to deepen the knowledge about the interrelations between the EGFR and PD-1/PD-L1 pathways.	4
Chow et al 2016	The current study aimed to report the safety and efficacy of a Fixed-dose regimen in an all-comer population of patients with R/M HNSCC, regardless of PD-L1 or HPV status, from a larger head	Phase Ib, multicenter, nonrandomized, multicohort study; n=118	Patients with advanced solid tumors treated with pembrolizumab between June 12, 2014, and October 8, 2014	Overall response rate (ORR) PFS OS	Of 132 patients enrolled, median age was 60, and 57% received two or more lines of therapy for R/M disease. ORR was 18% (95% CI, 12 to 26) by central imaging vendor and 20% (95% CI, 13 to 28) by investigator review. Median duration	A limitation of this study is the lack of a consistent method used to determine HPV status. HPV association was determined by the site investigator by using the method	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	and neck SCC (HNSCC) expansion cohort of the KEYNOTE-012 trial				of response was not reached (range, > 2 to > 11 months). Six-month progression-free survival and overall survival rates were 23% and 59%, respectively. By using tumor and immune cells, a statistically significant increase in ORR was observed for PD-L1–positive versus –negative patients (22% v 4%; P= .021). Treatment-related adverse events of any grade and grade>3 events occurred in 62% and 9% of patients, respectively.	of their choice; p16 IHC was used by the majority of sites. Whereas p16 IHC is a useful surrogate for HPV infection in oropharyngeal HNSCC, it has limited utility outside of the oropharynx where HPV is less prevalent. For that reason, patients with non-oropharyngeal HNSCC were considered to be HPV-negative regardless of p16 status	
Clement et al 2016	This report evaluates afatinib efficacy and safety in pre-specified subgroups of patients aged ≥65 and <65 years.	Phase III, open-label trial; n= 483	Patients were randomized (2:1) to 40 mg/day oral afatinib or 40 mg/m2/week intravenous methotrexate	PF OS ORR	Of 483 randomized patients, 27% were aged ≥65 years and 73% <65 years at study entry. Similar PFS benefit with afatinib versus methotrexate was observed in older and	Although patient numbers in then older subgroup were smaller than the overall population andnyounger subgroup	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					younger patients [2.6 versus 1.6 months, P = 0.052]. In older and younger patients, the median OS with afatinib versus methotrexate was 7.3 versus 6.4 months and 6.7 versus 6.2 months. ORRs with afatinib vs. methotrexate were 10.8% versus 6.7% and 10.0% versus 5.2%; DCRs were 53.0% versus 37.8% and 47.7% versus 38.8% in older and younger patients, respectively. In both subgroups, the most frequent treatment-related adverse events were rash/acne (73%–77%) and diarrhea (70%–80%) with afatinib, and stomatitis (43%) and fatigue (31%–34%) with methotrexate. Fewer treatment-related discontinuations were observed with afatinib (each sub-group 7% versus 16%). A trend	(particularly the methotrexate arm due to the 2:1 randomization scheme), and the study was not powered for formal statistical comparison of predefined subgroups, there is no indication that the benefit observed with afatinib would be adversely affected by advancing age	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					toward improved time to deterioration of global health status, pain, and swallowing with afatinib was observed in both subgroups.		
Cooper et al 2012	To report the long-term outcome of RTOG 9501 trial	Prospective randomized trial; n=410	Patients with high-risk resected head and neck cancers	local-regional control OS	At 10 years, the local-regional failure rates were 28.8% vs. 22.3% (P=. 10), DFS was 19.1% vs. 20.1% (P=. 25), and OS was 27.0% vs. 29.1% (P=.31) for patients treated by RT vs. RT þ CT, respectively. In the unplanned subset analysis limited to patients who had microscopically involved resection margins and/or extracapsular spread of disease, local-regional failure occurred in 33.1% vs. 21.0% (P=.02), DFS was 12.3% vs. 18.4% (P=.05), and OS was 19.6% vs. 27.1% (P=.07), respectively.	Now, with a median follow-up of 9.4 years for surviving patients, this analysis of RTOG 9501 shows no statistically significant differences for any of the major endpoints of L-R control (the primary endpoint), DFS, or OS (secondary endpoints). More-over, the longer follow-up has blunted the differences in outcome that were originally observed. We are unable to analyze	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						the potential effect of HPV infection on the outcome of this trial. Not recognized at the time this trial was designed and conducted, HPV-positive cancers are associated with a better prognosis, could have diluted the RTOG “high risk” group, and could have confounded the results.	
Del Campo et al 2011	This study investigated the pharmacodynamic and clinical effects of lapatinib in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).	Randomized phase II study; n=107	Therapy-naive patients with locally advanced SCCHN were randomized	Objective response rate Safety	In a subset of 40 patients that received X4 weeks of lapatinib or placebo, the objective response rate (ORR) was 17% (n¼4/24) vs. 0% (n¼0/16). In the lapatinib single-agent responders, all had EGFR overexpression, 50% had EGFR amplification, and 50% had HER2 expression by		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					immunohistochemistry (including one patient with HER2 amplification). Following CRT, there was a statistically non-significant difference in ORR between lapatinib (70%) and placebo (53%). Mucosal inflammation, asthenia, odynophagia, and dysphagia were the most commonly reported adverse events with lapatinib.		
Fonseca et al 2005	The present study compares the efficacy and safety of a new combination of cisplatin/docetaxel versus the 5-FU + cisplatin regimen in patients with squamous cell carcinoma of the head and neck (SCCHN)	A randomized phase II study; n=83	Chemotherapy-naıve patients	Overall response rate Median survival	Among 76 patients evaluable for response, the overall response rate in arm A was 70% (complete response (CR) 26%, partial response (PR) 44%) and in arm B 69% (CR16%, PR54%), respectively. Median survival in arm A was 7.6months (95%CI: 5.8–11.1) and 9.9months (95%CI: 7.4–14.6) for arm B. The most frequent grade 3/4 toxicity in arm A was	In conclusion, in our phase II trial, both schedules, cisplatin/docetaxel and cisplatin/5-FU, are active and useful combinations in patients with locally advanced SCCHN. The high response rates, and recent results of a phase III trial with better survival for docetaxel	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					neutropenia (34.1%) and diarrhea (9.8%) versus mucositis (29.3%) and neutropenia (19.5%) in arm B	combination, justify further evaluation of those chemotherapy combinations in major patient populations. Both schedules are well tolerated, with significant but different toxicity patterns, which are generally well manageable.	
Gilbert et al 2012	To evaluate the activity of bortezomib administered before irinotecan, versus the activity of bortezomib alone, followed by the addition of irinotecan at the time of progression	Randomized phase II 2-arm trial; n=71	Patients with histologically documented incurable, locally advanced, or metastatic squamous cell carcinoma of the head and neck. Patients were allowed up to 1 prior therapy for incurable, advanced disease, but treatment must have been	Response rate	The response rate of bortezomib and irinotecan was 13%. One patient had a partial response to bortezomib alone (response rate 3%). No responses were seen in patients with the addition of irinotecan at the time of progression on bortezomib.	The objective response rates in this study were 13.1% (a 90% CI of 3.6%–30.3%) with irinotecan and bortezomib (arm A) and 2.6% (a 90% CI of 0.4%–22.1%) with bortezomib alone (arm B). For either arm, the observed response rate was not different than the null hypothesis	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			completed at least 4 weeks before study entry. Patients could not have been previously treated with irinotecan or bortezomib.			(15% and 5% for arm A and arm B, respectively). Although the 90% confidence intervals for either arm include the targeted true response rates, the wide interval is probably due to the small number of patients on either arm.	
Gold et al 2018	To determine the response rate to therapy with erlotinib, an EGFR tyrosine kinase inhibitor, in patients with locoregionally recurrent or metastatic CSCC that was not amenable to curative treat- ment (NCT01198028)	An open-label, uncontrolled, single-center phase 2 study, N=39	Patients with histologically or cytologically confirmed CSCC that was not amenable to curative intent therapy, with either distant metastases or locoregional disease for which curative resection or definitive radiation were not feasible.	The primary endpoint was overall response rate according to RECIST 1.1 criteria. Other endpoints included toxicity, PFS and OS	A total of 39 patients received treatment during the trial; 29 of these patients were evaluable for response. ORR 10% (3/29); all responses were partial responses. DCR: 72% (21/29). The median PFS was 4.7 months (95% CI, 3.5-6.2 months); the median OS: 13 months (95% CI, 8.4-20.5 months). No unexpected toxicities were seen.	Erlotinib therapy was feasible for most patients with incurable CSCC and was associated with expected toxicities. However, only a modest response rate of 10% was observed. Further study of EGFR tyrosine kinase inhibitors in this patient population is not warranted.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Gregoire et al 2011	To assess the efficacy and safety of gefitinib given concomitantly and/or as maintenance therapy to standard cisplatin/radiotherapy for previously untreated, unresected, stage III/IV non-metastatic SCCHN	A phase II, randomized, double-blind, placebo-controlled study; n=226	Patients with III/IV non-metastatic SCCHN treated with gefitinib 250mg/ day, 500 mg/day or placebo in two phases, followed by a maintenance phase (gefitinib or placebo alone).	Primary endpoint was local disease control rate (LDCR) at 2 years; Secondary endpoints were LDCR at 1 year, objective response rate, progression-free survival, OS, and safety and tolerability	Gefitinib (250 and 500 mg/day) did not improve 2-year LDCR compared with placebo either when given concomitantly with chemoradiotherapy (32.7% vs. 33.6%, respectively; OR 0.921, 95% CI 0.508, 1.670 [1-sided p = 0.607]) or as maintenance therapy (28.8% vs. 37.4%, respectively; OR 0.684, 95% CI 0.377, 1.241 [1-sided p = 0.894]). Secondary efficacy outcomes were broadly consistent with the 2-year LDCR results. In both doses, gefitinib was well-tolerated and did not adversely affect the safety and tolerability of concomitant chemoradiotherapy.		2
Grob et al. 2020	To evaluate Pembrolizumab in recurrent or metastatic cutaneous SCC	Prospective single-arm study, Phase II, multicenter N=105	patients with recurrent or metastatic cSCC not amenable to surgery or radiation	Primary endpoint: ORR Secondary endpoints: DOR, DCR, PFS, OS, and safety.	Median FU: 11.4 months (0.4 to 16.3). ORR:34.3% (95% CI, 25.3; 44.2%)		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					4 CR, 32 PR, DCR: 52.4% (95% CI, 42; 62.2%) Median DOR: not reached (2.7 to 13.11 months); Median PFS: 6.9 months (95% CI, 3.1: 8.5). Median OS: not reached (95% CI, 10.7; not reached) Grade 3 to 5 treatment-related adverse events occurred in 5.7% (n=56) of patients.		
Halim et al 2012	To compare concomitant chemoradiotherapy based on weekly low-dose gemcitabine versus weekly low-dose paclitaxel in locally advanced head and neck squamous cell carcinoma	Prospective randomized phase III study; n=216	Patients with locally advanced, unresected stage III/IVA/IVB head and neck cancer	Median follow-up Response Survival	The median follow-up was 22 months. The scheduled protocol was exactly applied in 88 (80%) of patients in group A and in 96 (91%) of patients in group B (P = 0.02). Partial and complete response occurred in 86 out of 110 patients (78%) in group A and in 94 out of 106 patients (89%) in group B (P = 0.038). The 2-year progression-free	Although group B showed statistically significant better progression-free and OS, the differences between the survival figures were not enormous.	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					survival figures were 54 and 64% of groups A and B, respectively however, the 2-year OS figures were 56 and 67%, respectively		
Harrington et al 2013	To assess the activity and safety of concurrent chemoradiotherapy (CRT) and lapatinib followed by maintenance treatment in locally advanced, unresected stage III/IVA/IVB head and neck cancer	Randomized Phase II study; n=67		Survival	CRT dose intensities were unaffected by lapatinib: median radiation dose 70 Gy (lapatinib, placebo), duration 49 (lapatinib) and 50 days (placebo); median cisplatin dose 260 mg/m2 (lapatinib) and 280 mg/m2 (placebo). Lapatinib combined with CRT was well-tolerated. Grade 3/4 toxicities during CRT were balanced between arms, except for an excess of grade 3 diarrhea (6% vs. 0%) and rash (9% vs. 3%) and two grade 4 cardiac events in the lapatinib arm. CRR at 6 months post-CRT was 53% with lapatinib versus 36% with placebo	Prior to the study, the consensus view of an expert panel was that a 10–15% superiority of lapatinib would be the minimum requirement to justify planning a randomized phase III study. Although the 17% absolute difference in the primary end-point favoring lapatinib meets this threshold, this has to be considered in light of using a non-standard end-point measure (CRR at 6 months)	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					in the intent-to-treat population. The progression-free survival (PFS) and OS rates at 18 months were 55% vs. 41% and 68% vs. 57% for the lapatinib and placebo arms, respectively. The difference between study arms was greatest in p16-negative disease (median PFS >20.4 months [lapatinib] vs. 10.9 [placebo]).		
Harrington et al 2009	This study (EGF100262) sought to establish the recommended phase II dose of lapatinib with chemoradiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN).	Phase I, open-label, cohort study; n=31	Patients with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN).	Dose-limiting toxicities Overall response	Dose-limiting toxicities (DLTs) included perforated ulcer in one patient in the 500-mg cohort and transient elevation of liver enzymes in one patient in the 1,000-mg cohort. No DLTs were observed in the 1,500-mg cohort. Therefore, the recommended phase II dose was defined as lapatinib 1,500 mg/d with chemoradiotherapy.	This study has established the recommended phase II dose of lapatinib as 1,500 mg/d when combined with chemoradiotherapy in patients with LASCCHN. Furthermore, this dose is associated with an acceptable tolerability profile, similar to that	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					The most common grade 3 to 4 adverse events were radiation mucositis, radiation dermatitis, lymphopenia, and neutropenia. No patients experienced drug-related symptomatic cardiotoxicity, and no interstitial pneumonitis was reported. The overall response rate was 81% (65% at the recommended phase II dose).	observed with chemoradiotherapy alone. Given these findings, randomized phase II and III studies of lapatinib plus chemoradiotherapy have been initiated in LA SCCHN	
Huis in 't Veld et al 2018	To evaluate the effectiveness of Tumour necrosis factor α (TNF) and melphalan-based isolated limb perfusion (TM-ILP) as a limb-saving strategy for locally advanced extremity cSCC.	Retrospective analysis; n=30	Patients treated with TM-ILP for locally advanced cSSC of an extremity between 2000 and 2015.	Effectiveness of TM-ILP as a limb saving strategy	A total of 30 patients treated with TM-ILP for cSCC were identified, with a median age of 71 years (36–92) and 50% female. Response could not be evaluated in 3 patients. After a median follow-up of 25 months, the overall response rate was 81% (n = 22), with 16 patients having a complete response (CR, 59%). A total of 7 patients developed local	TM-ILP should be considered as an option in patients with locally advanced cSCC in specialized centers, resulting in a high limb salvage rate.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					recurrence, with a median time to recurrence of 9 months (Interquartile Range 7–10). Progressive disease was observed in 5 patients (19%). Limb salvage rate was 80%. The overall 2-year survival was 67%.		
Jehn et al 2008	To compare the safety and efficacy profiles of patients in the two treatment arms – cisplatin and cisplatin with liposomal formulation (lipoplatin).	A randomized, multicenter phase III trial; n=46	Patients with histologically confirmed SCCHN, age between 18-75 years with sufficient renal function.	Toxicities Response rate	Grade III and IV hematotoxicity were more frequent in the cisplatin arm (31.7% vs. 12%). The renal toxicity profile of both drugs also showed marked differences. In the cisplatin arm, 23.8% of patients suffered grade III toxicity. In contrast, no grade III or IV renal toxicity occurred in patients treated with lipoplatin. The efficacy results showed 38.8% objective partial remission in the cisplatin arm vs. 19% in the lipoplatin	This ongoing study has shown so far that the lipoplatin formulation reduces both the hematological and non-hematological toxicity profiles of cisplatin to a clinically relevant extent when combined with 5-FU. However, the authors feel that the high percentage of renal toxicity associated with the cisplatin arm in this study,	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					arm. However, 64% of the patients achieved stable disease while being treated with lipoplatin/5-fluorouracil (5-FU), vs. 50% in the cisplatin/5-FU arm.	especially the three patients suffering acute renal failure, does not fully reflect the experience at our institution with this drug	
Joseph et al 2019	To report the outcomes of using a combination of cetuximab with radiation therapy (Cetux-RT) to treat a selected group of patients with locally advanced (unresectable) cutaneous squamous cell carcinoma (LA-cSCC)	Propective pilot study; n=8	Patients with LA-cSCC received curative-intent treatment with Cetux-RT	Two-year efficacy and safety data	The median age was 81 years (range, 55–87). The ECOG performance status of all patients was between 0 and 2. With a median duration of follow-up of 25 months (range 10–48 months), five patients remain in complete response. After a partial response, another patient has relapsed and is receiving palliative chemotherapy, while two patients have died during the period of follow-up (one of whom died following the progression of disease, the other of an unrelated cause). Treatment in this group of patients was	Cetux-RT was well tolerated and provided durable disease control within this patient sample. Our data support the use of the Cetux-RT regimen for selected patients with inoperable LA-cSCC and adequate performance status.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					well tolerated, with most toxicities ≤ grade 2, and no toxicities of grade 4/5 reported.		
Lu et al 2015	To report the survival outcomes of patients with advanced cutaneous SCCHN treated with two chemotherapy regimens	Retrospective study; n=23	Patients with locally advanced cutaneous SCCHN treated with radiation and concomitant platinum (Pt)-based chemotherapy or cetuximab (Cx).	2-years DFS and OS	The majority (87%) of patients had stage III/IV disease and 9 (39%) patients had unresctable disease. All patients were being treated for recurrent disease. Aside from median age (59 Pt vs. 71 Cx, P=0.04), there were no significant differences in patient and tumor characteristics between those receiving Pt versus Cx therapy. At mean follow-up of 24 months, locoregional recurrence and distant failure were observed in 52% and 17% of all patients, respectively. Estimated 2-year disease-free survival and overall survival in the Cx versus Pt groups were: 50% versus 30% (P=0.25), and	Radiotherapy with either concurrent Pt or Cx appears to offer similar clinical outcomes in patients with locally advanced cutaneous SCCHN.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					73% versus 40% (P = 0.32), respectively.		
Martins et al 2013	To evaluate the efficacy of adding EGFR inhibition to standard cisplatin-radiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).	A phase I/II randomized clinical trial conducted at the Brazilian National Cancer Institute; n= 204	Patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).	Complete response rate (CRR) PFS	Patients on arm B had more rash, but treatment arms did not differ regarding rates of other grade 3 or 4 toxicities. Arm A had a CRR of 40% and arm B had a CRR of 52% (P _ .08) when evaluated by central review. With a median follow-up time of 26 months and 54 progression events, there was no difference in PFS (hazard ratio, 0.9; P =.71).	This randomized phase II trial showed that erlotinib did not improve the CRR or PFS in patients with locally advanced SCCHN when added to cisplatin-radiotherapy. Another possible explanation would be an imbalance in the number of p16-positive patients between the treatment arms because this was not a stratification factor. Results from the current study and RTOG 0522 suggest that EGFR-directed therapy in unselected patients does not	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						lead to an improvement in outcome compared with cisplatin-radiotherapy alone	
Maubec et al 2011	To evaluate the efficacy and safety of cetuximab	Open-label, uncontrolled phase II study; n=36	Patients with unresectable squamous cell carcinoma of the skin (SCCS) treated with cetuximab (initial dose of 400 mg/m2 followed by subsequent weekly doses of 250 mg/m2) for at least 6 weeks	Disease control rate PFS	DCR at 6 weeks was obtained in 25 of 36 patients (69%; 95% CI, 52% to 84%) of the intention-to-treat population. The best responses were eight partial responses and two complete responses. There were no cetuximab-related deaths. There were three related serious adverse events: two grade 4 infusion reactions and one grade 3 interstitial pneumopathy. Grade 1 to 2 acne-like rash occurred in 78% of patients and was associated with prolonged PFS.	As a first-line treatment in patients with unresectable SCCS, cetuximab achieved 69% DCR and may be considered as a therapeutic option especially in elderly patients. The low frequency of RAS mutations in SCCS makes SCCS tumors attractive for EGFR inhibition	3
Migden et al 2018	To report the results of the phase 1 study of cemiplimab for	Phase 1 study was an open-label, multicenter study	Patients with advanced cutaneous	Phase 1 study: The primary endpoint was the	In the expansion cohorts of the phase 1 study, a response to cemiplimab	Among patients with advanced cutaneous	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	expansion cohorts of patients with locally advanced or metastatic cutaneous squamous-cell carcinoma, as well as the results of the pivotal phase 2 study for a cohort of patients with metastatic disease (metastatic-disease cohort).	and a nonrandomized phase 2 study	squamous-cell carcinoma and patients with advanced solid tumors	safety and side-effect profile of cemiplimab; phase 2 study: The primary endpoint was the response rate, as assessed by independent central review. For both studies, secondary endpoints included the duration of response, progression-free survival, overall survival, and toxic effects.	was observed in 13 of 26 patients (50%; 95% confidence interval [CI], 30 to 70). In the metastatic-disease cohort of the phase 2 study, a response was observed in 28 of 59 patients (47%; 95% CI, 34 to 61). The median follow-up was 7.9 months in the metastatic-disease cohort of the phase 2 study. Among the 28 patients who had a response, the duration of response exceeded 6 months in 57%, and 82% continued to have a response and to receive cemiplimab at the time of data cutoff. Adverse events that occurred in at least 15% of the patients in the metastatic-disease cohort of the phase 2 study were diarrhea, fatigue, nausea, constipation, and rash;	squamous-cell carcinoma, cemiplimab induced a response in approximately half the patients and was associated with adverse events that usually occur with immune checkpoint inhibitors.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					7% of the patients discontinued treatment because of an adverse event.		
Migden et al 2020	To evaluate the safety and antitumor activity of cemiplimab in patients with locally advanced cSCC	Prospective pivotal open-label, phase 2, single-arm trial	Patients with locally advanced cutaneous squamous cell carcinoma and an Eastern Cooperative Oncology Group performance status of 0–1	Objective response, (proportion of patients with complete/partial response, as per RECIST 1.1 for radiological scans and WHO criteria for medical photography	78 patients were treated with cemiplimab. The median duration of study follow-up was 9.3 months (IQR 5.1–15.7) at the time of data cutoff. An OR was observed in 34 (44%; 95% CI 32–55) of 78 patients. The BOR was 10(13%) patients with a CR and 24 (31%) with a PR. Grade 3–4 treatment-emergent AE occurred in 34 (44%) of 78 patients; the most common were hypertension in 6 (8%) patients and pneumonia in four (5%). SAE occurred in 23 (29%) of 78 patients. One treatment-related death was reported that occurred after onset of aspiration pneumonia.	Cemiplimab showed antitumor activity and an acceptable safety profile in patients with locally advanced cutaneous squamous cell carcinoma	2
Montaudié et al 2020	To evaluated clinical outcomes of cetuximab as a single agent in patients with unresectable	Retrospective analysis; n=58	Patients with unresectable cutaneous squamous cell carcinoma (cSCC)	Disease Control Rate (DCR) at 6 weeks according to RECIST criteria. Secondary	Fifty-eight patients received cetuximab as monotherapy. The median age was 83.2 (range, 47.4 to 96.1).	Our study shows that cetuximab is safe and efficient for the treatment of patients, even	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	cutaneous squamous cell carcinoma (cSCC)			endpoints included DCR at 12 weeks, objective response rate (ORR) at 6 and 12 weeks, progression-free survival (PFS), overall survival (OS), and safety profile	The majority of patients was chemotherapy naïve. The median follow-up was 11.7 months (95% CI: 9.6-30.1). The DCR at 6 and 12 weeks was 87% and 70%, respectively. The ORR was 53% and 42%, respectively, at 6 and 12 weeks. The median PFS and OS were 9.7 months (95% CI: 4.8-43.4) and 17.5 months (95% CI: 9.4-43.1), respectively. Fifty-one patients (88%) experienced toxicity, and 67 adverse events related to cetuximab occurred. Most of them (84%) were grade 1 to 2.	elderly ones, with advanced cSCC. These results indicate that cetuximab is a promising agent to test in new combinations, especially with immune checkpoint inhibitors such as anti-PD-1 agents.	
Reigneau et al 2015	To address the question of the efficacy of induction therapy with cetuximab as neoadjuvant treatment for locally advanced NMSC.	Retrospective analysis; n=34	All consecutive patients with a diagnosis of unresectable locally advanced cutaneous SCC treated with neoadjuvant chemotherapy	The primary endpoint was the percentage of patients becoming amenable to surgery after three cycles of cetuximab and	Thirty-four patients, with a median age of 745 years, were evaluated. Twenty-five patients received CC. After three cycles of CC, 23 of 25 patients whose tumours were initially unresectable became	There was a good response in terms of resectability and tumour control in the majority of patients, with few relapses, despite the initially poor prognosis of these	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			containing cetuximab +/- cisplatin and 5-FU between February 2008 and February 2013 in one institution	chemotherapy, or cetuximab monotherapy. The secondary endpoints were as follows: (i) the percentage of histological tumour responses; (ii) the treatments received after induction therapy; (iii) progression-free survival (PFS), and overall survival (OS), (iv) the characteristics of relapses.	amenable to surgery (92%). A complete histological response was observed in 15 (65%) patients. The mean progression-free and mean overall survival in operated patients were 8.5 and 26.0 months, respectively.	tumours in this elderly group of patients. However, this therapeutic strategy needs to be validated in a prospective, randomized study.	
Seiwert et al 2016	To assess the safety, tolerability, and antitumor activity of pembrolizumab	Open-label, multicenter, multi-cohort phase 1b trial; n=60	Patients with PD-L1-positive squamous cell carcinoma of the head and neck	Adverse events Overall response	23 patients (38%) were HPV-positive and 37 (62%) were HPV-negative. Pembrolizumab was well tolerated, with 10 (17%) of 60 patients having grade 3–4 drug-related adverse events, the most common of which were increases in alanine aminotransferase and in	This study is the first to report the efficacy and safety of an anti-PD-1 antibody in patients with advanced PD-L1-positive recurrent or metastatic squamous cell carcinoma of the	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					aspartate aminotransferase, and hyponatremia, each occurring in two of 60 patients; one patient developed a grade 3 drug-related rash. 27 (45%) of 60 patients experienced a serious adverse event. There were no drug-related deaths. The proportion of patients with an overall response by central imaging review was 18% (8 of 45 patients; 95% CI 8–32) in all patients and was 25% (4 of 16 patients; 7–52) in HPV-positive patients and 14% (4 of 29 patients; 4–32) in HPV-negative patients.	head and neck. Pembrolizumab showed clinically significant activity in patients with heavily pretreated squamous cell carcinoma of the head and neck irrespective of HPV status. Greater antitumor activity was recorded in patients with squamous cell carcinoma tumors of the head and neck that expressed higher levels of PD-L1 and interferon-γ-related genes	
Stratigos et al 2020	To make recommendations on treatment, supportive care, education and follow-up of patients with invasive cutaneous squamous	Recommendations were based on evidence-based literature review, guidelines and expert consensus. Treatment	EDF-EADO-EORTC guideline	Treatment	Anti-PD-1 antibodies are the first-line systemic treatment for patients with metastatic or locally advanced cSCC who are not candidates for curative surgery or		1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	cell carcinoma (cSCC)	recommendations are presented for common primary cSCC (low risk, high risk), locally advanced cSCC, regional metastatic cSCC (operable or inoperable) and distant metastatic cSCC.			radiation, with cemiplimab being the first approved systemic agent for advanced cSCC by the Food and Drug Administration/European Medicines Agency. Second-line systemic treatments for advanced cSCC include epidermal growth factor receptor inhibitors (cetuximab) combined with chemotherapy or radiation therapy.		
Shin et al 2000	To assess the antitumor activity and toxicity profile of a combination of paclitaxel, ifosfamide, and carboplatin (TIC) in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN).	Phase II Study; n=56	Patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN).	Survival rates	A total of 32 patients (59%) responded to treatment; the complete response rate was 17% (9 of 54 patients). The median duration of the responses was 3.7 months (95% confidence interval [95% CI], 3.4–7.8 months) and that of complete responses was 9.7 months (95% CI, 7.4 months to the date of the last follow-up). The median duration of	The TIC regimen had high antitumor activity in patients with recurrent or metastatic SCCHN. The activity of TIC in patients with recurrent or metastatic SCCHN should be confirmed in a phase III randomized trial	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					follow-up care in all patients was 13.5 months. Median survival time for all patients was 9.1 months (95% CI, 7.9–12.2 months).		
Tortochaux et al 2011	To investigate the potential benefit of concurrent re-irradiation, fluorouracil and hydroxyurea versus methotrexate for patients treated with palliative intent for recurrent or second primary HNSCC in previously irradiated area	Randomized phase III trial (GORTEC 98-03); n=57	Patients treated with palliative intent for recurrent or second primary HNSCC in previously irradiated area	OS	All patients died in the two arms with a maximal follow-up of 5 years. 4 complete responses were achieved in R-RT arm, re-irradiation did not improve OS compared with methotrexate (23% vs. 22% at 1 year, NS). Sixteen patients experienced clinical grade P3 late toxicities (>6 months), 11 in R-RT arm and five in Ch-T arm.	There was no suggestion that concurrent re-irradiation, fluorouracil and hydroxyurea improved OS compared to methotrexate alone in patients treated with palliative intent for a recurrent or second primary HNSCC.	2
Tsukuda et al 2010	We compared concurrent chemoradiotherapy (CCRT) with docetaxel, cisplatin (CDDP), and 5-fluorouracil (5-FU) (TPF) with CCRT with	Randomized controlled phase II comparison study; n=100	Patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) were enrolled. The TPF group received	Overall response rate Safety	The overall response rates after CCRT were 98 with 90% of pathologically complete response (pCR) in the TPF group and 94 with 77% in the PFML group. For grade 3/4 adverse	The use of multiagent CCRT including CDDP appears to be more efficacious than CCRT with CDDP alone. Both regimens showed	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	CDDP, 5-FU, methotrexate and leucovorin (PFML) in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN)		CCRT with the TPF regimen. In the PFML group, patients received CCRT with the PFML regimen		events, mucositis was more frequent in the PMFL group, and the TPF group showed a higher incidence of hematological toxicity	high ORRs after CCRT completion (94%: PFML group; 98%: TPF group). The ORR, pCR rate and 3-year survival rate were almost identical to the results of previous studies on CCRT with PFML	
Vermorken et al 2014	Report the results of the ADVANTAGE study. To identify potential biomarkers of response to the combined cilengitide/ cisplatin, 5-fluorouracil, and cetuximab (PFE) treatment.	Randomized phase I/II ADVANTAGE trial; n=182	Patients treated with cilengitide combined (cilengitide 2000 mg once (CIL1W) or twice (CIL2W) weekly) with PFE in recurrent or metastatic (R/M)-HNSCC	PFS per investigator read Secondary objectives: OS ORR, disease control rates Duration of response Time-to-treatment failure (TTF) Confirm the safety profile of cilengitide plus	Median PFS per investigator read was similar for CIL1W + PFE, CIL2W + PFE, and PFE alone (6.4, 5.6, and 5.7 months, respectively). Accordingly, median OS and objective response rates were not improved with cilengitide (12.4 months/47%, 10.6 months/27%, and 11.6 months/36%, respectively). No clinically meaningful safety differences were observed between groups. None of the tested biomarkers	This study suggests that the combination of cilengitide and PFE offered no efficacy benefits compared with PFE alone in R/M HNSCCHN patients. Neither of the cilengitide-containing regimens demonstrated that a PFS benefit versus PFE alone and OS, OR, and disease control outcomes were similar across the	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				PFE To determine the pharmacokinetic (PK) profile.	(expression of integrins, CD31, Ki-67, vascular endothelial growth factor receptor 2, vascular endothelial-cadherin, type IV collagen, epidermal growth factor receptor, or p16 for human papilloma-virus) were predictive of outcome	three cohorts. Therefore, this combination cannot be recommended for further development in R/M-SCCHN patients.	

7.9.5. Literature

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8. Prevention and Surveillance

(AG Prävention und Nachsorge)

8.1. Question VII.1. Which procedures/examinations/tests based on stage should be recommended as surveillance evaluations? How frequently?

(Frage VII.1. Welche Untersuchungen sind im Rahmen der Nachsorge nach Stadien und in welchen Intervallen indiziert?)

Expert consensus

8.1.1. PICO

PICO – Scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Patients with SCC	Follow-up	n.a.	Efficacy

8.1.2. Database, search strategy, number of results

Database	Search strategy	Date	Number of results
1. Search			
Medline	(squamous[Title] AND (skin[Title] OR cutaneous[Title])) AND (follow-up*[Title/Abstract] OR surveillance [Title/Abstract])NOT “case report” AND (English[Language] OR	15th December 2016 (initial search)	203

Database	Search strategy	Date	Number of results
	German[Language])	Update 30th May 2017	210
		Update May 2020	308
Remarks and notes:-			

8.1.3. Selection criteria

Literature selection	
Number of total results	308
Inclusion criteria	Clinical trials (randomized and non-randomized), prospective and retrospective reviews, systematic reviews and case series with ≥10 patients included, with follow-up data available
Exclusion criteria	No follow-up data available
Number of results after abstract searching	26
Number of full texts reviewed	14

8.1.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Efird et al 2002	To determine the risk of subsequent	Retrospective review; n=822	Individuals with primary squamous	Subsequent cancer risk after SCSC	Patients were followed for	The results suggest that patients	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	cancer following squamous cell skin cancer		cell skin cancer (SCSC) and their comparison subjects matched for age, sex, race, residence area, and length of membership. Patients were included in the study if they had no prior history of cancer and received at least one multiphasic health checkup and questionnaire (MHC).	diagnosis	subsequent invasive cancer up to 24 years, with a mean follow-up time of 7.8 years. SCSC patients had a significantly greater risk [adjusted for body mass index (BMI) and education] for subsequent cancer overall (excluding non-melanoma skin cancer) [risk ratio (RR) =1.4, 95% confidence interval (CI) =1.2–1.6], and for basal cell skin cancer (RR =13.8, 95% CI = 8.8–21.9), digestive (RR =1.6, 95% CI =1.1–2.4), and genitourinary cancers (RR =1.5, 95% CI =1.0–2.0). An increased, but not statistically significant, adjusted risk (RR >=1.4) was also	diagnosed with SCSC may be at an increased risk of subsequent cancer at many sites, although several estimated risk estimates were within the limits of chance given no true association.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					observed for lip, oral cavity, and pharynx cancer (RR =3.9, 95% CI = 0.6–25.0); non-cutaneous squamous cell cancer (RR = 1.9, 95% CI = 0.9–4.4); and respiratory and intrathoracic cancer (RR = 1.4, 95% CI = 0.8–2.6). The addition of alcohol consumption, combined occupational exposure, marital status, and smoking history to the multivariate model did not materially change any significant positive associations with SCSC.		
Griffiths et al 2002	To establish the 5-year survival and outcome for	Retrospective cohort study; n=171	Patients with primary invasive squamous cell	Patient outcomes - either alive without recurrence or	Of these 171 patients, 157 were confirmed as	There is no evidence that the prognosis is superior after either	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients after conventional surgery, related to tumour characteristics and specific tumour measurements		carcinoma of the skin, followed for a minimum of 5 years after treatment with conventional excisional surgery, in one center, between 1990 and 1995.	metastasis at 5 years, dead of disease within 5 years or dead of other causes within 5 years.	having been treated for invasive squamous cell carcinoma, of whom 64 (41%) died within 5 years of treatment from causes other than squamous cell carcinoma, and were therefore defined as indeterminate. The remaining 93 patients were determinate patients; 85 lived without recurrence or metastasis for at least 5 years after treatment, and eight died of their disease. Comparing the groups who were alive or had died of disease at 5-year follow-up, the tumour diameter and tumour thickness were significantly	conventional surgery or Mohs' therapy, when series are compared for tumour thickness. Long-term follow-up and tumor-thickness measurements are required in all series after all treatments for meaningful comparisons to be made.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					greater in the eight patients who died (P = 0.02 and P =0.0057, respectively) but there were no significant differences between the two groups concerning age, deep resection margin clearance, lateral epidermal resection margin clearance, lymphocyte response or degree of tumour differentiation.		
Harris et al 2017	To evaluate which factors are predictive of recurrence and nodal spread and survival in patients with cHNSCC treated surgically	Retrospective review; n=212	Patients with CSCCs of the head and neck treated between January 1998 and June 2014. All patients undergoing primary surgery, with or without adjuvant therapy, with curative intent for	5-years DFS DSS OS Associations of patient and tumor characteristics with recurrence and survival	A total of 212 patients met inclusion criteria, with a mean age of 70.4 years; 87.3% were men. Mean tumor diameter was 3.65 cm, with an average depth of invasion of 1.38 cm. The mean	For advanced CSCCs of the head and neck, patients with recurrent disease, PNI, and poorly differentiated tumors are at the highest risk for local recurrence. Patients with tumors or the ear, cheek, temple, or	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			CSCC were included. Patients were excluded if they had distant metastases at presentation, were treated with palliative intent, and had <3 months of follow-up.	Factors independently associated with the presence of nodal metastasis at presentation	follow-up time was 35 months (median, 21.5), and over that period 67 recurrences were recorded, 49 of which were local. The 5-year Kaplan-Meier estimate of DFS for the cohort was 53.2%. On Cox multivariate analysis, recurrent disease, perineural invasion (PNI), and poorly differentiated histology were independent predictors of recurrence. On multinomial logistic regression, patients with primary tumors on the ear, cheek, temple, or lip, as well as those with PNI, were more likely to present with nodal metastasis.	lip, as well as those with PNI, are at increased risk of harboring nodal disease.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Analysis of OS and DSS was limited given incomplete cause of death data and the advanced age of the patient cohort.		
Kim et al 2018	Guidelines of care for the management of cutaneous squamous cell carcinoma	An expert workgroup 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. An evidence-based approach was used and available evidence was obtained by using a systematic search and review of published studies from PubMed and the Cochrane			After the diagnosis of a first SCC, screening for new keratinocyte cancers (BCC or cSCC) and for melanoma should be performed on at least an annual basis. Patients with a history of cSCC should be counseled on skin self-examination and sun protection. Topical and oral retinoids (eg, tretinoin, retinol, acitretin, and		1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Library databases from January 1960 through April 2015 for all identified clinical questions. A secondary search was subsequently undertaken to identify and review published studies from April 2015 to August 2016 to provide the most current information			isotretinoin) should not be prescribed to reduce the incidence of keratinocyte cancers in those with a history of cSCC, unless they are SOTRs. In the situation of SOTRs, only acitretin may be beneficial. Dietary supplementation of selenium and b-carotene is not recommended to reduce the incidence of future keratinocyte cancers in those with a history of cSCC. There is insufficient evidence to make a recommendation on the use of oral nicotinamide, DFMO, or celecoxib		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					in the chemoprevention of cSCC.		
Levine et al 2015	To compare outcomes in patients with 1 vs multiple cutaneous squamous cell carcinomas (CSCCs).	Retrospective, single-center cohort; n=985	Patients with dermally invasive (non–in situ) primary CSCC diagnosed from January 1, 2000, through December 31, 2009, from a tertiary center	Tumor stage (Brigham and Women's Hospital tumor stage) and outcomes (local recurrence [LR], nodal metastases [NM], and death due to CSCC) Outcomes were compared between patients with 1 vs more than 1 CSCC via multivariable competing-risk regression adjusted for other significant cofactors.	Of 985 patients with CSCC, 727 had 1 CSCC, 239 had 2 to 9 CSCCs, and 19 had 10 or more CSCCs. Most patients with 10 or more CSCCs were immunosuppressed (15 of 19 [78.9%]). The median follow-up time was 50 months (range, 2-142 months). Patients with more than 1 CSCC had a higher risk of LR (subhazard ratio for 2-9 CSCCs, 1.8; 95%CI, 1.1-4.3; and for ≥10 CSCCs, 3.8; 95%CI, 1.4 - 10.0) and NM (subhazard ratio for 2-9 CSCCs, 3.0; 95% CI, 1.4-6.5; and for ≥ 10 CSCCs, 4.2; 95%CI,	Patients with multiple CSCCs warrant frequent follow-up because they have an elevated risk of LR and NM. In particular, patients with 10 or more CSCCs have markedly elevated risks of recurrence and metastasis.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					1.4-10.4) compared with patients with 1 CSCC, adjusted for Brigham and Women's Hospital tumor stage. The 10-year cumulative incidence of LR and NM was higher in patients with 2 to 9 CSCCs and markedly higher in those with 10 or more CSCCs compared with patients who had 1 CSCC (10-year cumulative incidence for 1 CSCC: LR, 3.0%; 95%CI, 2.0%-4.5%; and NM, 2.3%; 95%CI, 1.5%-3.8%; for 2-9 CSCCs: LR, 6.7%; 95%CI, 4.2%-10.6%; and NM, 5.9%; 95%CI, 3.5%-9.6%; and for ≥10 CSCCs: LR, 36.8%; 95%CI, 19.2%-59.0%; and NM,		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					26.3%; 95%CI, 11.8%-48.8%).		
Mahajan et al 2019	To analyze the diagnostic performance of 18F-FDG-PET/CT in staging patients with newly diagnosed cSCC.	Retrospective analysis; n=23	Patients with biopsy-proven cSCC who underwent 18F-FDG scan at diagnosis in one institution from 2000 to 2016.	Sensitivity and specificity of 18F-FDG-PET/CT	Twenty-three cSCC patients who underwent 18F-FDG-PET/CT at diagnosis were evaluated. Primary sites were in head/neck (n=21), chest (n=1), and foot (n=1). All patients had 18F-FDG-positive scans with a total of 51 18F-FDG-positive lesions. All primary lesions (n=24) were 18F-FDG-positive (SUV: 2.3–22.8; mean 10.2), and additional 27 18F-FDG-positive lesions, including 21 nodes, four cutaneous, one osseous and one lung lesion, were noted in 13 patients. Mean size	18F-FDG-PET/CT has high sensitivity in the detection of cSCC lesions, including small cutaneous and nodal disease, and has a potential role in initial staging and management.	3-4?

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					of 18F-FDG-positive nodes was 0.9 cm (range: 0.4–2.5 cm), predominantly clinically impalpable. Pathology was available for 40/51 lesions; 31 sites positive for malignancy. SUV (mean ± SD) was 9.2 ± 6.2 for malignant and 2.7 ± 1.2 for benign lesions. Sensitivity, positive predictive value, and accuracy of 18F-FDG-PET/CT scan were 100, 77.5, and 77.5%, respectively. Overall, staging 18F-FDG detected nine prior unknown lesions in five patients that were proven metastatic disease by histopathology or follow-up; 18F-FDG-		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					PET/CT modified management in 5/23 (21.7%) patients		
McLaughlin et al 2017	To determine the rate of regional lymph node involvement in a large cohort of solid organ transplant patients with cutaneous head and neck squamous cell carcinoma (cHNSCC)	Retrospective chart review; n= 30 solid organ transplant patients; 383 cHNSCC ressections	All solid organ transplant recipients who underwent surgery between 2005 and 2015 for a cHNSCC at the Hospital of the University of Pennsylvania Department of Dermatology and/or Otorhinolaryngology	Rate of regional lymph node involvement Time from the first diagnosis to regional lymphatic disease	The average age of the patient was 63. Seven patients (5%) developed regional lymph node metastases (3 parotid, 4 cervical lymph nodes). The mean time from primary tumor resection to diagnosis of regional lymphatic disease was 6.7months. Six of these patients underwent definitive surgical resection followed by adjuvant radiation; one patient underwent definitive chemoradiation. 6 of the 7 patients died of disease	This is the largest study to date of cSCC in solid organ transplant patients. In addition, all of these lesions were limited to the head and neck. Despite the low rate of regional lymph node involvement demonstrated in these patients, their extremely poor prognosis makes managing an N0 neck in an immunocompromised patient a difficult clinical dilemma.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					progression with a mean survival of 15months. The average follow-up time was 3years (minimum 6months). Solid organ transplant recipients with cutaneous squamous cell carcinoma of the head and neck develop regional lymph node metastasis at a rate of 5%. Regional lymph node metastasis in this population has a poor prognosis and requires aggressive management and surveillance.		
Picard et al 2017	To search for somatic mutations of the HRAS, KRAS, NRAS, BRAF and	Multicenter retrospective study; n=31	Patients with confirmed advanced cSCC treated in two medical oncology	Incidence of somatic mutations of the RAS, BRAF and EGFR genes	31 samples of cSCC from 31 patients were analyzed. Only 2 RAS muated	Even in elderly patients (median age 86 years; range 48-96 years), cetuximab	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	EGFR genes in patients with advanced cSCC treated with cetuximab; and to investigate the efficacy and tolerance of cetuximab according to these mutations		departments in France between January 2008 and December 2014	and association with cetuximab efficacy with these mutations – Fisher test Disease control rate at week 6 PFS OS Safety	samples (6.5%) were identified. The first harbored an NRAS point mutation (c.35G>A) in codon 12, resulting in a p.G12D substitution. The second sample presented an HRAS point mutation (c.38G>T) in codon 13, resulting in p.G13V substitution. No mutation of KRAS, BRAF and EGFR genes at the investigated loci was found. Two patients with NRAS and HRAS mutations showed a partial and complete response to cetuximab, respectively. The mean duration of follow-up was 19 months. At week 6,	was efficacious and well-tolerated. This suggests that cetuximab is certainly warranted in the treatment of cSCC. However, it is also important to identify tumor-specific mutations that may determine response to treatment and prognosis for the disease. We have identified here that the incidence of RAS, BRAF and EGFR mutations is low in cSCC. The authors concluded that the incidence of RAS, BRAF and EGFR mutations is very low in cSCC. The search for mutations appears unnecessary before initiating a cetuximab treatment for advanced cSCC,	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					the disease control rate was 67.8%. The median OS was 13 months and the median PFS was 9 months. All patients could continue cetuximab treatment without dose reduction.	but ultimately mutational data are needed to better define the genetic landscape of this disease. Dr. Frederic Peyrade is a Merck board Member.	
Rose et al 2017	To review the outcomes for sporadic primary cSCC in one department, to identify a sub-group of "low-risk" cutaneous squamous cell carcinoma (cSCC) patients suitable for discharge to primary care without extended out-patient follow-up.	Retrospective review; n=320 patients; n= 336 primary invasive cSCC	Patients with primary invasive cSCC excised within a single plastic surgery department between 2011 and 2015	To identify a sub-group of "low-risk" cutaneous squamous cell carcinoma (cSCC) patients suitable for discharge to primary care without extended out-patient follow-up.	Tumours were staged by American Joint Committee on Cancer (AJCC e 7th Edition) and Brigham and Women's Hospital (BWH) classification systems. Tumours were then stratified into 4 risk groups: Group 1 (High-1), Group 2 (High-2), Group 3 (Intermediate) and Group 4 (Low). Follow-up practices for this "low-risk" Group 4 (Low) were	The primary aim of out-patient follow-up for cSCC is to screen for loco-regional recurrence. In conclusion, this data suggests it is unnecessary and costly to commit an elderly co-morbid population with adequately treated "low-risk" disease to specialist out-patient follow-up. The authors recommend a realistic approach to the follow-up of	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					then scrutinized using clinical-portal "e-health" records. The financial cost of "low-risk" disease to out-patient services, both locally and nationally, was estimated using publically available specialty-specific health service cost data. Group 4 (Low) patients consisted of 94 tumours (27.9%). There were no episodes of locoregional recurrence or SCC-related death in this group. At the time of analysis, 59 (67%) patients remained under active follow-up. Only 25 (26.6%) were discharged to primary care.	immunocompetent patients with "low-risk" tumours, single out-patient visit to review histopathology, council on sun protection and self-examination and then discharge to primary care.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Importantly, 18 (30.5%) Group 4 (Low) patients died of causes unrelated to their cSCC during their follow-up. 32 (34%) Group 4 (Low) patients developed further lesions. Most common were actinic keratosis (13.8%) and basal cell carcinoma (11.7%), only 6 (6.4%) developed a further cSCC. During the follow-up period Group 4 (Low) patients were reviewed in outpatient clinics on 536 occasions (a mean of 5.8 visits per patient; range 0e14). Presuming each out-patient appointment was allocated a standard 10-min		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					review consultation, this amounts to 89.3 h clinic time (almost 12x3-h out-patient clinics/year). Using a conservative estimate of £120 per out-patient appointment, this represents a total departmental cost of £64,320 over the study period (around £25,000/year). 3130 cSCC were registered in Scotland in 2014. If we extrapolated our data and follow-up practices nationwide, this would equate to around 873 “low-risk” cSCC patients treated, subsequently filling 5000 out-patient appointments and around 833 h of		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					clinic time (almost 111 x 3-h out-patient clinics/year), to a cost of £597'0000 (around £240,000/year).		
Ruiz et al 2018	To review utilization of radiologic imaging of high-stage CSCCs to evaluate whether imaging impacted management and outcomes.	Retrospective analysis; n=103	all patients with a diagnosis of cutaneous squamous cell carcinoma from January 1, 2000 through May 30, 2013	Disease-related outcomes (DRO: local recurrence, nodal metastasis, death from disease)	108 high-stage CSCCs in 98 patients were included. Imaging (mostly computed tomography, 79%) was utilized in 45 (46%) patients and management was altered in 16 (33%) patients who underwent imaging. Patients that received no imaging were at higher risk of developing nodal metastases (nonimaging, 30%; imaging, 13%; P = .041) and any DRO (nonimaging, 42%; imaging, 20%; P =	Radiologic imaging of high-stage CSCC may influence management and appears to positively impact outcomes. Further prospective studies are needed to establish which patients benefit from imaging.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					.028) compared to the imaging group. Imaging was associated with a lower risk for DRO (subhazard ratio, 0.5; 95% CI 0.2-0.9; P = .046) adjusted for BWH T stage, sex, and location.		
Supriya et al 2014	To evaluate the impact of whole-body positron emission tomography in comparison to staging by conventional methods alone in the management of patients with head and neck cutaneous squamous cell cancer (cSCC) with confirmed regional nodal metastasis.	Retrospective case cohort study; n=31	Patients with head and neck cSCC and regional nodal metastasis diagnosed from 1 January 2009 to 31 December 2010	Impact of 18F-FDG PET–CT on patient management	The original treatment plan based on conventional cross-sectional imaging and clinical examination were compared to the final treatment plan after additional PET staging to evaluate the impact of 18F-FDG PET–CT on patient management. Addition of 18F-FDG PET–CT did not change the management in 24/31 (77%) of	Overall the management in majority of head and neck cSCC patients with regional metastasis does not change by the addition of 18F-FDG PET–CT over conventional imaging.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients. In four cases the 18F-FDG PET-CT failed to pick up a biopsy-proven metastatic disease. Two patients who had reduced extent of surgery have shown no features of regional failure after one year of follow-up.		
Stratigos et al 2020	To make recommendations on treatment, supportive care, education and follow-up of patients with invasive cutaneous squamous cell carcinoma (cSCC)	Recommendations were based on evidence-based literature review, guidelines and expert consensus. Treatment recommendations are presented for common primary cSCC (low risk, high risk), locally advanced cSCC, regional metastatic cSCC (operable or inoperable) and distant metastatic	EDF-EADO-EORTC guideline	Follow-up	The frequency of follow-up visits and investigations for subsequent new cSCC depend on underlying risk characteristics.		1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		cSCC.					
Wassberg et al 1999	To report second primary cancers in patients with skin squamous cell carcinoma (SCC)	A population-based study; n=25947	Patients diagnosed with SCC in Sweden between 1958 and 1992.	Second primary cancers incidence	In total, 5,706 patients developed a second primary cancer at any site, compared with an expected number of 2,651 [standardized incidence ratio (SIR) = 2.15; 95% confidence interval (CI) = 2.10–2.21]. Men below 60 years of age at diagnosis of SCC had higher SIR (2.5; CI = 2.2–2.8) with the highest risk during the first year of follow-up (SIR = 9.2; CI = 6.9–12.2). If the second primary SCC was excluded, the SIR was reduced to 1.30 (CI = 1.25–1.34); the relationships by sex, age and time	Patients with SCC are at increased risk To develop new primary cancer, especially in skin, squamous cell epithelial and tobacco-related tissues. Common risk factors among the tumor types might explain our findings, however, an intrinsic susceptibility among SCC patients to develop cancer is also possible.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					since diagnosis remained similar. For skin cancer, the SIR for second SCC was markedly elevated (SIR = 15.6) and the risk of malignant melanoma was elevated 3-fold. Significantly increased risks were found for most second cancers in squamous cell epithelium: lip (SIR = 5.2), respiratory organs (SIR = 1.7), esophagus (SIR = 1.5), cervix uteri (SIR = 2.2), and vulva including vagina (SIR = 2.3). There was a generally increased risk of almost 2-fold for second cancer in hematopoietic or lymphoproliferative		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					tissues. Slightly increased rates (SIR = 1.0–1.5) were seen for second tumors in digestive tissues. Finally, a high SIR (SIR = 5.5) was observed for second primary cancer in salivary glands.		
Yoong et al 2009	To establish appropriate follow-up times and to determine the long-term risk of subsequent non-melanoma skin cancers and melanoma.	Retrospective study; n=40	Patients who had a primary invasive cutaneous SCC excised during 1996 were retrospectively identified from the databases of a dermatologist in private practice in south-east Queensland.	Lymph node status Patient's immunocompetency Presence of local recurrence, subsequent SCC, BCC and melanomas	The median follow-up time was 7.5 years. In the 10 years, there was one local recurrence of a well-differentiated SCC, which was detected at the 6 months follow up and following re-excision there was no further recurrence at the site and no metastases detected. In the entire audited group, 65% had a	These data which extended to 10 years, showed a significant rise in detection of further SCC as well as BCC in the period beyond 5 years. Of concern is the 10% who had their second SCC detected only in the 5–10 year follow-up period. The authors believe that these figures from our study would justify at least a 10-year follow up and we would strongly advise lifetime review.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					subsequent SCC detected. Half the patients developed a second SCC within 5 years of the index cutaneous invasive SCC, and 10% had a second SCC detected after only 5 years of follow-up. In the subgroup of patients followed up 5 years and more, 82.1% had a subsequent invasive SCC, 32.1% had invasive SCC detected within 12 months of the incident invasive SCC (this particular group had further invasive SCC detected in the audit period), 75% had invasive SCC detected in the 5–10 year follow up, and 14.3% had SCC detected only in the		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					5–10 year follow-up period. Of the entire audited group, 72.5% had a BCC within 5 years, and 82.5% at 10 years. The total number of BCC detected far exceeded that of invasive SCC, and 52.5% had BCC detected within 12 months of incident invasive SCC. One in eight patients had a subsequent melanoma detected.		

8.1.5. Literature

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8.2. Question VII.2 and VII.3. Which recommendations should be made for the primary prevention of AK and cSCC? Which preventive measures are specifically indicated for patients with high-risk features?

(Fragen VII.2 und VII.3. Welche Maßnahmen sind zur Primärprävention von AK und PEK geeignet? Welche präventiven Maßnahmen sind speziell für Risikogruppen indiziert?)

De novo Recherche

8.2.1. PICO

PICO – Scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Patients with SCC and AK	Primary prevention; Chemoprevention, Local therapies, Systemic therapies	No intervention	Efficacy; safety

8.2.2. Database, search strategy, number of results

Database	Search strategy	Date	Number of results
1. Search			
Medline	("chemoprevention"[MeSH Terms] OR "chemoprevention"[All Fields]) AND ("skin neoplasms"[MeSH Terms] OR ("skin"[All Fields] AND "neoplasms"[All Fields]) OR "skin neoplasms"[All Fields] OR ("skin"[All Fields] AND "cancer"[All Fields]) OR "skin cancer"[All Fields]) AND ("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields]) ("niacinamide"[MeSH Terms] OR "niacinamide"[All Fields] OR "nicotinamide"[All Fields]) AND ("skin neoplasms"[MeSH Terms] OR ("skin"[All Fields] AND "neoplasms"[All Fields]) OR "skin neoplasms"[All Fields] OR ("skin"[All Fields] AND "cancer"[All Fields]) OR "skin cancer"[All Fields]) AND ("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields]) AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields]) ("photochemotherapy"[MeSH Terms] OR "photochemotherapy"[All Fields] OR ("photodynamic"[All Fields] AND "therapy"[All Fields]) OR "photodynamic therapy"[All Fields]) AND ("skin neoplasms"[MeSH Terms] OR ("skin"[All Fields] AND "neoplasms"[All Fields]) OR "skin neoplasms"[All Fields] OR ("skin"[All Fields] AND "cancer"[All Fields]) OR "skin cancer"[All Fields]) AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields]) AND ("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields])	July 2017	177
Remarks and notes:-			

8.2.3. Selection criteria

Literature selection	
Number of total results	177
Inclusion criteria	Clinical trials (randomized and non-randomized), prospective and retrospective reviews, systematic reviews and case series with ≥10 patients included
Exclusion criteria	Case reports, studies not evaluating primary prevention, pre-clinical, animal models and cell line reports.
Number of results after abstract searching	18 (updated 01/2021)
Number of full texts reviewed	14

8.2.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Alberts et al 2004	To report the safety and efficacy of dose-Intensive oral vitamin A in subjects with sun-damaged skin. To determine whether the effects of taking the chemopreventive agent, vitamin A, in intermediate to moderately high daily oral doses would be well tolerated and could be quantitatively measured by	Randomized trial; n=129	All participants had moderate to severe sun damage with or without AKs on their posterior forearms at the time of enrollment into the study. Eligible participants could also have a history of two prior nonmelanoma skin cancers.	The primary study endpoints were the clinical and laboratory safety of vitamin A. The secondary endpoints included quantitative, karyometric image analysis and assessment of retinoid and rexinoid receptors in sun-damaged skin.	Patients were randomized to receive placebo or 25,000, 50,000, or 75,000 IU/day vitamin A for 12 months. There were no significant differences in expected clinical and laboratory toxicities between the groups of participants	The vitamin A doses of 50,000 and 75,000 IU/day for 1 year proved safe and equally more efficacious than the 25,000 IU/day dose and can be recommended for future skin cancer chemoprevention studies. The trial received was supported by a	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	karyometric and retinoid receptor analyses in the skin of individuals with visually and histologically normal, sun-damaged skin.				randomized to placebo, 25,000 IU/day, 50,000 IU/day, and 75,000 IU/day. Karyometric features were computed from the basal cell layer of skin biopsies, and a total of 22,600 nuclei from 113 participants were examined, showing statistically significant, dose-response effects for vitamin A at the 25,000 and 50,000 IU/day doses. These karyometric changes correlated with increases in retinoic acid receptor α, retinoic acid receptor β, and retinoid X receptor α at the 50,000 IU/day vitamin A dose.	grant from National Cancer Institute Grant CA-27502.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Carija et al 2016	To compare a single treatment of PDL-PDT with PDT for BCCs in terms of efficacy, aesthetic outcome, and pain in patients with multiple BCCs.	A prospective, controlled, intra-individual, investigator-blinded study; n= 15 patients, n= 62 BCCs	Patients with multiple BCCs treated at the Department of Dermatology, University Hospital Center, Split, Croatia. All patients were Fitzpatrick II and III skin types.	Primary outcomes were complete BCC regression at months 3 and 12. Secondary outcomes were pain immediately after treatment, and aesthetic outcomes evaluated by a blinded investigator.	The BCCs on an individual patient were divided into two similarly-sized groups, and treated with PDT (630nm LED light source, fluence rate=30mW/cm2, total dose of 150J/cm2) and 585 nm-PDL-PDT (spot size=7mm, fluence=10J/cm2, pulse duration=10ms, 10% overlap, three passes, and cooling). No significant difference was found in the therapeutic effect between the two treatments (P=0.285). Complete regression of BCCs at 3-months follow-	A single treatment with three passes of PDL-PDT is effective in clearing BCCs, but the recurrence rate is higher than in the case of conventional PDT. PDL-PDT is associated with low treatment-related pain, has similar cosmetic advantages as PDT but it requires less treatment time.	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					up occurred in 79% of the PDT treated area and 74% of the PDL-PDT area. At month 12, complete regression using PDT was 75% (95% confidence interval (CI) 0.55-0.89) compared to 59% (95% CI 0.41-0.75) for the PDL-PDT treated areas. Both treatments had low mean pain scores: 1.7 for PDT and 2.6 for PDL-PDT (P=0.049) and the aesthetic appearance was similar (P=0.763).		
Chen et al 2015	To assess the efficacy of oral nicotinamide for the chemoprevention of non-melanoma skin cancer in a high-risk population	A multicenter, phase 3, double-blind, randomized, placebo-controlled trial (Oral Nicotinamide to Reduce Actinic	Patients with at least two nonmelanoma skin cancers in the previous 5 years	The primary endpoint was the number of new nonmelanoma skin cancers (i.e., basal-cell carcinomas plus squamous-cell	Participants were evaluated by dermatologists at 3-month intervals for 18 months. At 12 months, the	Oral nicotinamide was safe and effective in reducing the rates of new nonmelanoma skin cancers and actinic	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Cancer [ONTRAC]); n=386		carcinomas) during the 12-month intervention period. Secondary endpoints included the number of new squamous-cell carcinomas and basal-cell carcinomas and the number of actinic keratoses during the 12-month intervention period, the number of nonmelanoma skin cancers in the 6-month postintervention period, and the safety of nicotinamide.	rate of new nonmelanoma skin cancers was lower by 23% (95% confidence interval [CI], 4 to 38) in the nicotinamide group than in the placebo group (P=0.02). Similar differences were found between the nicotinamide group and the placebo group concerning new basal-cell carcinomas (20% [95% CI, −6 to 39] lower rate with nicotinamide, P=0.12) and new squamous-cell carcinomas (30% [95% CI, 0 to 51] lower rate, P=0.05). The number of actinic keratoses was 11% lower in the nicotinamide	keratoses in high-risk patients. The trial was funded by the National Health and Medical Research Council	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					group than in the placebo group at 3 months (P=0.01), 14% lower at 6 months (P<0.001), 20% lower at 9 months (P<0.001), and 13% lower at 12 months (P=0.001). No noteworthy between-group differences were found concerning the number or types of adverse events during the 12-month intervention period, and there was no evidence of benefit after nicotinamide was discontinued.		
Dragieva et al 2004	To evaluate the efficacy and tolerability of topical photodynamic therapy with the new highly tumor-selective photosensitizer methyl	Prospective, randomized, double-blind, placebo-controlled study; n=17 patients; n=129	Transplant recipients with mild to moderate actinic keratosis treated during the period July 2001 to March	Complete resolution and reduction in the number or size of actinic keratoses within the lesional	The lesional areas treated with methyl aminolaevulinate were clinically cleared in 13 of 17 patients at 16	Photodynamic therapy using methyl aminolaevulinate is a safe and effective treatment for	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	aminolaevulinate vs. placebo in the treatment of actinic keratoses in transplant recipients.	moderate actinic ketratoses	2002 at the Department of Dermatology and the Transplantation Unit, University Hospital of Zurich.	area relative to the initial findings at weeks 4, 8 and 16 after treatment.	weeks. A partial response was recorded in a further three. No reduction in the size or number of actinic keratoses was observed in one area treated with methyl aminolaevulinate and in all placebo-treated areas. Adverse events, such as erythema, edema and crust formation, were mild to moderate, and treatment was well tolerated by all patients.	actinic keratoses in transplant recipients. It may also reduce the risk of transformation of actinic keratoses to invasive, potentially fatal, squamous cell carcinoma. Furthermore comprehensive, long-term trials are required.	
Drago et al 2017	To test the efficacy of oral nicotinamide in preventing and treating AKs in transplant recipients.	Randomized, case-control; n=38	Transplant patients with single or multiple AKs attending the Dermatologic Clinic of the University of Genoa, between	Efficacy	Group 1 took nicotinamide, 250 mg thrice daily, (cases) and Group 2 did not take any drug to treat AKs (controls).	Nicotinamide appears to be effective in preventing and treating AKs, although the mechanisms are	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			January and July 2015		For each case, one matching control was selected without randomization. The total area of AK was calculated for the group of cases and group of controls. At baseline, no statistically significant differences were observed between AK size of the two groups. After six months, among the cases, AKs had significantly decreased in size in 18/19 patients (88%). Among these 18 patients, seven patients (42%) had shown complete clinical regression and no	still unclear. Further studies with a larger sample of organ transplant recipients and a longer follow-up period are needed to further support our conclusions.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patient developed new AKs. Conversely, among the controls, 91% showed an increase in AK size and/or developed new AKs. Seven pre-existing AKs progressed to squamous-cell carcinoma.		
Elmets et al 2010	To evaluate the efficacy and safety of celecoxib, a cyclooxygenase 2 inhibitor, as a chemopreventive agent for actinic keratoses, the premalignant precursor of nonmelanoma skin cancers, and for nonmelanoma skin cancers, including cutaneous squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs)	A phase II-III, double-blind placebo-controlled randomized trial; n= 240	Eligible patients had a Fitzpatrick sun reactive skin type of I, II, or III. All subjects were required to have 10–40 actinic keratoses on the upper extremities, neck, face, and scalp at the time of entry into the study, and a previous histological diagnosis of at least one actinic keratosis and/or	The primary endpoint was the number of new actinic keratoses at the 9-month visit as a percentage of the number at the time of randomization. The incidence of actinic keratosis. The number of nonmelanoma skin cancers combined and SCCs and BCCs separately	Patients were randomly assigned to receive 200 mg of celecoxib or placebo orally twice daily. Subjects were evaluated at 3, 6, 9 (ie, completion of treatment), and 11 months after randomization. There was no difference in the incidence of actinic keratoses between	Celecoxib may be effective for prevention of SCCs and BCCs in individuals who have extensive actinic damage and are at high risk for development of nonmelanoma skin cancers.	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			nonmelanoma skin cancer. Patients were treated at eight US academic medical centers between January 18, 2001and November 3, 2006.	per patient at 11 months after randomization. The numbers of adverse events in the two treatment arms.	the two groups at 9 months after randomization. However, at 11 months after randomization, there were fewer nonmelanoma skin cancers in the celecoxib arm than in the placebo arm (mean cumulative tumor number per patient 0.14 vs 0.35; rate ratio [RR]=.43, 95% confidence interval [CI]=0.24 to 0.75; P=.003). After adjusting for age, sex, Fitzpatrick skin type, history of actinic keratosis at randomization, nonmelanoma skin cancer history, and patient time on study, the number of nonmelanoma skin cancers was lower in the		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					celecoxib arm than in the placebo arm (RR=0.41, 95% CI=0.23 to 0.72, P=.002) as were the numbers of BCCs (RR=0.40, 95% CI=0.18 to 0.93, P=.032) and SCCs (RR=0.42, 95% CI=0.19 to 0.93, P=.032). Serious and cardiovascular adverse events were similar in the two groups.		
Geng et al 2009	To assess the long-term tolerability of tretinoin 0.1% cream for chemoprevention of keratinocyte carcinomas (i.e. basal cell or squamous cell carcinomas) in the face and ears. The VATTC Trial.	A randomized, multicentre, double-blind, controlled trial, n=736 patients	Patients were veterans, had a history of two or more keratinocyte carcinomas over the previous 5 years and were treated in 6 different VA medical centers.	The main outcome measures were reported side-effects, frequency of cream application and attendance at study visits.	Participants were examined (by a study dermatologist) and interviewed every 6 months (for up to 5.5 years to May 2004). Treatment comprised tretinoin 0.1% cream or vehicle control cream once daily,	Overall, the tolerability level of topical tretinoin was high in this study population, with almost 40% of the tretinoin group reporting no side-effects, and the majority (67%) tolerating at least once-daily dosing at 6-month follow-up. High-dose	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					then twice daily as tolerated. Participants were instructed to step down application frequency to once daily or less if twice daily was not tolerated. The tretinoin group more commonly reported one or more side-effects at the 6-month follow-up than the control group (61% vs. 42%, P < 0.0001). Side-effects decreased over time in both groups, but to a greater extent in the tretinoin group, and the difference became nonsignificant at 30 months. Burning was the most common side-	topical tretinoin is feasible for long-term use in this population. This trial was supported by the VA Cooperative Studies Program (CSP#402), Office of Research and Development, Department of Veterans Affairs. Additional support was received from the American Cancer Society. M.A.W. is also supported by grants R01CA106592, R01CA106807, R25CA087972 and R01AR49342 from the National Institutes of Health. The study medication was donated by the OrthoNeutrogena	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					effect (39% tretinoin vs. 17% control, P < 0.0001). There was no difference in severity of side-effects among those affected. Of the participants who reported burning in either group, most reported mild burning; only 11% of those with burning in the tretinoin group reported it as severe (mild 62% tretinoin vs. 70% placebo; severe 11% vs. 5%; P = 0.4). Itching (24% vs. 16%, P = 0.01) and other local cutaneous reactions (12% vs. 6%, P = 0.01) were also more commonly reported by the tretinoin	division of Ortho-McNeil Pharmaceutical Inc.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					group at 6 months. There was no difference in numbness (2% vs. 2%, P = 0.9). Participants in the tretinoin group were less likely to apply cream twice daily at 6 months (29% vs. 43%, P = 0.0002). This difference persisted over the entire duration of follow-up. There was little difference between groups in attendance at study visits or completion of telephone interviews (92% vs. 95%, P=0.06). No unexpected adverse events were reported.		
Grau et al 2006	To explore the association of NSAID use and with the risk of basal cell carcinoma	Cohort study; n=702 of the 1,805 randomized subjects (39%) were	Patients included in the Skin Cancer Prevention Study that was a	To explore the association of NSAID use and with the risk of	Of the 702 patients with confirmed cancers, 570 had only BCCs, 51 had	In this closely monitored cohort of high-risk subjects, there	2/3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(BCC) and squamous cell carcinoma (SCC) using data from the Skin Cancer Chemoprevention Study.	included in the present analysis; n=1,952 microscopically confirmed new skin cancers - 1,747 BCCs, 204 SCCs and 1 basosquamous carcinoma.	randomized, double-blind trial of oral b-carotene for the prevention of non-melanoma skin cancer in patients with a recent history of these tumors. During the Skin Cancer Chemoprevention Study, 3,975 skin lesions in 1,093 participants (61%) were identified as possible cancers and removed. From this analysis were excluded lesions not confirmed microscopically (n=49), those that were recurrence of a previous cancer (n=286), malignant melanomas (n=3) and nonneoplastic	BCC and SCC.	only SCCs and 81 had both. The use of NSAIDs was reported in over 50% of questionnaires. For BCC, NSAIDs exhibited a weak protective effect in crude analyses, which attenuated markedly after adjustment. For SCC, the use of NSAIDs in the year previous to diagnosis reduced the odds by almost 30% (adjusted OR=0.71, 95% CI 0.48-1.04).	were only inconsistent, weak suggestions of an inverse association of use of aspirin and other NSAIDs with the incidence of NMSC in years following use. At most, our data suggest a weak chemopreventive effect of NSAID use on SCC in the year before diagnosis, and on the number of BCCs and SCCs.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			lesions (n=1,685).				
Kadakia et al 2011	To assess the efficacy of acitretin as a chemopreventive agent in non-transplantation patients at high risk for non-melanoma skin cancers (NMSC)	A prospective, randomized, double-blind, placebo-controlled clinical trial; n=70	Patients with history of ≥2 NMSCs and to have received previous treatment for all visible SCC and BCC, and could not have received any retinoids within 1 year of registration.	The primary outcome measure was the rate of new NMSC development.	Patients were randomized to receive either placebo (n=35) or acitretin 25 mg orally (n=35) 5 days per week. Initial history, skin examination, and laboratory studies were obtained less than 90 days before registration. Follow-up visits were scheduled at 1 month, 6 months, 12 months, 18 months, and 24 months. At the time of trial initiation and each subsequent follow-up, the skin was examined by the patients' dermatologists.	The original design was to have 110 patients per treatment arm, which would provide 80% power to detect a 33% difference in NMSC incidence rates. The attained sample size of 35 patients per group provided 51% power to detect a difference of incidence in NMSC of 11% versus 33%. This sample size provided 82% power to detect a difference in NMSC of 5% versus 33% or 11% versus 43%. Although there was not a statistically significant benefit observed with the use of acitretin,	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					During the 2-year treatment period, the patients who received acitretin did not have a statistically significant reduction in the rate of new primary NMSCs (odds ratio, 0.41; 95% confidence interval, 0.15-1.13; 54% vs 74%; P=0.13). However, using the incidence of new NMSC, the time to new NMSC, and total NMSC counts, an umbrella test indicated a significant trend that favored the use of acitretin (chi-square statistic, 3.94; P=0.047). The patients who received acitretin reported significantly more	this may have been the result of low statistical power. This work was supported by the US National Institutes of Health (grant CA-124477; principal investigator, Charles L. Loprinzi, MD) and by National Cancer Institute Community Clinical Oncology Program grant CA-37404.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					mucositis and skin toxicities compared with the patients who received placebo.		
Kreul et al 2012	To retrospectively assess the further incidence of skin cancer, other malignancies, and adverse events of patients accrued to our phase III skin cancer prevention study of alpha-difluoromethylornithine (DFMO). To establish what further incidence of malignancy (skin or otherwise) occurred after patients discontinued DFMO.	Retrospective review; n= 209 patients with post-study information	Clinical records of the original 291 subjects included in the phase III skin cancer prevention study of DFMO were reviewed	Rate of NMSC recurrence in the interval from going off-study from CO9737 to the date of last contact for this follow-up study Rate of skin cancer recurrence from randomization onto CO9737 to the date of last contact for this follow-up study	Previously, 291 participants (mean age, 61 years; 60% male) with a history of prior NMSC (mean, 4.5 skin cancers) were randomized to 500 mg/m2/day oral DFMO (n=144) or placebo (n=147) for 4 to 5 years in the phase III skin cancer prevention study of DFMO, University of Wisconsin Carbone Cancer Center (UWCCC) Protocol CO9737. Clinical records of 209 University of Wisconsin (UW) Health subjects	Follow-up data revealed a persistent but insignificant reduction in new NMSCs occurring in DFMO subjects without evidence of latent or cumulative toxicity relative to placebo subjects. The limitations of our follow-up study include the relatively small size of our study, the inability to review the full 291 patients from the original study (48 patient records were not affiliated with UW Health and	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					were reviewed, and 2,092.7 person-years of on-study (884.3 person-years) and post-study (1,208.4 person-years) follow-up for these patients were assessed for new NMSC events and recurrence rates from the on-study period, the post-study period, and the two study periods combined. No evidence of increased significant diagnoses or serious adverse events was observed in the DFMO participants. The initially observed, marginally significant	34 subjects from UW Health were lost to various reasons), the retrospective nature (follow-up guidelines from the prior study were not in place and subjects may have been more or less closely followed than previously), manual review process.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					reduction (P=0.069) in NMSC rates for DFMO subjects relative to placebo continued without evidence of rebound. Event rates after discontinuation from study for total NMSCs (DFMO 0.236 NMSC/person/year, placebo 0.297, P=0.48) or the subtypes of basal cell carcinomas (BCC; DFMO 0.179 BCC/person/year, placebo 0.190, P=0.77) and squamous cell carcinomas (SCC; DFMO 0.057 SCC/person/year, placebo 0.107, P=0.43) are listed in the full text.		
Pomerantz et al	To identify baseline	Randomized,	Participants of the	Safety and	One hundred and	In this study	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
2014	patient characteristics associated with adverse effects of topical tretinoin.	cohort study; n=324 patients	Veterans Affairs Topical Tretinoin Chemoprevention trial, which was a multicentre trial of high-dose topical tretinoin for the chemoprevention of keratinocyte carcinoma (KC) in a high-risk population. (Trial already described before - Geng et al 2009)	tolerability	ninety-seven patients (61% of those randomized to tretinoin) reported local adverse effects within 6 months. Clinical signs of severe photodamage at baseline [odds ratio (OR) 0.15, 95% confidence interval (CI) 0.04–0.54] and history of acne (OR 0.46, 95% CI 0.27–0.77) were associated with a decreased risk of adverse effects to tretinoin. The use of other topical medications at enrolment (OR 1.88, 95% CI 1.15–3.08) predicted an increase in adverse effects.	population, the common indications of topical tretinoin treatment were associated with lower risks of adverse effects. The concurrent use of other topical medications may worsen irritation caused by tretinoin. This study was supported by grant CSP 402 from the VA Cooperative Studies Program (CSP), Office of Research and Development, Department of Veterans Affairs (VA) and the American Cancer Society.	
Togsverd-Bo et al	To investigate the	Randomized	Patients were	The primary study	The interim	The interim data	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
2015	potential of long-term repeated photodynamic therapy (PDT) treatment applied to clinically normal skin to prevent the first onset of AK in high-risk renal transplant recipients (OTR). This report refers to the interim analysis of 25 patients as part of an on-going study evaluating the efficacy of repeated PDT treatment given over 5 years with a 1-year follow-up after the final PDT session.	control trial, n=25	recruited from and treated at the Department of Dermatology, Bispebjerg Hospital, between 2008-2011. Inclusion criteria were: renal transplant recipients aged 40–70 years, fair-skinned persons (Fitzpatrick skin type I–III [14]), stable graft function for >6 months, and unchanged immunosuppressive treatment regimen for >1 year before inclusion. Exclusion criteria were: pregnant or lactating women, previous or current AK, skin tumours and viral warts; and	endpoint is the total number of AKs at end of the study. The primary a priori endpoint of the interim analysis was the number of AK at the 3 years study visit. Secondary endpoints were the time to onset of first AK in the treatment areas and the number of non-melanoma skin cancers, comprising basal cell carcinoma (BCC) and SCC.	analysis evaluates the efficacy in 25 of 50 patients observed for 3 years out of 6 years follow-up period. Patients received PDT on inclusion and at 6-monthly intervals for 5 years. A blinded evaluation was performed at each visit. Prophylactic PDT significantly delayed onset of AK compared with untreated skin, p=0.020. At a 3-year follow-up, we observed AK in 63% of patients in untreated skin areas compared with 28% of patients in PDT-	analysis of this prospective study suggests a novel approach to early prevention of skin dysplasia in renal transplant recipients that may hold the potential to reduce morbidity from multiple AKs and SCCs in OTR.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			previous PDT treatment in study areas.		treated skin, with a total number of cumulated AKs in untreated skin (n=43) compared with PDT-treated skin (n=8), p=0.005.		
Weinstock et al 2009	To evaluate the relation of topical tretinoin, a commonly used retinoid cream, with all-cause mortality in the Veterans Affairs Topical Tretinoin Chemoprevention Trial (VATTC). The planned outcome of this trial was the risk of keratinocyte carcinoma, and systemic administration of certain retinoid compounds has been shown to reduce the risk of this cancer but has also been associated with	The VATTC Trial was a blinded randomized chemoprevention trial, with 2- to 6-year follow-up. (Results from the VAAT trial were also reported by Geng et al 2009 and Pomerantz et al 2014)	A total of 1131 veterans were randomized. Their mean age was 71 years. Patients with a very high estimated short-term risk of death were excluded.	Death, which was not contemplated as an endpoint in the original study design.	The authors report the halting of the VATTC Trial intervention 6 months before its scheduled end date because mortality in the tretinoin-treated group was higher than in the vehicle control group, and our evaluation of this potentially causal association between tretinoin therapy and increased mortality. Post hoc analysis of this difference	The authors observed an association of topical tretinoin therapy with death, but we do not infer a causal association that current evidence suggests is unlikely.	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	increased mortality risk among smokers.				revealed minor imbalances in age, comorbidity, and smoking status, all of which were important predictors of death. After adjusting for these imbalances, the difference in mortality between the randomized groups remained statistically significant.		
Willey et al 2009	To evaluate the potential benefit of cyclic photodynamic therapy (PDT) in the prevention of new SCCs in solid organ transplant recipients (SOTRs)	Prospective, open-label pilot study; n=12	Patients with SOTRs and progressive development of multiple SCCs and SCC in situ over the previous year treated in the University of Minnesota Department of Dermatology solid organ transplant clinic.	Number of new SCCs (invasive and in situ) in patients with SOTRs.	The median reduction in the 12- and 24-month post-treatment counts from the 1-month pre-treatment counts was 79.0% (73.3–81.8%) and 95.0% (87.5–100.0%), respectively. Treatments were well tolerated.	Cyclic PDT with 5-aminolevulinic acid may reduce the incidence of SCC in SOTRs. Additional studies with larger numbers of patients and optimized protocols are necessary to further explore the potential benefits of cyclic PDT in the prevention of skin	2-3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						cancer in this high-risk patient population.	

8.2.5. Literature

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9. Working group: Ocupational diseases associated with actinic keratosis and squamous cell carcinoma

(AG Berufsbedingte Erkrankung an PEK oder/und AK)

9.1. Question VIII.1. Diagnosis in patients with high UV occupational exposure

(Frage VI.1. Diagnostik bei Patienten mit berufsbedingter erhöhter UV-Exposition) Beantwortung durch Verweis auf LL Prävention

See S3-guideline for the prevention of skin cancer.

9.2. Question VIII.2. Reporting of suspected occupational skin cancer

(Frage VI.2. Meldung bei Verdacht auf einen berufsbedingten Hautkrebs) Beantwortung durch Verweis auf LL Prävention

See S3-guideline for the prevention of skin cancer.