Leitlinienprogramm Onkologie

Evidenztabellen zur S3-Leitlinie Aktinische Keratose und Plattenepithelkarzinom der Haut

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Evidenztabellen

DKG Krebsgesellschaft · Deutsche Krebshilfe Helfen. Forschen. Informieren. · AWMF

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 Deutschen 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 1.0, 2019 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

Literature selection	

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	Histological examination of the epidermis adjacent to and overlying	196 skin biopsy specimens showing iSCC from 79 women and 117	Prevalence of AK I-III lesions, ulceration and adnexal involvement	AK I, AK II and AK III lesions overlying iSCC: present in 63.8%, 17.9% and	Conclusion: All AK lesions have a potential risk of invasive	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	development of cutaneous invasive SCC (iSCC).	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)	men, mean age: 77.3 years Inclusion criteria: sun-exposed skin biospies >3mm, containing invasive tumours <25mm in diameter	overlying cutaneous iSCC	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 overlying AK I (39/125, 31.2%) than with AK II (8/35, 22.9%) and AKIII (5/36, 13.9%)	progression, regardless of the thickness of epidermal changes.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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 AK, were not examined due to the large number of medical records in the study: selection bias,	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						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) Anti-p53 (Bp53-11) primary antibody was used to stain p53 protein	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 cannot predict aggressiveness.	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 p53.	3
Jiyad et al 2016	To identify clinical features of actinic	Nested case-control study among	Cases: n=39 RTRs (renal transplant	OR: Association of actinic damage (as	Presence of an AK patch (AK greater	Study only assessed Caucasian OTRs (at	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	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.	participants of the STAR cohort (skin tumours in allograft recipients) (Australia)	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 sites	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.	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) % of area involving AK (>25% vs <25%): 5-fold higher risk of SCC/IEC (OR=5.33, 95% CI 1.53-28.56)	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 Various facial and upper limb skin sites were not of equal size	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Features of actinic damaged skin **not** associated with an significant higher risk of developing SCC or IEC within 18 months: <u>% of area involving erythema</u> (>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) <u>% of area involving pigmentation change</u> (>25% vs <25%): SCC/IEC (OR=1.6, 95% CI 0.46-6.22), SCC alone (OR=1.50, 95% CI 0.17-17.96)		
Pandey et al 2012	To examine the prognostic significance of follicular extension of atypical	Retrospective, case-controlled study	104 cases of AK with follicular extension and 104 cases of AK without follicular extension	Correlation of AK with follicular extension with history of prior SCC	OR=1.18, 95% CI 0,67-2.04, p=0.57	short follow-up Only one lesion per patient was chosen → might	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	keratinocytes in AKs.		out of a randomly selected pool of 1.000 biopsies. Follicular extension: presence of atypical keratinocytes extending into the isthmus of the hair follicle.		i.e. no increased likelihood that patients with AK with follicular extension would have past SCCs compared to those without follicular extension	undererstimate the results Selected cases were examined by two board-certified Dermatopathologists	
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 2: n=91 patients with 92 pathologically confirmed AKs at the same site of the subsequent SCC.	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) outcome. The study provided no data to calculate the absolute risk.	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 from AK to SCC among the different lesion sites (ANOVA, p=0.26)	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
			(45 women, 59 patients were older than 69 years)				
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 no field change (OR 20, 95% CI 2.1-195, n =4) compared with the one person with SCC but no	Representative population (all RTRs are referred to these clinics after transplantation for follow-up) Lack of knowledge of partcipants' history of skin cancer and AKs	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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)	prior to immunosuppression	

Remarks and notes: Papers not included

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
Remarks and notes:			

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 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 stage 2B or higher. 10 of 24 patients showed a high expression of MAGEA3	Cancer testis antigens as MAGEA3, MAGEA4 and MAGEA6 are selectively up-regulated in SCC. MAGEA3 may be a 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.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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	Review	Patients with metastatic cutaneous SCC	To report the known genetic events and	The authors report data from the following genes/genetic alterations available for SCC:		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	in high-risk and metastatic cutaneous SCCs, the known genetic events and molecular mechanisms, and identify avenues for further investigation and potential therapy			molecular mechanisms in high-risk primary cutaneous SCC and metastasis To identify avenues for further investigation and potential therapy.	TP53 family, NOTCH family, RAS family, CDKN2A, And the following topics: Protein tyrosine phosphatase 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 survival	Retrospective monocenter study; n=71	Patients with metastatic cutaneous SCC over a 15-year period treated in one center	Disease free survival (DFS) and OS	Poorly differentiated carcinoma was an independent predictor of poorer 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		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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, 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.		4
Bota et al. 2017	To review and compare the risk factors and clinical behavior of cSCC,	A comprehensive PubMed and MEDLINE database search was performed	Comparison of primary literature on cSCC, omSCC, and lip SCC	To review and compare the risk factors and clinical behavior of cSCC,	The American Joint Committee on Cancer (AJCC) has developed separate staging guidelines for both cSCC and omSCC.	Lip SCC exhibits rates of nodal metastasis and death that are	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	omSCC, and lip SCC, review tumor biology of squamous cell carcinoma, and compare work-up and treatment algorithms for lip SCC	with comparison of primary literature on cSCC, omSCC, and lip SCC.		oral mucosal SCC, and lip SCC, review tumor biology of squamous cell carcinoma, and compare work-up and treatment algorithms for lip SCC	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 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.	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 should consider that lip SCC may be more aggressive than cSCCs and portends a more worrisome outlook. Likewise,	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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),	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
					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. 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		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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. None- theless, 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	During a median follow-up period of 43 months, 26 (4%) of 615 patients developed metastases and 20 patients developed local recurrence (3%).	Only SCC greater than 2.0 mm in thickness are associated with a significant risk of metastasis. Tumours greater	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				time from date of diagnosis of the primary tumour to the date of diagnosis of metastasis or local recurrence	Tumours 2.0 mm or less in thickness did not metastasise. Metastases occurred in 12 (4%) of 318 tumours between 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]; p<0·0001) and desmoplasia (16.11 [6.57–39.49]; p<0.0001).	than 6.0 mm are associated with a high risk of metastasis and local recurrence. Desmoplastic growth is an independent risk factor for local recurrence.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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 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).	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
Brunner et al 2014	Assessment of the new nodal classification for	Retrospective study; n= 672	Patients with metastatic cutaneous SCC	Disease-specific survival (DSS) and OS.	The differentiation between N1 and N2 subgroups demonstrate	Although the current AJCC cutaneous SCC	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	cutaneous squamous cell carcinoma and its effect on patient stratification		from 2 prospective cancer center databases, treated with curative intent between 1980 and 2010		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 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.	nodal staging system is much more descriptive, the added complexity does not necessarily provide clinicians with a higher degree of useful prognostic information.	
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) tumors.	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
					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 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 has prognostic implications associated with lymph node metastasis and progression in CSCC	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 the prognostic implications of podoplanin expression in primary CSCCs, and highlights its relevance in predicting DFS	Retrospective study; n=94	Patients with SCC	Nodal progression (NP) and short DFS	Podoplanin expression was observed in 48.9% of 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	This article provides evidence supporting the implication of podoplanin expression as a marker of bad prognosis of CSCC	4
Chen et al 2014	To investigate p300 expression in cutaneous squamous cell carcinoma cSCC tissues and its effect on the outcome of	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 was	High p300 expression is associated with aggressive features of cSCC and will be a promising biomarker for	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients with cSCC				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	predicting clinical outcomes.	
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 Breslow depth did not correlate with the development of metastasis.	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-risk SCC	4
Ch`ng 2013	To assess whether primary tumor	Retrospective study; n= 239	Patients treated for metastatic cutaneous SCC	DSS, OS	On multivariable analysis, tumor differentiation (HR, 0.2; 95% CI, 0.1–0.8; p= .03) was	Pathological features of the	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	characteristics are independent prognostic factors.		from 1978 to 2010		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	primary lesion bear little importance in the presence of established nodal metastasis, other than tumor differentiation	
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 Zealand and tests the proposed staging system, with modifications for pathological staging	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 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.		4
Clark et al. 2013	To compare the 7th edition AJCC staging of nodal metastases from	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	The 7th edition of the AJCC Staging Manual for cSCC	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	cSCC with the N1S3 staging system				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 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 and N1S3 staging systems was similar despite the AJCC staging being more complex.	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.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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.		3
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	Lymph node metastasis at presentation (N1) or during follow up (N1f)	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	Local advanced tumors are at risk of lymph node metastasis. Increased risk is	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			October 1987 to November 2005	OS	N0 patients presented lymph node metastasis during follow up. Univariate analysis 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).	associated to previous lesions at tumor site. T4 classification have worse prognosis. Lymph node recurrences in N0 patients, once treated, did not affect survival.	
Erkan et al. 2017	To analyze the outcomes of multimodal treatment entailing the en bloc surgical resection and post-operative radiotherapy for	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, such as margin status, previous	Of 21 patients with clinical PNI from cutaneous HNSCC, 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	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
	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			treatment, zone involvement, and trigeminal involvement (branch-specific), as well as the pretreatment and post-treatment pain scores	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.		
Farasat et al 2011	To describe the AJCC cSCC staging system and rationale for the T (tumor characteristics) staging	Review for the rationale for and characteristics of the new AJCC staging system	Available published studies on 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	Classification of patients into primary tumor (T), regional lymph nodes (N), and distant metastasis (M).	A new AJCC cSCC T classification is 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.	The data available for analysis are still 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,	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			trials, case controlled studies, or multivariate analyses were prioritized over case series and retrospective reviews			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). 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	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 in this small group. Further studies are warranted in this population	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					positive nodes, extent of neck dissection and radiotherapy dosage delivered did not confer prognostic significance. Adverse prognostic implication of positive margins on DFS		
Gonzalez-Guerrero et al. 2017	To assess the correlation of tumor budding with the clinicopathologic features and the prognostic value of tumor budding in cutaneous squamous cell carcinoma (cSCC).	Retrospective study, n= 98	Samples from 49 primary nonmetastatic and 49 primary metastatic cSCCs to regional lymph nodes	To assess the relationship between tumor budding, clinicopathologic parameters, and patient survival	Tumor budding was observed in 45 cases of 98 (46%). 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).	This was a retrospective study limited to cSCCs of 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.	3
Griffiths et al 2002	Prognostic factors for primary squamous cell	Retrospective monocenter study; n= 71	A 6 year (1990-1995) cohort	OS and DFS Prognostic factors related to	64 (41%) died within 5 years of treatment from causes other than squamous cell carcinoma, and were therefore defined as inde-		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	carcinoma of the skin treated by conventional surgery			histologic parameters.	terminate. 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 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 of tumour differentiation.		
Haisma et al 2016	To identify independent risk factors for LN metastasis in patients with	Retrospective monocenter study; n=363	Patients with cHNSCC	The primary endpoint was time to LN metastasis.	Three hundred thirty-six patients with 545 primary HNcSCCs were included. The median follow-up period was		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	HNcSCC and to evaluate the impact of LN metastasis on prognosis			Further endpoints: LN metastasis-free survival, DSS, and OS.	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 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	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 ($P < 0.05$).	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
			Autonomous Region People's Hospital at Urumchi City, China		Wnt1 expression (P < 0.05) was found to be correlated with histopathological differentiation in CSCC, and negatively correlated with SFRP1 expression in CSCC (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 DFS (p= 0.014).	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
Hirshore, et al. 2017	To describe the clinical outcomes and prognostic	Retrospective single center study; n=149	Patients with node-positive cHNSCC who	OS	The median number of positive lymph nodes from 149 lymphadenectomies	Low total lymph node ratio is associated with	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	factors for patients with node-positive head and neck cutaneous SCC (cHNSCC) who underwent lymphadenectomy	lymphadenectomies	underwent lymphadenectomy	Locoregional control rates	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.	improved outcomes in node-positive cHNSCC	
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	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	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	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			Oncology Tumor Board		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 of six patients from the surgery alone group and one of 14 patients who received surgery plus radiation therapy experienced loco-regional relapse.	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	
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	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) were incorporated in the alternative	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	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			were also excluded.		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.	be a focus of high-risk CSCC study.	
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 Arizona Veterans Affairs Health Care System from January 29, 2001 to February 10, 2006	Comparisons included demographics, histology, immunohistochemical protein expressions (Ki-67, p53, E-cadherin, cyclin D1). Clinical outcomes	Demographic features were similar between cases (n=30) and controls (n=30). Non-well differentiated tumors were larger (1.8 cm versus 1.3 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,	Tumor differentiation and depth are important pathologic and prognostic criteria for cutaneous squamous cell carcinoma. Immunohistochemistry helps describe patterns of biomarker protein expression and may exemplify aggressive subtypes	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					and cyclin D1 between the two groups.		
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 without extra nodal spread (ENS).	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-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.		4
Krediet et al 2016	To quantify lymphangiogenesis in SCC.	Retrospective monocenter case-control	Patients diagnosed with SCC, who had	The association between the parameter tumor	Lymphatic vessel density, relative lymphatic vessel area, and lymphatic	Small colective	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	Vascular parameters were evaluated and compared with respect to their predictive power for tumor metastasis.	study; n=30 tumors	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	thickness and the lymphangiogenes is parameters LVD, LVA, and D2-40-Chalkley count.	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 immunohistoche mically 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 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	Small colective	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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	Small collective	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					mutations (p=0.040) were significantly related to shorter DSS. At multivariate Cox's regression only tumor size had an 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). Cox regression analysis indicated that CD200 could be an independent		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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
Maruyama et al 2016	To present our experience of SLNB in patients with cutaneous SCC (cSCC) and	Retrospective analysis; n=169	240 patients with cSCC that were evaluated in the Department of Dermatology, Tsukuba	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		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	compared the outcomes with those in cSCC patients who did not undergo concurrent SLNB		University Hospital, for medical treatment, etween 2004 and 2015		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		
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 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 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	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.	immunocompromised patient a difficult clinical dilemma.	
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. ECS and immunosuppression remained significant in the multivariable analysis.		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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 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 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 extent of the neck dissection, represented by the number of lymph nodes removed, as	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					the only statistically significant predictor of DSS. On multivariate analysis, pathological stage (poorly differentiated vs. well differentiated) and radiation 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)	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.	
Oddone et al 2009	To propose a prognostic score model in patients with regional metastatic cutaneous squamous cell	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	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 (range, 1.3-212 months) 70 of 250 patients (28%) developed recurrent	Patients who underwent surgery and received adjuvant radiotherapy had a better outcome compared with patients who underwent surgery	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	carcinoma of the head and neck		curative intent. Patients must have undergone surgery and had to have biopsy-proven cSCC to HN lymph nodes		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, 1.85-3.369); 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.	alone. Patients who 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
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 high tumor thickness index (metastases only from tumor thickness 2,4 mm and subcutaneous infiltration), desmoplasia and ulceration.		4
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	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 investigated loci was found. Two patients with NRAS and HRAS mutations showed a partial and complete response to	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	3 3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Safety	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.	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, but ultimately mutational data are needed to better define the genetic landscape of this disease.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						Dr. Frederic Peyrade is a Merck board Member.	
Roozeboom et al 2013	To identify clinical and histopathological prognostic factors for local recurrence and metastasis in cSCCs at any body site.	Retrospective monocenter study; n=224	Patients diagnosed with cSCC between 1 January 2005 and 31 December 2007 at Maastricht University Medical Centrum (MUMC).	DFS, local recurrence-free survival	The cumulative probabilities of 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 tumour diameter and tumour thickness were independent predictors for		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 lower risk for DRO (subhazard ratio, 0.5; 95% CI 0.2-0.9; P = .046) adjusted for BWH T stage, sex, and location.	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
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	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 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,	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				known prognostic risk factors.	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], 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]).	poor differentiation, perineural invasion, and ear, temple, or anogenital location were risk factors associated with poor outcomes	

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 (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		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 adjuvant therapies for high-risk cutaneous SCC (cSCC).	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	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 Histopathologic subtype Perineural invasions Lymphovascular invasion High-risk anatomical location	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 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	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.	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		searches: “high-risk cutaneous squamous cell carcinoma, guidelines, excision 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.		Immunosuppressed sate Incomplete excision	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 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.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Stevenson et al. 2016	Review metastatic cSCC at the study institution to evaluate whether the modified BWH staging system improved prognostication of the patients with poor outcomes	Retrospective monocenter study; n= 16; n= 32 control subjects	Patients with metastatic cSCC were identified at the New York University Dermatologic Associates and Cancer Associates from 1998 to 2013.	Comparison between two staging systems	Seven of 16 patients 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 odds ratio for high-risk lesions (defined as T2 or higher) between the same groups was 8.3 (95% confidence interval, 1.4–87).	The modified BWH 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,**	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						unbrauchbar, rein decriptiv	
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 subsequent neck dissection.	Rein dekriptiv, kleine Anzahl von metastasierten Patienten	4
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		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					metastasis group and the non metastasis lymph node 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.		
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	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 (HR 2.75, 95 % CI 1.57–4.82;p<0.001). 21% of the patients developed recurrence, with most	LNR is potentially an independent predictor of outcome in patients with metastatic cutaneous nodal SCC.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			Mary Cancer Centre (Westmead Hospital), Sydney		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 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	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	Association between clinical variables and lymph node metastasis. Lymph node metastasis -free 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-		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	locally advanced cutaneous squamous cell carcinoma of the trunk and extremities		cancer institutions in Brazil (Barretos Cancer Hospital and Amaral Carvalho Hospital) between 1997 and 2006	Cancer specific survival.	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 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 cancer-specific survival (CSS) than those with T4 tumors; patients with no lymph node involvement had		

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

Remarks and notes:

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 Expertkonsens

3.2. 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

3.3. 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

3.4. 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

3.4.1. 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)

3.4.2. 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) Update 17th May 2017	512 524
Remarks and notes: -			

3.4.3. 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

3.4.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Akay et al 2010	To investigate the frequency 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.	Prospective, single-centre study	n=80 patients (50 men, mean age: 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	Distribution and frequency of dermatoscopic criteria in the sample	Essential dermatoscopic features in facial AKs and 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%)	Lack of information regarding observers' blinding Conclusion: Histopathology still remains the gold standard for correct diagnosis.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Presence of brown to grey pseudonetwork: highly specific (90%) for PAK (p=0.028)		
Boone et al 2015	To design an algorithm for AK classification with high-definition optical coherence tomography (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.	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 years (range 38-93) Reference= 53 images of healthy skin; matching according to age, skin type, anatomic site	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 epidermal architecture (Phi=1, Se=100%, Sp=100%) and atypical honeycomb pattern (Phi=1, Se=100%, Sp=100%)	Severe (>300 µm) hyperkeratotic AKs not included: selection bias likely	2
Di Carlo et al 2014	To examine, by means of video thermography (VTG) and dermoscopy, the head and trunk	Single centre, prospective, diagnostic study	n=36 participants with 145 lesions (48 were BCC, 87 were AK) 12 women	Sensitivity (Se) Presence of characteristic patterns for BCC/AK	VTG showed the presence of a hyperthermic pattern in all AK cases, in all BCC	Small sample size Moderate interobserver agreement (k=0.4-	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	regions of chronic sun-exposed individuals showing clinical lesions suspected to be AK or BCC, in order: (i) to evaluate the diagnostic accuracy of VTG; and (ii) to compare the validity of each of these two methods as diagnostic tool for the clinicians.		Mean age: 64.3 years, range: 55-75 All participants: history of prolonged sun exposure		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 keratotic hair follicles	0.6 in 5 of 7 criteria)	
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)	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	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					-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) -well-demarcated dermo-epithelial junction (cross-sectional images) (3/5 studies)	No information regarding the data/information extraction process 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	Sensitivity (Se) Specificity (Sp) Positive predictive value (PPV) of the observers	<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%	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
			side served as controls. 15 AKs were histpathologically confirmed, 15 AKs were diagnosed according to clinical and conventional dermoscopic criteria.	Negative predictive value (NPV) of the observers Frequency of each confocal feature in the sample	<u>All 4 observers:</u> Se=90.84% Sp=77.50% PPV=80.65% NPV=89% <u>Frequency of each confocal feature:</u> 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%		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					-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 (LR+), or negative likelihood ratio (LR-) of dermoscopy as a real-time non-invasive diagnostic imaging technique for AK.	Prospective, diagnostic validation study Independent blinded comparison by expert dermoscopist. Histopathological diagnoses were used as gold standard	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 sensitivity and specificity of a diagnostic algorithm	Concordance: K=0.917 Se=98.7% Sp=95.0% PPV=99.4% NPV=90.5% LR+=19.74 LR-=0.01 Diagnostic algorithm that combined follicular openings and erythematous pseudonetwork: sensitivity: 95.6%, specificity: 95.0%	Lack of interobserver reliability (only one observer) Study was supported in part by a grant from the Carlos III Health Institute Research Fund for Research in Health Technology and by the Mutua Madrilen Foundation for Medical Research.	2
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	Sensitivity of detecting AK on digital photographs (given min. 1 AK clinically) was 88%	Observers had different degrees of experience. P-values for the correlation according to skin	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				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	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 ± 1 AK: Tb=0.758. Correlation regarding skin sites: lower face: Tb=0.816 forearm: Tb=0.408	sites missing: selective reporting bias likely Lack of inter-rater reliability. AKs were only diagnosed clinically.	
Lallas et al 2015	To evaluate whether specific	Retrospective, multicentre	n=143 patients with SCCs	OR: predictors of poorly/moderately/	<u>Poor differentiation:</u>	Exclusion: cases lacking	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	dermoscopic criteria can predict the diagnosis of poorly differentiated SCC compared with well- and moderately differentiated SCC.	evaluation of clinical and dermoscopic images of SCCs for the presence of pre-defined criteria.	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	well-differentiated SCCs	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)	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, by the Italian Ministry of Health (RF-2010-2316524).	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Well/moderately differentiation: predictors: scales/keratin, central distribution of scales/keratin, white structure-less areas, white halos, white circles, large vessel caliber		
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.	Small sample size Study was supported by the Italian Ministry of Health (RF-2010-2316524).	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Univariate analysis: Evident follicles (OR 12.45, 95% CI 5.34-29.06). sensitivity=78.6% specificity=94.3% AUC=0.94		
Lee et al 2014	To evaluate the dermoscopic features of AK in Asians. To assess changes in dermoscopic features following treatment, and to compare dermoscopic results with histopathological results.	Retrospective study with a follow-up of 6-12 months	n=34 AK lesions among 25 Korean subjects (4 men, 21 women, mean age: 77.8 years, range 62-88 years)	Frequency of dermoscopic features of AK	Keratin/scales (79.4%) Red pseudonetwork (73.5%) Targetoid-like appearance (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	Scaling might also be observed in SCC 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.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					disappearance of atypical keratinocytes.		
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 (HD_OCT) in the en-face (horizontal) and slice (vertical) imaging modes.	Diagnostic study HD-OCT: Lesions examined by an experienced investigator Histological evaluation: board-certified dermatopathologist	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 polymorphism in en-face mode: 80% -Parakeratosis in histology and irregular entrance signal in slice mode: 77% -Destruction of epidermal structure in histology with	Small sample size results in broad confidence intervals No statistically significant results No information regarding blinding of investigators 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	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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)	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 and were biopsied. Diagnosis based on imaging was compared with histopathology as standard reference.	Caucasian male subjects (n=30) with at least seven clinically appearing AKs on the face on three separate areas, mean age: 76 years, range: 67-93	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. Lack of information regarding Sp, PPV, NPV Two authors (including the main author) report conflict of interests mainly with respect to Michelson Diagnostics	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						(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 appearance of the lesions.	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 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)	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
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 and SCCs relative to histopathology.	Systematic review Literature search in PubMed, Embase, Cochrane library and Web of Science databases. Quality assessment of the eligible studies performed with the STROBE criteria.	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% Sp SCCs: not reported (results out of 1 study of which only 74% of the clinically suspicious lesions were biopsied)	Conclusions mostly based on case series and case control studies with low to moderate methodological quality. Small sample size in all studies Confidence intervals of Se/Sp not reported	2
Olsen et al. 2016	To estimate the diagnostic accuracy	Retrospective observer-blinded diagnostic study.	n=30 patients with AK lesions	Sensitivity (Se) Specificity (Sp)	<u>Unskilled observers (n=5):</u>	Only good quality OCT images were	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of optical coherence tomography in AKs.	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 and normal skin prior to evaluation for all observers	mean age: 72.2 years ±11.0, 13 female n=71 patients with healthy skin Mean age: 69.2 years±11.9, 40 female		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)	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 European Union.	
Peppelmann 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	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)	Small sample size Study is underpowered Obserevers: not blinded for the final diagnosis Inter-observer agreement (starting	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			compare vascular RCM features		-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	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	
Rishpon et al. 2009	To identify criteria for the diagnosis of SCC and AK by reflectance confocal microscopy (RCM)	Prospective, single centre study RCM imaging of lesions suspected clinically and/or dermoscopically to be SCC or AK, followed by RCM assessment of the	n=38 lesions in 34 patients (7AKs, 25 SCCs in situ, 3 invasive SCCs, 3 keratoacanthomas), mean age =69 years, range 30-91	Presence of dermoscopic and RCM features	Presence of the features in SCCs vs AKs: -Scales at the stratum corneum: 95% vs 100% -Polygonal nucleated cells at the stratum	Small sample size overestimates the results (only 7 AKs in the sample)	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		biopsy-proven SCCs and AKs. Evaluation by 3 observers.			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%		
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 histopathologically confirmed lesions were taken in vivo.	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	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 ($p<0.0001$).	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	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Perilesional unaffected skin served as control.		correlate OCT findings with histology.	A subgroup of histologically confirmed AKs (n=23) showed the same results. 2)>Stratum corneum: r=0.894 (p<0.0001) >Epidermis:r=0.951(p<0.0001)	No blinding of observer reported	
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	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
					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) 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.	n=46 AKs among 44 Caucasians (age range: 56-79 years, skin photo types II-III) Exclusion of lesions with hyperkeratosis	Correct identifications of two observers Sensitivity (Se) and specificity (Sp) for each RCM parameter	Observer 1: correct identification of AK by RCM: 46/46 lesions (100%) Observer 2: correct identification in 45/46 lesions (97.8%)	No calculation of PPV, NPV, Confidence intervals High inter-observer agreement, concordance values from 87% to 98.2%.	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		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.	10 normal skin sites served as control group.	compared to routine histology	<u>RCM parameters with highest sensitivity and specificity reported:</u> -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) <u>RCM parameters with the lowest sensitivity reported:</u> Lymphocyte rolling: Se=14.3%, Sp=100%, p=0.123 Exocytosis in the stratum granulosum:	Acknowledgements: The Vivascope 1500 used in this study was loaned by MAVIG. One author has served as a lecturer for MAVIG GmbH.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 invasive SCC before and after therapy (PDT or surgery).	Diagnostic, monocentric study Following RCM imaging, a biopsy was obtained from the skin site within the lesion. Follow-up: after 2 months and every 6 months thereafter for 2 years.	n=25 patients with histologically confirmed SCC. Lesions without obvious keratosis (n=14) underwent direct RCM examinations. Lesions with obvious keratosis (n=15) were gently debrided for further RCM.	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,	Small sample size/small number of lesions, only 1 patient with healthy skin as comparison No information about participants' skin types Blinding of obsevers unclear: detection bias likely	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			For comparison, 1 participant without dermatosis was recruited.		85.7% (12/14) non-debrided 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)	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	Prospective, multicentre diagnostic pilot study	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	Limitation: lack of testing of the specificity of the dermoscopic criteria in differentiating	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	assist the clinical diagnosis.	Histopathological diagnosis served as gold standard			pseudonetwork surrounding the hair follicles (95%) (ii) white-to-yellow surface scale (85%) (iii) fine, linear-wavy vessels surrounding the hair follicles (81%) (iv) hair follicle openings filled with yellowish keratotic plugs (66%) (i-iv) combined produced in 95% of cases a peculiar strawberry appearance	nonpigmented AKs from other nonpigmented skin lesions at this site Examination of the 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 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

3.4.5. Literature

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3.5. 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

3.5.1. PICO

PICO – Scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Patients actinic keratosis and SCC	Cytology	n.a.	Accuracy

3.5.2. 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:			

3.5.3. 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*

3.5.4. 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 malignant cases, eight were classified as BCC and five as	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 confused with BCC	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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.	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 keratosis (AK).	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 keratosis (AK).	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 sensitivity between the two staining methods was found		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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. 2000	Evaluate the diagnostic accuracy of cytologic examination in	Prospective trial; n= 45; 15 BCC patients; 30 SCC patients.	Samples from patients with BCC and SCC	Evaluate the diagnostic accuracy of cytologic examination in	Imprint cytology demonstrated to be of help in the rapid		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs), in order to assess its clinical value.			basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs), in order to assess its clinical value.	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 any therapeutic maneuver		

Remarks and notes:

3.5.5. Literature

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3.6. 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

3.7. 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

3.7.1. ICO

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

3.7.2. 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:			

3.7.3. 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*

3.7.4. 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	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.	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					T2 as any tumor between 2 and 4 cm diameter. The implications of 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	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 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
					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 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,		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					but these recommendations are left intentionally broad. Imaging modalities include computed 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		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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. None-theless, it has been suggested that PET/CT may have a role in surveillance of the N0 neck.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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 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.	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, currently offers the most predictive staging system available.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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.		
Czerwonka et al. 2017	To report on the usefulness of FDG PET as a baseline workup study for patients with cutaneous SCC (cSCC)	Retrospective study; n=12 patients	Patients with SCC and hight risk SCC in whom PET CT was performed between May 2000 and September 2003	To report on the usefulness of FDG PET as a baseline workup study for patients with cSCC	Primary lesions were detected in nine cases (83.3%), lymph 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.		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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	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		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	carcinoma of the head and neck (cHNSCC).				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 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	Retrospective study; n=215 patients	Patients treated with curative intent between	To identify potential prognostic factors using univariate and	All patients had surgery as their primary treatment;		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	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.		1987 and 2007 for metastatic HN cSCC to the parotid and/or neck were identified.	multivariate analyses. To elaborate a staging system and validated it externally.	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 significant predictors of survival. On Cox regression, the number of involved lymph nodes as single or multiple (P =.006) was significant. The N1S3 staging		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 according to the number of involved lymph nodes and size, and incorporates parotid as 1 of the regional levels. These 2		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 and PET negative (false-negative; n = 0); (iii) histologically positive and PET		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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.		
Ghafoori et al. 2015	To determine valuable sonographic features for	Prospective study; n= 63	Patients with head and neck SCC treated and referred to surgery clinic of	To determine valuable sonographic features for	The number of metastatic lymph nodes was 47, while the remaining 16		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	differentiating metastasis from benign nodes using gray scale and Doppler sonography.		Hazrat Rasoul Akram hospital from November 2010 to June 2012, with complaint of palpable cervical lymph node.	differentiating metastasis from benign nodes using gray scale and Doppler sonography.	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%, respectively.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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 patients is needed. Alternatively,	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						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 with than without a large (>3cm)		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Marrazzo et al. 2015	To investigate the 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).	Retrospective study; n=82 patients	Patients from a single center that had undergone head and neck imaging for hrSCC.	To investigate the 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).	Twenty-nine percent (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.		2
Ruiz et al. 2017	To review utilization of radiologic imaging of high-stage cutaneous SCC (cSCC) to	Retrospective study; n=98 patients; 108 high-stage cSCC	Patients diagnosed with cSCC from January 1, 2000, through May 30, 2013 treated in the	Disease-related outcomes (DRO): local recurrence, nodal metastasis, death from disease	Imaging (mostly computed tomography, 79%) was utilized in 45 (46%) patients and	Limitations: Single institution retrospective design and changes in	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	evaluate whether imaging impacted management and outcomes.		Brigham and Women's Hospital.		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.	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.	
Shetty et al. 2015	To evaluate the accuracy of preoperative clinical methods such as palpation, ultrasonography	Prospective study; n= 26 patients	Patients who were incisional biopsy proven cases of oral carcinoma requiring resection of tumor and	Accuracy of preoperative clinical methods To assess whether combining these	Palpation, USG, and CT findings were compared with histopathologic findings by Fisher's exact test and the		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(USG), and computed 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.		neck dissection treated in one center	techniques increases the specificity and sensitivity of LN metastasis diagnostic	"P" value for palpation, US and CT were 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	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 change 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		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	SCC (cHNSCC) with confirmed regional nodal metastasis.				reduced extent of surgery have shown no features of regional failure after one year of follow-up. Overall the management in majority of cHNSCC patients with regional metastasis does not change 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		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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. 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:

3.7.5. Literature

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Forest VI, Clark JJ, Veness MJ, et al. N1S3: a revised staging system for head and neck cutaneous squamous cell carcinoma with lymph node metastases: results of 2 Australian Cancer Centers. *Cancer* 2010;116(5):1298-304. doi: 10.1002/cncr.24855 [published Online First: 2010/01/07]
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Marrazzo G, Thorpe R, Condie D, et al. Clinical and Pathologic Factors Predictive of Positive Radiologic Findings in High-Risk Cutaneous Squamous Cell Carcinoma. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]* 2015;41(12):1405-10. doi: 10.1097/dss.0000000000000526 [published Online First: 2015/10/31]
Ruiz ES, Karia PS, Morgan FC, et al. The positive impact of radiologic imaging on high-stage cutaneous squamous cell carcinoma management. *J Am Acad Dermatol* 2017;76(2):217-25. doi: 10.1016/j.jaad.2016.08.051 [published Online First: 2016/10/07]
Shetty D, Jayade BV, Joshi SK, et al. Accuracy of palpation, ultrasonography, and computed tomography in the evaluation of metastatic cervical lymph nodes in head and neck cancer. *Indian journal of dentistry* 2015;6(3):121-4. doi: 10.4103/0975-962x.163032 [published Online First: 2015/09/24]
Supriya M, Suat-Chin N, Sizeland A. Use of positron emission tomography scanning in metastatic head and neck cutaneous squamous cell cancer: does it add to patient management? *American journal of otolaryngology* 2014;35(3):347-52. doi: 10.1016/j.amjoto.2014.01.006 [published Online First: 2014/02/08]
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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 (rate of participants with 75%

PICO – Scheme			
	• Imiquimod • Resiquimod • MAL-PDT, ALA-PDT • Retinoids Tbc.		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 [Title/Abstract] OR placebo[Title/Abstract] OR trial[Title/Abstract]) NOT case report AND (German[language] OR English[language])	12nd January 2017 (initial search)	269 280

Database	Search strategy	Date	Number of results
		Update 17th May 2017	

Remarks and notes:

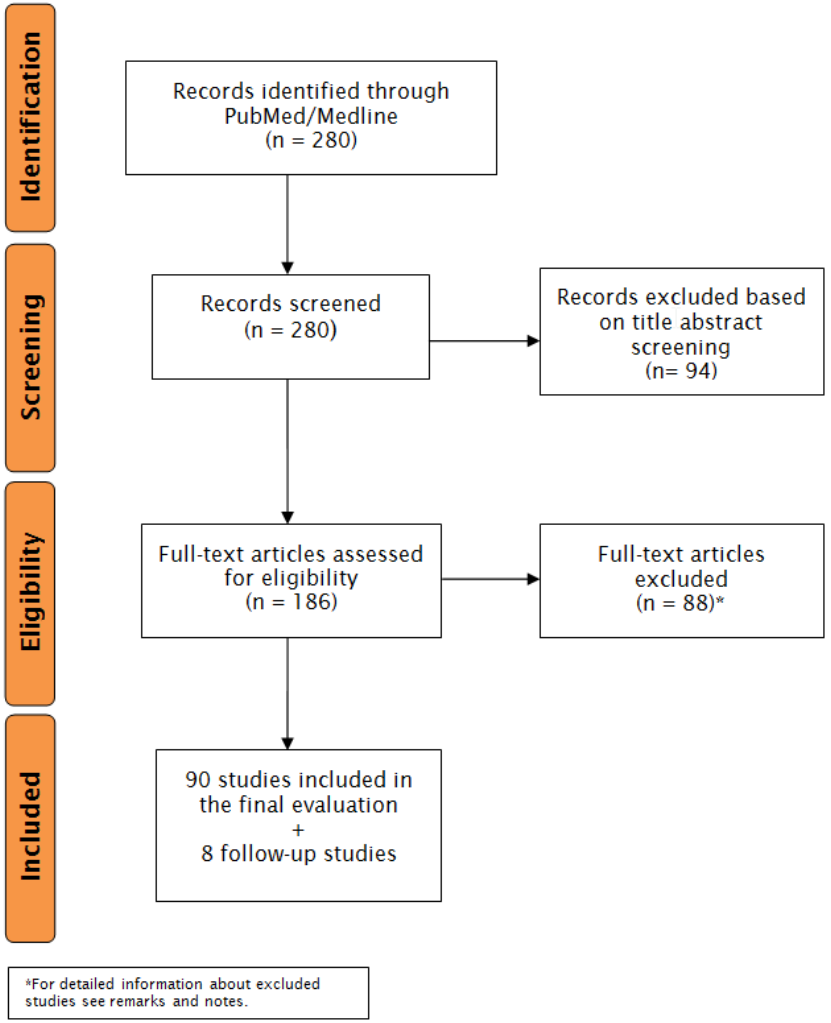
Some of the studies were already thoroughly analyzed in a Cochrane Review by Gupta, Paquet et al. (2012). The review served as supporting document for the evidence tables displayed here. Articles which were included in the review are highlighted with an asterisk (★).

4.1.3. Selection criteria

Literature selection	
Number of total results	280
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) • 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 **Outcomes**:

Literature selection	
	only per-lesion-efficacy reported without information on the subject of randomization (participant in inter-individual studies **Intervention:** Different (sequential) therapies and combination therapies
Number of results after title and abstract screening	186
Records excluded after full text review	**88**
Records included	90 + 8 follow-up studies

4.1.4. Flow chart of the literature search



4.1.5. Evidence table

4.1.5.1. 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, 5% 5-FU augmented	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 withdrawing from the study as a result of adverse events	<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) 0.5% 5-FU; 79%	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</u>	2

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
			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		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 100% lesion clearance</u> (N=4): 5% 5-FU vs cryotherapy: OR=10.8 (95% CI: 1.2-94.9) 0.5% 5-FU	<u>available in the evidence table:</u> Jorizzo et al. 2002 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
					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) <u>Cosmetic outcome (N=1, assessed at 3 months):</u> 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 cryotherapy and 81% of patients treated with imiquimod showed an excellent cosmetic outcome (based on scarring, atrophy, and induration).		

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					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 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		
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	N=83 RCTs comparing the treatment of actinic keratoses with either placebo, vehicle, or another active therapy with a total of 10036 participants	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-	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	1

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
		2010), and LILACS (from 1982)	The RCTs covered 18 topical treatments, 1 oral treatment, 2 mechanical interventions, and 3 chemical interventions, including PDT.		3.66; 3 studies with 420 participants) 0.5% 5-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 following photosensitisers:	had a high risk of reporting bias.	

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					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> 313 with 3% diclofenac compared to 127 with 2.5% hyaluronic acid; 136 with 0.5% 5-fluorouracil		

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

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					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.		
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	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),	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 change 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	1

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
		outcome "participant complete clearance" Literature search can be obtained from the Cochrane Review Gupta 2012	IMB (n=3, N=560), MAL-PDT (n=7, N=557) and placebo (n=32, N=2520).			had a high risk of reporting bias.	
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 ((actinic or solar) and keratosis) and (random OR randomized). Review articles and reference lists were used as well.	n=5 randomized, double-blind trials Lasted 12-16 weeks and treated 1293 patients 90% were men Mean age: range: 64-71 years 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	Participant complete clearance rate Number needed to treat (NNT) for one patient to 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	Imiquimod vs vehicle Participant complete clearance rate: 50% vs 5% 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%),	Quality scores were high; all trials reported being both randomized and double blind, scoring 3 or more of the maximum 5 points. Limitations: Two of the five studies used histological rather than clinical diagnoses of AK. QORUM guidelines were followed Unclear risk for publication bias	1

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
			(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.	information on over 1200 patients) Relative risk for serious adverse events (RR sAE) NNT to cause one additional withdrawal Relative risk to withdraw due to adverse events	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: 1.5 (95% CI: 0.8-2.7)		
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,	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	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	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	1

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
		vehicle controlled trial, and precancerous skin lesions The medication names were also incorporated. 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	the vehicle treatment groups, the mean age was 62.9 years, 85.8% of the patients were male and 93.6% had a Fitzpatrick skin type of I or II.		the 1-, 2-, and 4-week 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 number of lesions present by increasing the length of therapy	evaluated the treatment of AKs present on the face, and therefore the results may not be relevant to the 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
					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 concentrations: 0.0025%, 0.005%. 0.01%, 0.015%, or 0.05%), and imiquimod 2.5%/3.75% (IMI) for	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 Cochrane Database of	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 same study): age slightly older (>70 years)	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%-6.3% -IMB vs vehicle/ placebo: 42.2% vs 3.7%	No sequential or combination treatments included Risk of bias assessment with the Cochrane Collaboration “risk of bias” assessment tool with risk of bias being mostly low to unclear	2

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
	AKs on the face, forehead, and scalp.	Systematic Reviews, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and BIOSIS. Cross-references and conference websites were searches as well.	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		<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%	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	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 the cumulative ranking curve (SUCRA), ranking from 0-1 (0=worse treatment with no uncertainty,	<u>Complete clearance rates, OR, SUCRA score (%)</u> -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): 54.8% (95% CI:	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)	2

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
		-1 diclofenac 3% in 2.5% hyaluronic acid (DCF) -1 0.5% fluoruracil (5-FU) -1 ingenol mebutate (IMB)		1=best treatment with no uncertainty)	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 studies, N=322): 39.9% (95% CI: 15.6–64.2%), 8.7	Repeated applications were not studied in the NMA 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	

Study	Aims	Design	Population	Outcomes	Results	Comments/ Linked studies	LoE
					(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% (95% CI: 5.5–8.3%), 1 (reference), 0.0%	Wolf et al. 2001 Rivers et al. 2002 Gebauer et al. 2003 Lebwohl et al. 2012 Swanson et al. 2010 Hanke et al. 2010	

4.1.5.2. Individual studies (n=91)

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 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.	Randomized, active-controlled, double-blind, parallel-group study 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	n=16 patients with AKs (10 male, mean age=64 years, range:50-82 years) Majority: photo skin types II and III Exclusion criteria: Patients with ≥15 lesions or with very extensive lesions	Complete healing Reduction rate in number of AKs at 1 month Mean reduction of lesions counts at 1 month	1% colchicine group vs 0.5% colchicine group <u>Complete healing:</u> 6/8 vs 7/8 <u>Reduction rate in number of AKs:</u> 73.9% (48/65) vs 77.7% (52/67), p<0.001 <u>Mean reduction of lesion counts:</u> 0.7±1.3 vs 0.66 ±1.7,p > 0.05	Insufficient detail reported about the method used to generate the 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.	2
Akarsu et al 2011	To compare the effects of topical 3% diclofenac sodium plus hyaluranon (DFS) gel, 5% imiquimod (IMQ)	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,	Complete clearance rates =CR Total Thickness Score=TTS from 0-4	CR at the end of the treatment vs follow-up: DFS: 19.1% vs. 14.3% IMQ: 20% vs. 45%	Results not generalizable due to use of TTS and PGII (self-report scale)	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	cream, and base cream (BC) in 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.		mean age=65.71 years ±11.60, disease duration (years): 2.68±2.34 Basal TTS: 3.95±0.22 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	Patient Global Improvement Index=PGII from 0-6 Both outcomes assessed at 0, 4, 8, 12, 16, 20 and 24 weeks	BC: 0% Average TTS value 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	Efficacy of DFS seemed to decrease after cessation of treatment	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					expensive than DFS (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	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	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
		1 month run-in period with placebo ointment				Grant PO1 CA27502. 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	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	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
		systemic steroids 4 weeks before			treatment: on the 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). Intervention: Imiquimod 5%	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	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	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	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	cream or vehicle once daily, 3 days per week,	days per week, N=130 to vehicle			the face (64.6%) 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)	but not the 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		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					LSRs (96.9% and 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 pain)	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
					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		
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 with AKs.	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	Participant complete clearance Participant partial clearance (≥75%) Reduction in AK count from baseline at week 8	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 Pharma.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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.		the full face or to 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.	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		

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).		
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	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).	≥75% clearance of baseline lesions 100% clearance Type and severity of LSR	Imiquimod group vs vehicle group ≥75% clearance of baseline lesions: 72% (21/29), (1st course 45%, 13/29;	Small sample size N=5 dropouts (intervention: 4 vs control:1) High risk for attrition bias	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	(solar keratosis) within a field of treatment. Intervention: Application of study cream or vehicle three times a week.		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 Subjects with <75% clearance of the baseline SK number were treated with a second course of study cream	Mean SK counts (baseline vs vehicle)	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: 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	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 selection and peromance bias This study was supported by 3M Pharmaceuticals. Statement regarding potential conflict of interest is missing.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Vehicle: 10.8 to 9.3, p=0.0017		
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 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	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 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.	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 lesions per patient: 6.3±1.5 Placebo: N=76, mean lesions per patient. 6.4±1.4	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 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	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 light sources This study was sponsored by Biofrontera Bioscience GmbH.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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 600 to 750 nm, and the recommended light dose is 100 J/cm².	Randomization BF-200 ALA: MAL cream: placebo: 3:3:1			<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% <u>Occurrence of Adverse events:</u> 96.4% vs 98.0% vs 72.4% Most common and most severe AEs: erythema, burning and pain <u>Mean VAS score:</u>		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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-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	See Dirschka et al 2012	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Overall new lesions: 41.7% and 41.8% in BF-200 ALA, 20.6% and 56.1% in placebo and 48.7% in MAL		
Dragieva et al 2004★	To evaluate the efficacy and 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.	Prospective, single-centre, randomized, double-blind, placebo-controlled, intraindividual study	n=17 OTRs with 129 mild to moderate AKs 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)	Complete response rate at 16 weeks after 2nd treatment Partial response rate Overall lesion complete response rate Adverse events VAS score	Complete response rate vs partial 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,	Small sample size 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	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	Sites were illuminated with 75 J/cm² of visible light delivered at 80 mW/cm² by a noncoherent light source.				discomofort higher for MAL than placebo Mild to moderate AEs such as erythema, oedema and crust formation reported <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	pain reception and consequently the VAS-score (underestimation) Unclear risk of 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	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
						Statement regarding potential conflict of interest is missing.	
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 mean change from baseline in the average lesion area 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) ≥10% decrease in average lesion area: Significantly hgher in the CPA group than the placebo group at weeks 3 (P=0.05) and 6	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
					(P=0.02), and showed a trend at week 12 (P=0.06) 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	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	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>	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	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	Imiquimod: 3-times-per-week for 3-4 weeks, up to two courses		Randomization 1:1		98.7% (306/310) vs 93.6% (234/250), p=0.0420 Patient complete 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/dryn	Withdrawal rates: 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
					ess, scabbing/crusting Conclusion: 12-month lesion 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	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	Patient Complete clearance rates Incidence of AEs Change in local skin response score at day 4 between treatment cycles (mean composite LSR score)	Complete clearance: 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): Complete clearance of AKs present at week 8: 46.7% vs 18.4%, p<0.01	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
	present in the field at 8 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.		follow-up ingenol mebutate 0.015% (N=92) or vehicle gel (N=49) for three consecutive days.		Emergent AKs: 59.5% vs 25.0%, p=0.01 After 12 months: AKs present at 8 weeks: 18.5% vs 4.1%, p=0.02 Emergent AKs: 31.0% vs 15.0%, p=0.10 12-month clearance rate (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)		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Most common LSR: erythema and flaking/scaling AEs: 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%) <u>Follow-up:</u> 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	Randomized, double-blind, placebo-controlled,	n=150 patients (89 men, 61 women) Mean age: 68 years (range: 27-87 years)	Mean lesion-count reduction	Diclofenac group vs placebo	Study was conducted in Australia (higher	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	with placebo (2.5% hyaluronan gel alone) in the treatment of patients with SK. Intervention: Application of 0.25g gel to 5cm² twice daily until lesions resolved or for 12 weeks.	multicentred, parallel group study	Random allocation to active treatment (N=73) or placebo (N=77) Patients applied 0.25g of gel to a designated 5cm² study area twice daily over 12 weeks.	Complete lesion resolution >50% lesion reduction Adverse events	At 16 weeks: highly significant <u>decrease in number of lesions:</u> 6.2±7.5 (56.1% reductions) vs 2.4±4.3 (23.6% 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.	prevalence rate of SKs : results are limited to this population, results have to be interpreted 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 :	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Patients were highly compliant	Gel and placebo are nearly identical: small risk of allocation bias and unblinding 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.	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	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	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
			Combined placebo = pooled result of all placebos (=placebos of 2,3,5 or 7 times per week)		20.0% vs 36.7% (p=0.002) <u>Median percentage lesion reductions:</u> 25.0%, 50.6%, 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	considered compliant Study was not 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
					itching (59.1%), pain (39.6%), burning (15.4%)) Author's <u>conclusion:</u> 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-	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%)	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	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	filtered spectrum 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 absolute irradiance was 150 mW/cm2, the application time 10-11 min and the				<u>Patient complete clearance rates:</u> PD750 vs Wa1200L: After 1 month: 85% vs 91%, p=0.51 After 3 months: 79% 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	Additional cooling with cold air was offered during treatment. 17% did not need it (all from P750 group)	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	absolute irradiation dose was 100 J/cm2 with the control of an individual interactive measuring system.						
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 once daily applied as a 3-week on/off/on regimen.	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 Investigator Global Integrated Photodamage (IGIP) score Safety (adverse events, LSR)	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% (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%	Drop-outs: N=27 Limitations: Local effects of imiquimod, including erythema, may have led to investigator and subject bias (performance and detection bias/Hawthorne effect) Investigator selected the treatment area for each subject (face or balding scalp)-> selection bias participants applied the cream once	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					(p<0.001 each imiquimod vs placebo) Mean IGIP score: 0.7±1.1, 23.4% vs 2.0±1.1, 62.3% vs 1.8±1.1, 70.9%) Adverse events: 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 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%)	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 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	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
						Graceway Pharamceuticals.	
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	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
					greater extent than patients without 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	Randomized, observer-blinded, intrapatient, single-centre, comparison study	n=28 patients with ≥5 AKs in two comparable anatomical areas on the head	Total lesion count reduction Complete clearance Treatment failure	TCA vs ALA PDT: Total lesion count reduction (ITT): 31.9% vs 58.0% (p=0.006)	Drop-outs at 12 month follow-up: N=5: moderate risk for attritions bias Patients were instructed to	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	cancerization 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 PDT 1200, 600 – 740 nm, using a dose of 75 J/cm² at an	Follow-up: 1, 3, 6 and 12 months after treatment .	Mean age: 70.0 years±7.6 (range 56-88) N=4 female	(number of AK greater than 50% of the baseline count) Adverse events, treatment related pain (mean VAS score 0-10) Cosmetic outcome (excellent, good, fair and poor)	Mean Complete clearance rate: 48.8%±35.1 vs 73.7%±29.5 (p=0.011) Treatment failure N patients (%): 7 (25%) vs 2 (7.1%) Mean VAS score: 7.5±2.3 vs 5.1±2.6, p=0.04 Scarring was only seen in TCA group (n=6, 21.4%) Cosmetic outcome (excellent): N=11 (44.0%) vs N=19 (76.0%), p=0.202	regularly apply sunscreen until completion of study.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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						
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, and 10 J/cm²) to treat multiple AKs on the face and scalp.	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 2 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 single PDT according to varying light doses Application site reactions during	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%), increase in CR rate was significant (p=0.013)	Hyperkeratotic, hypertrophic grade 3 AKs were excluded because of previous experience suggesting these did not respond well to PDT: selection bias High risk of performance bias: non-blinded	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
				illumination and after treatment	Partial response: 12 (17%) vs 12 (17%) 16 weeks for ALA PDT: 4 (6%) Number of cleared lesions at week 8: 0: 5 (14%) vs 25 (71%) 1: 14 (40%) vs 8 (23%) 2: 16 (46%) vs 2 (6%) CR rate of AKs 8 weeks after a single PDT according to varying light doses: 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 Subjective signs during/after ALA PDT: burning/stinging (most frequently	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
					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% Adverse events: Itching = most frequently reported application site reaction	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: selective reporting bias likey Only statistically significant results were reported, results for AEs and	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					LSR: Erythema and scabbing/crusting (16% of patients rated them as severe)	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 vehicle cream cream once daily for 1, 2 or 4 weeks.	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 Physician Global Assessment of Improvement Adverse events	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) 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,	Unclear risk of allocation concealment and random sequence generation. No placebo cream was used to conceal the treatment duration. Study was partly double-blinded and partly open. High risk for performance and detection bias. Unclear which type of analysis was used: High risk for attrition bias	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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%), 4-week fluorouracil (96%), and vehicle (65%) study group	Several data were not reported (eg PGAI, sd on mean percentages etc): selective reporting bias likely This study was supported by Dermik Laboratories.	
Kang et al 2003★	To determine the safety and efficacy of adapalene gel 0.1% vs 0.3% vs placebo in the	Multicentre, randomized, placebo-controlled, active-controlled,	n=90 participants 69 men, 21 women Mean age: 63, range 43-83	Mean reduction/changes of lesion count at 9 months	Adalpene gel 0.1% vs 0.3% vs vehicle Mean reduction of lesion count	No follow-up Authors pooled together selected PGAI data, i.e. for	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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.	assessor-blinded, parallel-group study Randomization: 1:1:1	79% white, with skin phototypes I and II	Physician global assessment improvement Tolerability Adverse events	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) 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,	clear, marked, moderate improvement to reach statistically significant difference: selective reporting bias likely This study was supported by Galderma Corporation, Texas, US.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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 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-	Multicentre, randomized, open, active-controlled, intraindividual,	n=121 participants with 1343 lesions 78 men, 43 women Mean age: 69 years, range: 39-89	Mean percentage of reduction in lesion counts	MAL-PDT vs cryotherapy (PP) <u>Mean percentage reduction in lesion</u>	Sd of mean percentage reduction in lesion counts were not	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	PDT vs cryotherapy in patients with AK on the extremitites. Intervention: Treatment with PDT using MAL 160 mg/g cream or conventional cryotherapy.	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.		Cosmetic outcome assessed by investigator and participants Participant preference Adverse events	count: 78% vs 88% (p=0.002) Investigator's assessment of cosmetic outcome: 79% vs 56%, (p<0.001) Patients' assessment: 50% vs 22% (p<0.001) Patients' preference: 59% vs 25% (p<0.001) Both treatment regimens: safe and well tolerated	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 better and positive value if MAL-PDT isd better. This could influence the participant perception. This study was supported by Galderma.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
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 placebo IPL.	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 satisfied – not satisfied) at follow-up Investigator evaluation (0-4, 0= no improvement) 10 weeks after treatment 3 Adverse events	MAL-IPL vs placebo IPL Complete AK clearance per hand: 54.5% vs 3.0%, p<0.0001 (after 10 weeks) Complete AK clearance rates per lesion: 69% vs 15%, p<0.001 Per hand: 55% vs 3%, p<0.001 Mean VAS score at treatment 3: 4.9±2.1 vs 4.3±2.1, 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	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
					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 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.	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 Vehicle group: N=250	Participant complete clearance rates for all lesions at 8 weeks post-treatment Partial clearance rates for all lesions at 8 weeks post-treatment Median percentage reduction of baseline lesion Adverse events	Imiquimod vs vehicle Complete clearance rates: 48.3% (117/242) vs 7.2% (18/250), p<0.001 Partial clearance rates: 64.0% (155/242) vs 13.6% (24/250), p<0.001 Median percentage reduction of	This study was supported by 3M Pharmaceuticals. Skin quality rating not reported for placebo: selective reporting bias	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
				Local skin reactions	baseline lesions: 86.6% vs 14.3% Adverse events: 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 Local skin reactions: common and occurred in both groups, most frequently reported: erythema, flaking/scaling/dryness and 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-	Multicentre, randomized, double-blind, vehicle-controlled, parallel-group study	n=146 patients with completely cleared AKs 131 imiquimod treated, 15 vehicle treated	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)	The study was conducted with financial support from 3M Pharmaceuticals.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	treatment visit in the phase III studies. Intervention: application of 5% imiquimod 3 times per week or twice per week.		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.		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.		
Kose et al 2008★	To compare the efficacy and safety of topical 3% diclofenac gel plus hyaluronic acid and 5% imiquimod cream in the treatment of AK. Intervention: Application of Diclofenac 3% natrium in 2.5% HA gel once daily or 5% imiquimod cream	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% diclofenac gel once daily to their lesions N=25 patients: 5% imiquimod cream three times a week for 12 weeks	Investigator and participant global improvement indices at the end of treatment (IGII and PGII) Local skin reactions and adverse events	Diclofenac vs imiquimod group (no sign. differences between the two groups) IGII: Participant complete response: 12% vs 22% PGII: Participant complete response: 28% vs 23%	No blinding: high risk for performance and detection bias No data reported for participant partial clearance: high risk for selective reporting bias No information regarding participants' compliance: this	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	three times a week for 12 weeks.				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	might skew the data. Statement regarding potential conflict of interest is missing.	
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-	Single-centre, randomized, active-controlled, parallel-group study Randomization to one or two courses of cryosurgery (20–40 s per lesion),	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	Cryosurgery vs 5-FU vs IMIQ: Initial clinical clearance: 68% (17/25) vs 96% (23/24) vs 85% (22/26), p=0.03	No information regarding blinding: risk for performance and detection and bias Lack of information regarding patients	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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 times a week for 4 weeks (up to two courses).	topical 5-FU (twice daily for 4 weeks), or one or two courses of topical imquimod (three times per week for 4 weeks each)		end of the treatment Adverse events Cosmetic outcome 12 months after EOT	Histological total clearance rate: 32% (8/25) vs 67% (16/24) vs 73% (19/26), p=0.02 Recurrence rate: 25% vs 24% vs 16%, p<0.01 Sustained clearance rate of intitially cleared lesions: 28% (7/25) vs 54% (13/24) vs 73% (19/26), p<0.01 Sustained clearance of the total treatment field: 4% (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)	adherence to the treatment No detailed information regarding adverse events: selective reporting bias likely.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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 imiquimod 5% cream once daily, 2 days per week for 16 weeks.	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 reduction in baseline lesions at 8 weeks post-treatment Adverse events Application site reactions Local skin reactions	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: 39.5%-55.1%) Median % reduction in AK lesions: 83.3% vs 0% Severe LSR: erythema: 17.7% vs 2.3%	High risk for attrition bias (9 drop-outs in intervention, 11 in control group) Not all outcomes reported: selective reporting bias likely No information provided regarding patients' adherence This study was supported by 3M Pharmaceuticals.	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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% 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%	Multicenter, randomized, double-blind, parallel-group, placebo-controlled study	N=547 patients in the face/scalp group (277 received ingenol mebutate gel 0.015%, 270 placebo)	Participant complete clearance at 57 days Participant partial clearance	Ingenol mebutate vs placebo **Face and scalp** <u>Complete clearance</u> 42.2% vs 3.7%, p<0.001	Data were pooled Face/scalp group: 3 drop-outs in the ingenol mebutate group, 8 drop-outs	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	for trunk and extremities).	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=458 in the trunk/extremities group (N=226 received ingenol mebutate 0.05%, 232 placebo) Mean age: 65.1 years	Median reduction of AKs Mean maximum composite score (0-24)	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%) **Trunk and extremities** Complete clearance 34.1% vs 4.7%, p<0.001 Partial clearance: 49.1% vs 6.9%, p<0.001	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.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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: long term follow up-study of **Lebwohl et al 2012** and three other studies	To assess 12-month recurrence rates and safety associated with ingenol mebutate gel treatment in patients who previously had achieved complete clearance of actinic keratoses.	Observational follow-up study of patients who had achieved complete clearance of AK in 4 studies, results are pooled from 4 studies Randomization 1:1	Population: N=108 patients with complete clearance of face or scalp lesions; N=76 patients with complete clearance of trunk or extremity lesions.	Recurrence rate Median time to recurrence Safety	12-month recurrene rate: 87.2% (face/scalp) and 86.8% (trunk/extremities) Estimated median times to recurrence: 365 days (face/scSlp) and 274	The study was supported by LEO Pharma.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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.		To enroll in the follow-up studies, patients had to have achieved complete clearance in a prespecified 25-cm2 area at day 57 of their original trial.		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.		
Loven et al. 2002	To compare the 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	Randomized, multicenter, 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	n=24 patients 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)	Reduction of number of AK lesions (absolute and %) Adverse events Patients' treatment preference (questionnaire)	0.5% vs 5% FU 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:	Study was only single blind (evaluator-blinded): high risk for detection bias/patients compliance might bias the results Small sample size (n=24)	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	cream twice daily for 4 weeks.	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.	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.		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%) 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%)	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. Statement regarding potential conflict of interest is missing.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
			Of the 18 patients who 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		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		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
			applied to both sides of the face.				
McEwan et al 1997 ★	To study the efficacy and tolerability of topical 3% diclofenac in 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.	Single-centre, randomized, double-blind, placebo-controlled, parallel-group study Self-application twice/day and also sunscreen once/day for 24 weeks	n=130 participants 73 men, 57 women Age range: 48-87 Active treatment: N=65 Control group: N=65	Complete response rate Partial response rate Adverse events	Active vs placebo <u>Complete response rate:</u> 29% (95%CI: 19-42) vs 17% (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	High risk for attrition bias: N=31 drop-outs in the intervention group and N=16 in 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.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
Misiewicz et al 1991★	To compare the efficacy and tolerability of arotinoid methyl sulfone (Ro 14-9706) cream with tretinoin cream in the treatment of AK. Intervention: Application of 0.05% Ro 14-9706 cream and tretinoin cream twice daily for 16 weeks.	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 Apllication twice daily for 16 weeks, each as a 0.05% cream to opposite sides of the face	Overall response at 16 weeks (Complete response, no response) Mean % decrease in the number of lesions at 16 weeks Tolerability scoring	Ro 14-9706 vs tretinoin <u>Complete response:</u> 0 (0%) vs 2 (8%) <u>Partial response:</u> 12 (48%) vs 10 (40%) <u>No response:</u> 13 (52%) vs 11 (44%) Worsening: 0 (0%) vs 2 (8%) <u>Mean % decrease:</u> 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) <u>Tolerability:</u> Ro 14-9706: better tolerated, local inflammation was slight/absent in most ptients	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
					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 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.	Comparative, intra-patient, split-face, single-centre, investigator-blinded, randomized 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	n=22 patients with 311 AKs 18 men, 4 women 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	Complete remission rate at 90 days 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	IMB vs DL-MAL-PDT Complete remission rate: 75.8% vs 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	Small sample size Open study: performance and detection bias likely Self-application by patients might bias the results (compliance): results might be over/underestimate.	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
		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 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.	and preferences of the patients.		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		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
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 likely.	2
Moloney et al 2007★	To compare the efficacy and adverse effects of MAL-PDT with ALA-PDT in the treatment of scalp AK. Intervention:	Single-centre, randomised, 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	Field complete clearance rates at 1 month post-treatment Mean reduction in lesion counts at 1	ALA-PDT vs MAL-PDT <u>Field complete clearance rate:</u> 40% vs 46.7% = clearing of 87% of AKs treated with ALA-	Small sample size consisting of only men: Interpretation of the results is limited to this study	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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.		or ALA as first or second treatment. MAL cream was applied for 3 h; 20% ALA cream was applied for 5 h.	month post-treatment Adverse events Pain (VAS score at 3,6,12,16 minutes) Duration of discomfort Participant preference	PDT vs 71% treated with MAL-PDT Mean reduction from baseline in AK counts: 6.2±1.9 vs 5.6±3.2 (p=0.588) → no sign. difference in efficacy Adverse events: no AEs apart from mild erythema in all treated sites and superficial erosions in two patients Pain: All patients experienced pain 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	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	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					most significant one) Duration of discomfort: longer following treatment with ALA when compared with MAL-PDT (p=0.044) Patient preference: 2 (13.3%) vs 10 (66.7%)		
Moriarty et al 1982★	To investigate the efficacy of etretinate (tigason) in the treatment of AK. Intervention: 75mg etretinate as first or second treatment and placebo consequently either as first or second treatment per os once daily for 2 months.	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 or placebo) given for two months, order of administration was randomized.	Participant complete clearance rates Partial remission rates (50% reduction in size of 75% of lesions) Adverse events	Etretinate vs placebo group Participant complete clearance rate: 22.7% (5/22) vs 0% Partial remission: 63.6% (14/22) vs 4.3% (1/23) **After crossover:** Complete or partial response: 84% (37/44) vs 5% (2/42)	N=3 dropouts in the intervention group and N=2 dropouts in the control group: Risk for attrition bias unclear Random sequence generation and allocation concealment unclear Unclear if second part of the study	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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%	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 for the treatment of AK. Intervention: Subjects received both one treatment session of MAL-PDT (illumination with with a narrowband red light (average wavelength approximately 630 nm, light dose 37	Multicentre, randomized, open-label, active-controlled, intraindividual, right-left comparison study Lesions with a noncomplete response were retreated after 12 weeks	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 Lesion complete response rates of baseline lesions at 12 and 24 weeks Participant preference Cosmetic outcomes Investigator preference	MAL-PDT vs cryotherapy Mean % lesion reduction from baseline (PP): 86.9% vs 76.2%, p<0.001 (week 12); 89.1% vs 86.1%, p=0.20, week 24 Lesion complete response rate: 85.8% vs 82.5%, regardless of lesion location and severity (week 24)	Study design was open since 2 physically distinct treatments were compared: risk for performance and detection bias Standard deviations for the mean percentages of reduction in lesion counts were not reported: selective reporting bias likely	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	J/cm²) from a standard light-emitting diode (LED) light source) and a double freeze–thaw cryotherapy.			Mean VAS score (pain) Adverse events	Cosmetic outcome (investigator) Rated as excellent: 70.8% vs 57.5% (week 12), 77.2% vs 49.7%, week 24 Participant preference (cosmetic outcome, efficacy, skin discomfort): 44.7% vs 9.9%, p<0.001 Investigator preference: 52.2% vs 15.9%, p<0.001 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	This study was supported by Galderma France.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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 at 6 months Pain (mean VAS score during and after treatments, 0-10)	DL-PDT vs LED-PDT <u>Patient complete response rate:</u> 42.9% (15/35) vs 68.6% (24/35), p=0.030 <u>Lesion complete response rate:</u> 89.2% vs 72.4%, p=0.0025 <u>Mean VAS score:</u> 1.53 (range: 0.1-6.0) vs 4.36 (range: 0.3-8.4), p<0.001	Random sequence generation and allocation concealment unclear Detailed information of the 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	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Conclusion: DL-PDT is less costly and less effective than LED-PDT	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 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.	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 reduction Local skin reactions Application site reactions Adverse events	Imiquimod vs vehicle <u>Patient complete clearance:</u> 45% vs 0% <u>Partial clearance</u> (>50%): 82% vs 50% <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%	Small sample size N=1 lost to follow-up: risk for attrition bias is low Self-application of the treatment by the participants: compliance might differ which might bias the results This study was supported by 3M Pharmaceuticals.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					hzeadache and influenza-like symptoms: 25% in imiquimod group No serious AEs reported No results were statistically significant		
Ortonne et al 2010	To compare cross polarized light photography (CPL) and fluorescence diagnosis (FD) using methyllevulinic 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	Randomized, double-blind, vehicle-controlled, parallel-group, 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	n=12 patients with at least 5 clinically visible AK lesions in a single 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	Mean reduction Adverse event	Mean reduction in lesion count: Imiquimod group: 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	Small sample size The study was funded by 3M Pharmaceuticals.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	and after treatment with imiquimod 5% cream or vehicle	daily, 3 days per week for 4 weeks. After a 4-week break, a second course followed.					
Ostertag et al 2006★	To compare the recurrence rates and the improvement of actinic-damage 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).	Single-centre, randomized, double-blind, active-controlled, parallel-group study Follow-up=1 years	n=55 participants 50 men, 5 women Mean age: 72 years, range: 52-85 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).	Recurrence rates at 3, 6, and 12 months post-treatment RR of recurrence in FU group vs LA group Mean % lesion cleared Adverse events Additional outcome: Photoaging score (simplified form of the Glogau score to classify photoaging)	FU group vs LA group <u>Recurrence rates:</u> <u>3 months:</u> 61.5% (95% CI: 48.6-71.0) vs 21.7% (95%CI: 10.9-36.3), p=0.005 <u>6 months:</u> 57.7% (95%CI 44.8-67.3) vs 21.7% (95%CI: 10.9-36.3), p=0.011 <u>12 months:</u> 60.0% (95%CI: 46.1-71.3) vs 25.9% (95%CI: 15.4-38.8), p=0.013 <u>RR (95% CI) of recurrence in FU group vs LA:</u> 3 months vs 6 months vs 1 year:	Unclear allocation concealment. Self-application of the treatment: lack of information regarding patients' compliance Standard deviations associated with mean values were not reported: high risk for selective reporting bias	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					2.83 (1.34-6.45) vs 2.65 (1.24-6.15) vs 2.31 (1.19-4.62) <u>Photoaging score:</u> 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 months <u>Mean % lesion cleared:</u> 6 months: 79.2% vs 94.4%, p=0.022 12 months: 76.6% vs 91.1%, p=0.048 <u>Side effects:</u> more frequently in the laser group, esp. erythema and hypopigmentation		
Pariser et al 2016	To evaluate the effect of short-incubation time and	Randomized, multicenter, vehicle-controlled,	n=234 participants ith 6-20 grade 1 or	Median AK clearance rate for subjects at week 12	Median AK lesion clearance rate: ALA-PDT vs vehicle PDT	Unclear randomization scheme	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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 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.	investigator-blinded study	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 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	Complete clearance rate Partial clearance rate Participant complete clearance rate at week 12 Subject satisfaction and acceptability of treatment (4-point scale) at follow-up Safety	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 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	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 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
					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 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		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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 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		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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%) 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,		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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 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).	Multicenter, double-blind, randomized, vehicle controlled study	100 Caucasian patients with 4-10 previously untreated nonpigmented, 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	Complete lesion response rate 3 months after EOT Patient response rate at 3 months after EOT Adverse events	MAL-PDT vs vehicle-PDT 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%	4 patients with 36 lesions were 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	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
			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)		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) 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)	PhotoCure ASA, Oslo, Norway.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
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. 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.	Multicenter, randomized, double-blind, placebo-controlled study	n=80 patients with 4-10 previously untreated, mild to moderate nonpigmented 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 31-84 N=38 in the placebo group with 242 lesions 34 male Mean age: 67 years, range 39-84	Complete lesion response rate Patient complete response rate Cosmetic outcome, assessed by patient and investigator on a 4-point rating scale Safety: Adverse events	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%-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%)	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 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	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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 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	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
					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 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	Multicentre, randomized, two-arm, parallel-group, open-label, intraindividual study Randomization (1:1) of two treatment areas to simultaneous or sequential treatment with ingenol mebutate gel (0.015% and 0.05%): Simultaneous group: N=101 Sequential: N=98	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%, sequential 43.6%)	Complete AK clearance at week 8 Percentage reduction in AKs at week 8 Local skin response score after 3 days of first application Adverse events Patient satisfaction (mean TSQM score, 0-100)	Simultaneous vs sequential group <u>Complete AK clearance rate:</u> 52.7% vs 46.9%, p=0.34 Face/scalp: 53.3% 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:	Unclear random sequence generation and allocation concealment Drop-outs: N=9 in the simultaneous 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	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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 mebutate gel from day 1 (Visit 1) and then treated the second area 8 weeks later.				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 groups, most common treatment-related AEs: pruritus and pain at application site <u>Patient satisfaction:</u> mean: 64.6 vs 67.4, p=0.37	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
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% vs 34.5% <u>Adverse events:</u> 29 occurred (5 sAEs, unrelated to treatment): most common: pruritus (5 cases)	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
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 or 6 months.	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
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.	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	Lesion complete response rate at week 8 Participant complete clearance at week 8 Participant partial clearance at week 8	Active vs vehicle Lesion complete response rate: 83% vs 31%; Week 12: 91% vs 25% Complete clearance: 66% vs 11%; Week 12: 73% vs 8%	Unblinded investigator for safety assessments: high risk for performance and detection bias Per protocol analysis was used: intervention: 7 drop-	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	Intervention: 20% ALA or vehicle in combination with visible blue light PDT 14 to 18 hours later.		14 to 18 hours by PDT Follow-up visits: 24 hours, 1,4,8, and 12 weeks following PDT	Application site reactions LSR Adverse events	<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 1.6%, hypertension: 1.7% vs 0%, skin hypertrophy: 1.7% vs 0% <u>Adverse events:</u>113 AEs, 92%: mild/moderate, 7% severe	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.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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 up to 4 weeks.	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) Median time to require the first spot AK treatment: 6.2 months vs 6.0 months	High risk population was under investigation: might overestimate the results No adherence/compliance of participants reported The study was supported by the Office of Research and Development Cooperative Studies Program, US Department of Veterans Affairs	3
Reinhold et al 2016	To evaluate the efficacy, safety and cosmetic outcome of BF-200 ALA	Randomized, double-blind, phase III, multicentre,	n=94 patients were enrolled with 4-8 mild-to-moderate AKs in the face	Patient complete clearance rate	BF-200 ALA vs placebo after a maximum of 2 PDTs:	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
	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± 9 nm) until a total light dose of 37 J/cm² was achieved.	placebo-controlled, parallel-group study Randomization: 2:1 If residual lesions remained at 3 months after treatment, PDT was repeated.	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	Lesion complete clearance rate Histopathologically confirmed response rate Patient partial response % of treatment-emergent AEs in the two groups Local skin reactions Cosmetic outcome at 12 weeks pain (VAS score) patient satisfaction	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-emergent AEs: 100% vs 69% most commonly reported: application site TEAEs: application site pain, erythema, pruritus, scab, exfoliation, oedema and vesicles		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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 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	Multicentre, double-blind, placebo-controlled, parallel-group study	n=195 patients with ≥5 AKs 73% male	Target lesion number scores (TLNS)	Active treatment vs placebo (60 day groups)	N=11 drop-outs: Risk for attrition bias rather low	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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.	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.		Cumulative lesion number scores (CLNS) Lesion total thickness score (TTS) Patient global improvement indices (IGII and PGII) Adverse events	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%, p<0.05 Adverse events:: 10 sAEs: 7 in the active treatment (pruritus, application site reaction, paraesthesia, rash,	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 (measured by comparing expected and actual use of gel and records in the patient diaries) This study was supported by Hyal Pharmaceutical Corporation.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					oedema, contact dermatitis), 6 probably related to treatment; 4 sAEs in placebo group	Statement regarding potential conflict of interest is missing.	
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 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.	Multicenter, randomized, vehicle-controlled, intraindividual, investigator-blinded phase 2 study application of ALA/VEH to both dorsal hands/forearms for 3-hours before blue light treatment Treatment was repeated at week 8 if any AK lesion remained.	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 right extremity were randomized to be occluded or without occlusion during the incubation period.	Median AK lesion clearance rate at week 12 Complete lesion clearance rate at week 12 Subject complete clearance rate at week 12 Subject partialclearance rate at week 12 Subject satisfaction Tolerability/safety	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%, 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>	Participants were not blinded: performance bias likely Unclear random sequence generation and allocation 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	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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, 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	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
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 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.	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±8.60	average number of lesions before and after treatment average reduction of lesions Investigator and Patient Global Improvement Scores (modified versions) Adverse events	Diclofenac vs 5-FU <u>average number of lesions before and after treatment:</u> <u>diclofenac</u>: 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 <u>Investigator 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:	Small sample size 3 drop-outs in 5-FU group: Risk for attrition bias unclear Study is underpowered, estimated sample size was 52 patients. No information regarding patients' compliance/adherence provided. Compliance might bias the results Blinded investigator only evaluated photographic pictures Unclear random sequence generation and	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					sign. Higher in 5-FU group	allocation concealment Study was open: performance and detection bias likely	
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 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.	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-lesion" MAL-PDT (LT side) and the other side with 1 session of field MAL-PDT (FT side).	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 side) versus 9 ± 1.2 (FT side)	Participant complete and partial response at 3 and 9 months Mean lesion reduction at 3 and 9 months Mean number of new AKs 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 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>	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
					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 (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	Multicentre, exploratory, open, randomized, prospective, two-armed, observer-blinded phase 2 study	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	5-FU/SA vs cryosurgery <u>Mean change in lesion count:</u> -5.2 vs -5.7	Small patient population Open study: performance and detection bias likely	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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).	Randomization to receive 6 weeks of once-daily topical 0.5% 5-FU/SA, or up to two cryosurgery treatments (3 weeks apart).		posttreatment follow-up) AEs, local skin reactions Physicians global assessment Patients' assessment regarding clinical improvement, and cosmetic outcome	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 frequently in 5-FU/SA group) Physicians global assessment: very good/good outcome: 84.9% vs 83.9% Patients' assessment:	This study was sponsored by Almirall, S.A.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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. Intervention: Application of 0.025%, 0.05%, 0.075% ingenol derivate (LEO 43204) or IMB once daily for 2 consecutive days.	Single-centre, randomized, intrapatient, active-controlled, investigator-blinded Randomization to 0.025%, 0.05% and 0.075% LEO 43204 gel (ingenol derivate) and 0.05% ingenol mebutate gel, application once daily for 2 consecutive days	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 All patients had previously been treated for AKs, predominantly cryosurgery	LSR_{max} Score Mean LSR Score (range 0-24) Adverse events % change in the number of visible AKs Clearance rate	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 treatments) <u>Mean LSR_{max} score:</u> 9.2 vs 10.1 vs 11.2 vs 10.0 <u>Most frequent AEs</u> (across all treatments), N=172 AEs: application site pruritus (82%),	High-risk cohort (95% had previous history of skin cancer), results are limited to this study and population Intrapatient design reduces the risk for confounding Unclear random sequence generation and allocation concealment	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
			95% had a previous history of skin cancer		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%	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 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	Randomised, active-controlled, parallel-group study. Randomization of face/scalp to receive either application of ALA for 1 hour followed by activation with blue	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 Complete lesion clearance: 50% vs 50% vs 8% Partial clearance: 75% vs 75% vs 42%	Small sample size Unclear risk of random sequence generation and allocation concealment Lost to follow-up: N=1 (intolerance	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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 4 weeks.	light (Blue) or 595 nm pulsed dye laser (PDL-PDT) or topical 5-FU 0.5% cream (once or twice daily for 4 weeks).			<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 average score for crusting and erosion peaked at visit 3 for 5-FU (2), other treatments below 0.3	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 given except for stinging: selective reporting bias very likely. This study was supported by DUSA laboratories. Statement regarding potential conflict of interest is missing..	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
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 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)	Histological clearance rate Patient complete clinical clearance % of lesions cleared Physician's and subject's reported assessment Tolerability Safety/adverse events	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 at week 20</u>:74.5% vs 54.6% vs 35.5% <u>Physicians reported assessment:</u> Very good/good: at week 20: 54.9% vs 92.0% vs 73.8% <u>Subject's reported assessment</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
					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 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.	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-	Lesion recurrence rate Clinical improvement Patients assessment	5-FU/SA group vs vehicle vs diclofenac/HA: Lesion recurrence rate: 85.8% vs 79.8% vs 81.0% (12 months)	See Stockfleth 2011	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	Intervention: 0.5% 5-FU/SA once daily, its vehicle or diclofenac/HA twice daily for a maximum of 12 weeks.		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)	Recommendation of the treatment Side effects	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% 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.	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	Participant complete clearance rates at 14 weeks Participant partial clearance rates	Imiquimod (PP analysis) Participants complete clearance rate: 84% (95% CI: 64-95%)	Drop-outs: N=16, 25 patients remained in the group treated with imiquimod and 11 in the control group: moderate risk for attrition bias	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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.		Mean age: 68 years, range: 45-85	Local skin reactions Adverse events Recurrence Compliance	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 both group	Results are only presented for experimental group, not for the control group LSR and AEs were presented graphically Unclear random sequence generation 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	Randomized, multicenter, double-blind, vehicle-controlled study Randomization 2:1 (5-FU:vehicle)	n=166 patients Mean age: 72.2 years±7.1 87.7% male N=111 received 5-FU/SA,	Complete clinical clearance 8 weeks after EOT Partial clearance 8 weeks after EOT	5-FU/SA vs vehicle Complete clinical clearance: 49.5% vs 18.2% [OR: 3.9 (95% CI: 1.7-8.7), p=0.0006]	Self-application of the treatment: compliance might skew the results Higher incidence of local skin reactions	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	treatment of AK lesions. Intervention: Self-application of 5-FU/SA or verhicle once daily for 12 weeks.	Treatment was self-administered once daily for 12 weeks	N=55 vehicle	Proportional reduction from baseline in the total number of AK lesions per patient Safety Physician Global Assessment mean scores in the DLQI questionnaire (week 12 and 8 weeks after last treatment) Patient satisfaction	Partial clearance: 69.5% vs 34.6% [OR: 4,9 (95% CI: 2.3-10.5), p<0.0001] Proportional reduction from baseline in the total number of AK lesions per patient: 78.0% vs 46.9%, p<0.0001 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	in the 5-FU/SA group might have compromised the blinding of the study This study was funded by Almirall S.A.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					8 weeks follow-up: -0.667 vs -0.133, p=0.0725 <u>Inicidence of treatment-emergent adverse events:</u> 99.1% vs 83.6% Erythema: 88.9% vs 52.7%, pain: 69.4% vs 41.8%, irritation: 59.3% vs 27.3%		
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	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	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	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	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	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	interval between cycles.	interval between cycles.		Adverse events	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> 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,	performance bias likely Data for safety were reported differently in the published record and protocol This study was supported by Graceway Pharmaceuticals LLC.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					application site pruritus, fatigue, and nausea) Local skin reactions: greater incidence of patients experiencing LSRs, and severe LSRs, with increasing imiquimod 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	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:	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	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	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	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
	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 treatment period was followed by 2 weeks without treatment and then a compulsory second 2-week treatment period.	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	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 absolute reduction in AK lesions from baseline to EOS	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% 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	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	See lebwohl et al. 2004 and Swanson et al. 2010	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	three-week cycles of daily dosing. 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.				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.		
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)	Resiquimod 0.01% vs 0.03% vs 0.06% vs 0.1% Overall complete clearance rates: 77.1% vs 90.3% vs 78.1% vs 85.3% Complete clearance rates PP: 78% vs 95% vs 76% vs 92% Complete clearance rates after course 1:	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	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
				Discontinuation rate due to adverse events or local skin reactions Incidence of severe adverse events and local skin reactions (possibly treatment-related)	40.0% vs 74.2% vs 56.3% vs 70.6% Overall partial clearance rates: 63% vs 81% vs 63% vs 76% Discontinuation due 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%	suggestion that intensity of local skin reactions may have an association with 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	Multicentre, randomized, double-blind, vehicle-controlled, parallel-group study	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	Imiquimod vs vehicle Participant complete clearance rate: 57.1% vs 2.2%, p<0.001	ITT analysis was used, but some lost to follow-up participants were missing for the description	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	and balding scalp including pretreatment and posttreatment biopsy specimens. Intervention: Application of imiquimod 5% cream or vehicle cream once/day, 3 days per week for 16 weeks	Randomization to either imiquimod 5% cream (N=147) or vehicle cream (N=139).		weeks post-treatment Local skin reactions/ Adverse events	<u>Partial clearance rate:</u> 72.1% vs 4.3%, p<0.001 <u>Adverse events and local skin reactions:</u> 70.7% vs 48.2% of which 46.3% vs 11.5% were application site reactions <u>Incidence of sever AEs:</u> 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	10 dropouts in the intervention group, 18 drop-outs in the control group: attrition bias likely Not all skin quality outcomes were 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	Multicentre, randomized, double-blind, placebo-controlled, parallel-group study	n=115 participants 91 men, 24 women Age range: 41-90	Participant complete response rates at 3 months after last treatment	MAL PDT vs placebo PDT <u>Participant complete response rate:</u> 68.4% vs 6.9%,	Unclear allocation concealment. This study was supported by Photocure ASA.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	treatment of multiple AKs. Intervention: Application of MAL or placebo cream 3 hours before illumination with noncoherent red light (LED); treatment was repeated 1 week later.	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.		Lesion complete response rates at 3 months post-treatment Adverse events Local skin reaction	OR=39.5, 95% CI: 10.5-149.2, p<0.001 <u>Lesion complete response rates:</u> 83.3% (95% CI: 79.3-86.7%) vs 28.7% (95% CI: 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),	Statement regarding potential conflict of interest is unclear.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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 AK with BF-200 ALA vs placebo. Intervention: Illumination was performed 3 h after the application of the gel with a 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.	Multicentre, randomized, double-blind, placebo-controlled, interindividual, two-armed study Randomization to BF-200 ALA (N=81) or placebo (N=41).	n=122 participants with 4-8 mild to moderate AK lesions 105 men, 17 women Mean age: 71 years, range: 57-85	Participant complete clearance rate Lesion complete clearance rate Local skin reactions Adverse events Cosmetic outcomes	PDT BF-200 ALA vs placebo PDT <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:	Use of light source depends on the study centre: 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.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					(96% and 99%, respectively, PhotoDyn: 53% vs 70%) <u>Cosmetic outcome</u> (investigator-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		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Incidence of pain, itching and burning was much higher in subjects irradiated with the Aktilite, severe symptoms 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/foreahead and burning on the bald scalp		
Tanghetti et al 2007★	To compare the efficacy and tolerability of	Multicentre, randomized, assessor-blinded,	n=36 patients with ≥4 AKs	Total AK count (baseline and week 24)	5% 5-FU vs imiquimod <u>Total AK count:</u>	Lack of sociodemographic information of patients	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	imiquimod with 5-FU. Intervention: Application of 5% 5-FU twice daily for 2-4 weeks or imiquimod 5% cream twice weekly for 16 weeks.	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		Mean % reduction in lesion counts at week 24 Participant complete and partial (<66%) clearance Physician's grading of erythema Local skin reactions Mean scores for patients discomfort (1-4, 1=very painful)	Baseline: 646 vs 490 At week 24: 40 vs 167, p<0.05 Mean % reduction in lesion counts: 94% vs 66%, p<0.05 Participant complete clearance: 84% vs 24%, p<0.01 Participant partial clearance: 100% vs 53% Local skin reactions: similar: 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	Unclear random sequence generation and allocation concealment Performance bias likely: dosing scheudles 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
					remained mild the entire time of treatment (investigator assessment) <u>Mean scores patients' perception of discomfort:</u> 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 <u>Lesion complete response rate:</u> 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%)	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	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Participant complete clearance rate: 89% (95% CI: 81-94%) vs 80% (95% CI: 71-87%) 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	This study was supported by PhotoCure ASA. Statement regarding potential conflict of interest is missing.	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					the lesions in each treatment group		
Taub et al 2011	To compare the efficacy and tolerability of PDT using 20% 5-ALA and blue 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.	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 treatment Partial reduction in lesion count (50%) Subject satisfaction Adverse events	20% 5-ALA vs vehicle <u>Mean lesion count reductions:</u> 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	Small sample size Intrapatient design reduces the risk for confounding 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.	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
Thompson et al 1993★	To examine the effect of the regular use of sunscreen on the appearance of new solar 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.	Single-centre, randomized, placebo-controlled, parallel group study Study was conducted in Australia	n=588 white participants randomized, 431 evaluable participants 180 men, 251 women Mean age: 63 years, range: 40-93 N=210 subjects in the base-cream group (vehicle), N=210 subjects in the sunscreen group	Mean reduction/increase in lesion counts at 7 months Mean % of lesions remitting throughout the study New lesions Participants' compliance	Sunscreen group vs base group <u>Mean reduction/increase in lesion counts:</u> -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) <u>Mean % of lesions remitting throughout the study:</u> 25% vs 18% <u>New lesions:</u> 333 vs 508 (1.6 vs 2.3 mean lesions per subject) <u>Compliance:</u> 81% of pat. reported applying the cream daily for at least 80% of the study	Unclear allocation concealment, blinding of outcome assessment was not stated: unclear 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	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					period; no difference in the amount of cream used by the two groups	and cancer Foundation, 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.	
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	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
						Lack of information regarding patients compliance Standard deviations associated with mean values were not provided: high risk of selective 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	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	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%	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.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	three consecutive days per week for 16 weeks.	days per week for 16 weeks.			Possibly/probably related AEs: Imiquimod: application site reaction (5/29), fatigue 81/29), headache (1/29), diarrhea (1/29), nausea (1/29), rash (1/29), skin disorder (1/29), and leucopenia (1/29) Erythema and ersosion were mild to moderate	This study was supported by 3M Pharamceuticals.	
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	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 week and 24 months Average % reduction of lesions at 20 weeks	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%	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'	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	weeks to adefined are of 50 cm.			Recurrence rate Adverse events	<u>Average % reduction in the individual lesion count:</u> 53% vs 17% <u>Recurrence rate:</u> 55% after an average of 9.3 months <u>Adverse events:</u> mild to moderate erythema, desquamation, itching, inflammation, edema	adherence or compliance to the study medication: over/underestimation of the results might be possible. Discrepancy in the number of participants completely cleared between abstract and report: selective reporting bias likely This study was supported by Shire Pharamceuticals.	
Von Felbert et al 2010★	To compare pain intensity, efficacy, safety and cosmetic outcome of MAL-PDT with two different light sources in an investigator-initiated, randomized, double-blind study.	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 maximum pain (VAS score) Cosmetic outcome	VIS + wIRA PDT (with spray cooling) vs VIS + wIRA PDT (without) vs LED PDT with spray cooling vs without spray cooling <u>Complete clearance rate:</u>	Unclear random sequence generation and allocation concealment. Attrition bias likely: PP analysis was used, 1 drop-out in the intervention	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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.			Adverse events and local skin reactions	*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	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 AK on the balding scalp (25cm²-250cm²).	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	Percentage reduction in AK count from baseline Complete and partial clearance at week 8	0.037% vs 0.05% vs vehicle: Reduction in AK count: 72.7% vs 78.5% vs 12.6%, p<0.001, no stat. difference between	Only men participated: results of this study are only limited to this population and might not be generalizable.	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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 Randomisation: 2:2:1 to receive ingenol disoxate 0.037%, 0.05% or vehicle gel once daily for two consective days	n=163 were reandomised 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.	Patients satisfaction (Treatment Satisfaction Questionnaire for Medication TSQM score at week 8, range 0-100) Local skin responses Adverse events	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 for both doses of	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
					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 moderate AEs within		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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= most commonly reported AE, usually	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 not provided: selective reporting bias likely	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					mild to moderate; dryness, burning and erythema were the most commonly reported clinical signs and symptoms of facial irritation in all groups.	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 application of a sunscreen of sun protection factor 20, MAL was applied to the entire treatment area. Immediately after, patients left the clinic 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) Local adverse reactions: erythema and pustular eruptions	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 <u>Mean pain score during dPDT:</u> 1.3±1.5, decreased to 0.5±0.7 the day	Blinding was not stated, participants were exposed to light for different periods of time: performance bias likely Additional outcomes were reported that were not describe in the methodological part: unclear risk of selective reporting bias This study was supported by	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	exposed themselves to either 1.5 hours or 2.5 hours of daylight.			Participant's satisfaction	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 Increased severity of erythema was related to an increased light dose	Department of dermatology, Bisebjerg Hosptal, Copenhagen	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					(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 study. Intervention: After gentle lesion preparation and application of a	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 Complete response	Grade I vs grade II vs grade III: <u>Mean lesion response rate:</u> 75.9% vs 61.2% vs 49.1% (p<0.0001) No difference between 1.5h and 2.5h groups	This study was supported by Department of dermatology, Bisebjerg Hosptal, Copenhagen Blinding was not stated, participants were exposed to light for different	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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.				Complete response: 73% vs 63% vs 55% Complete response rate: 75.9% vs 61.2% vs 49.1%	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 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.	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 Lesion complete response rate Mean complete response rate according to AK grade Pain scores Erythema scale	16% MAL-dPDT vs 8% MAL-dPDT <u>Mean reduction in lesion count:</u> 75% vs 79% <u>Absolute decrease:</u> 429 vs 420 <u>Lesion complete response rate:</u> 76.9% vs 79.5%, p=0.37 <u>Mean complete response rates:</u> grade I: 80.2%,	Intrapatient design reduces the risk for confounding Number of participants and average time spent 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	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	Immediately after, patients left the hospital with instructions to spend the remaining day outside at home in daylight.			Participant's preference	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 the two groups Preference: 17 patients had previously been treated with conventional PDT, 12 (71%) preferred dPDT	Linear association was found between increasing light dose and increasing response rate (p=0.005, r^2=0.27)	
Wiegell et al 2008★	To compare response rates and	Single centre, randomized,	n=30 patients 23 men, 7 women	Mean and absolute reduction in lesion	Daylight vs LED	The 2 treatments were physically	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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 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.	assessor-blind, active-controlled, intraindividual study	Mean age: 78 years, age range: 63-90	counts at 3 months post-treatment Pain (scale: 0-10) Adverse events Participant's preference	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 severe in the sun-exposed area in 10 patients (42%), in the LED area in 5 patients (21%) Preference: 62% daylight exposure, 14% LED	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 Memorial Foundation.	
Wolf et al 2001★	To explore the therapeutic	Multicentre, randomized,	N=120 patients were enrolled, 118	TLSN (target lesion number score)	Active treatment vs placebo	Unclear random sequence	2

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	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.	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).	received treatment, 117 analysed hepp	CLNS (cumulative lesion number score) Investigator improvement indices (IGII) Patient improvement indices (PGII) Adverse events	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 (pruritus: 55% vs 49%, application site reaction: 34% vs 20%, dry skin: 36% vs 17%)	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 This study was supported by Hyal Pharmaceutical Co. Statement regarding potential conflict of interest is missing.	
Zane et al 2016	To compare treatment outcomes of MAL-PDT and IMB.	Single-centre, randomized, open-label,	n=35 patients with 437 lesions Mean age: 68.0 years, range: 52-90	Complete lesion response at 3 months	IMB vs MAL-PDT	Clear description of the IMB intervention is not provided (e.g.	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	Intervention: Two symmetrical contralateral areas with a similar number of AKs were either treated with a single session of conventional MAL-PDT or 3 days of daily application of IMB.	intraindividual, split-face study Randomization of two symmetrical contralateral areas with a similar number of AKs to 3 days of an IMB treatment cycle or a single session of MAL-PDT.	34 men, 1 woman	Mean % reduction at 3 months Participant complete response at 3 months Pain (mean VAS score) Local skin reaction (LSR) score Cosmetic outcome Patient preference Time to healing (days)	Complete lesion response: 62.9% vs 67.1%, n.s. Mean % reduction: 65.8±33.0 vs 67.6±31.2, n.s. 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%	dosage): selective reporting bias likely Small sample size 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	

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Time to healing: 12.91±4.86 vs 8.20±2.75, p<0.01		
Zane et al 2014a	To compare the treatment results and cost-effectiveness of MAL-PDT and 3% diclofenac plus 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.	Single-centre, open-label, prospective, nonsponsored, randomized controlled clinical trial Randomization 1:1 (MAL-PDT:DHA, N=100 in each arm)	n=200 patients with 1674 AKs 58 women Age range: 42-93	Overall lesion response rate Patient complete remission rate/partial remission rate after 90 days Cosmetic outcome (patient- and investigator-assessed) Patients' overall satisfaction	MAL-PDT vs DHA Overall lesion response rates: 85.9% vs 51.8%, p<0.0001 Patient complete remission rate: 68% vs 27% Patient partial remission rate: 30% vs 48%, p<0.0001 Cosmetic outcome: 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%	Study was open: performance and detection bias likely 42 patients needed 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	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					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 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	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 an scalp (543 AKs total) 72 women Age range: 39-98	Lesion complete remission (after 90 days) Participant complete and partial remission (after 90 days) Recurrence rate Cosmetic outcome (patient- and investigator-assessed) Patient satisfaction	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)	Study was open: performance and detection bias likely	3

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
	frozen rim was achieved. Laser: A single session of CO^2 laser ablation 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.			Safety	At 12 months: 53 vs 14 <u>Recurrence rate:</u> 27.4% vs 78.1%, p<0.0001 <u>Cosmetic outcome:</u> *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 <u>Patient satisfaction:</u> fair: 0% vs 18.4% Good: 40.2% vs 57.1% Excellent: 59.8% vs 24.5%, p<0.0001		

Study	Aims and intervention	Design	Population	Outcomes	Results	Comments and methodological assessment	LoE
					Safety: cryotherapy: erythema, edema, hemorrhagic vesicles and blisters, erosions, crusts 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)

- Berlin 2008†
- Campione 2010
- Dragieva 2004†
- Galitzer 2011
- Grimaître 2000
- Jenni 2016†
- Lawrence 1995
- Nguyen 2016
- Perras 2004†
- Puviani 2017

Defined efficacy outcomes not reported, outcomes unclear (n=45)

- Babilas 2007
- Babilas 2008
- Braathen 2009
- Buinauskaite 2014
- Buinauskaite 2013
- Calzavara-Pinton 2016
- Carducci 2015
- Choi 2015†
- Choi 2017†

Combination therapies assessed (n=34)

- Alexiades 2017
- Bercovitch 1987
- Berlin 2008†
- Berman 2014a
- Berman 2014b
- Choi 2015†
- Choi 2017†
- Dragieva 2004†
- Eibenschutz 2016
- Goldenberg 2013

No original data reported, doublettes (n=3)

- Gupta 2015
- Swanson 2013†
- Perras 2004†

Small sample size (n=1)

- Seckin 2009

- Scarpa 1970
- Serra-Guillen 2009
- Thai 2004
- Weiss 2013
-
- Deonizio 2011
- Di Nuzzo 2015
- Edwards 1990
- Edwards 1986
- Ericson 2004
- Faghihi 2016
- Falagas 2006
- 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
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- Togsverd-Bo 2012
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4.1.6. Literature

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4.2. Question III.2. For which patients should preventive measures be recomended?

(Frage III.2. Für welche Patienten sind welche präventiven Therapiemaßnahmen geeignet?) Verweis auf Präventionsleitlinie

5. Working group: Squamous cell carcinoma treatment

(AG Therapie des PEK)

5.1. Question IV.1. Which treatment is recomended for the primary tumor?

(Frage IV.1. Welche Therapie des Primärtumors wird empfohlen?) Beantwortung durch

5.2. Question IV.2. Should sentinel lymph node biopsy be recomended? In which cases?

(Frage IV.2. Ist die Entfernung des Wächterlymphknotens indiziert? In welchen Fällen?) Beantwortung durch Systematische Recherche

5.2.1. PICO

PICO – Scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Patients with SCC	Sentinel lymph node biopsy	Observation	Efficacy (diagnostic accuracy)

5.2.2. 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) Update 30th May 2017	122 127
Remarks and notes:			

5.2.3. Selection criteria

Literature selection	
Number of total results	127
Inclusion criteria	Clinical trails (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	21
Number of full texts reviewed	*15*

5.2.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Ahmed et al 2014	Analyze the feasibility and reliability sentinel lymph node biopsy (SLNB) for cutaneous head and neck SCC (HNSCC). Identify risk factors associated with a positive SLN.	Systematic review; n= 221 articles; were screened of these 11 publications with 73 patients were selected; 3 case series; 8 prospective cohorts.	MEDLINE, PubMed, Cochrane, and ASCO databases searches conducted (1946-2013).	Analyze the feasibility and reliability SLNB for HNSCC. Identify risk factors associated with a positive SLN.	Studies ranged from 1 to 15 patients (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.		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Tumor diameter was not associated with SLN status (P = .09; 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		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					for a tumor localized at a high-risk area were 72.63%, 100% and 96.74%, 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.		
Demir et al 2011	To evaluate and identify the role of lymphocintigraphy and sentinel lymph node biopsy in patients with high-risk cutaneous SCC	Prospective study; n= 19	Patients with high-risk cSCC treated in one center	To evaluate and identify the role of lymphocintigraphy 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,		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(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				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 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		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 of SLNB for regional staging of SCC on the head and neck (HNSCC).	Retrospective review; n=53	Patients with HNSCC, at high risk for nodal metastasis 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.	Sentinel node (SN) identification rate SLNB positivity rate Local recurrence Regional nodal recurrence Distant recurrence.	In 53 patients with 54 tumors the SN identification rate 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	Rigorous study of SLNB for cutaneous SCC incorporating 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	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 the presence of nodal disease.	specimen for accurate diagnosis. Use of the NCCN guidelines may facilitate identification of patients with SCC at high risk for nodal metastasis.	
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		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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) 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	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 (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		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	factors should be considered “high-risk,” and to decide whether a randomized controlled trial is feasible.				controlled trial with 80% power to detect a significant difference in DFS.		
Hirshoren et al 2017	To describe the clinical outcomes and prognostic factors for patients with node-positive cutaneous head and neck SCC (cHNSCC) who underwent lymphadenectomy.	Retrospective single center study; n=149 lymphadenectomies	Patients with node-positive cHNSCC treated surgically at a single tertiary center between June 1, 2001, and December 31, 2014.	OS Locoregional control rates Prognostic factors	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		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					nodes divided by the total number of nodes; multivariate analysis [MVA]; HR, 1.13; p = .019).		
Krediet et al 2015	To evaluate risk factors for metastasis in patients with cutaneous SCC (cSCC) in a large cohort study with long-term follow-up and to determine the value of SLNB.	Retrospective review; n= 143	Patients who underwent excision of cSCC between January 2005 and August 2009 at a tertiary referral center	To evaluate risk factors for metastasis in patients with cSCC in a large cohort study with long-term follow-up. To determine the value of SLNB.	The risk for metastases from a cSCC is associated with tumor thickness > 4 mm and tumor 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.		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 Dermatology, Tsukuba University Hospital.	Efficacy of sentinel lymph node biopsy for cSCC. Compared the outcomes with those in cSCC patients who did not undergo concurrent SLNB.	Patients who were followed up for at least 6 months or developed metastases within the follow-up period 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		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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	This is the largest study to date of cutaneous SCC in 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	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 transplant recipients with cutaneous squamous cell carcinoma of the head and neck develop regional lymph node metastasis at a rate of 5%. Regional	extremely poor prognosis makes managing a N0 neck in an immunocompromised patient a difficult clinical dilemma.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 define a high risk cutaneous SCC (HRcSCC) and the feasibility of performing sentinel lymph node biopsy in this group of patients	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 and Spanish	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'' or ''squamous cell carcinoma'' AND ''cutaneous'' or ''skin'' AND ''sentinel lymph node.''	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 metastasis and might benefit from SLNB	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 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		1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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.		
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		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					false-negative results were 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.		
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	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		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Cancer (AJCC) criteria and a recently proposed alternative staging system are most closely associated with positive SLNB findings in non-anogenital cSCC.	(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 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		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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	Embase, CENTRAL, and MEDLINE were searched for published studies, clinical trials, and guidelines on high-risk cutaneous SCC	Patients with high-risk cSCC	To compare two different guidelines (NCCN and AJCC) in what concerns SCC high risk features discrepancies and omissions.	The AJCC TNM staging system considers the following high-risk features when determining the primary tumor (T)	Future studies are required to evaluate the extent to which the inclusion of these additional high-risk features would improve	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	excision, high-grade/desmoplastic lesions, perineural invasion (PNI), lymphovascular invasion, immunosuppression	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, immuno-suppression, depth, recurrence, sirolimus, cyclosporine, azathioprine, sentinel lymph node biopsy, superficial parotidectomy, elective neck		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	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 present. Currently, there is no unanimous consensus on the	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.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		dissection, and Mohs micrographic surgery." All records obtained from our searches were screened by title and abstract for selection.			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 include incomplete excision as a feature warranting a tumor's treatment as high-risk cSCC. As a compounding		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					in cases of cSCC. SNB should be considered in cases where tumor thickness is ≥ 2 mm and actively performed in cases ≥ 5 mm.		

Remarks and notes:

5.2.5. Literature

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5.3. Question IV.3. For which patients should lymph node dissection be recomended?

(Frage IV.3. Für welche Patienten ist welche Lymphknotendissektion zu empfehlen?) Beantwortung durch Systematische Recherche

5.3.1. 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

5.3.2. 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])	15th December 2016 (initial search)	30

Database	Search strategy	Date	Number of results
	("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 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
Remarks and notes:			

5.3.3. 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	12
Number of full texts reviewed	*11*

5.3.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Bergstrom et al 2008	To review the available information on the high risk SCC patients treatment To define patients which may benefit from lymph node dissection	Review	n.a.	n.a.	Staging systems, which accounts only for the horizontal 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	New data from SCC studies help to predict high-risk 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 wich are “bad actors”. The role of HPV in SCC	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					biopsy: elective neck dissection remains the standard of care for invasive SCC of the head and neck.	carcinogenesis continues to be elucidated, and represents a potential approach to targeted therapy and prevention.	
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 (cSCCHN).	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 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		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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 with 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 <		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					.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 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		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 on both clinical and pathological data.		
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 head and neck SCC (HNSCC).	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 is estimated to exceed 20%; however,		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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. Appropriate work-up for occult nodal		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 (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. Fifty-six of 250 patients		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(22%) died from another cause.		
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 patient 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		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients is not justified.		
Takeda et al 2013	To compare pre-surgical aspects data between two groups: patients with lymph node metastasis and patients without lymph node metastasis	Retrospective review; n=164 patients	Patients with cSCC from one center	Detection rate from lymph node metastasis of the SLNB	The following factors were compared 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		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					the sentinel lymph node biopsy of cSCC using the blue dye technique has sufficient detection rates.		
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 per cent, respectively). There was no significant difference in five-year OS (61% vs 57%, respectively) or five-year DFS (74%		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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	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 process for	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients. 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%).	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 whith 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		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					utility compared to observation. Given the current available evidence, a wait-and-see approach is justified in patients with a probability of occult metastases < 19 %.		

Remarks and notes:

5.3.5. Literature

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5.4. Question IV.4. For which patients should adjuvant radiotherapy or post-operative radiotherapy (R1;R2) be recomended?

(Frage IV.4. Für welche Patienten wird eine adjuvante Strahlentherapie bzw. eine postoperative Radiatio (R1;R2) zu empfohlen?)
Beantwortung durch LL Adaption

5.4.1. 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

5.4.2. 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) Update 30th May 2017	116 120

Database	Search strategy	Date	Number of results
Remarks and notes:			

5.4.3. Selection criteria

Literature selection		
Number of total results		120
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		25
Number of full texts reviewed		*18*

5.4.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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 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		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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.	Paterns 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		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					and cause-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 survival rates were 58% and 72%, respectively.		3
Erkan et al 2017	To analyze the outcomes of multimodal treatment entailing the en bloc surgical	Retrospective review; n= 21	Patients with clinical PNI from cHNSCC between the years 2006 and 2012 in one center.	DFS OS	Of 21 patients with clinical PNI from cHNSCC, 7 patients (33%) were previously treated for their disease with primary	The retrospective study of this rare clinical entity	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	resection and post-operative 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			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	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 margins portended poorer survival outcomes in this study.	demonstrates that multimodal treatment can achieve favorable survival outcomes.	
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	Few studies addressed the effectiveness of adjuvant RT in patients who have SCC with PNI.	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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% to 55%, respectively. Adjuvant RT was associated in selected patients with 100% local control.	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.	
Jambusaria-Pahlajani et al 2009	To compare reported outcomes of high-risk SCC treated with surgical monotherapy (SM) with those of surgery plus adjuvant	Systematic review; n= 2,449	Medline reports of high-risk SCC treated with SM or S+ART that reported outcomes of interest: local recurrence, regional or distant	Local recurrence, regional Distant metastasis	There were no controlled trials. Of the 2,449 cases of 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	High cure rates are achieved in high-risk cutaneous SCC when clear surgical	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	radiotherapy (S+ART).		metastasis, or disease-specific death, between January 1, 1980, and June 30, 2006. Case reports containing less than 5 cases were excluded	Disease-specific death.	(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%(po.001), and disease-specific death 1% versus 7% (p=.001).	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 involvement of larger nerves imparting a worse prognosis.	
Lansbury et al 2013	To assess the effects of treatments for non-metastatic invasive SCC of the skin	Systematic review of observational studies; n=118 papers;	Patients with non-metastatic invasive SCC of the skin reported in observational	Effects of treatments for non-metastatic invasive SCC of the skin	Pooled estimates of recurrence of SCCs were lowest after		1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	using evidence from observational studies, given the paucity of evidence from randomised controlled trials.		studies in Medline or Embase, to December 2012.	Recurrence	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 was 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 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		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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).		
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 centrally towards the central nervous system. Patients with incidental PNI have a local control rate of 80% to 90% compared with about 50%	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	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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%.	disease after surgery is high and the chance of successful salvage is modest. Patients with parotid-area node metastases are optimally treated with surgery and postoperativ e RT.	
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	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	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			or carboplatin area under the curve 2).			to undergo surgery.	
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 in 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. 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	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 demonstrate	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 years vs patients not receiving adjuvant therapy: 80 years; p = 0.07) and comorbidities (p = 0.9).	d a favorable RFI/OS in patients with cSCC recurrent disease 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	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						beneficial even in patients presenting with small primary tumors.	
Tang et al 2013	To report outcomes, failure patterns, and toxicity after stereotactic radiosurgery (SRS) for recurrent head and neck cutaneous squamous cell carcinoma with gross perineural invasion (GPNI).	Retrospective study; n=10	Patients from one center, who received SRS as part of retreatment for recurrent head and neck cutaneous squamous cell carcinoma with GPNI, between December 2003 and September 2009.	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 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.	Although there is excellent in-field control with this approach, the rate of out-of-field failures remains unacceptably high. We found that the majority of failures occurred in previously clinically uninvolved CNs often just outside treatment	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						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 (cSCCHN).	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 metastatic involvement of >=2 lymph nodes, positive margins, or extracapsular invasion.	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 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.	For high-risk cSCCHN, adjuvant chemoradiation was associated with a better recurrence-free survival than adjuvant radiation alone.	3
Veness 2005	To discuss the treatment of patients with high-risk cutaneous SCC (cSCC) and, where applicable, also present the current	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		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	role of radiotherapy in the management of these patients				nodes in all patients is inappropriate. Patients with adequately excised and previously untreated lesions are usually not candidates for further treatment. Patients with more 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.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					METASTATIC SCC TO LYMPH NODES: Patients with 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 imperative if early loco-regional recurrence is		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 function is not compromised, re-excision should be considered. If re-excision is not appropriate, a course of adjuvant RT (55–60 Gy) is		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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	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	In patients with metastatic cutaneous head and neck SCC, surgery and adjuvant RT provide the best chance	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			2002 in one Australian center		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 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.	of achieving locoregional control and should be considered best practice.	
Veness et al 2003	To present the experience of one Australian center on treating cutaneous SCC (cSCC) metastatic to cervical non-	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% 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),		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	parothid lymph nodes.				metastatic spread to multiple nodes (p=0.5) and the presence of extra nodal spread (p= 0.01) all predicted for worse survival. Patients undergoing combined modality treatment had a lower relapse rate (15%) and a significant 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 significantly better 5-		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 with cutaneous SCC (cSCC), specifically as it relates to those	Retrospective review	PubMed publications obtained using the search terms ‘‘squamous cell carcinoma,’’ ‘‘cutaneous squamous cell carcinoma,’’ ‘‘radiotherapy,’’	n.a.	There is no strong evidence for or against the use of surgical excision (SE) with ART versus SE alone in the treatment of cSCC with PNI. Certain researchers suggest treating all cSCC with PNI, even microscopic, with		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	CSCCs that undergo perineural invasion (PNI).		and ‘‘perineural invasion’’ for reports dealing with cSCC with PNI.		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.		

Remarks and notes:

5.4.5. Literature

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5.5. Question IV.5. Which treatment is recomended for local or local regional recurrence?

(Frage IV.5. Welche Therapie des lokalen bzw. loko-regionären Rezidivs wird empfohlen?) Beantwortung durch LL Adaption und orientierende Recherche

5.5.1. PICO

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

5.5.2. 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) Update 30th May 2017	171 177

Database	Search strategy	Date	Number of results
Remarks and notes:			

5.5.3. Selection criteria

Literatur 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 approaching therapy in this setting	
Number of results after abstract searching		32
Number of full texts reviewed		*20*

5.5.4. 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	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	Regionally metastatic cHNSCC is an aggressive disease associated with high recurrence rates. Adjuvant therapy may provide clinical benefit but patients	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	rates for patients treated for regionally metastatic cutaneous head and neck SCC (cHNSCC) 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				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 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.	with tumors >2 cm and ECS have poorer OS despite adjuvant treatment.	
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	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	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	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	To identify the survival difference with END compared with observation for patients with a cN0 neck				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% 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%).	routinely performed but was found to be associated with a survival advantage and reduced regional recurrence rate.	
Chen et al 2007	To analyze the management of parotid-area metastasis from	Retrospective study; n=36	Patients treated with radiation therapy for	Local (parotid) control OS	After treatment, 7 patients experienced a subsequent parotid	The present study shows that surgery and postoperative	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	cutaneous squamous cell carcinoma with radiation therapy		cutaneous squamous cell carcinoma involving the parotid-area lymph nodes		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 (parotid) control rate of 86%. OS rate for the entire patient population at 5 years was 63%	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 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)	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	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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	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.	
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	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

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(16.7%). Three out of the 24 patients developed interstitial pneumonia (12.5%).		
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 nodes treated at Westmead Hospital, Sydney	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 median survival of patients was 18.5 months	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 decision not to offer combined treatment may have been related to the concern of surgeon in regards to limb edema.	3
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	One hundred six patients had 412 primary invasive cSCC. Eighty-five percent were AJCC-7 T1, and 15% T2. Risks of NM and PO	Low T-stage cSCC account for most poor outcomes. Brigham and Women's Hospital staging criteria better risk stratifies	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				To report poor outcomes	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.	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 immunocompromised patients. Better risk stratification of low T-stage cSCC in immunosuppressed 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	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						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 rates ranged from 50% to 61% in imaging-positive patients and from 86% to 100% in imaging-negative patients	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 render their results and conclusions difficult to validate or compare	3
Harris et al 2017	To evaluate which factors are predictive of	Retrospective review; n=212	Patients with cHNSCC treated between January	5-years DFS DSS	A total of 212 patients met inclusion criteria,	For advanced cHNSCC, patients with recurrent	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	recurrence and nodal spread and survival in patients with cutaneous head and neck SCC (cHNSCC) treated surgically		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.	OS Associations of patient and tumor characteristics with recurrence and survival Factors independently associated with the presence of nodal metastasis at presentation	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 disease, perineural invasion (PNI), and poorly differentiated histology were independent predictors of recurrence. On multinomial logistic regression, patients with primary tumors	disease, PNI, and poorly differentiated tumors are at 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.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 patient cohort.		
Hong et al 2005	To present diagnostic methods, interval between index lesion and metastasis, treatment methods, and outcome	Retrospective review; n=20	Patients confirmed to have parotid bed metastases of squamous cell carcinoma treated in the University of Wisconsin Tumor Registry and Head and Neck Oncology Tumor Board, during a period of 10y from 1989 to 1999	Treatment Recurrence Survival	After diagnosis of parotid bed metastases, 14 (70%) of 20 patients underwent primary surgery with postoperative radiotherapy to the parotid bed and ipsilateral neck. Three patients (15%) manifested local recurrence in the parotid bed during their follow-up	Most patients in this series underwent superficial parotidectomy, with total parotidectomy reserved for the 20% of patients with partially fixed lesions or preoperative facial nerve involvement. This rationale is based on several studies,	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					period. The minimum follow-up time for patients in this series was 24 months. Cumulative OS was 12 of 20, or 60%.	which have demonstrated that most intraparotid lymph nodes lie lateral to the facial nerve.	
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 49 months. No survival differences emerged between	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
					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 recurrence and distant failure	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
					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		
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 cHNSCC had	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	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					dramatically lower outcomes	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 statistically significantly with P stage. The 5-year DSS rate was 68%.		3
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 cutaneous SCC 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	Limitations: Single institution retrospective design and changes in technology overtime. Radiologic imaging of high-stage cSCC may influence	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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.	management and appears to positively impact outcomes. Further prospective studies are needed to establish which patients benefit from imaging.	
Schweinzer et al 2017	The aim of this retrospective study was to investigate whether the use of immunohistological staining (immuno-histochemistry, IHC) with anti-cytokeratin AE1/AE3 anti- body in 3D-histology-controlled excisions	Retrospective review; n=116 patients with histological con-firmed DSCC; 18 samples included	Patients with histological confirmed DSCC who underwent surgery at the Tuebingen University Hospital/Departmen t of Dermatology between 01/2006 and 12/2014	Local recurrence rate Early diagnosis	In 55.6% (n = 10), the margins of 3D-histology still showed no evidence of neoplastic lesions in both stainings. In contrast, we found neoplastic lesions in 5 of 18 cases (27.8%) with cytokeratin AE1/AE3		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	can help to detect extensions of the lesion and to reduce the rate of local recurrence in comparison to conventionally used H&E-staining in patients with desmoplastic SCC (DSCC)				staining, while H&E-staining remained negative. In addition, neoplastic lesions were found in both, H&E as well as cytokeratin AE1/AE3 staining in three cases (16.7%). The data presented show improvement of diagnosis in 27.8% of cases using IHC and 3D-histology. This method is suitable to improve the diagnosis of DSCC.		
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	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	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:	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,	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	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	measures, surgical options, and adjuvant therapies for high-risk cutaneous SCC (cSCC).	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, superficial parotidectomy, elective neck dissection, and Mohs micrographic surgery.” All records obtained from our		Tumor size Depth of invasion Recurrent setting Poorly differentiated lesions Histopathological subtype Perineural invasions Lymphovascular invasion High-risk anatomical location Immunosuppressed sate Incomplete excision	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 present. Currently, there is no unanimous consensus on the high-risk features of cSCC. Although NCCN Guidelines and the AJCC TNM	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.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		searches were screened by title and abstract for selection.			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 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.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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 in 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. Patients with adjuvant treatment demonstrated a 5y-RFI and OS rate of 78 and 79 %, respectively, while	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 adjuvant radiotherapy. Locoregional metastases in the lymphatic basin might be more frequent than	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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:	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
					76 years vs patients not receiving adjuvant therapy: 80 years; p = 0.07) and comorbidities (p = 0.9).		
Stratigos et al 2015	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 cSCC is excellent, with an overall five-year cure rate of greater than 90%, which is much	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 are based on current standards of	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					better than other SCCs of the head and neck area	care, existing guidelines and expert panel opinion	
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	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						imaging findings, we did not score such instances as GPNI.	

Remarks and notes:

5.5.5. Literature

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5.6. Question IV.6. Which treatment is recomended for patients with metastatic disease, in first and second line?

(Frage IV.6. Welche Therapie wird für Patienten im fernmetastasierten Stadium (First- und Second Line) empfohlen?) Beantwortung durch De novo Recherche

5.6.1. PICO

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

5.6.2. 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) Update 30th May 2017	114 120
Remarks and notes:			

5.6.3. Selection criteria

Literature selecti	
Number of total results	120
Inclusion criteria	Trials evaluating therapy in locally advanced SCC (Seiwert et al , Chow et al) 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 neoadjuvant or adjuvant therapies,
Number of results after abstract searching	37
Number of full texts reviewed	*28*

5.6.4. 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 Head and Neck	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-year Kaplan–Meier projections for OS for Arm A versus Arm B were 48% versus 50% (P =0.55)	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 be	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						pointed out that this study did not address the role of primary surgical resection in the management of these patients.	
Bauml et al 2017	To evaluated pembrolizumab, an anti-programmed death 1 receptor antibody, in this platinum- and cetuximab-pretreated population with poor prognosis (Keynote 055)	Multicenter, phase II, single-arm study; n=171	Eligible patients were ≥18 years old with confirmed recurrent or metastatic HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx resistant to both platinum and cetuximab. Concurrent platinum and cetuximab treatment was not required, but patients were required to have had progressive	ORR Safety	75% of the patients received two or more prior lines of therapy for metastatic disease, 82% were PD-L1 positive, and 22% were HPV positive. At the time of analysis, 109 patients (64%) experienced a treatment-related adverse event; 26 patients (15%) experienced a grade ≥3 event. Seven patients (4%) discontinued treatment, and one died of treatment-related adverse events. Overall response rate was 16% (95% CI, 11% to 23%), with a median duration of response of 8 months (range, 2+ to 12+ months); 75% of responses were ongoing at the time of		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			disease or recurrence within 6 months of the last dose of each therapy. Additional eligibility criteria included measurable disease, provision of newly obtained core or excisional biopsy for PD-L1 expression analysis, Eastern Cooperative Oncology Group performance status of 0 to 1, and adequate organ function.		analysis. Response rates were similar in all HPV and PD-L1 subgroups. Median progression-free survival was 2.1 months, and median OS was 8 months. Pembrolizumab exhibited clinically meaningful antitumor activity and an acceptable safety profile in recurrent or metastatic HNSCC previously treated with platinum and cetuximab.		
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	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 moderately	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	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	with aggressive skin SCC.				tolerable; 29% of patients in the treatment arm required dose reductions for grade 3 or 4 toxicities	available retrospective data from M.D. Anderson Cancer Center (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 end point or to detect a significant difference between arms in either recurrence or SPT alone,	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						limiting the interpretation of our results	
Buglione et al 2017	To report a subgroup analysis primarily focused on human papillomavirus (HPV)-related oropharyngeal cancer (OPC) from the Cetuximab Plus Radiotherapy Versus Cisplatin Plus Radiotherapy in Locally Advanced Head and Neck Cancer (CTXMAB+RT;NCT01216020) trial comparing radiation therapy with concomitant cisplatin (CDDP) versus concomitant cetuximab (CTX) as first-line treatment of locally advanced head and neck cancer.	Sub-group analysis of an open-label randomized phase II study; n=30	Patients included in CTXMAB+RT trial	Locoregional control (LC) metastasis-free survival Cancer-specific survival (CSS) OS Re-analysis of severe and fatal infectious complications to more thoroughly investigate the association between CTX treatment and potentially life-threatening reactions.	A total of 33 patients had OPC. The HPV status was available for 30 of the 33 patients. Thus, 3 patients treated with CDDP but with unknown HPV status were excluded from the survival analysis. The small number of patients in each group did not allow for significance to be reached for any of the outcomes analyzed. A trend favored the CDDP arm in the p16-positive group for the 2-year LC and OS/CSS rates (100% vs. 72.9% and 100% vs. 77.8% for CDDP vs. CTX). In this group of patients, the hazard ratio for the treatment arm (CTX vs. CDDP) was 4.7 (95% confidence interval [CI] 0.5-40.3) for LC, 3.4 (95% CI 0.4-30.5) for OS, and 2.4 for CSS (95% CI 0.2-23.2). A survival benefit favoring the CDDP arm was not evident in the p16-negative OPC group or for	In patients with p16-positive OPC in the CTXMAB+RT trial, CTX had lower efficacy than CDDP, with possible implications for treatment selection in this clinical setting.	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients with cancer located in other sites. Serious or fatal infectious complications occurred only in the CTX arm.		
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 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)	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 (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).	Although response data for our experimental arm look encouraging, the hypothesis of a 35% activity, expressed as capability to induce a CR, cannot be accepted according to our statistical methods. The achievement of a CR following primary chemo-therapy is an important prognostic factor for	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						these patients, and, if a survival advantage is to be expected with induction chemo-therapy followed by locoregional treatment, the achievement of a CR after primary chemotherapy is an important step.	
Chow et al 2016	The aim of the current study was 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 and neck SCC	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 of response was not reached (range, > 2 to > 11 months).	A limitation of this study is the lack of a consistent method used to determine HPV status. HPV association was determined by the site	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(HNSCC) expansion cohort of the KEYNOTE-012 trial				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.	investigator by using the method 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	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						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 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 dis-	Although patient numbers in the older subgroup were smaller than the overall population and younger subgroup (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	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					continuations were observed with afatinib (each sub-group 7% versus 16%). A trend toward improved time to deterioration of global health status, pain, and swallowing with afatinib was observed in both subgroups.	no indication that the benefit observed with afatinib would be adversely affected by advancing age	
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	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						endpoints). More-over, the longer follow-up has blunted the differences in outcome that were originally observed. We are unable to analyze 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		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						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, 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 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.		2
Fonseca et al 2005	The present study compares the efficacy and safety of a new	A randomized phase II study; n=83	Chemotherapy-naıve patients	Overall response rate	Among 76 patients evaluable for response, the overall response rate in arm A was	In conclusion, in our phase II trial, both schedules,	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	combination of cisplatin/docetaxel versus the 5-FU + cisplatin regimen in patients with squamous cell carcinoma of the head and neck (SCCHN)			Median survival	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 neutropenia (34.1%) and diarrhea (9.8%) versus mucositis (29.3%) and neutropenia (19.5%) in arm B	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 combination, justify further evaluation of those chemotherapy combinations in major patient populations. Both schedules are well tolerated, with	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						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 completed at least 4 weeks before study entry. Patients could not have been previously treated with irinotecan or bortezomib.	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 addition of irinotecan at 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	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						hypothesis (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.	
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,	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	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%,		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	unresected, stage III/IV non-metastatic SCCHN			year, objective response rate, progression-free survival, OS, and safety and tolerability	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.		
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 survival figures were 54 and 64% of groups A and B, respectively however, the 2-year OS figures were 56 and 67%, respectively	Although group B showed statistically significant better progression free and OS, the differences between the survival figures were not enormous.	2
Harrington et al 2013	To assess the activity and safety of concurrent	Randomized Phase II study; n=67		Survival	CRT dose intensities were unaffected by lapatinib: median radiation dose 70 Gy	Prior to the study, the consensus	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	chemoradiotherapy (CRT) and lapatinib followed by maintenance treatment in locally advanced, unresected stage III/IVA/IVB head and neck cancer				(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, with the exception of 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 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]).	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)	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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. 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).	This study has established the recommended phase II dose of lapatinib as 1,500 mg/d when combined with chemoradiotherapy in patients with LASCCHN. Further more, this dose is associated with an acceptable tolerability profile, similar to that observed with chemoradiotherapy alone. Given these findings, randomized phase II and III studies of lapatinib plus chemoradiothe	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						rapy have been initiated in LA SCCHN	
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 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.	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	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						cisplatin arm in this study, especially the three patients suffering acute renal failure, does not fully reflect the experience at our institution with this drug	
Magrini et al 2016	To compare radiotherapy (RT) with concomitant cisplatin (CDDP) versus concomitant cetuximab (CTX) as first-line treatment of locally advanced HSCC in terms of compliance, toxicity, and efficacy.	Non-profit, phase II, multi-institutional, prospective, open-label, randomized trial; n=70 Patients were randomly assigned in a 1:1 ratio to receive either CDDP 40 mg/m2 once per week or CTX 400 mg/m2 as loading dose followed by CTX 250 mg/m2 once per week concomitant to radical RT.	Eligibility criteria included an age of 18 years or older; histologically confirmed diagnosis of stage III (excluding T1N1), IVA, or IVB squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or supraglottic larynx; Eastern Cooperative Oncology Group performance status of 0 or 1; and adequate	Local RFS Metastasis-free survival Cancer-specific survival OS For primary end points, compliance to treatment was defined as number of days of treatment discontinuatio	The study was discontinued early because of slow accrual after the enrollment of 70 patients. RT discontinuation for more than 10 days occurred in 13% of patients given CTX and 0% given CDDP (P = .05). Drug dosage reduction occurred in 34% given CTX and 53% given CDDP (difference not significant). Toxicity profiles differed between the two arms, with hematologic, renal, and GI toxicities more frequent in the CDDP arm, and cutaneous toxicity and the need for nutritional support more frequent in the CTX arm.		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			hematologic, hepatic, and renal function.	n and drug dosage reduction.	Serious adverse events related to treatment, including four versus one toxic deaths, were higher in the CTX arm (19% v 3%, P = .044). Locoregional control, patterns of failure, and survivals were similar between the treatment arms. CTX concomitant to RT lowered compliance and increased acute toxicity rates. Efficacy outcomes were similar in both arms. These results raise the issue of appropriately selecting patients with head and neck cancer who can benefit from CTX in combination with RT.		
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	This randomized phase II trial showed that erlotinib did not improve The CRR or PFS in patients with locally advanced	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					events, there was no difference in PFS (hazard ratio, 0.9; P =.71).	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 lead to an improvement in outcome compared with	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						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
Rischin et al 2010	Results in a randomized phase II trial with the	Open-label, randomized phase III trial; n=861	Patients with previously untreated stage III	2y OS rate	2-year OS rates were 65.7% for CIS and 66.2% for TPZ/CIS (TPZ/CIS – CIS: 95% CI, -5.9%	No evidence that the addition of	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	hypoxic cytotoxin tirapazamine combined with cisplatin radiation		or IV (excluding T1-2N1 and M1) squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx		to 6.9%). There were no significant differences in failure-free survival, time to locoregional failure, or quality of life	TPZ to chemoradiotherapy, in patients with advanced head and neck cancer not selected for the presence of hypoxia, improves OS	
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 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	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 head and neck. Pembrolizumab showed clinically	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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.	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	
Shin et al 2000	To assess the antitumor activity and toxicity profile of a combination	Phase II Study; n=56	Patients with recurrent or metastatic squamous cell carcinoma of the	Survival rates	A total of 32 patients (59%) responded to treatment; the complete response rate was 17% (9 of 54 patients). The	The TIC regimen had high antitumor activity in patients with	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of paclitaxel, ifosfamide, and carboplatin (TIC) in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN).		head and neck (SCCHN).		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 date of last follow-up). The median duration of 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).	recurrent or metastatic SCCHN. The activity of TIC in patients with recurrent or metastatic SCCHN should be confirmed in a Phase III randomized trial	
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	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						second primary HNSCC.	
Tsukuda et al 2010	We compared concurrent chemoradiotherapy (CCRT) with docetaxel, cisplatin (CDDP), and 5-fluorouracil (5-FU) (TPF) with CCRT with CDDP, 5-FU, methotrexate and leucovorin (PFML) in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN)	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 CCRT with the TPF regimen. In the PFML group, patients received CCRT with the PFML regimen	Overall response rate Safety	The overall response rates after CCRT were 98 with 90% of a pathologically complete response (pCR) in the TPF group and 94 with 77% in the PFML group. For grade 3/4 adverse events, mucositis was more frequent in the PMFL group, and the TPF group showed a higher incidence of hematological toxicity	The use of multiagent CCRT including CDDP appears to be more efficacious than CCRT with CDDP alone. Both regimens showed high ORRs after CCRT completion (94%: PFML group; 98%: TPF group). The ORR, pCR rate and 3-year survival rate were almost identical to results of previous studies on	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						CCRT with PFML	
van den Bosh et al 2017	To investigate whether de-escalation of elective radiation dose and the introduction of an intermediate dose-level for borderline sized lymph nodes in the treatment of head and neck cancer will result in less radiation sequelae and improved quality of life after treatment without compromising the recurrence rate in the electively treated neck.	Multicenter, phase III, single-blinded, randomized controlled trial; n= 300 (expected)	Patients to be treated with definitive radiation therapy for a newly diagnosed stage T2-4 N0-2 M0 squamous cell carcinoma of the oropharynx, hypopharynx or larynx are eligible.	The primary endpoint is 'normalcy of diet' at 1 year after treatment (toxicity). The secondary endpoint is the actuarial rate of recurrence in electively irradiated lymph nodes at 2 years after treatment (safety).	No results available yet	A total of 6 head and neck centers (or affiliated) will participate and include: the Radboudumc Nijmegen, University Medical Center Utrecht, VU University Medical Center Amsterdam, MAASTRO clinic Maastricht, Radiotherapie groep Arnhem and Radiotherapeutisch Instituut Friesland. The first patient was included in august 2016 and accrual is	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						expected to continue for 4 years.	
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 PFE To determine the pharmacokinetic (PK) profile.	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 (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	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
						three cohorts. Therefore, this combination cannot be recommended for further development in R/M-SCCHN patients.	
Yamasaki et al 2017	To evaluate the efficacy of cisplatin and fluorouracil (CF)-based combination neoadjuvant chemotherapy on the outcome of patients with resectable locally advanced esophageal squamous cell carcinoma (ESCC). To compare the recurrence-free survival (RFS) associated with CF plus Adriamycin (ACF) with that	Randomized, phase II; n=162	Patients with resectable advanced ESCC were randomly assigned to either ACF (Adriamycin 35 mg/m2, cisplatin 70 mg/m2 i.v. on day 1, fluorouracil 700 mg/m2 continuous infusion for 7 days) every 4 weeks or DCF (docetaxel 70 mg/m2, cisplatin 70 mg/m2 i.v. on day 1, fluorouracil 700 mg/m2 continuous infusion for 5 days) every 3 weeks. Surgery was scheduled after	Primary endpoint: RFS, analyzed by the intention-to-treat Secondary endpoints: OS R0 resection rate Histopathological response rate Postoperative complications	The R0 resection rates for the ACF and DCF groups were equivalent (95.9% versus 96.2%, P = 0.93). The 2-year RFS and OS rates for DCF versus ACF were 64.1% versus 42.9% (hazard ratio 0.53, 95% confidence interval 0.33-0.83, P = 0.0057) and 78.6% versus 65.4% (P = 0.08), respectively. Compared with ACF, DCF chemotherapy was associated with prolonged RFS for patients with resectable advanced ESCC. Thus, DCF chemotherapy has potential as a standard neoadjuvant therapy for resectable ESCC.		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	associated with CF plus docetaxel (DCF)		completion of two cycles of chemotherapy. Recruitment was done between October 2011 and October 2013	Safety.			
Zheng et al 2017	To confirm the superiority of paclitaxel, cisplatin and McKeown esophagectomy with total two-field lymphadenectomy compared with surgery alone for esophageal ESCC.	Phase III, multicenter, open label, randomized controlled study. n=528 (expected)	Histologic diagnosis of squamous cell thoracic EC stage IIA to IIIB, not previously treated.	Primary endpoint: OS Secondary endpoints: DFS R0 resection rate Complication rate Perioperative mortality Days of hospitalization Quality of life (QOL)	No results available		2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Neoadjuvant chemotherapy response rate Pathologic response rate Toxicities of neoadjuvant chemotherapy Prognostic factors Predictive factors PFS Adverse events			

Remarks and notes:

5.6.5. Literature

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6. Working group: Prevention and surveilance

(AG Prävention und Nachsorge)

6.1. Question V.1. Which procedures/examinations/tests, based on stage, should be recomended as surveillance evaluations? How frequent?

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

6.1.1. PICO

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

6.1.2. 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 German[Language]	15th December 2016 (initial search) Update 30th May 2017	203 210

6.1.3. Selection critera

Literature selection	
Number of total results	210
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	20
Number of full texts reviewed	14

6.1.4. Evidence table

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
DiMonta et al 2017	To evaluate electrochemotherapy efficacy in treatment of locally advanced stage III SCC, in which surgical procedures would have entailed wide tissue sacrifice.	Retrospective single center study; n=22 consecutive patients	Patients with extensive cSCC that were referred to the National Cancer Institute of Naples from January 2011 to December 2015	Efficacy Safety	Overall response to electrochemotherapy treatment was observed in 18 (81.8%) patients. Clinical response with necrosis of tumor mass was observed from the first session and lasted for all follow up period that ranged between 5 and 48 months with a median of 34		3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					months. Overall the treatment was well tolerated with a very low complication rate. Electrochemotherapy shows a high rate of OR rate, avoiding demolitive surgery and providing oncological efect with good aesthetical and functional preservation.		
Efird et al 2002	To determine the risk of subsequent cancer following squamous cell skin cancer	Retrospective review; n= 822	Individuals with primary squamous 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	Subsequent cancer risk after SCSC diagnosis	Patients were followed for 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	The results suggest that patients 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.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			cancer, and received at least one multiphasic health checkup and questionnaire (MHC).		(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 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 =		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 patients after conventional surgery, related to tumour characteristics and specific tumour measurements	Retrospective cohort study; n=171	Patients with primary invasive squamous cell carcinoma of the skin, followed for a minimum 5 year after treatment conventional excisional surgery, in one center, between 1990 and 1995.	Patient outcomes - either alive without recurrence or metastasis at 5 years, dead of disease within 5 years or dead of other causes within 5 years.	Of these 171 patients, 157 were confirmed as 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	There is no evidence that the prognosis is superior after either conventional surgery or Mohs' therapy, when series are compared for tumour thickness. Long-term follow-up and tumour-thickness measurements	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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	are required in all series after all treatments for meaningful comparisons to be made.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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 disease, perineural invasion (PNI), and poorly differentiated histology were	For advanced CSCCs of the head and neck, patients with recurrent disease, PNI, and poorly differentiated tumors are at 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
					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 patient cohort.		
Leiter et al 2016	This article describes prevention options current therapy options, and follow-up recomendations.	Review article		Surgical therapies Sentinel lymph node biopsy Systemic therapy	The extent of excision should be dependent on tumor size, radius and thickness. actinic keratoses are not included. Especially		5

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					for extensive excisions first a complete excision Of the invasive component and later minimally destructive or local therapeut treatments are possible. The execution of SLNB goes along with a low morbidity compared to other tumor entities, such as, malignant melanoma. In the presence of metastasis, that cannot be treated by surgery or radiotherapy (advanced PEKs), medication therapies as cytotoxic chemo-therapies, targeted therapies and immunotherapies or		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					combinations can be used.		
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 terciary 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, 1.4-10.4)	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
					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, 26.3%;		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					95%CI, 11.8%-48.8%).		
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 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 cSCC in 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 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.		
Picard et al 2017	To search for somatic mutations of the HRAS, KRAS, NRAS, BRAF and EGFR genes in patients with advanced cSCC	Multicenter retrospective study; n=31	Patients with confirmed advanced cSCC treated in two medical oncology departments in France between	Incidence of somatic mutations of the RAS, BRAF and EGFR genes and association with cetuximab efficacy with these	31 samples of cSCC from 31 patients were analyzed. Only 2 RAS muated samples (6.5%) were identified. The firs harbored a NRAS	Even in elderly patients (median age 86 years; range 48-96 years) cetuximab was efficacious and well-tolerated. This	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	treated with cetuximab; and to investigate the efficacy and tolerance of cetuximab according to these mutations		January 2008 and December 2014	mutations – Fisher test Disease control rate at week 6 PFS OS Safety	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 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	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	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					median PFS was 9 months. All patients could continue cetuximab treatment without dose reduction.	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.	
Rose et al 2017	To review the outcomes for sporadic primary cSCC in one department, with the objective of identifying 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 Com- mittee 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).	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.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Follow-up practices for this “low-risk” Group 4 (Low) were then scrutinised 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 loco-regional recur-rence 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	The authors recommend a realistic approach to the follow-up of immuno- competent patients with “low-risk” tumours e a 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
					primary care. 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 review consultation, this		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 practises nationwide, this would equate to around 873 “low-risk” cSCC patients treated, subsequently filling 5000 out-patient appoint- ments and around 833 h of clinic time (almost 111 x 3-h out-		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patient clinics/year), to a cost of £597'0000 (around £240,000/year).		
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 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 crosssectional imaging and clinical examination was 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 patients. In four cases the 18F-FDG PET-CT failed to pick up biopsy proven metastatic	Overall the management in majority of head and neck cSCC patients with regional metastasis does not change by addition of 18F-FDG PET-CT over conventional imaging.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					disease. Two patients who had reduced extent of surgery have shown no features of regional failure after one year of follow-up.		
Topin-Ruiz et al 2017	To confirm the efficiency of wide surgical excision of the nail unit with full-thickness skin graft reconstruction on a series of patients with subungual squamous cell carcinoma (SUSCC) with an extended follow-up and to evaluate short- and long-term postoperative morbidity and patient satisfaction.	Consecutive serie; n=55	Patients with biopsy-proven SUSCC without bone invasion treated by wide surgical excision of the nail unit followed by full-thickness skin graft reconstruction from January 1, 2000, to August 31, 2012 in one center	Demographic data Pathologic characteristics of tumors Ppostoperative follow-up Recurrences Patients' satisfaction with surgery Quality of life Delayed postoperative morbidity (functional outcome and sensory disorders)	Among the 55 patients (23 women and 32 men; mean age, 64 years), the mean follow-up was 6.6 years (range, 5.0-11.2 years), with a minimum follow-up of 5 years. Fifty-two questionnaires (95%) were returned. Two recurrences were observed. Minor early postoperative complications, such as graft infection and delayed wound healing, were seen in 6 patients; 8 patients		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					experienced severe pain. Late postoperative complications included hypersensitivity to mechanical shocks (39 of 51 patients [76%]), mildly increased sensitivity to cold (38 of 51 patients [75%]), loss of fine touch sensation (17 of 35 patients [49%]), and epidermal inclusion cysts (9 of 51 patients [18%]). Most patients were very satisfied with cosmetic and global outcomes of the surgery.		
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	Patients with SCC are at increased risk To develop new primary cancer, especially in skin, squamous cell epithelial and	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					[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 second primary SCC was excluded, the SIR was reduced to 1.30 (CI = 1.25–1.34); the relationships by sex, age and time 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.	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.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Wei et al 2017	To evaluate Oculocutaneous albinism 2 (OCA2)/ HECT and RLD Domain Containing E3 Ubiquitin Protein Ligase 2 (HERC2) (OCA2/HERC2) locus variants for impact on time to develop cutaneous squamous cell carcinoma (cSCC) in organ transplant recipients (OTRs) who are at elevated risk of developing cSCC.	Data from two trials were included: The Ohio State University (OSU) study design was a case-control with prospective follow-up; n= 125 The University of California San Francisco (UCSF) study design was a national cross-sectional survey with retrospective chart review; n=261	Solid organ transplant recipient with at least five years follow-up post-transplant from two different centers	Time to first cSCC diagnosis after transplant	OCA2 variants rs12913832 and rs916977 were significantly associated with time to first cSCC post-transplant. OTRs homozygous for the brown eye alleles of rs916977 (GG) and rs12913832 (AA) had significant delays of time to first cSCC post-transplant compared to individuals homozygous for the blue eye alleles [HR=0.34, p<0.001and HR=0.54, p=0.012, respectively]. Both variants were highly associated with eye color in combined studies (p<0.001).		4
Yoong et al 2009	To establish	Retrospective study; n=40	Patients who had a primary invasive cutaneous SCC	Lymph node status	The median follow-up time was 7.5 years. In the 10-year	These data which extended to 10	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	appropriate follow-up times and to determine the long-term risk of subsequent non-melanoma skin cancers and melanoma.		excised during 1996 were retrospectively identified from the databases of a dermatologist in private practice in south-east Queensland.	Patient's immunocompetency Presence of local recurrence, subsequent SCC, BCC and melanomas	period, there was one local recurrence of a well-differentiated SCC, which was detected at the 6 month 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 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	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.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					subsequent melanoma detected.		

Remarks and notes:

6.1.5. Literature

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6.2. Question V.2. Which recomendations should be made for actinic keratosis and squamous cell carcinoma pimary prevention? (Frage V.2. Welche Maßnahmen sind zur Primärprävention von PEK und AKs geeignet?) Beantwortung durch De novo Recherche

6.2.1. PICO

PICO – Scheme			
Population	**Intervention**	**Comparison**	**Outcome**
Patients high at risk for SCC and AK (immunosuppressed Patients)	Primary prevention; Chemoprevention, Local therapies, Systemic therapies	No intervention	Efficacy; safety

6.2.2. 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])	July 2017	177

Database	Search strategy	Date	Number of results
	("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])		
Remarks and notes:			

6.2.3. Selection critera

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	17
Number of full texts reviewed	14

6.2.4. 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	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 end points were the clinical and laboratory safety of vitamin A. The secondary end points included quantitative, karyometric image analysis and assessment of retinoid and rexinoid receptors	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	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
	would be well tolerated and could be quantitatively measured by karyometric and retinoid receptor analyses in the skin of individuals with visually and histologically normal, sun-damaged skin.			in sun-damaged skin.	participants 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 outcome 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 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 Can-	Patients with at least two nonmelanoma skin cancers in the previous 5 years	The primary end point was the number of new nonmelanoma skin cancers (i.e., basal-cell carcinomas plus squamous-cell carcinomas) during	Participants were evaluated by dermatologists at 3-month intervals for 18 months. At 12 months, the rate of new	Oral nicotinamide was safe and effective in reducing the rates of new nonmelanoma skin cancers and actinic keratoses in high-risk patients.	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		cer [ONTRAC]); n=386		the 12-month intervention period. Secondary end points 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.	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 with respect to new basal-cell carcinomas (20% [95% CI, −6 to 39] lower rate with nicotinamide, P=0.12) and new squamous-cell carcino- mas (30% [95% CI, 0 to 51] lower rate, P=0.05). The number of actinic keratoses was 11% lower in the nicotinamide group than in the	The trial was funded by the National Health and Medical Research Council	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 with respect to 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 tumour-selective	Prospective, randomized, double-blind, placebo-controlled study; n=17 patients; n=129 moderate actinic ketratoses	Transplant recipients with mild to moderate actinic keratosis treated during the period July 2001 to March 2002 at the Department of	Complete resolution and reduction in the number or size of actinic keratoses within the lesional area relative to the initial findings at	The lesional areas treated with methyl aminolaevulinate were clinically cleared in 13 of 17 patients at 16 weeks.	Photodynamic therapy using methyl aminolaevulinate is a safe and effective treatment for actinic keratoses in transplant	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	photosensitizer methyl aminolaevulinate vs. placebo in the treatment of actinic keratoses in transplant recipients.		Dermatology and the Transplantation Unit, University Hospital of Zurich.	weeks 4, 8 and 16 after treatment.	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, oedema and crust formation, were mild to moderate, and treatment was well tolerated by all patients.	recipients. It may also reduce the risk of transformation of actinic keratoses to invasive, potentially fatal, squamous cell carcinoma. Further more 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 January and July 2015	Efficacy	Group 1 took nicotinamide, 250 mg thrice daily, (cases) and Group 2 did not take any drug to treat AKs (controls). For each case, one matching control	Nicotinamide appears to be effective in preventing and treating AKs, although the mechanisms are still unclear. Further studies with a larger	2

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 patient developed new AKs. Conversely, among the controls, 91%	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
					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 nonmelanoma skin cancer. Patients were treated at eight US academic medical	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 per patient at 11 months after randomization.	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 the two groups at 9 months after random- ization. However, at 11 months after	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
			centers between January 18, 2001and November 3, 2006.	The numbers of adverse events in the two treatment arms .	randomization, there were fewer nonmelanoma skin cancers in the cele- coxib 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, his- tory of actinic keratosis at randomization, nonmelanoma skin cancer history, and patient time on study, the number of nonmelanoma skin cancers was lower in the celecoxib arm than in the placebo arm (RR=0.41, 95% CI=0.23 to 0.72,		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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, then twice daily as tolerated.	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 topical tretinoin is feasible for long-term use in this population.	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Participants were instructed to step down application frequency to once daily or less if twice daily was not tolerated. he 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-effect (39% tretinoin vs. 17% control, P < 0.0001). There was no difference in	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 Insti-tutes of Health. The study medication was donated by the OrthoNeutrogena division of Ortho-McNeil Pharmaceutical Inc.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 (BCC) and squamous-cell carcinoma (SCC) using data from the Skin Cancer Chemoprevention Study.	Cohort study; n=702 of the 1,805 randomized subjects (39%) were included in the present analysis; n= 1,952 microscopically confirmed new skin cancers - 1,747 BCCs, 204 SCCs and 1 basosquamous carcinoma.	Patients included in the Skin Cancer Prevention Study that was a 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.	To explore the association of NSAID use and with the risk of BCC and SCC.	Of the 702 patients with confirmed cancers, 570 had only BCCs, 51 had only SCCs and 81 had both. The use of NSAIDs was reported in over 50% of questionnaires. For BCC, NSAIDs exhibited a weak	In this closely monitored cohort of high risk subjects, there 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.	2/3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			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 lesions (n=1,685).		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).	At most, our data suggest a weak chemopreventive effect of NSAID use on SCC in the year prior to diagnosis, and on the number of BCCs and SCCs.	
Kadakia et al 2011	To assess the efficacy of acitretin as a chemopreventive agent in non-transplantation patients at high risk	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	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.	The original design was to have 110 patients per treatment arm, which would provide 80% power to detect a 33% difference in NMSC	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	for non-melanoma skin cancers (NMSC)		1 year of registration.		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 at each subsequent follow-up, the skin was examined by the patients' dermatologists. 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,	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, 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,	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 mucositis and skin toxicities compared with the patients who received placebo.	MD) and by National Cancer Institute Community Clinical Oncology Program grant CA-37404.	
Kreul et al 2012	To retrospectively assess the further incidence of skin cancer, other malignancies, and adverse events of patients accrued to	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	Previously, 291 participants (mean age, 61 years; 60% male) with a history of prior NMSC (mean, 4.5 skin cancers) were	Follow-up data revealed a persistent but insignificant reduction in new NMSCs occurring in DFMO subjects	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	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.			Rate of skin cancer recurrence from randomization onto CO9737 to the date of last contact for this follow-up study	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 were reviewed, and 2,092.7 person years of on study (884.3 person years) and poststudy (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	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 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
					poststudy 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 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,		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 2014	To identify baseline patient characteristics associated with adverse effects of topical tretinoin.	Randomized, cohort study; n=324 patients	Participants of the 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)	Safety and tolerability	One hundred and 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	In this study 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.	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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.	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 2015	To investigate the potential of long-term repeated photodynamic therapy (PDT) treatment applied to clinically normal skin with the intention of preventing the first onset of AK in high-risk renal transplant recipients (OTR). This report referes to the interim analysis of 25	Randomized control trial, n=25	Patients were recruited from and treated at the Department of Dermatology, Bispebjerg Hospital, between 2008-2011. Inclusion criteria were: renal trans-plant recipients aged 40–70 years, fair skinned persons (Fitzpatrick skin type I–III [14]), stable graft function	The primary study endpoint is total number of AKs at end of study. Primary a priori end point of the interim analysis was 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	The interim 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. Blinded evaluation was performed at each visit.	The interim data 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.	3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	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.		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 previous PDT treatment in study areas.	cancers, comprising basal cell carcinoma (BCC) and SCC.	Prophylactic PDT significantly delayed onset of AK compared with untreated skin, p = 0.020. At 3-year follow-up, we observed AK in 63% of patients in untreated skin areas compared with 28% of patients in PDT-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 mortal- ity in the Veterans Affairs Topical	The VATTC Trial was a blinded randomized che- moprevention trial, with 2- to 6-year follow-up. (Results from the VAAT trial were also reported	A total of 1131 veterans were randomized. Their mean age was 71 years. Patients with a very high esti- mated short-term	Death, which was not con- templated as an end point 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	The authors observed an association of topical tretinoin therapy with death, but we do not infer a causal association that current	1

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	Tretinoin Chemopre- vention Trial (VATTC). The planned outcome of this trial was risk of keratinocyte carcinoma, and systemic administration of certain retinoid compounds has been shown to reduce risk of this cancer but has also been associated with increased mortality risk among smokers.	by Geng et al 2009 and Pomerantz et al 2014)	risk of death were excluded.		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 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.	evidence suggests is unlikely.	
Willey et al 2009	To evaluate the potential benefit of cyclic photodynamic	Prospective, open-label pilot study; n=12	Patients with SOTRs and progressive development of	Number of new SCCs (invasive and	The median reduction in the 12- and 24-month post-	Cyclic PDT with 5-aminolevulinic acid may reduce the	2/3

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	therapy (PDT) in the prevention of new SCCs in solid organ transplant recipients (SOTRs)		multiple SCCs and SCC in situ over the previous year treated in the University of Minnesota Department of Dermatology solid organ transplant clinic.	in situ) in patients with SOTRs.	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.	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 cancer in this high-risk patient population.	

Remarks and notes:

6.2.5. Literature

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7. Working group: Ocupational diseases associated with actinic keratosis and squamous cell carcinoma

(AG Berufsbedingte Erkrankung an PEK oder/und AK)

7.1. Question VI.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

7.2. Question VI.2. Reporting of suspected occupational skin cancer

(Frage VI.2. Meldung bei Verdacht auf einen berufsbedingten Hautkrebs) Beantwortung durch Verweis auf LL Prävention