European consensus-based interdisciplinary guideline for invasive cutaneous squamous cell carcinoma. Part 1: Diagnostics and prevention - Update 2026

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European consensus-based interdisciplinary guideline for invasive cutaneous squamous cell carcinoma. Part 1: Diagnostics and prevention - Update 2026

On behalf of EADO[A], EDF[B], ESTRO[C], UEMS-DV[D] and EORTC[E]

[A] European Association of Dermato-Oncology, [B] European Dermatology Forum, [C] European Society for Radiotherapy and Oncology, [D] European Union of Medical Specialists (Union Européenne des Médecins Spécialistes)-Dermatology Venereology, [E] European Organization for Research and Treatment of Cancer

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ABSTRACT

Invasive cutaneous squamous cell carcinoma (CSCC) is one of the most common cancers in white populations, accounting for 20% of all cutaneous malignancies. A collaboration of multidisciplinary experts from the European Association of Dermato-Oncology (EADO), the European Dermatology Forum (EDF), the European Society for Radiotherapy and Oncology (ESTRO), the European Union of Medical Specialists (UEMS)-Dermatology Venereology, and the European Organization of Research and Treatment of Cancer (EORTC), was formed to update guideline recommendations on CSCC (previous version 2023), based on current literature and expert consensus. Part 1 of the guidelines addresses diagnostics and prevention in immunocompetent as well as immunosuppressed patients. CSCC may be classified as easy-to-treat (vast majority) or difficult-to-treat, common primary CSCC, and is further defined as low risk or higher risk depending on the risk of recurrence or metastasis. A new classification of five groups of difficult-to-treat CSCC (DTT-CSCC) is proposed, published in 2025 by EADO experts and reflecting the commonly encountered clinical challenges. Difficult-to-treat (DTT) CSCC includes DTT-common CSCC groups 1 and 2 (which correspond to a subgroup of common CSCC that are complex to treat due to tumor and/or patient characteristics or multiplicity), DTT-CSCC group 3 corresponding to locally advanced CSCC, and DTT-CSCC groups 4 and 5 corresponding to CSCC with locoregional or distant metastases, respectively. The first step of diagnostics is based on clinical and dermatoscopic features, and is always confirmed by histopathology. The presence of risk factors characterizes higher risk CSCC, and the more risk factors, the higher the risk. After the histological diagnosis of CSCC has been established, the second step includes staging procedures, such as physical examination and, when indicated, imaging. In the third and final step, the clinical,

histologic and radiologic findings are incorporated into staging systems. The more widely used staging systems are the American Joint Committee on Cancer 8th edition (AJCC8) and the Brigham and Women's Hospital (BWH) systems. Prevention strategies include oral nicotinamide and sun protection measures.

Key words: invasive cutaneous squamous cell carcinoma; advanced; low-risk; high-risk; common primary CSCC; locally advanced CSCC; metastatic CSCC; diagnosis; prognosis; staging; imaging; prevention; chemoprevention; immunosuppression

1. INFORMATION ABOUT THE GUIDELINES

1.1. Societies in charge

This guideline was developed on behalf of the European Association of Dermato-Oncology (EADO), the European Dermatology Forum (EDF), in collaboration with the European Society for Radiotherapy and Oncology (ESTRO) and the European Union of Medical Specialists (Union Européenne des Médecins Spécialistes, UEMS) -Dermatology Venereology. In order to guarantee the interdisciplinary character of these guidelines, they were developed in cooperation with the European Organization for Research and Treatment of Cancer (EORTC). Alexander J. Stratigos in collaboration with Clio Dessinioti, Claus Garbe and Josep Malvehy coordinated the authors' contributions as part of the EADO Guideline Program in Dermato-oncology. Collaboration on guideline development with EDF, ESTRO, UEMS-Dermatology Venereology, and EORTC guaranties the interdisciplinary quality of the guideline.

1.2. Disclaimer

Medicine is subject to a continuous development process. Therefore, all statements, including those on diagnostic and therapeutic procedures, can only reflect the state of scientific knowledge at the time this guideline went to press. The treating physician who refers to the recommendations of this guideline must consider scientific progress since the guideline was published.

1.3. Scope

This guideline has been written to assist clinicians in the diagnosis, follow-up and treatment of patients with invasive cutaneous squamous cell carcinoma (CSCC). This update was initiated mainly due to advances in diagnostics, new evidence on prognostic risk factors, and prevention. The use of these guidelines in clinical routine should improve patient care.

1.4. Target population

These two parts of the CSCC guideline contain recommendations for the diagnosis, prevention, treatment and follow-up of patients with invasive CSCC. The guideline is addressed to the attending physicians and the medical nursing staff. An attempt has been made to write the guideline in a way that is easy to understand, so that patients can also understand the recommendations.

1.5. Principles of methodology

We focus on invasive CSCC (hereafter CSCC), excluding actinic keratoses (AK), Bowen's disease (in situ), and mucosal SCCs such as those located in the genital area, or those in the labial-buccal-nasal area, which are often mixed with CSCC under the label of 'head and neck' tumors. Particular emphasis is given to the definitions of CSCC, the diagnosis, risk classification, updated staging systems and treatment modalities. Patient education and prevention issues are also addressed. Formulation of clear sections has been made to support clinicians in their practice.

The European Interdisciplinary Guidelines on invasive squamous cell carcinoma of the skin are written as a uniform text and then published in two separate but integral parts: Part 1 on definitions, epidemiology, etiopathogenesis, diagnosis, risk classification, staging and prevention and Part 2 on treatments, supportive care, patient education and follow-up (Stratigos et al. Part 2. 2026).

The guideline published here are an update of the existing European consensus-based interdisciplinary guidelines for the management of invasive CSCC version 2023 [1, 2] and are additionally informed by other up-to-date guidelines, including the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for squamous cell skin cancer (version 1.2026)[3], and the British Association of Dermatologists guidelines for the management of people with cutaneous squamous cell carcinoma (version 2020).[4] *De novo* literature search was conducted by the authors by Medline search in English language publications with last search date on October 13, 2025. The literature search begun from the last literature search performed for the guideline 2023 on 10 March 2023. Search terms included: 'cutaneous squamous cell carcinoma', 'squamous cell carcinoma', and 'advanced, locally advanced, low-risk, high-risk, common primary CSCC, locally advanced CSCC, metastatic CSCC'. These terms were combined with 'diagnosis, prognosis, staging, imaging, prevention, chemoprevention, guidelines, treatment, surgical excision, radiotherapy, adjuvant, systemic, anti-PD-1 antibody, cemiplimab, pembrolizumab, chemotherapy, cetuximab, EGFR-inhibitors, clinical trials, follow up, patient education'. The references cited in selected papers were also searched for further relevant publications. The guideline methodology was based on the standards of the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument[5].

Recommendations are based on the level of best quality available evidence and good clinical practice points (GPP). The levels of evidence were graded according to the Oxford classification (Supplementary Table 1)[6]. In brief, level 1 indicates strongest evidence based on systematic review of well-designed studies, level 2 based on randomized or well-designed cohort or cross-sectional studies, level 3 based on non-randomized adequately designed studies, and levels 4 and 5 indicate the weakest evidence based on small number of patients or poor quality. Level may be graded down based on study quality, imprecision, indirectness, because of inconsistency between studies, or because the absolute effect size is very small. Level may be graded up if there is a large or very large effect size. (Supplementary Table 1). The grades of recommendation were also classified as A, B, C, X. In this update we introduced color-coded recommendations: green for strong, light green for medium strength, yellow for weak recommendation, red for strong contraindication and white for a good clinical practice point. (Table 1).

Expert consensus was provided wherever adequate evidence is not available (described in Supplementary Appendix-guideline part 1). The changes in the guideline update 2026 compared with the guideline version 2023 are presented in Supplementary Appendix-guideline part 1. In view of the regulatory approval of adjuvant cemiplimab for CSCC at “high risk of recurrence”, the classification of CSCC was revised to “low-risk” and “higher-risk” throughout the guideline. Also, the previously termed “high-risk” factors were revised to “risk factors” to avoid confusion with the tumors at high risk of recurrence eligible for adjuvant cemiplimab.

The guideline manuscripts were additionally externally reviewed by reviewers from each participating society, who were not included as authors of the guidelines.

Table 1. Grades of recommendation

Grade of recommendation	Description	Syntax	Color
A	Strong recommendation	Shall	Green
B	Medium strength recommendation	Should	Light green
C	Weak recommendation	May/can	Yellow
X	Contraindication	Shall not/should not	Red
GPP	Good clinical practice point	Based on consensus, when adequate evidence was not available	White

1.6. Financing

The authors did this work on a voluntary basis and did not receive any honorarium. The authors paid their own travel expenses for participation in the consensus conferences. Accommodation costs were in part reimbursed by EADO.

1.7. Audience and period of validity

This set of guidelines will assist healthcare providers in managing their patients according to the current standards of care and evidence-based medicine. The guidelines published here reflect the best published data available at the time the report was prepared. Caution should be

exercised in interpreting the data; the results of future studies may modify the conclusions or recommendations in this report. In addition, it may be necessary to deviate from these guidelines for individual patients or under special circumstances. Just as adherence to the guidelines may not constitute defense against a claim of negligence (malpractice), deviation from them should not necessarily be deemed negligent. These guidelines will require updating approximately every two years (expiration date: December 2028) but advances in medical sciences may demand an earlier update.

2. Definitions

Cutaneous SCC (CSCC) is a common skin cancer characterized by the malignant proliferation of epidermal keratinocytes and it is classified as a keratinocyte carcinoma together with basal cell carcinoma. It is distinguished into *in situ* (Bowen's disease) and invasive form. These guidelines focus on invasive CSCC (CSCC).

Depending on the extent of the disease, CSCC is classified as common primary, by far the most frequent, and advanced CSCC. Common primary CSCCs are non-metastatic CSCC, usually easy-to-treat lesions, which can be further classified as low-risk or higher-risk, depending on the risk of recurrence. Higher-risk CSCC is defined as invasive CSCC without locoregional (in transit or regional nodal metastasis) or distant metastasis (staged as N0 and M0), that has features associated with a higher risk for local recurrence and metastasis (detailed in section 6, box 4), and that is amenable to curative surgery or RT.[7, 8] Advanced CSCC is classified as either locally advanced (laCSCC), or metastatic (mCSCC).

LaCSCC shall be defined as non-metastatic CSCC, not amenable to either surgery or radiotherapy with reasonable hope for cure, because of multiple recurrences, large size, bone erosion or invasion, or deep infiltration beyond subcutaneous tissue into muscle or along nerves, or tumors in which curative resection would result in unacceptable complications, morbidity or deformity.[9] This corresponds to unresectable T3/T4 (tumor invading deep structures) according to the 8th edition AJCC and 9th edition UICC staging classification.[10-12] MCSCC includes loco-regional metastatic CSCC with in-transit metastases or metastases of regional lymph nodes, or distant metastatic CSCC requiring systemic treatments. CSCC with regional nodal metastasis corresponds to stage III or IV according to the 8th edition AJCC or UICC staging classification. Metastatic CSCC with distant metastasis corresponds to stage IV. The presence of in-transit metastases is not included in the 8th edition AJCC/UICC staging systems.

In addition, an operational classification of five groups of difficult-to-treat CSCC (DTT-CSCC) based on independent clustering by EADO experts was published in 2025. Five groups of DTT-CSCC were defined spanning the common and advanced CSCC definitions. In particular, DTT-common CSCC group 1 includes common CSCC that is complex to treat due to tumor and/or patient characteristics (such as comorbidities or tumor location), and DTT-common CSCC group 2 includes multiple common CSCCs when the number is the main problem. DTT-CSCC group 3 corresponds to locally advanced CSCC, while DTT-CSCC groups 4 and 5 correspond to CSCC with regional metastases (nodal or cutaneous) or distant metastases, respectively.[13] (Figures 1, 2)

Recommendation 1. (updated from 2023)

Definitions and classifications of invasive CSCC	Guideline 2026 Evidence- based statement
Grade of recommendation: A	Common primary CSCC shall be classified as low-risk or higher-risk. Higher-risk CSCC is defined as invasive CSCC without locoregional (in transit or regional nodal metastasis) or distant metastasis (staged as N0 and M0), that has features associated with a higher risk for local recurrence and metastasis (see Recommendation Box 4). Advanced CSCC shall be classified as locally advanced (LaCSCC), locoregional metastatic or distant metastatic CSCC (mCSCC). LaCSCC shall be defined as non-metastatic CSCC, not amenable to either surgery or radiotherapy with reasonable hope for cure, because of multiple recurrences, large size, bone erosion or invasion, or deep infiltration beyond subcutaneous tissue into muscle or along nerves, or else tumors in which curative resection would result in unacceptable complications, morbidity or deformity.
Level of evidence: 1	Meta-analysis[7, 8], phase 1 and phase 2 cohort studies[9]
	Strength of consensus: 100%

3. Epidemiology and etiology

3.1. Epidemiology

CSCC is the second most common form of skin cancer, accounting for 20% of keratinocyte carcinomas. Reliable population-based CSCC incidence data are limited, but indicate that rates are increasing in most white populations globally and are predicted to continue to increase.[14-17] International incidence data are presented in Supplementary Table 2.[15, 16, 18-22] Rates increase with age, male sex (SIR, 2.1; 95% CI, 2.06-2.14) and low latitude and multiplicity is

strongly correlated with age.[22, 23]. The associated public health burden of CSCC is substantially underestimated.[14, 24] Markedly increased rates of CSCC have been reported in immunocompromised individuals, and in particular patients with[25] solid organ transplants [26-28], hematologic malignancy including chronic lymphocytic leukemia (CLL) [29-32] and human immunodeficiency virus (HIV) infection [33].

Common primary CSCC are typically indolent tumors, rarely giving rise to metastasis, when they are treated early and correctly.[14, 34-37] Most CSCC tumors have a very good prognosis, with five-year cure rates of greater than 90%.[37-39] The rate of recurrence was reported to be 4.6% in a large single center study of more than 900 patients with CSCC followed for approximately 10 years, 3.7% for nodal disease and 2.1% for disease-specific death.[39, 40] European data on metastatic risk from the UK National Cancer Registration and Analysis Service reported a cumulative incidence of loco-regional or distant metastasis after a median follow up of 15.2 months was 2.1% (1.1% in women, 2.4% in men) in 2013-2015: most mCSCC (85.2%) were diagnosed within 2 years from the primary CSCC and the usual site of metastasis was the head and neck or parotid lymph nodes (73.6%).[37] The risk of metastasis is higher for tumors with multiple risk factors.[41] Of note, disease-specific death has been reported to occur not only as a result from metastasis but also due to local complications and underlying tissue destruction in laCSCC.[42] In addition, several studies have shown worse outcomes for CSCC in immunosuppressed patients compared to immunocompetent patients.[34, 43-46] In immunosuppressed patients, loco-regional recurrence was more common[43], the risk of metastatic CSCC at least doubled[37] and outcomes for advanced disease were significantly worse[47]. Patients with epidermolysis bullosa also have a high risk of early-onset, aggressive

and often multiple CSCCs developing at sites of chronic skin blistering and scarring and a particularly high rate of disease-specific death.[48]

3.2. Etiology

Beside ultraviolet radiation (UVR) exposure (sun exposure and use of tanning beds), which is by far the most important causal factor for CSCC [49], other factors implicated [50, 51] include immunosuppression and immunosuppressive drugs (e.g. azathioprine and ciclosporin) [52, 53], non-immunosuppressive drugs such as BRAF inhibitors [54], voriconazole [55], and hydrochlorothiazide diuretics[53, 56, 57], chronic inflammation[51], toxins such as arsenic and polyaromatic hydrocarbons[51], human papillomaviruses, particularly β-HPV types[50, 51, 58-60], smoking[61, 62], alcohol[63], genodermatoses responsible for defects in DNA repair and genomic stability (e.g., xeroderma pigmentosum, recessive dystrophic epidermolysis bullosa (RDEB), epidermodysplasia verruciformis (EV), oculocutaneous albinism, Fanconi anemia and Lynch/Muir Torre syndrome and porokeratosis[50, 51, 58].

Genome-wide association studies have also highlighted germline single nucleotide polymorphisms associated with CSCC risk, including *MC1R, ASIP, TYR, SLC45A2, OCA2, IRF4*, *BNC2*, the metastasis suppressor gene *CADM1, AHR*, a transcription factor that regulates cell proliferation, *SEC16A* involved in secretion and cellular proliferation, and other loci involved in pigmentation phenotypes (*TYRP1, TRSP1*) in tumor immunosuppression (HLA variants, BACH2), invasion and metastasis (*SETDB1, ECM1*, and *CERS2*).[58, 64-68].

While most CSCCs arise in the context of actinic keratoses (AKs) and in patients with chronic photoaging, the rate of transformation of clinically evident AKs into CSCC is very low (less than

1/1000 per year during a 5-year follow up) and the risk factors and molecular drivers for progression are uncertain.[50, 51, 69, 70]

3.3. Molecular pathogenesis

CSCC are complex genetic tumors with a high tumor mutational burden (median 45.2 mutations per megabase of genomic DNA).[71-73] Most CSCC harbor a spectrum of aberrant genes dominated by UV-induced signatures with characteristic C>T or CC>TT dinucleotide mutations.[50, 51] These genetic mutations drive progression, but tumor microenvironmental processes including stromal interactions and local immunomodulation also play key roles in tumor growth and advances in understanding of epigenetic alterations and skin microbiome factors have added further complexity to current concepts of CSCC pathogenesis. [50, 51]

In UV-induced CSCC alterations occur in genes responsible for cell cycle control *TP53*, *CDKN2A, NOTCH1* and *NOTCH2*, epigenetic regulators *KMT2C, KMT2D, TET2*, members of the Hippo pathway and of the SWI/SNF chromatin remodeling complex, with inactivating mutations of TGFβ receptor genes [72-74]. Potentially targetable genetic alterations are infrequent but theoretically include PIK3CA, FGFR3, MEK, and EGFR [75, 76]. Normal skin accumulates mutations in a linear fashion with cumulative UV exposure, increasing the mutation load and clone size, which correlates with keratinocyte cancer risk. Normal sun-exposed skin and AK have a lower mutation rate than SCC, but most of them already have driver mutations in NOTCH1 and TP53 [77-79]. Other genetic alterations have been identified in CSCCs which are in part or exclusively due to non-UV risk factors. For example, specific genetic signatures have been found in CSCC

associated with chronic azathioprine exposure [72]. In RDEB-CSCC a clock-like mutational profile associated with APOBEC deaminase editing has been reported[80], defective DNA mismatch repair with microsatellite instability and accelerated ageing may also contribute and PLK-1 over-expression is a possible candidate for targeted therapy [81].

Data from humans and mouse models suggest that progression of premalignancy to CSCC can be considered a disease continuum from differentiated towards more progenitor-like cellular states.[82] This transition is driven by combinations of genetic mutations involving *TP53*, *NOTCH1, TGFβ*, and the RAS-MAPK signaling cascade, and corresponding transcriptomic analyses showing coordinated downregulation of genes involved in epidermal differentiation and reorganization of the epidermal differentiation complex and epigenetic changes such as in methylation and long non-coding RNAs[83-85]. As CSCC acquires more progenitor-like characteristics, the immune landscape shifts markedly, with an increased presence of innate immune cells (such as dendritic cells, neutrophils, monocytes, and macrophages) and expanded populations of immunoregulatory cells, including regulatory T cells and Th2 lymphocytes.[50, 51, 86] Notably, advanced progenitor-rich tumors display elevated expression of immune checkpoint molecules like PD-1, TIGIT, LAG3 and CTLA4 [51, 86-89] and subpopulations of tumor specific keratinocytes are proposed to act as a hub for interactions with the tumor microenvironment[86]. Cancer-induced nerve injury in perineural invasion also appears to trigger chronic inflammatory signaling via ATF3, IFN-I, and IL-6 pathways in neurons, leading to recruitment of immunosuppressive immune cells in the perineural niche, dampening antitumor immunity. Blocking this pathway could restore immune response and improve anti-PD-1 therapy efficacy.[90]

The importance of the gut microbiome in immune modulation, cancer progression and therapeutic responses is now widely accepted and preliminary evidence suggests a possible association of the cutaneous bacterial microbiome and CSCC progression. [90, 91] The skin virome, specifically HPV, has been more extensively investigated and whilst high-risk alpha-HPV E6 and E7 oncoproteins are important carcinogens in anogenital SCC, β-HPV oncoprotein also play a causal but different mechanistic role in cooperation with UV in inherited EV-associated CSCCs.[92] In contrast, a role is not confirmed in non-EV CSCC, and although meta-analyses show that AK/CSCCs harbor HPV DNA more frequently than normal skin with higher viral loads in AK in immunosuppressed versus immunocompetent individuals, they are not usually transcriptionally active[52, 58]. A 'hit-and-run' mechanism may be one explanation, but more recent experimental studies show that immune selection by beta-HPV specific CD8+ T cells may control UV-induced, p53-mutated keratinocytes, thus suppressing tumorigenesis. Loss of this protective immunity in immunosuppressed patients may underlie the association with CSCC, independent of keratinocyte-intrinsic oncogenic mechanisms, with potential implications for future therapeutic and preventative approaches.

4. Diagnostic approach in primary CSCC

4.1. Clinical diagnosis

CSCC may have variable clinical presentations depending on tumor size, differentiation, pigmentation, location and skin type. It most commonly arises on sun-exposed sites (head, neck,

forearms, dorsum of the hands). The presence of multiple AK represents an established predictor of CSCC development in previously unaffected individuals. [69, 70]

In its early minimally invasive phase, CSCC is usually a small flesh-colored papule or plaque, often with a scaly/hyperkeratotic surface, not easily distinguishable from a hyperplastic/hyperkeratotic AK or *in situ* SCC (Bowen's disease). It enlarges over time at a variable rate, often with ulceration and crusting. There is usually some induration upon palpation. CSCC may be pigmented, displaying a light to dark brown color, especially in non-white skin populations. Well-differentiated CSCC usually manifests as a hyperkeratotic and verrucous tumor, sometimes with a crateriform appearance. Poorly differentiated CSCC may appear as red-colored non-keratotic tumor, is frequently ulcerated or bleeding and may be difficult to distinguish from other non-pigmented tumors like amelanotic melanoma, Merkel cell carcinoma, atypical fibroxanthoma and other less frequent neoplasms. CSCC may be tender on palpation or spontaneously painful, and this may be a sign of perineural involvement.

LaCSCC may result either from tumors with a particularly aggressive biological potential, from multiple relapses after inadequate initial management of primary CSCC or from neglected lesions. This results in large, indurated tumors that infiltrate the surrounding skin and may invade regional anatomic sites such as the orbits or sinuses with pain and other associated symptoms. The actual tumor extent, infiltration and depth of invasion are not easily predictable by simple clinical examination. In mCSCC, the tumor may present with in-transit, nodal or distant metastasis. Clinical examination of the draining basins and imaging in addition to clinical diagnosis of the primary tumor, has to be considered for staging in CSCC with a risk factor, when metastases need to be ruled out.

The clinical differential diagnosis includes in early cases inflamed seborrheic keratosis, high-grade AK, or keratotic basal cell carcinoma and melanocytic tumors in the case of pigmented CSCC. Less differentiated cases may be confused with amelanotic melanoma, or with rarer neoplasms such as atypical fibroxanthoma, Merkel cell carcinoma or adnexal tumors among others.

Adequate documentation of the cutaneous tumor with measurement of the maximum clinical diameter in the patient's medical file is necessary prior to biopsy and surgery. Recording symptoms and photographic documentation (clinical and, whenever possible, dermatoscopic) is recommended prior to biopsy. Recording the clinical diameter is important as this is a critical parameter in risk classification and staging of CSCC unlike the size recorded in the histological report, which is usually reduced due to the shrinkage during sample-processing techniques.

Keratoacanthoma has been re-classified in the new WHO classification of skin tumors, 5th edition. It is no longer classified as well-differentiated CSCC. It is classified as a clinically and pathologically distinctive, self-limiting squamous tumor of infundibular-trichilemmal origin characterized by rapid growth, stabilization and spontaneous regression often leaving a deep scar. Clinically, keratoacanthoma manifests as a solitary dome-shaped nodule capped with keratin in the center, usually arising on sun-exposed skin areas. [93]

4.2. Dermatoscopy and other non-invasive techniques

Dermatoscopy represents an integral part of clinical examination for the assessment of skin tumors. The dermatoscopic features of CSCC have been extensively investigated and shown to

depend on the grade of histopathological differentiation (Figure 3).[94-96] Well-differentiated CSCC is dermatoscopically dominated by a white color that might be present in the form of keratin masses, white structureless areas, white perifollicular circles or white perivascular halos, the latter surrounding hairpin or coiled vessels (Figure 3A, 3C).[95] Each one of these features has a particular diagnostic significance, according to the clinical differential diagnosis. Keratin masses, although very frequent in CSCC, are not specific, since several other, benign and malignant, tumors may display signs of keratinization.[97] White structureless areas, possibly corresponding to extensive acanthosis, were shown to predict CSCC over AK.[98] White circles surrounding follicles which are frequently dilated and filled with keratin plugs, are considered as a specific sign of CSCC over several other nodular tumors, including BCC, seborrheic keratosis, nevi, warts and others.[94] White perivascular halos are seen in CSCC and other keratinizing tumors as well, such as seborrheic keratosis (mainly irritated subtype) or common warts. However, the distribution of the vessels (and the surrounding halos) differs, being irregular in CSCC as compared to the homogeneous arrangement in benign tumors.[99]

Keratoacanthoma is typified by a peculiar dermatoscopic pattern consisting of a central mass of keratin surrounded by radially arranged hairpin or coiled vessels, usually surrounded by a white halo.[94]

Poorly differentiated CSCC is substantially different in terms of its dermatoscopic characteristics. It is predominated by a red color, resulting from a rich vascularity composed of dotted, coiled, hairpin, short linear and linear irregular vessels (polymorphous vascular pattern). Hemorrhage is also very frequent and signs of keratinization are absent (Figure 3B, 3D).[95]

Moderately differentiated CSCC displays mixed dermatoscopic criteria, including white-colored and vascular structures.[94-96]

Other non-invasive techniques such as in vivo Reflectance Confocal Microscopy (RCM), Line field confocal OCT (LC-OCT), and Optical Coherence Tomography (OCT) have been used in case series. A possible role for RCM and LC-OCT in clinical practice would be to differentiate CSCCs from BCCs or other skin tumors in clinically and dermoscopically equivocal lesions [100-103]. Although RCM and LC-OCT have good histopathologic correlations (i.e. parakeratosis, atypical keratinocytes, and vascular alterations), the limited laser penetration frequently hampers the full-thickness examination of the tumor. LC-OCT and OCT, in different modalities, provides deeper vertical sections of the tissue, and may thus help to distinguish *in situ* versus early invasive CSCC.[104-106]. However, there is currently insufficient evidence for routine diagnostic use of these non-invasive techniques in the diagnosis of CSCCs.

Recommendation 2. (updated from 2023)

Clinical and non-invasive diagnosis of the primary CSCC	**Guideline 2026** **Consensus-based statement**
GPP	Clinical diagnosis of the primary CSCC includes description of the lesion, recording of symptoms and location and measurement of the diameter. Photographic documentation is recommended. Dermatoscopy can help in the differential diagnosis of CSCC pre-operatively.
	Strength of consensus: 100%

4.3. Histopathological diagnosis

The gold standard for the diagnosis of CSCC is histology. A biopsy or excision and histological confirmation should be performed in all clinically suspected CSCCs. A lower threshold for biopsy of suspicious lesions has been proposed for solid organ transplant recipients.[107] Depending on the size of the tumor and treatment approach, an incisional biopsy, i.e., incision or punch biopsy or an excisional biopsy of the entire lesion can be performed initially. Preoperatively, the longest clinical diameter of the lesion (including the peripheral rim of erythema) should be recorded and noted on the surgery report as it is part of further prognostic staging.[108]

CSCCs consist of atypical epithelial tumor cell formations that extend beyond the epidermis into the underlying dermis. Like the cells of the stratum spinosum of the epidermis, the cells tend to cornify and horny pearls are formed. [109] [110] CSCC may be classified according to the WHO classification of skin tumors (4th edition, 2018) [111] as presented in Supplementary Table 3. Not yet included in the WHO classification is desmoplastic CSCC with a high proportion of stroma and narrow cell strands, which grows markedly infiltrative, perineurally or perivascular.[112]

Clinical information to be noted on the biopsy as well as the excision request should include patient demographics, the location and the clinical diameter of the lesion as the latter is necessary for staging. The final histopathological report (after excision) should include histological risk factors that are relevant for the staging and prognosis of CSCC including the thickness, depth of invasion, the presence or absence of perineural invasion (PNI), the grade of differentiation, desmoplastic type and margins status. Additional useful histologic features may be recorded including the histological subtype, lymph vascular invasion and caliber of nerves

affected by PNI if ≥ 0.1 mm (Table 2). According to the AJCC 8th edition cancer staging manual, for CSCC, the maximum vertical tumor thickness is measured in mm, from the granular layer of the adjacent normal epidermis, or 'shoulder' of the tumor, to the deepest part (base) of the tumor.[113] The depth of invasion reports the invasion or not into the subcutaneous fat (Clark level V), or even below for more aggressive tumors. For PNI, there is need for standardization in reporting.[114] The histopathological subtypes that have been associated with higher risk for local recurrence or metastases include desmoplastic-type, adenosquamous or sarcomatoid subtypes, and their presence is a NCCN high-risk criterion. The guideline author group proposes the use of a standardized definition for desmoplasia, based on the criteria by Breuninger et al.[112], also used in subsequent studies [42, 115, 116]. Desmoplastic-type CSCC is diagnosed when at least one third of the tumor specimen shows infiltrating nests of atypical squamous epithelial cells, often featuring single cell strands, surrounded by a distinct sclerotic stromal reaction. The degree of differentiation may classify CSCC into well-differentiated subtypes with low metastatic potential and into poorly differentiated, more aggressive subtypes.[109].

Recommendation 3. (same with recommendation 2023)

Pathology report	**Guideline 2026** **Consensus-based statement**
GPP	If invasive SCC is suspected, a histopathological diagnosis shall be made. The following histological characteristics shall be included in the pathology report: type of specimen (e.g. shave, punch, excisional), histological thickness or depth of invasion, grade of differentiation, presence of perineural invasion, desmoplastic type and margins status.

	It may also include histologic subtype, lymph vascular invasion and caliber of affected nerves with PNI if ≥0.1 mm.
	Strength of consensus: 100%

5. Risk factors for local recurrence, nodal metastasis, disease-specific death

Higher-risk CSCC is defined as invasive CSCC without locoregional (in transit or nodal) or distant metastasis (staged as N0 and M0), that has features associated with a higher risk for local recurrence and metastasis (Box 4).[117] The assessment of the prognostic risk is particularly relevant for common CSCC to identify the few with a higher risk of local recurrence, metastasis, or death, among all the other low-risk tumors. The ascertainment of risk prognostic factors defining higher risk CSCC has an impact on further management, with more aggressive surgical treatment and more frequent follow up recommendations. The variability of risk factors proposed in current guidelines is due to the variability of reported evidence.[3, 4, 39, 43, 112, 115, 116, 118-132] Nevertheless, similar risk factors are proposed in the BAD guidelines, the NCCN guidelines and the European guidelines, regarding the risk associated with local recurrence and nodal metastasis (Table 3).

A list of nine risk factors with evidence-based data portending a greater individual risk of local recurrence or nodal metastasis was proposed in the previous European guidelines 2023 and updated in Box 4. The risk factors may be classified as intrinsic (tumor-related) or extrinsic (patient- and treatment- related). These proposed risk factors include clinical features (tumor diameter, location, symptomatic PNI), histological features (thickness or deep invasion, poor differentiation, desmoplasia, lymph vascular invasion, PNI), radiologic features (radiological

perineural spread, bone erosion), immunosuppression, and positive histological margins. Recurrence has not been included as a risk factor for subsequent recurrence, considering that local recurrence is a prognostic outcome and not a risk factor *per se*. In the current update, histological PNI is defined in more detail as PNI in named nerve, nerve ≥ 0.1 mm or beyond dermis, or extensive PNI. [126, 133]

Each risk factor may differentially affect the risk of subsequent local recurrence, or nodal metastasis or disease-specific death. [8, 42, 45, 134] (Supplementary Tables 4-7) The 5-year cumulative incidences for these poor prognostic outcomes were practically below 1% for CSCC with one "high-risk" NCCN feature, as shown in a retrospective study in 8727 CSCC patients. There was a higher 5-year cumulative incidence of 9.4% for local recurrence, 7.3% for nodal metastasis, 3.9% for distant metastasis and 10.5% for disease-specific death for CSCC with a "very high-risk" feature according to the NCCN guideline risk groups. (Supplementary Table 8) [135] In the systematic review and meta-analysis by Zakhem et al., a greater than 10% prevalence of local recurrence, nodal metastasis, or disease-specific death was shown only for higher stages, and in particular for AJCC8 T3 or T4, and for BWH T2b or T3 [136](Supplementary Table 9)

In addition, the number of risk factors should be considered. As shown in the BWH staging system, the presence of 3 or more risk factors (among poor differentiation, large caliber PNI, clinical diameter of 2 cm or larger and invasion beyond subcutaneous tissue) had 2 to 4 times the risk of a poor outcome compared with tumors with 2 risk factors, even though they would be classified in the same BWH stage T2b. Importantly, a 5-year incidence greater than 10% for a poor prognostic outcome was shown only for CSCCs having 3 or 4 BWH risk factors [41] (Table 4)

A prognostic model (riSCC) developed by Jambusaria Pahlajani et al., provides a personalized estimate of risk of LR, in-transit metastases, nodal metastases, distant metastases, and disease-specific death (DSD) for CSCC, after incorporating patient- and tumor-related risk factors, including age, sex, tumor location, diameter, invasion into fat, differentiation, perineural invasion, lymph vascular invasion, immunosuppression, recurrence and prior surgery type (available as a web-based application at: https://riscc.scoutconsortium.org).[137] Another prediction model by Rentroia-Pacheco et al., includes eight variables (age, sex, number of prior CSCCs, tumor location, diameter, invasion into fat, differentiation, and perineural or lymph vascular invasion) to predict metastatic risk (available as a web-based application at:. https://emc-dermatology.shinyapps.io/CSCC-abs-met-risk/*).* [138]

Artificial intelligence analysis is an emerging approach studied to identify CSCC associated with metastasis in whole slide images.[139, 140] In addition, the use of a 40-gene expression profile (GEP) test combined with clinicopathological risk factors has been studied to predict the metastatic risk of CSCC.[141, 142] (See section 6)

Recommendation 4. (updated from 2023)

	Guideline 2026 **A list of intrinsic (tumor-related) and extrinsic and patient- and treatment-related) risk factors for local recurrence or nodal metastasis of CSCC**
Grade of recommendation: B	1. tumor diameter (>20 mm) 2. localization on lip/ear/temple 3. thickness >6mm or invasion beyond subcutaneous fat

	4. poor differentiation in histology 5. desmoplasia[a] or lymph vascular invasion 6. PNI: histological (in named nerve, nerve ≥ 0.1 mm or beyond dermis, or extensive[b]), symptomatic, or radiological PNI 7. bone erosion 8. immunosuppression[c] 9. positive histological margins Note: The presence of multiple risk factors confers significantly higher risk
Level of evidence: 2	Systematic review and meta-analysis Quality of evidence low to moderate.[7, 8] Retrospective study in patients treated with microscopically controlled surgery[116, 128] Retrospective studies[43, 112, 116, 119-127, 131] Prospective studies[39, 115, 132] Systematic review showing worse prognosis with clinical PNI compared to histological PNI[129] Systematic review on CSCC with bone invasion[130] Scoping review[133]
	Strength of consensus: 100%

[a] Other histologic types have been reported to portend a higher recurrence risk, such as acantholytic or adenosquamous type, but with less supportive evidence.

[b] Extensive PNI defined as 5 or more distinct involved nerves per histological section[126]

[c] Immunosuppression defined as: organ transplantation, HIV, chronic lymphatic leukemia or another hematologic malignancy[42, 131]; Immunosuppression not specifically defined in the meta-analyses[7, 8]. Zakhem et al., reported organ transplantation and HIV predilecting for a higher risk of local recurrence and organ transplantation for nodal metastases. (Supplementary Tables 4-7)

6. Gene expression profiles (GEP)

The 40-GEP was validated to predict risk of nodal/distant metastasis in high-risk, localized CSCC.[141] Subsequent work shows that integrating 40-GEP with established systems (AJCC-8, BWH, NCCN risk groups) improves discriminatory performance and supports risk-aligned management and risk classification when combined with clinicopathologic factors.[142, 143] Multi-center analyses suggest 40-GEP classes correlate with metastasis-free and local-recurrence-free survival and may help specify who benefits from adjuvant radiotherapy (ART) (signal for benefit in Class 2B, potential de-escalation in Class 1).[144-146] Economic modeling indicates possible cost savings when guiding ART. These data are encouraging but non-randomized.[147] A systematic review/meta-analysis of three studies supports added prognostic value of 40-GEP [141, 142, 148, 149], while critical commentaries highlight limitations (industry sponsorship, retrospective designs, generalizability), underscoring the need for prospective, outcome-driven European studies. [150]

How-to-use practice points

Order on primary-tumor tissue after complete histopathologic work-up and conventional risk scoring (e.g., AJCC-8, BWH, NCCN risk groups). Use results in multidisciplinary discussion to refine risk-aligned surveillance and, in carefully selected cases, ART decisions.

Do not base SLNB, margin management, or systemic therapy decisions solely on a GEP result. Evidence in immunosuppressed patients and for predicting outcomes beyond metastasis risk is insufficient. Consider local availability/reimbursement and communicate test limitations (most data from U.S. cohorts; prospective outcome data limited).

Summary

A validated 40-gene expression profile (40-GEP; commercially: DecisionDx-SCC) can be considered as an adjunct to established clinicopathological risk stratification in selected patients with localized, high-risk CSCC, where the result is likely to change management (e.g., intensity of follow-up imaging, consideration of adjuvant radiation therapy [ART]). GEP must not replace histopathologic assessment or clinical staging and should not be used in low-risk disease. Evidence remains largely retrospective/observational, with growing—but still limited—data on decision impact; therefore, routine use in all patients is not recommended.

7. Staging work-up

Recommendations for the staging work-up of CSCC are shown in Figure 4. Staging for recurrent CSCC is the same as for primary CSCC.

7.1. Physical examination

The diagnosis of CSCC should prompt a complete and careful physical examination including primary tumor, total-body skin examination for the presence of other skin disorders as dermatoheliosis, AK, other skin cancers, chronic inflammatory diseases or signs of diseases with increased risk of CSCC (albinism, xeroderma pigmentosum, etc.) and evaluation of the skin surface of the primary site to rule out in-transit metastasis.[151]

Although the overall risk of lymph node involvement in invasive CSCC is relatively low (up to 5%) [40], all patients should undergo a careful physical examination and palpation of the regional

lymphatic basins.[39, 152] This approach is sufficient in most low-risk CSCC. In case of a clinically or radiologically detected regional node, a fine needle aspiration cytology (FNAC) is recommended.[153] As an alternative to FNAC, ultrasound-guided core biopsy can be done.[153] (Figure 4).

7.2. Nodal imaging

The need for staging procedures is not well established due to limited data for CSCC from the literature. In patients with common primary CSCC but without palpable lymph nodes imaging for staging is recommended only in patients with CSCC with an EADO risk factor (Box 4) (Figure 4). Imaging methods such as ultrasonography (US), computed tomography scan (CT) or positron emission tomography computed scan (PET-CT) are more sensitive than clinical examination. [152-154] There are limited data on the use of US for nodal metastasis for CSCC. There is some evidence in patients with vulvar CSCC or head/neck SCC. A study of 44 patients with vulvar CSCC and suspected inguinal lymph node metastases reported that US had a higher sensitivity and negative predictive value than CT, but lower specificity and positive predictive value. [155] A meta-analysis (17 studies) in patients with HNSCC (not CSCC) evaluated radiological imaging modalities including US, US-guided FNAC (USgFNAC), CT, and MRI for the detection of lymph node metastases. USgFNAC showed the highest diagnostic odds ratios. US performed significantly better than MRI. Mean sensitivity of 87% was highest for US and specificity of 98% was highest for USgFNAC. However, there were only 2 studies addressing the evaluation of clinically N0 necks.[154] In a retrospective study of baseline and surveillance imaging in 87 high-risk CSCC, disease was detected in 26 (30%) cases of which 18 were subclinical.[156] In a larger

retrospective study in 246 high-risk HNCSCC, who underwent baseline ultrasonographic imaging of their lymph nodes (cervical and parotid), this was more sensitive (sensitivity 91%, specificity 78%) than clinical examination alone (sensitivity 50%, specificity 96%) for the detection of lymph node metastasis. The authors concluded that the high sensitivity of US for surveillance detection of nodal metastases should be evaluated against the high rate of false-positive findings, as explored with FNAC biopsy.[157]

As lymph node metastases from CSCC may be more superficial and easier to detect on US than those from mucosal SCC, US performed by experienced physicians may be a cost-effective minimally invasive staging modality for lymph nodes.[152]

7.3. Imaging for laCSCC and distant metastasis

For staging of advanced CSCC, consultation in a multidisciplinary tumor board including a radiologist is mandatory to optimize the use of imaging modalities. In large CSCC or those with possible involvement of underlying structures (orbital invasion, PNI), additional imaging tests, such as CT or MRI may be required to accurately assess the extent of the tumor and the presence of metastatic spread.[129, 158-160] MRI is indicated for subtle intracranial disease, perineural spread[119], and imaging of tumor invasion in surrounding soft tissue,.[158, 160] CT scan and PET-CT are excellent techniques for the detection of metastatic involvement in distant organs [160] (Figure 4).

One critical question is how these radiological investigations help the therapeutic choice with an impact on the course of the disease. A retrospective study of radiologic imaging for high-stage

BWH T2b and T3 CSCC in 45 patients reported mainly CT (79%), PET/CT or MRI, while there was no patient in this cohort that underwent imaging with ultrasound. Imaging changed management in 16 (33%) patients.[161] Another study in 394 CSCCs reported imaging in 35% of tumors due to staging or treatment planning, and more common imaging modalities were CT (59%), PET/CT (42%), and MRI (37%), while US was used only in one CSCC. Imaging changed management in 47.2% of tumors.[162]

Recommendation 5. (updated from recommendation 2023)

Imaging for staging	**Guideline 2026** **Evidence-based recommendation**
Grade of recommendation: B	Patients with low risk CSCC should undergo physical examination only with no need for imaging studies unless indicated by physical examination Patients with primary common CSCC with risk factors* should be staged for non-palpable lymph node involvement, preferably by US or by CT scan. For suspected underlying tissue involvement (bone or soft tissue), CT or MRI should be done to determine extent of local infiltration. LaCSCC should undergo imaging to rule out metastasis. CSCC with nodal involvement should undergo a full skin examination and imaging studies to rule out distant metastatic disease.
Level of evidence: 3	There are no precise clinical guidelines for radiologic evaluation for CSCC [158] Meta-analysis of studies for the detection of lymph nodes metastases in HNSCC (only 2 studies addressing the evaluation of clinically N0 necks)[154] Retrospective studies [155, 157, 161-166] Review of studies on nodal staging of higher-risk CSCC[152]

	Strength of consensus: 100%

* Specification of risk factors for imaging for non-palpable regional nodal metastasis cannot be given, as the independent effect of risk factors has not been consistently reported. CSCC at higher risk for nodal metastasis include (but are not restricted to) AJCC8 T3/T4, BWH T2b/T3 stages.

7.4. Sentinel lymph node biopsy (SLNB)

SLNB for patients with CSCC aims at the detection of occult nodal metastasis with the hope that their early management may improve prognosis[2]. Published systematic reviews report rates of positive SLNB ranging from 0% to 12.3% and up to 29.8%, depending on high-risk criteria. [167-170] In the meta-analysis of Schmitt et al., (19 studies, 130 patients with non-anogenital CSCC) the risk of having a positive sentinel lymph node increased with the number of risk factors, varying from 0% in AJCC T1 tumors to 60% in AJCC T4 tumors, and reached 7.1% (6/85) in BWH T2a, 29.4% (5/17) in BWH T2b and 50% (3/6) in BWH T3 stages.[169]

Regarding CSCC, in the systematic review of Tejera-Vaquerizo et al., in 2018 (23 studies), there were no studies reporting on predictors of SLN involvement or on the prognostic utility of SLN following adjustment for confounders.[168] Two more recent studies revealed a survival benefit of SLNB versus observation.[171, 172] In a multicenter study, SLNB was independently associated with a reduced risk of nodal recurrence, disease-specific mortality and all-cause mortality in immunocompetent patients.[171] A retrospective SEER registry study reported a benefit in disease-specific survival of SLNB versus observation for CSCC of the head and neck specifically in patients with multiple risk factors.[172] Nevertheless, clear evidence about the prognostic impact of this recommendation in terms of overall survival is lacking.

Whether a completion lymph node dissection (CLND) after a positive SLN is needed in CSCC, is also a matter of debate due to the absence of good level of evidence. Kesmodel et al., looked at a cohort of 2730 patients identified from the U.S. National Cancer Database (NCDB) with CSCC, of whom 42.3% underwent SLNB (15.4% positive). Patients who underwent CLND demonstrated a non-significant trend towards an improved survival (HR: 0.63, 95% CI: 0.30–1.33, p=0.221).[173]

Huis In 't Veld et al., reported a 5-year disease-specific survival of 52% in patients with CSCC with nodal involvement treated with therapeutic lymph node dissection (of whom 65% also received adjuvant radiotherapy), indicating that lymph node dissection +/- adjuvant radiotherapy can achieve durable survival in approximately half of regionally metastatic CSCC cases. None of these patients, however, had a positive SLNB. [174] It is obvious that despite curative intent surgery + adjuvant radiotherapy, these patients are at high risk of recurrence/metastases, and would potentially benefit from additional effective systemic therapy.

Recommendation 6. (same with recommendation 2023)

Sentinel lymph node biopsy (SLNB) for CSCC	**Guideline 2026** **Evidence-based recommendation**
Grade of recommendation: X	SLNB is currently not recommended in the management of CSCC as a standard of care.
Level of evidence: 3	No evidence of prognostic advantage in the detection of occult metastatic disease by SLNB [167, 168, 175] Meta-analysis[168, 176] Systematic review [170, 177, 178]
	Strength of consensus: 100%

8. Staging systems for CSCC

After risk factors have been identified, and the tumor spread has been assessed by physical examination or imaging as appropriate (Figure 4), in the last step, the clinical, histologic and radiologic findings are incorporated into staging systems.[179] The more widely used staging systems include the UICC 9th edition (Union for International Cancer Control)[12] (pathological classification of head/neck CSCC shown in Table 5, clinical and pathological classification of non-head/neck CSCC shown in Supplementary Table 10), the AJCC 8th edition (American Joint Committee on Cancer) (pathological classification and staging shown in Tables 5, 6) [11], and the Brigham and Women's Hospital (BWH) classification system (Table 7) [180] . Notably, the recently released UICC TNM classification and staging 9th edition for CSCC, taking effect as of January 2026, is the same with the previous 8th edition, with two differences: 1) including the lip vermillion border and commissure, and 2) re-defining perineural invasion for T3 as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in or involvement of five or more nerves per section, without foramen or skull base invasion or transgression.[10, 12] Furthermore, there are two additional staging systems for nodal disease of the head and neck (N1S3 [181] and ITEM [182]) (Supplementary Table 11).

The T stage of the UICC and the AJCC staging system are traditionally based upon the diameter of the tumor, including tumor thickness and perineural invasion as additional risk factors. The BWH system is built up of similar risk factors of tumor diameter ≥2 cm, poorly differentiated histology, perineural invasion of nerve(s) ≥0.1 mm in caliber, or tumor invasion beyond subcutaneous fat, however the risk category increases with the number of risk factors (Table 7). Unlike the staging systems for Merkel Cell Carcinoma and melanoma, the current

staging systems for CSCC do not include satellitosis or in-transit metastases (S-ITM), even though S-ITM has been identified as an independent factor of poorer prognosis.[183, 184]

The past years many groups have studied the validity of the various systems for predicting the risk of recurrence or metastasis. Ruiz et.al. compared AJCC and BWH in a population of 680 head and neck CSCC. [185] Higher risk CSCC (AJCC8 (T3/T4) and BWH (T2b/T3) accounted for 121 (18%) vs 63 (9%) of total cases, 17 (71%) vs 16 (70%) of metastases, and 11 (85%) vs 12 (92%) of deaths. The AJCC8 T2 and T3 comprised 23% of cases and had statistically indistinguishable outcomes. The authors report a higher specificity (93%) and positive predictive value (30%) for identifying cases at risk for metastasis or death by BWH. There was no difference for local recurrence (LR) and overall survival (OS).[185] The validation study of Venables et al., investigated the performance of AJCC8, BWH, Tubingen staging systems and Salamanca T3 refinement in predicting metastasis on 887 metastatic CSCC and 887 nonmetastatic CSCC. The BWH system showed the highest specificity (92.8%, 95% confidence interval (CI) 90.8–94.3%) and c-index (0.84, 95% CI 0.82–0.86).[186] They concluded that although BWH showed the highest overall discriminative ability, positive predictive value was low for all staging systems. However, the study does have some limitations like the fact that the authors assume that the diameter criterion of ≥ 0.1 mm must have been met if PNI was reported, so a currently included T3 tumor might be a T1 tumor if PNI is in a nerve < 0.1mm. In another study Roscher et.al. compared AJCC 7, AJCC 8, BWH and Breuninger's staging system.[187] They found that in the systems used by Breuninger et. al. and the BWH system gave the best result in predicting the risk of metastasis. Using the system by Breuninger et. al., the risk of metastasis was 3-fold for the high co-risk factors (OR: 3.27; 95%CI:1.54-6.96). The BWH staging system gave ORs for metastasis at 6.58 (95%CI: 2.90-

14.90) for the T2a category and 35.34 (95%CI: 9.76-128.06) for the T2b category. They also state that current staging systems for CSCC are unsatisfactory in identifying non-selected patients with CSCC at higher risk for metastasis. [187] Other studies reported similar performance for BWH and AJCC8 staging systems for predicting poor outcomes for head/neck and non-head/neck CSCCs, however sensitivity and positive predictive value were low.[188, 189]

9. Primary and secondary prevention

Increased UV exposure, both chronic or intermittent, professional or recreational, from natural or artificial sources, in childhood and adulthood is associated with an increased risk for CSCC. As up to 95% of keratinocyte carcinoma can be attributed to UV exposure, photoprotection is the mainstay of the cSCC primary prevention.[17, 190, 191] Multi-component strategies are considered as most effective for inducing changes in sun exposure behaviors of the population, such as mass media campaigns, environments offering shaded areas, family-oriented behavioral counselling for the early childhood interventions and increasingly, digitally delivered interventions.[192-196] Messages of UV protection, avoidance of sunbathing and tanning are useful but these interventions are struggling with strong social trends valuing pleasure associated with sunbathing and seaside vacations, the perception of suntan considered as aesthetic as well as the false concept that tan is marker of good health. Fair-skinned individuals and persons at high-risk for skin cancer should be advised to avoid sunbathing and the use of tanning beds and to use photo-protection measures starting from an outdoor UV index of 3 or higher. These measures include seeking shade and avoiding direct sun exposure at solar noon, wearing

protective clothing like long-sleeved tops, longer skirts or trousers, wide-brimmed hats and sunglasses and using broad spectrum, UVA and UVB sunscreens with SPF> 30 on the skin areas that cannot be covered by clothes.[191]

Regular use of sunscreen, in addition to other photoprotective measures, has been reported to be effective in reducing the incidence of AK and CSCC in four randomized controlled trials and several non-randomized experimental prospective studies, in the general population and organ transplant recipients.[197-200] However, in two meta-analyses there was no significant effectiveness of sunscreen for preventing either melanoma or nonmelanoma skin cancers, but these included also retrospective studies and studies that analyzed use of only UVB filters.[201, 202] Thus, recommendation for regular sunscreen use remains as a third measure for effective sun protection if sun exposure cannot be avoided, on skin areas that cannot be otherwise protected, along with seeking shade and the wearing of clothing to cover the skin**.** A clear message of strict photoprotection measures should be given to all patients who have already developed CSCC.

Specific situations may require specific preventive and screening measures: In 2010, the International Commission on non-ionizing radiation published a statement on necessary protection of workers against ultraviolet radiation, and in several countries keratinocyte cancer is officially recognized as an occupational disease in outdoor workers.[203, 204] Risk-tailored screening procedures were developed for organ transplant recipients in Australia and the UK and similar efforts are under way in the USA.[26, 205, 206]

Recommendation 7. (updated from 2023)

Prevention	Guideline 2026 Evidence-based recommendation
GPP	All individuals at high risk for CSCC shall be educated about sun protection measures including avoidance of sun bathing and tanning, the use of shade, protective clothing, regular use of sunscreens and avoidance of artificial UVR tanning.
Level of evidence 1	Measures of photoprotection should be recommended when outdoors UV index is 3 or higher, including seeking shade, the use of protective clothing, regular use of sunscreens on uncovered skin areas. Systematic review of randomized controlled trials, RCT [192-196, 207-210]
Level of evidence 2	Regular use of sunscreens shall be recommended RCT confirmed reduction in CSCC rate. Guidelines. [191, 197-200]
	Strength of consensus: 100%

10. Chemoprevention

Chemoprevention aims to reduce the risk of the development of new CSCC, especially for patients at risk of developing numerous and/or aggressive CSCC.[211] Systemic agents studied for the chemoprevention of CSCC include nicotinamide, retinoids, and non-steroidal anti-inflammatory drugs (NSAIDs). Nicotinamide is a water-soluble form of vitamin B_3 (niacin). It may enhance repair of photodamaged DNA and prevent the immune-inhibitory effects of UVR.[212]. A metanalysis of nicotinamide in skin cancer (552 patients, 5 trials) in 2022, reported that nicotinamide for 6-12 months significantly reduced the rate of new CSCC, compared with placebo-controls in higher risk patients and SOTRs (rate ratio 0.48 (95% CI, 0.26-0.88).[213] There

is only one randomized controlled trial in 386 immunocompetent patients with a history of at least two nonmelanoma skin cancers. At 12 months, there was a lower rate of new CSCCs with nicotinamide 500 mg twice daily (reduction by 30% compared to placebo, p=0.05) The positive effect was limited to the active treatment period. [214] This benefit appears to be supported by a large retrospective cohort study in 33822 veterans which found a reduction in the incidence rates of subsequent skin cancers (including CSCC) in patients who received at least 30 days of nicotinamide 2x500mg/day.[215] Nicotinamide is reported safe and generally well tolerated. [213, 214]

Oral retinoids studied include acitretin and isotretinoin[211, 216-218], which were shown to be effective in reducing the incidence of new CSCC at least during the duration of treatment in higher risk patients. They are, however, not routinely recommended, due to risk of teratogenicity and the dose-related toxicities that are not well tolerated by patients**.**[219, 220] NSAID use was associated with a reduced risk of CSCC in a meta-analysis (2015), with significant study heterogeneity [221]**.** In a UK population-based case-control analysis in patients with incident CSCC, there was a slightly decreased risk of CSCC in regular users of any NSAID (OR: 0.89, 95% CI: 0.82-0.97).[222] An Australian cohort study reported inconsistent patterns of association of NSAID use that did not provide convincing evidence that NSAID may reduce subsequent CSCC risk. [223] For anti-oxidants, phytochemicals and selenium, the current evidence is inconclusive. Vitamin D3 plus calcium had no statistically significant effect in reducing new self-reported NMSC in a RCT in 36,282 postmenopausal women.[224] Vitamin D supplementation alone had no significant effect on reduction of CSCC in a RCT of 2259 individuals [225]

Topical treatments for chemoprevention include 5% 5-fluorouracil (5-FU)[226] that was shown to be effective in reducing the risk of CSCC requiring surgery by 75% in one RCT. A 2-4 weeks course appeared to have a protective effect for one year, with non-significant effect thereafter. 92% of participants in the fluorouracil group reported erythema and 61% had mild-to-moderate crusting [226] Addition of calcipotriol to 5-FU has been shown to increase the benefit.[227] Topical tretinoin has no significant effect in preventing CSCC.[228]

Recommendation 8. (updated from 2023)

Nicotinamide chemoprevention in immunocompetent patients	**Guideline 2026** **Evidence-based recommendation**
Grade of recommendation C	Nicotinamide 500 mg twice daily may be offered to immunocompetent patients with a history of multiple keratinocyte skin cancers considering the favorable safety profile.
Level of evidence 3	A phase 3, double-blind randomized controlled trial showed significantly lower risk (by 30%) of new CSCC with nicotinamide at 12 months, p=0.05)[214] A large retrospective cohort study showed 21% risk reduction of new CSCC. The risk reduction rose to 53%, when nicotinamide was initiated after the first keratinocyte skin cancer.[215] Systematic review[213]
	Strength of consensus: 96% (25 agree, 1 abstential)

11. **Prevention in immunocompromised patients**

Current evidence for CSCC prevention in immunocompromised individuals has mainly focused on organ transplant recipients (OTRs), but potential strategies are also relevant to other immunocompromised patient groups.[229-231]

11.1. Primary prevention

Strict photoprotection is usually recommended in immunocompromised individuals.[231] Evidence that sunscreen is effective in CSCC prevention is limited to a non-randomized, open-label trial in Germany which showed that sunscreen was associated with a significant reduction in CSCC at 24 months, although vitamin D levels were lower [200, 232]. As azathioprine is associated with UVA-photosensitivity and mutagenicity, patient should be advised on sunscreen use and sun avoidance year-round.[233] There is evidence that photoprotection advice is better recalled and implemented if provided in a specialist clinical setting.[234, 235] Although behavioral interventions (e.g. written material, mobile apps and videos) can improve photoprotective behavior, whether this translates into CSCC prevention has not been confirmed.[230]

11.2. Secondary prevention

This has mainly focused on treatment of premalignancy, systemic chemoprevention, modification of immunosuppression and skin cancer surveillance. Evidence for guiding treatment selection, thresholds for initiation and optimal sequencing of these strategies in immunocompromised individuals is mainly based on expert consensus.[231, 236]

11.2.1 Topical chemoprevention

Most RCTs of lesion and field-directed AK treatments have excluded immunocompromised individuals and current guidance is largely based on expert consensus. [231, 236] In a Delphi study which considered interventions for actinic damage, consensus was reached for use of cryotherapy for scattered AK; field therapy (no consensus on type) for grouped AK; and combination lesion-directed and 5-fluorouracil-based field therapy for field cancerized skin.[231]

However, the effectiveness of these recommendations in CSCC prevention requires validation in future prospective studies.

11.2.2 Systemic chemoprevention

Retinoids

Three RCTs confirm that systemic retinoids confer a significant chemopreventive effect in OTRs [237-239], with an estimated 54% overall reduction in CSCC [240] and case series also signal a chemopreventive effect in other immunocompromised patients.[241] The risk of teratogenicity and mandatory pregnancy prevention with double reliable contraception (during treatment and for 3 years after acitretin discontinuation) is an important consideration for females with pregnancy potential. Dose limiting adverse effects include cheilitis, xerosis, alopecia, headache, arthralgia and hyperlipidemia [240, 242-244] and a rebound in CSCCs 3-4 months after discontinuation is common and retinoid chemoprevention should therefore be viewed as long term strategy and requires laboratory monitoring [219, 242]. However, there is no clear consensus regarding when to initiate retinoid chemoprevention.[231] Optimal dosing regimens are also uncertain although acitretin is usually started at low dose (e.g., 10 mg/day) and escalated as tolerated to an effective maintenance dose (e.g., 25-30 mg/day) [231]

Nicotinamide

Nicotinamide is a vitamin B3 derivative and has few adverse effects, does not require laboratory monitoring and is low-cost. The 2015 ONTRAC phase 3 RCT in immunocompetent individuals with at least 2 KCs in the preceding 5 years in Australia demonstrated a 30% reduction in the incidence of new CSCC with nicotinamide 500mg twice daily over 12-months compared with placebo, but evidence in immunocompromised individuals is inconsistent to date.[214] Two small prospective RCTs in OTRs provided a signal of chemopreventive efficacy but were underpowered [245, 246]. The 2023 ONTRANS phase 3 RCT in 158 OTRs in Australia failed to confirm a statistically significant reduction in CSCC compared with placebo although a trend towards reduced CSCC incidence was seen and it has been argued that possible benefit was underpowered due to low recruitment.[247, 248] Although a subsequent small, retrospective, single center OTR

observational cohort study showed benefit[249], a larger multicenter observational retrospective study in a Veterans Affairs OTR cohort failed to confirm an overall chemopreventive effect, although there was a reduction in CSCC incidence if initiated after the first 1-2 KCs.[215] Given the conflicting data, prospective RCT evidence from the ongoing SPRINTR trial in Canada are now awaited (NCT05955924).

Capecitabine

Limited observational data for this 5-fluorouracil prodrug suggest it has a CSCC chemopreventive effect in OTRs: [250-253]. However, dose-limiting side effects (fatigue, hand-foot syndrome, diarrhea, nausea/vomiting, mucositis, anemia, hyperuricemia/gout) resulted in up to 43% of patients discontinuing treatment and further clinical trials are required to establish optimal patient selection, dosing, safety and long-term efficacy [253, 254].

Modification of immunosuppression (MOI)

This is a potential approach to secondary CSCC prevention and is relevant in the context of pre- and post-transplant CSCC, and re-transplantation.[231, 255] It remains uncertain when and how MOI should be undertaken and it requires a multidisciplinary approach, with consideration of factors including type of allograft, risk and implications of rejection, prognosis of individual tumors, and patient preferences [231].

There is no robust measure for overall immunosuppressive intensity to guide decision-making and relatively limited evidence on relative risk of specific drug classes. [231] Of the anti-proliferative agents, azathioprine confers an increased CSCC risk compared to mycophenolate but there is less evidence for significant differences between calcineurin inhibitor (CNIs) [256, 257] and uncertain whether the selective T-cell costimulatory blockade agent, belatacept, is associated with a lower risk of CSCC [258] However, several RCTs have demonstrated that conversion from CNIs to mTOR inhibitors after the first post-transplant CSCC reduces risk of subsequent CSCC, with a non-significant reduction if undertaken after more than one CSCC, but do not have a primary protective effect [259, 260]. A reduction of 56% in keratinocyte cancers with mTORi use was confirmed in a meta-analysis of 5876 OTR from 21 RCTs; an overall increase

in mortality was also reported [261], although this may reflect the higher doses of mTORi used in early trials [262]. Adverse effects of mTORi including delayed wound healing, diarrhoea, mucositis, proteinuria and peripheral oedema, lead to high rates of discontinuation [263].

Sequencing of CSCC secondary prevention approaches

At what stage, in whom and in what order possible preventive interventions should be introduced remains an area of considerable clinical uncertainty. [231, 236, 264] In Delphi expert consensus study, for OTR CSCC prevention, consensus was reached on use of photoprotection and topical treatment in OTRs with photodamage, AK and field change, but no consensus was reached on prevention strategies after the first invasive CSCC, with concerns regarding adverse effects of mTORi conversion despite RCT evidence supporting this.[231] In OTRs with multiple CSCC accruing at a low rate, MOI was recommended together with introduction of systemic chemoprevention, although no agreement was reached as to how MOI should be undertaken and which systemic chemopreventive agent should be started: With higher rates of CSCC accrual (>10/year), acitretin was recommended and was similarly first choice in the event of a high-risk CSCC developing. [231]

11.3. Surveillance

Expert consensus recommends that patients should be counselled on self-monitoring and provided with access to rapid evaluation of suspicious skin lesions. [231, 265] Many post-transplant clinical guidelines advise that all OTRs should be offered skin cancer surveillance at least annually [266], but its evidence supporting effectiveness on CSCC prevention is sparse [267, 268] and the cost-effectiveness of pre-transplantation screening strategies has similarly yet to be validated.[230] More risk-stratified approaches for timing of baseline surveillance using the SUNTRAC tool [268-271] and subsequent surveillance pre- and post-CSCC [206, 265] have been proposed. Most evidence on risk stratification, screening and surveillance in immunocompromised patient cohorts has focused on OTR, but other immunocompromised groups may also potentially benefit, and this has been particularly promoted in patients with CLL and inflammatory bowel disease.[30, 272-274]

Recommendation 9. (updated from 2023)

Prevention of CSCC in solid organ transplant recipients	**Guideline 2026** **Evidence-based recommendation**
GPP	Education about routine skin surveillance, sun protection measures and use of sunscreen should be recommended. Oral retinoids should be considered in OTRs with one or more CSCC Conversion to mTOR inhibitors in OTRs with one or more CSCC should be discussed with transplant physicians. Modification of immunosuppression in OTRs with one or more CSCC can be discussed with transplant physicians.
Level of evidence: 4	Sunscreen: one non-randomized case-control study of sunscreen in OTRs showed a reduction of CSCC [200].
Level of evidence: 3	Oral retinoids: RCTs and systematic reviews confirm CSCC prevention in small numbers of OTRs [237-240].
Level of evidence: 2	Conversion to mTOR inhibitors: CSCC prevention shown in RCTs and systematic reviews [259-263, 275-278].
Level of evidence: 3	Modification of immunosuppression: non-randomized evidence that CSCC may be reduced in OTRs by modification of immunosuppression [231, 256-258].
	Strength of consensus: 100%

Summarizing box of recommendations

Practice points	Recommendation	GOR
1. Definitions and classifications of invasive CSCC	Common primary CSCC shall be classified as low-risk or higher-risk. Higher-risk CSCC is defined as invasive CSCC without locoregional (in transit or regional nodal metastasis) or distant metastasis (staged as N0 and M0), that has features associated with a higher risk for local recurrence and metastasis (Box 4). Advanced CSCC shall be classified as locally advanced (LaCSCC), locoregional metastatic or distant metastatic CSCC (mCSCC). LaCSCC shall be defined as non-metastatic CSCC, not amenable to either surgery or radiotherapy with reasonable hope for cure, because of multiple recurrences, large size, bone erosion or invasion, or deep infiltration beyond subcutaneous tissue into muscle or along nerves, or else tumors in which curative resection would result in unacceptable complications, morbidity or deformity.	A
2. Clinical and non-invasive diagnosis of the primary CSCC	Clinical diagnosis of the primary CSCC includes description of the lesion, recording of symptoms and location and measurement of the diameter. Photographic documentation is recommended. Dermatoscopy can help in the differential diagnosis of CSCC pre-operatively.	GPP
3. Pathology report	If invasive SCC is suspected, a histopathological diagnosis shall be made. The following histological characteristics shall be included in the pathology report: type of specimen (e.g. shave, punch, excisional), histological thickness or depth of invasion, grade of differentiation, presence of perineural invasion, desmoplastic type and margins status. It may also include histologic subtype, lymph vascular invasion and caliber of affected nerves with PNI if ≥0.1 mm.	GPP

4. Risk factors for local recurrence or nodal metastasis	1. tumor diameter (>20 mm) 2. localization on lip/ear/temple 3. thickness >6mm or invasion beyond subcutaneous fat 4. poor differentiation in histology 5. desmoplasia[a] or lymph vascular invasion 6. PNI: histological (in named nerve, nerve ≥ 0.1 mm or beyond dermis, or extensive[b]), symptomatic, or radiological PNI 7. bone erosion 8. immunosuppression[c] 9. positive histological margins Note: The presence of multiple risk factors confers significantly higher risk	B
5. Imaging for staging	Patients with low risk CSCC should undergo physical examination only with no need for imaging studies unless indicated by physical examination Patients with primary common CSCC with risk factors* should be staged for non-palpable lymph node involvement, preferably by US or by CT scan. For suspected underlying tissue involvement (bone or soft tissue), CT or MRI should be done to determine extent of local infiltration. LaCSCC should undergo imaging to rule out metastasis. CSCC with nodal involvement should undergo a full skin examination and imaging studies to rule out distant metastatic disease.	B
6. SLNB	SLNB is currently not recommended in the management of CSCC as a standard of care.	X
7. Prevention	All individuals at high risk for CSCC shall be educated about sun protection measures including avoidance of sun bathing and tanning, the use of shade, protective clothing, regular use of sunscreens and avoidance of artificial UVR tanning.	GPP
8. Nicotinamide chemoprevention in	Nicotinamide 500 mg twice daily may be offered to immunocompetent patients with a history of multiple	A

immunocompetent patients	keratinocyte skin cancers considering the favorable safety profile.	
9. Prevention of CSCC in solid organ transplant recipients	Education about routine skin surveillance, sun protection measures and use of sunscreen should be recommended. Oral retinoids should be considered in OTRs with one or more CSCC. Conversion to mTOR inhibitors in OTRs with one or more CSCC should be discussed with transplant physicians. Modification of immunosuppression in OTRs with one or more CSCC can be discussed with transplant physicians.	GPP

GOR: grade of recommendation, GPP: good clinical practice point, SLNB: sentinel lymph node biopsy

* Specification of risk factors for imaging for non-palpable regional nodal metastasis cannot be given, as the independent effect of risk factors has not been consistently reported. CSCC at higher risk for nodal metastasis include (but are not restricted to) AJCC8 T3/T4, BWH T2b/T3 stages.

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Tables & Figures

Table 1. Grades of recommendation

Grade of recommendation	Description	Syntax	Color
A	Strong recommendation	Shall	Green
B	Medium strength recommendation	Should, or should not	Light green
C	Weak recommendation	May/can, or may not/can not	Yellow
X	Contraindication	Shall not/should not	Red
GPP	Good clinical practice point	Based on consensus, when adequate evidence was not available	White

Table 2. Basic features included in the histopathological report of a CSCC diagnosis (modified from[1, 279])

HISTOPATHOLOGIC REPORT of CSCC		
Type of specimen	☐ punch ☐ shave	☐ excisional
Histologic subtype:	☐ Common ☐ Acantholytic ☐ Spindle cell SCC ☐ Verrucous	☐ Clear cell SCC ☐ Other:
Degree of differentiation	☐ Well differentiated ☐ Moderately differentiated ☐ Poorly differentiated	
Tumor histological thickness*	..... mm	
Invasion beyond subcutaneous fat	☐ No ☐ Yes	
Perineural invasion, in named nerve, nerve caliber ≥ 0.1 mm or beyond dermis, or extensive	☐ No ☐ Yes	
Desmoplasia	☐ No ☐ Yes	
Lymphatic/vascular invasion	☐ No ☐ Yes	
Complete excision -clear histological margins: Clear deep margins Clear lateral margins	 ☐ No ☐ Yes ☐ No ☐ Yes	

*Tumor thickness measured from the granular layer of adjacent normal epidermis to the base of the tumor (per 8th TNM classification for carcinomas of the skin)

Table 3. Similarity of risk factors in current guidelines for CSCC with higher risk for poorer prognosis

Present European Guideline 2026 - Risk for local recurrence or metastasis	**NCCN 1.2026 [3] – Very high-risk for local recurrence, metastasis, or disease-specific death**	**BAD Guideline 2020** [4] **- Very high-risk for local recurrence, nodal metastasis, or disease-specific death**
Diameter >20 mm	Diameter >40 mm	Diameter >40 mm
Localization on lip/ear/temple	-	-
Thickness >6 mm	Thickness >6 mm	Thickness >6 mm
Invasion beyond subcutaneous fat	Invasion beyond subcutaneous fat	Invasion beyond subcutaneous fat
Bone erosion	-	Bone invasion
Histology: desmoplasia or lymph vascular invasion	Adenosquamous or sarcomatoid in any portion of the tumor Lymphatic or vascular involvement	Histological subtype: desmoplastic, adenosquamous, spindle/sarcomatoid/metaplastic
Poor differentiation	Poor differentiation	In-transit metastasis
Immunosuppression	–	Immunosuppression
PNI (histological (in named nerve, nerve ≥ 0.1 mm or beyond dermis, or extensive), symptomatic or radiological)	Histological PNI of a nerve deeper than the dermis or ≥ 0.1 mm	Histological PNI in named nerve, nerve ≥ 0.1 mm or beyond dermis
Positive histological margins	-	One or more involved or close (<1 mm) histological margin in a high-risk tumor

NCCN: National Comprehensive Cancer Network, BAD: British Association of Dermatologists

Table 4. 5-year cumulative incidence depending on the number of risk factors included in the Brigham and Women's Hospital (BWH) T staging system (from Ran et al., 2025)[41]

	Local recurrence	Nodal metastasis	Distant metastasis	Disease-specific death
BWH risk factors*	**5-y incidence (95% CI)**	**5-y incidence (95% CI)**	**5-y incidence (95% CI)**	**5-y incidence (95% CI)**
4	33.0% (19.0-47.0)	28.0% (15.0-42.0)	8.4% (2.6-19.0)	25.0% (12.0-39.0)
3	16% (11.0-22.0)	20% (15.0-26.0)	7.9% (4.6-12.0)	11% (6.7-16.0)
2	8.8% (7.0-11.0)	11% (9.2-13)	2.35% (1.4-3.4)	5.4% (4.0-7.0)
1	5.0% (4.1-5.9)	3.6% (2.9-4.4)	1.1% (0.7-1.6)	1.9% (1.4-2.7)
0	1.7% (1.5-2.0)	0.6% (0.4-0.7)	0.2% (0.1-0.3)	0.3% (0.2-0.4)

* Risk factors: diameter of 2 cm or larger, poorly differentiated histology, tumor extension beyond subcutaneous fat, and invasion of a nerve of large caliber.

Table 5. AJCC 8th edition/UICC pTNM classification 9th edition – for CSCC of head and neck (excluding eyelid for UICC).[10, 11]

AJCC 8th/UICC pTNM classification 9th edition – for CSCC of head and neck			
pT – Primary Tumor		**pN – Regional Lymph Nodes**	
TX	Primary tumor cannot be identified	NX	Regional lymph nodes cannot be assessed
T0	No evidence of primary tumor	N0	No regional lymph node metastasis
T1	Tumor ≤ 2 cm in greatest dimension	N1	Metastasis in a single ipsilateral lymph node <3 cm in greatest dimension without ENE
T2	Tumor >2 cm and ≤ 4 cm in greatest dimension	N2a	Metastasis in single, ipsilateral lymph node <3 cm with ENE or, >3 cm and ≤6 cm in greatest dimension without ENE
T3	Tumor >4 cm in greatest dimension or minor bone erosion or PNI or deep invasion[a,b]	N2b	Metastasis in multiple ipsilateral lymph nodes, all <6 cm in greatest dimension without ENE
T4a	Tumor with gross cortical bone/marrow invasion	N2c	Metastasis in bilateral or contralateral lymph node(s), all <6 cm in greatest dimension without ENE
T4b	Tumor with axial skeleton invasion including foraminal involvement and vertebral foramen involvement to the epidural space	N3a	Metastasis in a lymph node >6 cm in greatest dimension without ENE
		N3b	Metastasis in a lymph node >3cm in greatest dimension with ENE or multiple ipsilateral, or any contralateral or bilateral node(s) with ENE
		M – Distant Metastasis	
		M0	No distant metastasis
		M1	Distant metastasis

ENE: extranodal extension

[a] In AJCC staging, perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression

In UICC 9th edition staging, perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in or involvement of five or more nerves per section, without foramen or skull base invasion or transgression.

[b] Deep invasion defined as invasion beyond the subcutaneous fat or > 6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor)

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

N classifications shown in pink include the nodal criteria eligible for adjuvant cemiplimab treatment included in the C-POST trial[280]

Table 6. Staging based on UICC TNM classification 9th edition (2025) for all locations of CSCC excluding eyelid, perianal, vulva and penis, and based on AJCC TNM classification 8th edition (2017) for CSCC of the head and neck [11, 12]

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IVA	T1,T2,T3	N2, N3	M0
	T4	Any N	M0
Stage IVB	Any T	Any N	M1

Table 7. BWH classification system[180]

BWH risk factors
Tumor diameter ≥2 cm
Poorly differentiated histology
Perineural invasion of nerve(s) ≥0.1 mm in caliber
Invasion beyond subcutaneous fat (excluding bone invasion, which upgrades tumor to BWH stage T3).
T1 0 risk factors T2a 1 risk factor T2b 2-3 risk factors T3 4 risk factors or bone invasion

Figures

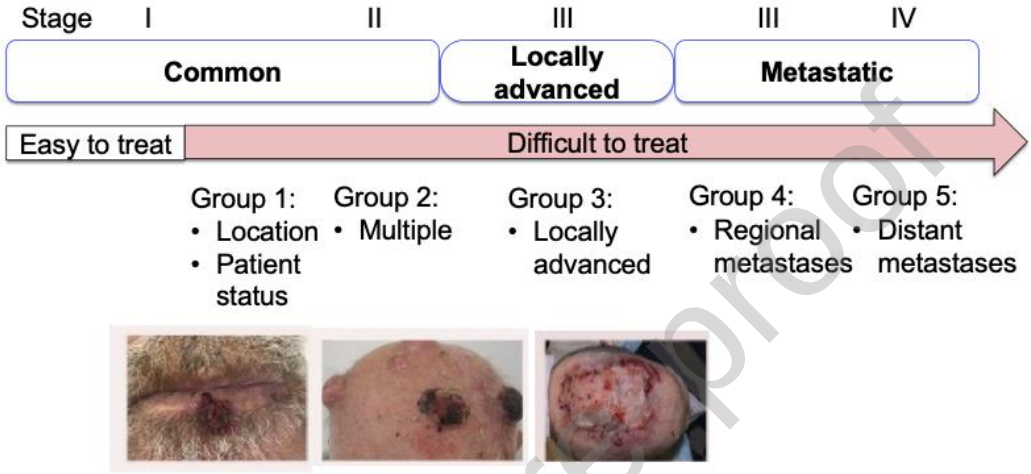


Figure 1. Summary schematic showing the EADO difficult-to-treat CSCC classification corresponding to the traditional definitions and stage.[13]

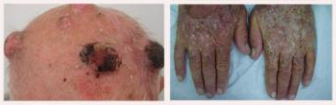
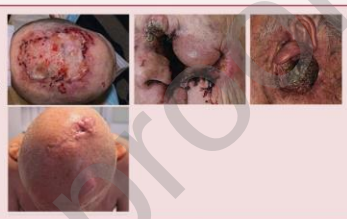
	Stage	Characteristics		Illustrative pictures	Classification group
Common cSCC	I	Easy to treat cSCC	cSCC (TN0M0) easily manageable None of the other groups characteristics **Surgical excision recommended*		Not included in the experiment
	IIA	Complex to treat	cSCC (TN0M0) complex to treat due to tumor and/or patient characteristics* **Surgery is likely to be curative but functional or cosmetic consequences and/or other factors (general status, immunosuppression, comorbidities, tumor history..) may lead to therapeutic discussion including radiotherapy with curative intention and/or medical treatments*		Group 1 *n* = 65
	IIB	Multiple tumors	Multiple cSCCs (TN0M0) when the number is the main problem for management, whatever the background (genetics, immunosuppression…) **Multimodal approach with either surgery/ radiotherapy/systemic therapy* ***when the characteristics of at least one cSCC, is the main problem and not the number itself, patients must be classified in other relevant groups according to the most problematic cSCC*		Group 2 *n* = 24
Advanced cSCC	IIC	Locally advanced without regional metastases	Locally advanced cSCC (TN0M0) **surgery and/or radiotherapy are unlikely to be curative indication for systemic therapy / radiotherapy/ palliative care according to patient's performance status*		Group 3 *n* = 69
Metastatic cSCC	III	Regional metastases	cSCC with regional metastases either nodal or cutaneous metastases distant from the primary (TN+M0) whatever the severity and number of cSCC **Multimodal approach with either surgery/ radiotherapy/systemic therapy*		Group 4 *n* = 59
	IV	Distant metastases	cSCC with distant metastases (TNM+), whatever the severity and number of cSCC **Multimodal approach with systemic therapy, radiotherapy or palliative care according to patient's performance status*		Group 5 *n* = 31

Figure 2. EADO classification for CSCC. Six-group classification derived from the interpretation of the five consensual clusters and the addition of the easy to treat group. Each definition is the best formulation found by the experts to describe the common points between cases in each given consensual cluster. The numbers indicate the number of cases initially included in each consensual cluster. (From: Gaudy-Marqueste C, Grob JJ, Garbe C, Ascierto PA, Arron S, Basset-Seguin N, et al. Operational classification of cutaneous squamous cell carcinomas based on unsupervised clustering of real cases by experts. J Eur Acad Dermatol Venereol. 2025;39:612–21. Creative Commons CC BY-NC-ND license, [13])

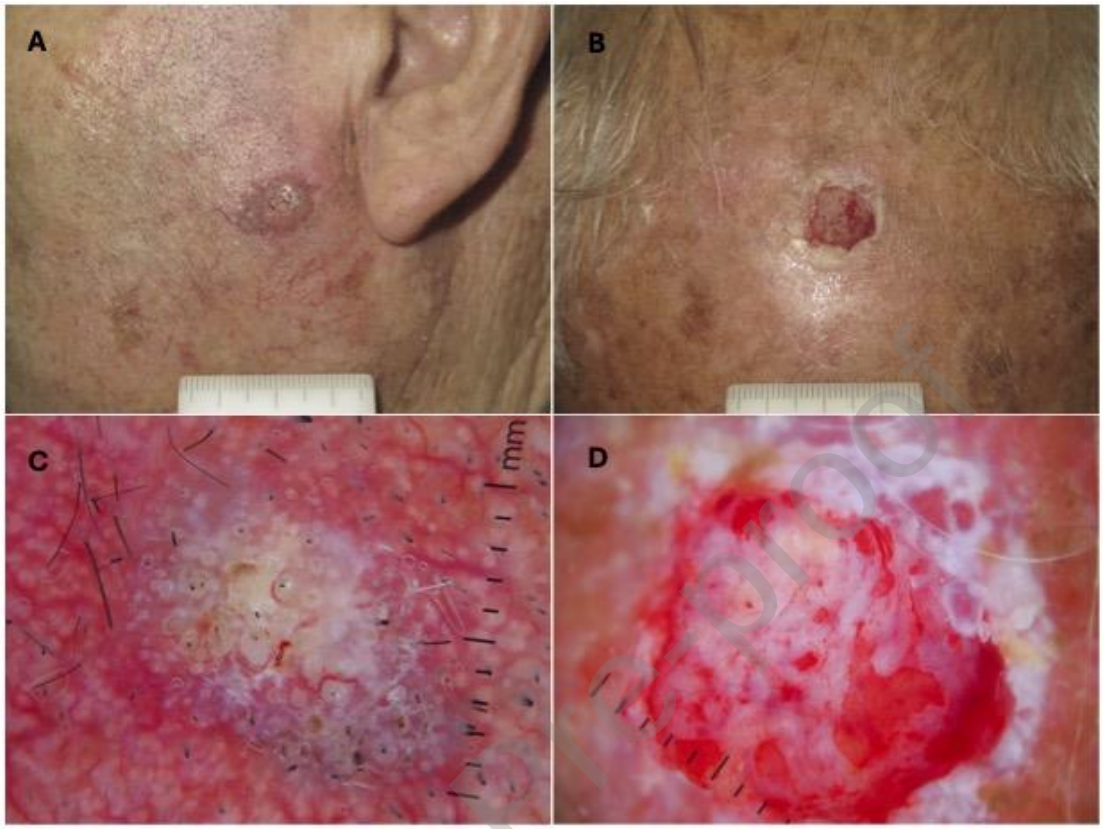


Figure 3. Clinical (upper panel) and dermatoscopical (lower panel) characteristics of CSCC. **A, C**: A typical example of well-differentiated SCC, dermatoscopically typified by a white predominant color, white perifollicular circles, rosettes and hairpin and linear irregular vessels. **B, D**: A typical example of poor-differentiated SCC, dermatoscopically predominated by a red color and a polymorphous vascular pattern combining coiled, linear irregular and hairpin vessels. (Photos courtesy of Aimilios Lallas)

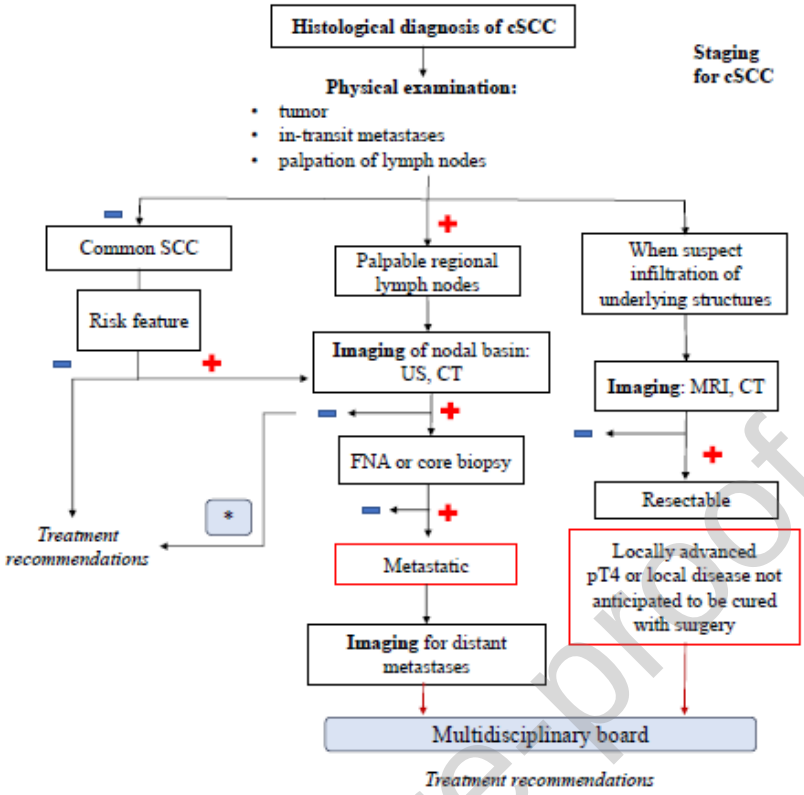


Figure 4. Algorithm for the diagnostic approach and staging in patients with CSCC (updated from 2023). Strength of consensus: 100%

* Multidisciplinary board is recommended for:

1) recurrent CSCC with non-nodal criteria at high risk of recurrence, as defined in the CPOST trial (clinical and /or radiologic involvement of named nerves, or T4 lesions with invasion of cortical bone or skull base, or recurrent cSCC plus ≥1 additional feature of ≥T3, or poorly differentiated histology and ≥ 20 mm diameter)
2) CSCC BWH T2b/T3, to consider adjuvant RT.

BWH T2b: 2-3 risk factors, T3: 4 risk factors or bone invasion. BWH risk factors: diameter ≥20 mm, poor differentiation, histological PNI ≥0.1 mm, tumor invasion beyond fat.
Refer to Guideline 2026 part 2 for detailed treatment recommendations.

Declaration of Interest Statement

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Highlights

- Multidisciplinary guideline on invasive CSCC diagnostics and prevention.
- CSCC may be classified as easy-to-treat or difficult-to-treat.
- Clinical and dermatoscopic features are confirmed by histopathology.
- Clinical, histologic and radiologic findings are incorporated into staging systems.
- Prevention strategies include oral nicotinamide and sun protection measures.