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REVIEW

Guidelines for the diagnosis and treatment of cutaneous squamous cell carcinoma: a GRADE approach for evidence evaluation and recommendations by the Italian Association of Medical Oncology

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Cutaneous squamous cell carcinoma (CSCC) accounts for ∼20%-25% of all skin tumors. Its precise incidence is often challenging to determine due to limited statistics and its incorporation with mucosal forms. While most cases have a favorable prognosis, challenges arise in patients presenting with locally advanced or metastatic forms, mainly appearing in immunocompromised patients, solid organ transplantation recipients, or those facing social difficulties. Traditionally, chemotherapy and targeted therapy were the mainstays for advanced cases, but recent approvals of immunotherapeutic agents like cemiplimab and pembrolizumab have revolutionized treatment options. These guidelines, developed by the Italian Association of Medical Oncologists (AIOM) using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach, aim to guide clinicians in diagnosing, treating, and monitoring patients with CSCC, covering key aspects from primitive tumors to advanced stages, selected by a panel of experts selected by AIOM and other national scientific societies. The incorporation of these guidelines into clinical practice is expected to enhance patient care and address the evolving landscape of CSCC management.

Key words: cutaneous squamous cell carcinoma, CSCC, anti-PD-1, cemiplimab, skin cancer, keratinocyte carcinoma, GRADE, guidelines

INTRODUCTION

Cutaneous squamous cell carcinoma (CSCC) accounts for ∼20%-25% of skin tumors. However, the precise incidence data for this neoplasm are not well-defined due to limited statistics and its frequent inclusion with mucosal forms.[1] In Italy, the 2015 Italian Cancer Registry Association (AIRTUM) report estimated that ∼19 000 new cases of CSCC will be diagnosed in 2018, with higher incidence in males, especially after the age of 65 years, and a typical North–South gradient.[2]

In New South Wales, Australia, where one of the highest frequency of nonmelanoma skin cancers (NMSCs) has been recorded, the overall incidence rate of CSCC from 2016 to 2019 was 856 cases per 100 000 people.[3] In the United States, estimates in 2006 reported 2.2 million people treated for NMSCs, with ∼600 000 identified as having squamous cell carcinoma (SCC). Another United States study estimated that between 4000 and 9000 patients died from CSCC in 2012.[4,5] Across Europe, in the past 20 years, there has been considerable variability in the incidence of CSCC, likely related more to differences in national case registration methods than to genuine phenotypic variation.[6] In a 2019 national study in England, covering 2013-2015,

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the age-standardized rates for the first registered CSCC were 77.3 per 100 000 person-years for men and 34.1 for women. Within 36 months, 1.1% of women and 2.4% of men with this carcinoma developed metastases.[7]

Despite a favorable prognosis in over 90% of cases, some patients with primary CSCC, particularly those who are immunocompromised or face social challenges, may develop locally advanced or metastatic forms, presenting a growing clinical concern.[4] Traditionally, chemotherapy and targeted therapy were the only available options for such cases, with limited response rates, of short duration (months) and with significant toxicities. However, recent approvals of immunotherapeutic agents, such as cemiplimab and pembrolizumab, have established immunotherapy as the standard of care for patients who are ineligible for curative surgery or radiotherapy, marking a significant advancement in the treatment landscape.[8,9]

The recommendations presented here were developed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach by the Italian Association of Medical Oncologists (AIOM), aiming to provide guidance to health care practitioners dealing with patients diagnosed with CSCC. These guidelines encompass recommendations pertaining to diagnosis, treatment, and post-treatment monitoring, covering settings ranging from early-stage tumors to those that are locally advanced or metastatic. The prioritized aspects of CSCC management were identified by a panel of experts chosen by AIOM in collaboration with other national scientific societies. The application of these guidelines in routine clinical settings is anticipated to enhance the quality of patient care.

METHODS

The AIOM Guidelines Panel for Cutaneous Squamous Cell Carcinoma includes clinicians with extensive expertise in dermato-oncology, hailing from all medical fields involved in the diagnosis and treatment of skin cancers (medical oncology, dermatology, surgery, pathology, and radiotherapy), in addition to members specialized in clinical research methodology. This multidisciplinary team annually updates the guidelines. Before the final publication on the AIOM website (www.aiom.it), the work is reviewed by external reviewers from the leading Italian dermato-oncological scientific societies (Italian Melanoma Intergroup; Italian Society of Medical, Surgical and Aesthetic Dermatology and of Sexually Transmitted Diseases; Italian Association of Radiotherapy and Clinical Oncology; Italian Society of Pathology; Italian Society of Oncologic Surgery; Italian Society of Medical and Interventional Radiology).

Development of clinical questions

The following clinical questions all follow the PICO format, including Population (P), Intervention (I), Comparator (C), and Outcomes (O):

- Question 1: Should sunscreen creams with solar protection factor 30-50 be recommended in subjects who are exposed to solar UV radiation (UVR) to reduce the incidence of CSCC?
- Question 2: Should dermoscopy be recommended in subjects with suspicious skin lesions compared to visual inspection only for the detection of CSCC?
- Question 3: Should chemoprevention be recommended in subjects at high risk of developing CSCC?
- Question 4a: Should dermatological follow-up be carried out in immunosuppressed subjects?
- Question 4b: Should clinical—instrumental follow-up be carried out in immunosuppressed subjects?
- Question 5a: In patients with operable low-risk CSCC, should excision with margins $\geq$4 mm be recommended over $<$4 mm?
- Question 5b: In patients with operable high-risk CSCC, should excision with margins $\geq$6 mm be recommended over $<$6 mm?
- Question 6: In recurrent or high-risk CSCCs, should Mohs surgery be recommended over traditional excision?
- Question 7a: In non-recurrent and operable CSCC, should surgical excision with clear margins be recommended over radiotherapy?
- Question 7(b-c): In non-recurrent and operable CSCC, should surgical excision with clear margins be recommended over (b) cauterization or (c) cryotherapy?
- Question 8: Should adjuvant radiotherapy be recommended after surgical excision of high-risk CSCC?
- Question 9: Should sentinel lymph node biopsy be recommended in high-risk CSCC?
- Question 10: Should prophylactic lymphadenectomy be recommended in high-risk CSCC?
- Question 11: Should baseline radiological tumor assessment be recommended in subjects with high-risk CSCC?
- Question 12: Should radiological tumor assessment be recommended in the follow-up of subjects with high-risk CSCC?
- Question 13: Should concomitant chemoradiation be recommended over post-operative radiotherapy alone in patients with CSCC and histopathological high-risk factors?
- Question 14: Should cemiplimab be recommended over chemotherapy for patients with recurrent and/or metastatic CSCC who are not eligible for curative treatment?
- Question 15: Should concomitant chemoradiation be recommended over exclusive curative radiation therapy in patients with non-resectable CSCC?
- Question 16: Should platinum-based chemotherapy be recommended over palliative care/best supportive care for patients with recurrent and/or metastatic CSCC who are not eligible for curative treatment?
- Question 17: Should early integration of palliative care with oncological treatment be recommended in patients with advanced/metastatic CSCC over the 'solo practice model'?

The outcomes were identified by the panel members as either 'critical' or 'important', based on their degree of priority.

Search strategy and quality of evidence evaluation

For each PICO, a systematic and cross-checked literature search was conducted on PubMed, Embase, and Cochrane Library [details about the search string and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart are reported in the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2024.103005]. Systematic literature reviews and randomized clinical studies were included. Where unavailable, non-randomized studies were retrieved. Narrative reviews and case reports were excluded.

The quality of the evidence was assessed using the GRADE approach, which includes the evaluation of study limitations, imprecision, indirectness, inconsistency, and publication bias. Randomized controlled trials start from a high certainty, but any limitation found in one of these domains downgrades the certainty of the evidence. A judgment is then expressed among the following: high, moderate, low, and very low. A final summary of these judgments has been reported in the dedicated tables (Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2024.103005).

Evidence to decision

The decision-making process is conducted and reported transparently in the evidence to decision (EtD) framework.[10] The evidence is reported in relation to the priority of the problem while considering the certainty of the evidence, the balance of desirable and undesirable effects, patient values, resource use, equity, acceptability, and feasibility.

Based on this, the panel can then formulate a vote between the intervention and the comparison: favorable, uncertain/favorable, uncertain/unfavorable, and unfavorable. The panel also votes on the strength of the recommendation: strong in favor, conditional in favor, conditional against, and strong against the intervention. The reporting of the recommendations was done according to the Appraisal of Guidelines for Research and Evaluation (AGREE) reporting checklist.[11]

CLINICAL QUESTIONS

Primary prevention

Risk factors associated with the development of CSCC include exposure to UVR, both natural and artificial, age, and fair skin phototype. The most significant environmental risk factor for the occurrence of CSCC is chronic cumulative exposure to UVR, which also explains the drastic increase in incidence with advancing age. Incidence is higher at lower latitudes, correlating with higher environmental light intensity. In 90% of cases, the tumor arises in anatomical areas chronically exposed to sunlight, such as the head/neck region and the dorsal surfaces of the hands and forearms, and is more common in individuals who work outdoors. Moreover, artificial sources of UVR, such as Psoralen and UVA (PUVA) therapy and indoor tanning devices, are implicated in the pathogenesis of CSCC, with a higher risk for individuals who are exposed at a younger age.[11,12]

Sun protection is implemented through different effective means, with the use of sunscreen creams being one, but not the only, method. It also includes the use of clothing, hats, and protective eyewear, as well as avoiding direct sunlight. The significant role played by UVR in the development of skin cancer emphasized the importance of developing prevention strategies and adequate photoprotection and sun exposure. Measures to consider in this regard include raising awareness among individuals about the consequences of excessive sun exposure, protection from direct UVR exposure with appropriate clothing and hats, seeking shaded areas, and the regular and correct use of sunscreen creams. For roles requiring occupational exposure to sunlight, personal protective equipment (PPE) can be used as a secondary measure. However, it is crucial to emphasize that PPE, such as protective clothing, sunglasses, hats, and sunscreen, should not replace efforts to limit sunlight exposure.[12]

Notably, case-control or cohort epidemiological studies have analyzed the effects of sunscreen cream use on the development of skin neoplasms, with conflicting results. In the review conducted by Burnett and Wang in 2011, the analysis of literature data indicated that the application of sun protection creams led to a decrease in the incidence of CSCC without noteworthy reductions in vitamin D levels or adverse effects on overall health.[13] Additionally, consistent and proper use of sunscreen creams has demonstrated effectiveness in diminishing the occurrence of actinic keratoses (AKs), a recognized indicator of prolonged sun-induced damage.[14]

An Australian study showed that the fraction of cutaneous cancers that could be prevented through proper application of sunscreen creams was 9.3% for CSCC and 14% for melanoma.[15]

Genetic factors, such as fair skin phototype, make the skin more sensitive to chronic UVR exposure and often enhance the effects of environmental factors in carcinogenesis (synergistic effect). An increased incidence of CSCC has also been reported in patients with genodermatoses, such as mucocutaneous albinism, xeroderma pigmentosum, and epidermodysplasia verruciformis. Finally, chronic long-term inflammatory processes, as present in some genetic diseases (e.g. epidermolysis bullosa), chronic wounds, burns, scars, and lower limb ulcers, can contribute to the development of CSCC.[1]

Another significant risk factor for the development of CSCC is immunosuppression, which can promote the development and progression of CSCC due to reduced immune surveillance against cancer cells or human papillomavirus (HPV) infection. Immunosuppression may be caused by solid organ or hematopoietic stem cell transplant, autoimmune condition requiring systemic immunosuppression, advanced solid organ malignancy, or a hematologic malignancy, such as lymphoma or leukemia, which are associated with an increased risk of CSCC. All

immunosuppressive agents and biologic drugs have an impact on this risk, but to varying degrees. Iatrogenic immunosuppression is typically exemplified by organ transplant recipients, who have a 65-250 times higher risk of developing CSCC compared to the general population.[16,17] Other treatments, such as BRAF inhibitors, can promote the onset of eruptive CSCC through different mechanisms, for example, by enhancing the effectiveness of pre-existing mutations in chronically sun-exposed areas or by reducing defenses against HPV.[18]

Question 1: Should sunscreen creams with solar protection factor 30-50 be recommended in subjects who are exposed to solar UVR to reduce the incidence of CSCC?

Recommendation: In subjects who are exposed to solar UVR, sunscreen creams with solar protection factor 30-50 may be considered as a first option measure to reduce the incidence of CSCC.

Strength of recommendation: Conditional in favor

Overall quality of evidence: Very low

Motivation/comments on the benefit/risk balance: In the review and meta-analysis by Sánchez et al. in 2016, the only randomized study aimed at assessing the impact of sunscreens on the risk of developing both basal cell carcinomas (BCCs) and CSCC is the Nambour trial, named after the Australian region where it was conducted.[19,20] A total of 1621 individuals were randomly assigned to four different groups: daily application of sunscreen with a sun protection factor of 15 plus β-carotene supplementation; sunscreen plus placebo in tablet form; only β-carotene; or only placebo.[20] A total of 1383 participants underwent full skin examination by a dermatologist in the follow-up period. The endpoint was the incidence of carcinomas after a 4.5-year follow-up.[20] The results did not show any difference in the number of patients developing both BCC and CSCC across the various groups.[20] However, although no difference was observed in the number of patients developing CSCC in the different groups, a significant reduction in the number of SCCs was noted in the group of patients applying sunscreen with a risk ratio (RR) of 0.61 [95% confidence interval (CI) 0.46-0.81].[20] The considered outcome was the number of patients developing new skin carcinomas, and the RR was 0.88 (95% CI 0.50-1.54). The risk of developing clinically and histologically confirmed CSCC was 3 out of 100 in both groups (with and without sunscreen). Regarding the risk of developing AKs, the RR was 0.95 (95% CI 0.75-1.20). However, concerning the number of CSCC, an RR of 0.61 (95% CI 0.46-0.81) was obtained, with an absolute value of 184 per 100 in the group without sunscreen and 100 per 100 in the group with sunscreen.[20]

This question represents an issue, and the available evidence is of low quality. It has been established that there is no significant uncertainty or variability regarding the assessment of the primary outcome, and the overall balance did not favor the intervention or comparator. There was no impact on equity, and the intervention was deemed acceptable by the parties involved, with potential for improvement. The overall recommendation was in favor of the intervention. The difficulties in conducting such studies and obtaining reliable results are associated with various factors, including the time required for a thorough assessment of the potential onset of these neoplasms, the presence of potential confounding factors, and the challenges in measuring solar radiation intensity and defining the use of sun protection creams. These aspects need to be considered when designing appropriate prospective studies that allow for adequate follow-up periods to assess the development of neoplasms such as BCC, which may potentially require a long induction period. See Supplementary Material (Question 1), available at https://doi.org/10.1016/j.esmoop.2024.103005, for EtD results, quality of evidence, and implications for future results.

Secondary prevention

Secondary prevention aims to detect disease at early stage. The clinical and dermoscopic diagnosis of CSCC presents greater challenges compared to that of BCC. These difficulties primarily stem from the diverse stages in which CSCC clinically manifests. While fully developed nodular CSCC usually does not represent a diagnostic challenge, early forms may resemble BCC or even inflammatory diseases, for which histopathological confirmation is generally not carried out in daily routine. Depending on the stage of tumor progression, CSCC may present as plaque or nodule exhibiting a dermoscopic vascular pattern of initially coiled vessels with yellow scales and hemorrhages and later a polymorphic pattern, with irregular linear vessels, corkscrew vessels, and glomerular vessels. Additionally, in hyperkeratotic varieties, the presence of whitish keratin material and, in ulcerated forms, the presence of ulceration and blood spots conceal and modify the dermoscopic characteristics of the lesion, consequently complicating the diagnosis.[21] The pigmented variant of AK shares many features with lentigo maligna, both clinically and dermoscopically: in these cases, carrying out a biopsy, even incisional, is mandatory to confirm the diagnosis.[22-24] Currently, there are no controlled studies in the literature specifically validating, for CSCC, procedures that improve diagnostic accuracy compared to clinical examination alone, such as dermoscopy or other non-invasive diagnostic methods like confocal microscopy.

Individuals at high risk of developing CSCC encompass diverse groups, including those with lowered immunity, a history of NMSC, rare genetic disorders (e.g. xeroderma pigmentosum), and exposure to specific factors such as trauma, arsenic, albinism, or psoralen and ultraviolet A treatment. Noteworthy subsets at elevated risk include individuals with precursor lesions, previous NMSCs, and those with compromised immunity due to organ transplants or conditions like human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS). Additionally, specific genetic conditions like albinism and recessive dystrophic epidermolysis bullosa contribute to an increased susceptibility to CSCC. Understanding and addressing these

varied risk factors are crucial for developing targeted preventive strategies and interventions.[25]

Chemoprevention is the use of dietary or pharmacologic agents to inhibit or reverse cancer development and is a promising approach for individuals at high risk of NMSCs.[25] Oral retinoids, such as isotretinoin and acitretin, have been shown to effectively reduce the number of new NMSCs in high-risk patients.[26-28] Other potential chemopreventive agents include difluoromethylornithine, T4 endonuclease V, and polyphenolic antioxidants.[29]

Question 2: Should dermoscopy be recommended in subjects with suspicious skin lesions compared to visual inspection only for the detection of CSCC?

Recommendation: In subjects with suspicious skin lesions, the use of dermoscopy should be recommended as the first option compared to visual inspection only for the detection of CSCC.

Strength of recommendation: Conditional in favor—expert opinion

Overall quality of evidence: No included studies

Motivation/comments on the benefit/risk balance: In the current literature, aside from anecdotal cases, there are no studies validating dermoscopy or other non-invasive diagnostic methods, such as confocal microscopy, as procedures that enhance diagnostic accuracy compared to clinical examination alone, specifically for the diagnosis of CSCC. However, studies on the effectiveness of dermoscopy for diagnosing melanoma and other skin conditions suggest the significant role of this technique in the differential diagnosis of skin lesions. It has been established that this question posed an issue. There is no significant uncertainty or variability regarding the assessment of the primary outcome, the overall balance favors the intervention, there is no impact on equity, and the intervention is deemed acceptable by the parties involved. The overall recommendation was in favor of the intervention.

Question 3: Should chemoprevention be recommended in subjects at high risk of developing CSCC?

Recommendation: Chemoprevention treatment may be considered as a primary option compared to no treatment in individuals at high risk of developing CSCC.

Strength of recommendation: Conditional in favor

Overall quality of evidence: Low

Motivation/comments on the benefit/risk balance: Few studies have been conducted in individuals with higher risk of developing CSCC to assess whether a chemoprevention strategy could reduce this risk.[25] These studies have also evaluated different drugs, specifically one study on nicotinamide[26]; three on retinoids: acitretin versus placebo,[27] oral retinol versus oral isotretinoin versus placebo,[28] acitretin versus placebo[30]; two on antioxidants: one study on oral selenium versus placebo,[31] one on β-carotene versus placebo[32]; and finally, one more recent study on nonsteroidal anti-inflammatory drugs, specifically celecoxib.[33]

The benefit endpoint considered is the incidence of new lesions. Regarding nicotinamide, the standardized mean incidence of new lesions in the 386 patients treated in the study was comparable to that in untreated subjects (ranging from 0.2 lower to 0.2 higher).[26] In studies with retinoids, the overall standardized mean difference was 0.63 lower (ranging from 1.16 lower to 0.09 lower),[27,28,30,34] while with antioxidants, it was 0.14 times higher (ranging from 0.03 higher to 0.25 higher).[31,32] Finally, regarding celecoxib, in a single study involving 240 patients, the incidence was 0.41 times lower (ranging from 0.66 lower to 0.16 lower).[33] Overall, in the eight randomized studies, considering a total of 626 patients, the standardized mean incidence in subjects who underwent chemoprevention was 0.23 times lower than in untreated patients (with a range from 0.44 lower to 0.02 lower). Overall, the evaluation of randomized studies considering a chemoprevention strategy versus no treatment has shown a reduced but evident benefit (the CI of differences in standardized mean incidence does not intersect the value 0). Differences between the various analyzed drugs have been highlighted; for nicotinamide and antioxidants, there is no significant impact (CI around 0), whereas for celecoxib and retinoids, the benefit is confirmed (CI <0), especially for retinoids, which have an evaluation in three studies, while only one study is available for celecoxib.

Regarding the outcome of harm represented by adverse events associated with drug intake, the toxicity profile was described in Bavinck et al. (1995) for acitretin and analyzed exclusively in Chen et al. (2015) for nicotinamide, showing an increase of 0.33 in the odds ratio (OR) in 386 patients for hepatotoxicity (ranging from 0.01 to 8.19) and similarly 0.33 for nephrotoxicity (low-quality evidence).[26,27]

The evidence for favorable effects has been confirmed but judged as low. The assessment regarding the balance between positive and negative effects was considered to probably favor the intervention. It was also evaluated that there is probably no impact on equity for the implementation of the intervention. See Supplementary Material (Question 3), available at https://doi.org/10.1016/j.esmoop.2024.103005, for EtD results, quality of evidence, and implications for future results.

Question 4a: Should dermatological visits be carried out in immunosuppressed subjects?

Recommendation 1: Dermatological visits versus no dermatological visits may be considered as a primary option in immunocompromised individuals.

Strength of recommendation 1: Conditional in favor—expert opinion

Recommendation 2: Dermatological follow-up visits versus no dermatological follow-up visits may be considered as a primary option in immunocompromised solid organ transplant recipients (SOTR)

Strength of recommendation 2: Strong in favor—expert opinion

Overall quality of evidence: No included studies

Motivation/comments on the benefit/risk balance: The magnitude of the problem is significant, as the reference populations, i.e. immunocompromised subjects and SOTRs, are on the rise. It is not possible to provide an assessment of the desired/undesired effects with a more intensive follow-up since comparative studies are lacking. The potential risks from a strategy of dermatological checks are

probably very limited, while the benefits could be moderate or substantial (although there are no literature data on this), derived from the early diagnosis of potentially aggressive lesions. Taking all this into consideration and considering the risk of the population to be sufficiently high to anticipate the need for early diagnosis of disease recurrence or the appearance of a new lesion, the possibility of dermatological follow-up is moderately favored, especially in the subpopulation of immunocompromised patients undergoing solid organ transplantation. Dermatological follow-up in immunocompromised patients does not pose a major obstacle to the feasibility and equity of this approach and should be acceptable to the main stakeholders. There is no uncertainty or variability in how individuals may assess this approach. See Supplementary Material (Question 4a), available at https://doi.org/10.1016/j.esmoop.2024.103005, for EtD results, quality of evidence, and implications for future results.

Question 4b: Should clinical—instrumental follow-up be carried out in immunosuppressed subjects with a diagnosis of CSCC?

Recommendation: Clinical—instrumental follow-up versus no clinical—instrumental follow-up may be considered as a primary option in immunocompromised individuals with a diagnosis of CSCC.

Strength of recommendation: Conditional in favor—expert opinion

Overall quality of evidence: No included studies

Motivation/comments on the benefit/risk balance: The magnitude of the problem is significant, as the reference population is on the rise. It is not possible to express an assessment of the desired/undesired effects with a more intensive follow-up since comparative studies are lacking. The potential risks from a strategy of clinical and instrumental checks are probably moderate, arising mainly from false-positive suspicious lesions requiring invasive diagnostic procedures (further radiological investigations that may expose to radiations; histological confirmation procedures that may cause complications, such as biopsies on visceral lesions). Considering all this and deeming the risk of the population to be sufficiently high to anticipate the need for early diagnosis of disease recurrence or the appearance of a new lesion, the possibility of such a follow-up path is moderately favored. The follow-up will be personalized based on the type of transplant, the degree of immunosuppression, the drug used to reduce the risk of rejection, and the characteristics of CSCC (extension, recurrence, type of treatment received). Clinical—radiological follow-up in this population of immunocompromised patients does not pose a major obstacle to the feasibility and equity of this approach since the number of patients to monitor is well limited compared to all patients with CSCC. There is probably not much uncertainty or variability in how individuals may assess this approach and, in its acceptability, especially given the increased risk of cutaneous recurrence or new cutaneous or extracutaneous neoplasms that this population may present due to sustained immunosuppression. See Supplementary Material (Question 4b), available at https://doi.org/10.1016/j.esmoop.2024.103005, for EtD results, quality of evidence, and implications for future results.

Treatment of primary resectable CSCC

The treatment of CSCC is based on complete surgical excision. Surgical removal allows histological examination and confirmation of the clinical diagnosis as well as evaluation of surgical margins, either intraoperative or post-operative, with very high rates of effectiveness and healing rates of 95%. There may be conditions in which alternative techniques to surgery are used in daily clinical practice. In patients where CSCC arises on multiple AKs or in areas with multiple *in situ* tumors, different destructive modalities (cryotherapy, curettage and electrocoagulation, photodynamic therapy with aminolevulinic acid or methyl-aminolevulinic acid) or topical agents (imiquimod 5% or 3.75%; diclofenac gel 3%, ingenol mebutate 500 μg/g or 150 μg/g) are also employed to clear the field of cancerization, although these therapeutic procedures do not allow for histological margin analysis.[35] There are no studies comparing the therapeutic efficacy of these options to traditional surgery in invasive carcinomas. However, a multicentric placebo-controlled randomized study compared the rate of complete clinical responses for non-invasive SCCs/Bowen's disease in a group of 225 lesions, with randomization into four arms (photodynamic therapy with aminolevulinic acid, cryotherapy, topical 5-fluorouracil, and placebo photodynamic therapy). Photodynamic therapy achieved the highest response rate (93%), followed by cryotherapy (86%) and 5-fluorouracil (83%).[36] Another randomized study compared photodynamic therapy and topical therapy with 5-fluorouracil, finding a higher rate of complete clinical responses for photodynamic therapy (88% versus 67%) with a lower recurrence rate (6.8% versus 27.3%) after 12 months of follow-up.[37] A retrospective study on 263 non-invasive lesions/Bowen's disease compared photodynamic therapy, cryotherapy, and surgical excision in terms of recurrence rates after 8 years of follow-up. The recurrence rate after photodynamic therapy (18%) was significantly higher than that with surgery (0.4%) and cryotherapy (5%). However, the lesions treated with photodynamic therapy were larger and more infiltrated than those treated with cryotherapy.[38] In cases where there is clinical uncertainty about the invasiveness of the lesion or doubt between *in situ* tumor and invasive CSCC, surgical excision or a biopsy followed by histological examination confirms the non-invasive nature of the lesions.

Question 5a: In patients with operable low-risk CSCC, should excision with margins $\geq$4 mm be recommended over $<$4 mm?

Recommendation: In subjects with operable low-risk CSCC, surgical excision with margins $\geq$4 mm should be

considered as a first-line option compared to excision with margins <4 mm.

Strength of recommendation: Conditional in favor—expert opinion

Overall quality of evidence: No included studies

Motivation/comments on the benefit/risk balance: The guidelines unanimously emphasize the importance of radical surgical excision with clear margins. However, there are no available clinical studies specifying the minimum appropriate dimensions for clear margins, and thus, there is no consistent guidance in this regard. The American National Comprehensive Cancer Network (NCCN) guidelines based their recommendations on the findings of a prospective American study by Brodland and Zitelli in 1992.[39] The results highlighted for well-defined low-risk CSC, with a diameter of <2 cm, that excision with a margin of 4 mm from the clinical margins of the lesion resulted in complete excision of the neoplasm in over 95% of cases. For larger low-risk lesions exceeding 2 cm, the recommended margin to ensure histologically complete removal of the neoplasm is 6 mm.[39] European guidelines from the European Dermatology Forum (EDF), European Association of Dermato-Oncology (EADO), and European Organization for Research and Treatment of Cancer (EORTC) recommended a standardized minimum margin of 5 mm for low-risk carcinomas, i.e. tumors with a vertical thickness <6 mm and no risk factors.[40] Carrying out excisions with larger clear margins could inevitably lead to a higher incidence of treatment-related complications, such as surgical outcomes, scarring, pain, and bleeding.

It has been established that the question represented an issue, with no significant uncertainty or variability regarding the assessment of the primary outcome, a balance favoring the intervention, no impact on equity, and the intervention being deemed acceptable by all parties. The overall recommendation is in favor of the intervention.

Question 5b: In patients with operable high-risk CSCC, should excision with margins ≥6 mm be recommended over <6 mm?

Recommendation: In subjects with operable high-risk CSCC, surgical excision with margins ≥6 mm may be considered as a first-line option compared to excision with margins <6 mm.

Strength of recommendation: Conditional in favor—expert opinion

Overall quality of evidence: No included studies

Motivation/comments on the benefit/risk balance: The guidelines unanimously emphasize the importance of radical surgical excision with clear margins. However, there are no clinical studies available to determine the minimum appropriate dimensions for free margins, and therefore, there are no consistent indications in this regard. The margins free from disease after surgical excision must be assessed based on tumor size and aggressiveness according to clinical—pathological parameters.

The American NCCN guidelines based their recommendations on the results of a prospective American study by Brodland and Zitelli in 1992.[39] For lesions >2 cm, the recommended margins to ensure complete histological removal of the neoplasm are 6 mm. For high-risk locations (scalp, ears, eyelids, nose, lips) or other high-risk characteristics (histological grading ≥2, invasion of subcutaneous tissue), lesions with diameters <1 cm, 1-1.9 cm, or >2 cm should require free margins of 4 mm, 6 mm, and 9 mm, respectively. The guidelines of the German Dermatology Society indicate that for SCCs >2 cm in diameter, or lesions with a thickness >6 mm, or with other high-risk prognostic features (poor cellular differentiation, recurrent tumors, perineural invasion, deep extension into the subcutaneous layer, and/or localization on the ear or lip), a free margin of at least 6 mm is necessary to achieve a 95% complete response at 5 years.[41]

The European EDF/EADO/EORTC guidelines recommend, for tumors with a thickness <6 mm but with high-risk features (histologically undifferentiated, perineural invasion, recurrent tumors) and for tumors with a histological vertical thickness >6 mm, a free margin of 6-10 mm.[40] Carrying out excisions with larger free margins could inevitably lead to a higher incidence of treatment-related complications, such as surgical outcomes, scarring, pain, and bleeding.

It has been established that the issue represents a problem, and there is no significant uncertainty or variability regarding the assessment of the main outcome. The balance favors the intervention, and there is no impact on equity. The intervention is certainly acceptable to all parties. The overall recommendation is in favor of the intervention.

Question 6: In recurrent or high-risk CSCCs, should Mohs surgery be recommended over traditional excision?

Recommendation: In subjects with high-risk or recurrent CSCC, the Mohs technique may be considered over simple excision.

Strength of recommendation: Conditional in favor

Overall quality of evidence: Very low

Motivation/comments on the benefit/risk balance: From the available literature, we considered five retrospective monocentric studies. The 2008 study by Brantsch et al. included 615 patients with CSCC treated with traditional surgery over a period of 10 years, with a median follow-up of 43 months (range 1-163 months).[42] The 2002 study by Cherpelis et al. included 200 cases of CSCC treated with Mohs micrographic surgery (MMS) from 1988 to 1998, with a follow-up ranging from 6 months to 10 years.[43] The study by Pugliano-Mauro and Goldman (2010) included 260 high-risk CSCC patients treated with MMS, with a mean follow-up of 3.9 years, involving neoplastic lesions in the H zone of the face, tumors >2 cm, or rapidly growing tumors with perineural involvement, and lesions occurring in immunosuppressed patients.[44] Of these lesions, 231 (89%) were primary, and 29 (11%) were recurrences, with 20% of the patients being immunosuppressed.[44] The study by Vuyk and Lohuis (2001) reported the experience of a single surgeon on 56 patients with CSCC treated with MMS over an 8-year period, with a mean follow-up of 33 months (range 1-99 months), of which 3 (5%) were recurrent lesions.[45] The study by Silapunt et al. (2005) included 144 CSCCs in 117

patients with lesions located on the ear treated with Mohs surgery, with a mean telephone follow-up of 34.6 months (range 7-67 months).[46] Of these cases, only 122 were subjected to follow-up, and the remaining ones were not reachable.[46]

Our objective was to compare MMS and standard excision in the treatment of CSCC in a high-risk population or with recurrent CSCC. We relied on the analysis of multiple benefit outcomes (essential: percentage of local recurrence, number of re-interventions, percentage of metastasis) and harm outcomes (essential: scarring outcomes; important: infections, bleeding).

The benefit outcomes had limited importance, with a local recurrence rate of 2.7% in the population of 1045 individuals collected from four observational studies,[42,44-46] while the rate of distant metastasis was 12.4% in a population of 460 patients collected from three observational studies.[42-44] None of the studies reported the benefit outcomes of re-excision and the undesirable ones (scar results, infections, and bleeding).

Regarding the population's perception of the importance of outcomes, there was no significant uncertainty or variability, and this aspect is not analyzed in the studies under consideration. Moreover, it was not assessable whether the balance between desirable and undesirable results favors one technique over the other due to the lack of studies on this topic.

The Mohs technique is likely more expensive than traditional surgery because, despite the absence of pharmacoeconomic studies comparing the two techniques, the Mohs technique involves a greater number of professionals and more hours of surgical activity.[45] No studies analyzed the required resources or considered whether the cost-effectiveness balance favors one technique over the other.

The equity of the Mohs technique probably appeared reduced because the high costs and the need for specialized personnel would prevent a widespread and uniform distribution nationwide.

The Mohs technique, compared to traditional surgery, could be considered depending on the figures involved in the process under consideration. Therefore, it might be considered economically unsustainable despite the potential superiority of the MMS technique, yet to be demonstrated. The Mohs technique was probably not very implementable for the reasons mentioned.

The high-risk patient or those with recurrent SCC could undergo treatment with true MMS if carried out in specialized and competent centers. See Supplementary Material (Question 6), available at https://doi.org/10.1016/j.esmoop.2024.103005, for EtD results, quality of evidence, and implications for future results.

Question 7a: In non-recurrent and operable CSCC, should surgical excision with clear margins be recommended over radiotherapy?

Recommendation: In patients with non-recurrent and operable CSCC, surgical excision with clear margins may be considered as a first-line option over radiotherapy.

Strength of recommendation: Conditional in favor

Overall quality of evidence: Very low

Motivation/comments on the benefit/risk balance: There are no randomized studies comparing surgery with radiotherapy; literature consists solely of case series of patients treated with either method. The considered benefit outcomes were the percentage of recurrences and relapse-free survival, while the harmful outcomes included surgical complications and the incidence of radiodermatitis. Four observational studies involving a total of 395 cases of CSCC were analyzed.[47-50] The rate of recurrences after surgery was 3.5%, while that of surgical complications was 8.7% (41/469 patients).[47-50]

The balance of effects in terms of benefit/harm was indicated as probably in favor of surgery. The question was evaluated as definitely representing a clinical problem, with anticipated positive effects being moderate, and unknown negative effects. There is probably significant uncertainty or variability regarding the assessment of outcomes. Concerning equity, it was assessed as probably having no impact, and the intervention was deemed acceptable to stakeholders.

Note: In an observational radiotherapy study by Barysch et al., involving a total of 180 high-risk CSCC patients, the percentage of relapse-free survival at 10 years was 80.6% (35 recurrences/180). The percentage of recurrences after a median follow-up of 4.9 years was evaluated in two observational studies and was 8.1%.[50] Data on the side-effects of radiotherapy were not available in the same studies.[50,51]

See Supplementary Material (Question 7a), available at https://doi.org/10.1016/j.esmoop.2024.103005, for EtD results, quality of evidence, and implications for future results.

Question 7(b-c): In non-recurrent and operable CSCC, should surgical excision with clear margins be recommended over cauterization or cryotherapy?

Recommendation: In subjects with non-recurrent and operable CSCC, surgical excision with clear margins may be considered as a first-line option compared to cauterization or cryotherapy.

Strength of recommendation: Conditional in favor (for cauterization); expert opinion (for cryotherapy)

Overall quality of evidence: Very low (for cauterization); no included studies (for cryotherapy)

Motivation/comments on the benefit/risk balance: Surgical excision is the treatment of choice as it allows histological confirmation and assessment of resection margins. Surgery is rarely contraindicated, even in elderly patients or in cases of tumors that are challenging to treat due to extensive size and anatomical locations with potential functional and cosmetic consequences, provided that these patients are managed appropriately by experienced personnel. There are no randomized studies comparing surgery with diathermocoagulation/cauterization or cryotherapy. There is only one retrospective observational study published in 2002 by Werlinger et al., comparing surgical excision to curettage

and diathermocoagulation in a cohort of 268 patients with cutaneous BCC or SCC, of which 110 underwent surgical excision and 158 underwent curettage and diathermocoagulation.[52] These were small-sized tumors (median diameter 7 mm), and only 76 were SCCs.[52] The considered benefit outcomes were the rate of recurrences and relapse-free survival, while the harmful outcomes included complications and the outcomes of different techniques. The study results did not show significant differences in recurrences between the two methods, although the study is burdened by a very high risk of bias due to its retrospective nature, lack of stratification, and a high number of patients lost to follow-up (8 in the surgery group and 32 in the curettage and diathermocoagulation group). However, when analyzing only the group of patients with CSCC, the recurrence rate for patients with available follow-up was 0/20 (0.0%) for those treated with surgery and 2/56 (3.6%) for those treated with other methods. For this study, the risks of inconsistency and imprecision were evaluated as not serious, while the risks of imprecision were considered serious due to the low number of events.

The retrospective observational study by Nordin and Stenquist in 2002 reported data on 100 cases of NMSC located on the auricle, mostly BCCs, with only 13 invasive and 6 *in situ* CSCCs, showing only 1 recurrence in 76 cases followed over time. In a prospective study of 100 cases of superficial and non-facial NMSCs, including 11 *in situ* and 6 invasive SCCs treated with the same method (curettage + cryosurgery), there were no recurrences evident at a 1-year follow-up.[53]

The quality of the evidence is low; however, the panel deemed this issue very relevant and considered that there are no uncertainties regarding its evaluation, and no additional costs or equity problems are expected.

Note: In patients where CSCC arises on multiple AKs or areas with multiple *in situ* tumors, various destructive modalities (cryotherapy, curettage and electrocoagulation, photodynamic therapy) or topical agents (imiquimod 5% or 3.75%; diclofenac gel 3%, ingenol mebutate 500 μg/g or 150 μg/g) can be used, as reported in the EDF guidelines (Werner, 2015)[54] on AK and EDF/EADO/EORTC on CSCC.[55] See Supplementary Material (Question 7b), available at https://doi.org/10.1016/j.esmoop.2024.103005, for quality of evidence and implications for future results.

Question 8: Should adjuvant radiotherapy be recommended after surgical excision of high-risk CSCC compared to no adjuvant treatment?

Recommendation: In subjects with resected high-risk CSCC, adjuvant radiotherapy may be considered compared to no treatment.

Strength of recommendation: Conditional in favor

Overall quality of evidence: Moderate

Motivation/comments on the benefit/risk balance: After a systematic literature review,[56-59] the working group concluded that the recommendation proposed in the American Society for Radiation Oncology (ASTRO) guidelines addressed was applicable to the Italian context.[60] Moreover, the ASTRO guidelines were of excellent quality according to the AGREE II assessment. For these reasons, the panel has decided to adopt the ASTRO guidelines. Specifically, the adoption is referred to the following risk factors: Key Question 2, points 1 (clinically or radiologically evident perineural invasion), 3 (CSCC operated after previous resection with clear margins), 4 [T3 and T4 tumors according to American Joint Committee on Cancer (AJCC) eighth edition staging], and 5 (desmoplastic or infiltrative cutaneous SCC in the context of chronic immunosuppression).[60]

Question 9: Should sentinel lymph node biopsy be recommended in high-risk CSCC?

Recommendation: In subjects with high-risk CSCC, sentinel lymph node biopsy should not be considered as a primary option compared to only follow-up.

Strength of recommendation: Conditional against

Overall quality of evidence: Very low

Motivation/comments on the benefit/risk balance: In a retrospective monocentric observational design study by Maruyama et al., including 169 treated patients (with neoplasms more advanced than *in situ* tumors and without baseline metastasis) followed up for at least 6 months (average follow-up of 31.4 months), 49 patients underwent sentinel lymph node biopsy during the same period.[61]

The considered benefit outcomes were the recurrence rates, disease-free survival (DFS), and overall survival (OS); the harmful outcomes were the surgical complications of the sentinel lymph node biopsy.

DFS had a risk of 11% with only follow-up, while with the sentinel lymph node biopsy, it was 6% (range 2%-21%), resulting in an RR of 0.55 (range 0.1-1.85). Consequently, there were 5 fewer disease recurrences per 100 patients undergoing sentinel lymph node biopsy, with a 95% CI ranging from 9 fewer to 10 more patients.

Regarding OS, no reported differences were found between the population undergoing sole follow-up and patients undergoing sentinel lymph node biopsy. Concerning harmful outcomes, three cases of surgical complications were reported: one case of bacterial lymphangitis in a 77-year-old man, one case of lymphorrhea in a 49-year-old man, and one case of post-operative bleeding, all successfully treated.

There was no likely uncertainty or variability regarding how the population evaluated these outcomes. Undesirable effects were considered small compared to irrelevant desirable effects. Therefore, the balance of effects between desirable and undesirable outcomes probably favors sole follow-up over sentinel lymph node biopsy. The procedure would be easily implementable, considering it is already in use for other types of neoplasms and is carried out in non-specialized centers. Consequently, the distribution would be widespread from the beginning, allowing facilities to implement this technique without excessively high costs or insurmountable technical—logistic difficulties. See Supplementary Material (Question 9), available at https://doi.org/10.1016/j.esmoop.2024.103005, for quality of evidence and implications for future results.

Question 10: Should prophylactic lymphadenectomy be recommended in high-risk CSCC?

Recommendation: Prophylactic lymphadenectomy should not be considered for high-risk CSCC compared to sole follow-up.

Strength of recommendation: Conditional against—expert opinion

Overall quality of evidence: No included studies

Motivation/comments on the benefit/risk balance: Based on the literature, no studies addressing this issue were identified. The panel, therefore, proceeded to formulate a recommendation based on its clinical experience. It was concluded that carrying out prophylactic lymphadenectomy in the high-risk population affected by CSCC is not recommendable. Prophylactic lymphadenectomy is not recommended also due to potential side-effects, such as lymphedema, surgical site infection, and regional paresthesia. See Supplementary Material (Question 10), available at https://doi.org/10.1016/j.esmoop.2024.103005, for quality of evidence and implications for future results.

Medical therapy, staging, and follow-up

The prognosis for patients with CSCC is generally favorable, with a 5-year cure rate exceeding 90%.[62] In a cohort of over 900 patients with CSCC followed for ∼10 years, 4.6% experienced recurrence, 3.7% had lymph node metastasis, and 2.1% succumbed to disease progression.[63] In patients with >10 CSCC, the incidence of local recurrences and lymph node metastases was 37% and 26%, respectively, compared to 3% and 2% in those with a single CSCC.[63] The risk of distant metastases is low, <5% after 5 years of follow-up in most patients.[63] About 85% of metastases involve regional lymph nodes, while distant metastases are more frequent in the lungs, liver, brain, skin, and bones.[63]

There are no definitive recommendations regarding the use of instrumental staging procedures after the surgical removal of histologically confirmed SCC. NCCN guidelines suggest carrying out instrumental investigations for tumors with deep bone or soft tissue involvement or perineural invasion.[64] Apart from the suggested use of magnetic resonance imaging in the presence of perineural involvement, there are no indications on the specific type of instrumental investigation to be employed. The early identification of regional nodal relapse could be of benefit in terms of surgical salvage. Therefore, according to EDF/EADO/EORTC guidelines, high-risk CSCC cases (diameter >2 cm, deep-infiltrating tumors, aggressive histology, perineural involvement, recurrent tumors, and those located on the lip or ear) should undergo nodal ultrasound every 3 months for the first 2 years, every 6 months for an additional 3 years, and then annually.[65]

Operated CSCC represents a highly heterogeneous category of disease. Within this, the definition of 'high risk' is used to identify a group of patients with a higher risk of locoregional or distant recurrence. This includes patients with head and neck cutaneous disease who have intraparotid lymph nodes or cervical lymph nodes related to a primary cutaneous lesion with one or more of the following characteristics: presence of two or more lymph nodes, size >3 cm, or extracapsular extension of disease. High risk is also determined for the primary tumor when it has dimensions >5 cm (T3) or features of invasion into nearby tissues resulting in a T4 stage. For these patients, postoperative radiation therapy is suggested. However, for the definition of high risk based on T characteristics, there is no perfect concordance in the literature. EADO/EDF/EORTC guidelines define concepts only partially overlapping with ASTRO guidelines.[65]

CSCC is predominantly treated with surgery, but in cases of recurrent disease where surgical options are limited, radiation therapy may offer disease control. The presumed advantage of radiation therapy is often derived from results obtained in squamous carcinomas of the head and neck with mucosal origin. It should also be considered that in head and neck mucosal cancers, chemotherapy with platinum agents or treatment with anti-epidermal growth factor receptor (EGFR) antibodies has shown overall improvement in prognosis (both disease control and OS) compared to radiation alone.[66]

In cases of recurrent CSCC that is not amenable to curative surgical or radiation approaches, it often poses a dilemma for clinicians. Recurrence is a clinical challenge due to infections, bleeding, or pain. Additionally, patients often have comorbidities, toxicity from previous treatments, and age-related issues that may hinder the therapeutic path with chemotherapy. Due to the inherent fragility of patients with this type of disease, exacerbated by the complications created by the pathology itself, concurrent care pathways are often initiated from the beginning of treatment. In this regard, the main clinical question concerns the possibility of administering systemic oncological treatments alongside the already established best supportive care. The literature on this subject is relatively limited. An alternative to systemic chemotherapy, which can be challenging due to patient comorbidities or frailty, may be immunotherapeutic treatment.[66,67] Initial data on a relatively small sample of patients are particularly encouraging and may represent a shift in the therapeutic approach for patients in this stage of the disease.

Recent years have witnessed a paradigm shift in the therapeutic landscape of CSCC with the advent of immunotherapy. Immunotherapy, particularly anti-programmed cell death protein 1 (PD-1) agents, has emerged as a groundbreaking approach in the treatment of advanced CSCC, capitalizing on the tumor's high mutational burden and the presence of neoantigens. This transformation necessitates a multidisciplinary evaluation of each case to optimize treatment strategies in a population often burdened by severe comorbidities.[66]

The breakthrough status of immunotherapy is underscored by robust preclinical rationale, linking CSCC's etiology to chronic UVR exposure and its subsequent high somatic mutation rate. Studies indicate a direct correlation between tumor mutational burden (TMB) and immunotherapy efficacy, with CSCC exhibiting the highest TMB

among tumors. Age-related considerations, such as the increased likelihood of immunotherapy benefit in older patients, and the tumor's elevated programmed death-ligand 1 expression further support the rationale for anti-PD-1 immunotherapy.[67,68]

The CARSKIN trial and subsequent KEYNOTE-629 trial demonstrated the efficacy of pembrolizumab in unresectable CSCC, leading to Food and Drug Administration (FDA) approval.[9,69] Cemiplimab, approved by both FDA and European Medicines Agency (EMA), showcased significant clinical benefits in the EMPOWER-CSCC 1 trial, with an overall response rate (ORR) of 46.1% and a disease control rate (DCR) of 72.5%. The study highlighted the importance of considering cemiplimab as a first-line treatment, particularly in cases where curative surgery or radiotherapy is not feasible due to various factors.[8]

A retrospective study conducted in Italy further supported the real-world safety and activity of cemiplimab on 131 patients, with an ORR of 58% and a DCR of 71.7%.[70] Clinical and biochemical factors associated with response were identified, emphasizing the need for personalized treatment approaches.

While chemotherapy has historically yielded short-lived responses with considerable toxicities, immunotherapy, especially with cemiplimab, offers durable responses, improved quality of life, and a manageable safety profile. The EGFR inhibitor cetuximab, though less explored, demonstrated response rates in advanced CSCC. However, the overall efficacy and tolerability of immunotherapy make it a preferred choice in cases where curative surgery or radiotherapy is not suitable.[66,70,71]

In conclusion, the integration of immunotherapy has revolutionized the therapeutic landscape for advanced CSCC. Comprehensive evaluations considering patient characteristics and tumor factors are crucial for optimal treatment selection, ensuring the highest chances of long-term outcomes. The evolving evidence from prospective trials and real-world studies underscores the continued advancement and refinement of immunotherapeutic strategies for CSCC.

Question 11: Should baseline radiological tumor assessment be recommended in subjects with high-risk CSCC?

Recommendation: In subjects with high-risk CSCC, a baseline instrumental staging may be considered for the detection of extracutaneous metastases.

Strength of recommendation: Conditional in favor

Overall quality of evidence: Very low

Motivation/comments on the benefit/risk balance: The considered benefit outcomes encompassed the rate of extracutaneous recurrences, DFS, and OS, while complications associated with radiological procedures were evaluated as adverse outcomes. In the observational study conducted by Ruiz et al. in 2017, a cohort of patients with stage T2b or T3, consisting of 45 individuals who underwent staging procedures (for 48 CSCCs) at the initial diagnosis, was compared with 53 patients who did not undergo such procedures.[72] Computed tomography was the most frequently used exam. Results from 65% of radiological procedures revealed abnormal findings, and in 33% of cases, the radiological procedure influenced the clinical management. There appeared to be no substantial uncertainty or variability in how the population assesses the analyzed outcomes. The balance of effects between desirable and undesirable outcomes favored the performance of staging procedures over not conducting staging. The recommended intervention seemed easily implementable, given its existing application for other types of neoplasms, even in non-specialized centers. Consequently, the distribution would likely be widespread from the outset, allowing facilities to incorporate this technique without excessively high costs or insurmountable technical—logistic difficulties. See Supplementary Material (Question 11), available at https://doi.org/10.1016/j.esmoop.2024.103005, for EtD results, quality of evidence, and implications for future results.

Question 12: Should radiological follow-up tumor assessment be recommended in subjects with high-risk CSCC?

Recommendation: Radiological follow-up tumor assessment may be considered as first option in subjects with high-risk CSCC.

Strength of recommendation: Conditional in favor

Overall quality of evidence: Very low

Motivation/comments on the benefit/risk balance: The considered benefit outcomes included the rate of extracutaneous recurrences, DFS, and OS. The adverse outcomes involved complications related to radiological procedures. In the observational study by Ruiz et al., the percentage of lymph node metastases was higher in the group that did not undergo instrumental staging.[72] Mortality in the two groups was statistically different, with 19 out of 45 patients deceased in the instrumental staging group (42.2%) and 32 out of 53 (60.4%) in the group without instrumental procedures (RR 0.70, range 0.47-1.05). The risk/benefit balance was assessed as probably favoring the intervention based on available data, particularly in identifying lymph node metastases. The panel deemed the issue a clinical priority, with no impact on equity given the widespread availability of clinical and instrumental investigations in every health care facility across Italy. Consequently, the feasibility of this intervention is substantially guaranteed, along with its potential acceptability by individuals and involved institutions. See Supplementary Material (Question 12), available at https://doi.org/10.1016/j.esmoop.2024.103005, for EtD results, quality of evidence, and implications for future results.

Question 13: Should concomitant chemoradiation be recommended over post-operative radiotherapy alone in patients with CSCC with histopathological high-risk factors?

Recommendation: Concurrent chemoradiation should not be considered as a first-line therapeutic option for patients with surgically resected high-risk CSCC.

Strength of recommendation: Conditional against

Overall quality of evidence: Very low

Motivation/comments on the benefit/risk balance: The considered benefit outcomes were DFS and OS, while the

detrimental outcomes included incremental toxicities due to treatment and the worsening of quality of life. The radiosensitizing treatment with carboplatin was investigated in a randomized trial published in 2018 by Porceddu et al.[73] The primary objective was the improvement of locoregional disease control. A total of 321 patients with head and neck region CSCCs were randomized.[73] The study did not demonstrate an advantage in the primary endpoint [freedom from locoregional relapse (FFLRR)], as well as in secondary outcomes of DFS [hazard ratio (HR) 0.85 (95% CI 0.55-1.29)] and OS [HR 0.95 (95% CI 0.58-1.57)], and in quality of life. FFLRR at 2 and 5 years was 88% (95% CI 83% to 93%) and 83% (95% CI 77% to 90%) in the radiotherapy-only group, while it was 89% (95% CI 84% to 94%) and 87% (95% CI 81% to 93%; HR 0.84, 95% CI 0.46-1.55, $P = 0.58$) in the carboplatin + radiotherapy group, respectively. No increase in radiotherapy toxicities, such as mucositis, dysphagia, and acute or late dermatitis, was observed in the experimental arm. However, acute differences between the two arms appeared unfavorably in the chemotherapy-treated group for side-effects such as constipation, fatigue, and dysgeusia. Additionally, as expected, there were increased marrow toxicities related to the chemotherapy drug in the acute phase. Overall, the benefit-to-harm balance does not favor the addition of systemic radiosensitizing treatment in high-risk subjects after surgical intervention due to increased toxicities with no improvement in various outcome parameters. See Supplementary Material (Question 13), available at https://doi.org/10.1016/j.esmoop.2024.103005, for EtD results, quality of evidence, and implications for future results.

Question 14: Should cemiplimab be recommended over chemotherapy for patients with recurrent and/or metastatic CSCC who are not eligible for curative treatment?

Recommendation: Cemiplimab should be recommended as a first-line option over chemotherapy in patients with recurrent and/or metastatic CSCC who are not eligible for curative treatment.

Strength of recommendation: Strong in favor

Overall quality of evidence: Low

Motivation/comments on the benefit/risk balance: After carefully examining the issue and conducting a systematic literature review, the working group concluded that the recommendation proposed in the National Institute for Health and Care Excellence (NICE) guidelines addressed the question of interest, and its content was applicable to the Italian context.[74] Furthermore, the NICE guideline was of excellent quality according to the AGREE II evaluation. For these reasons, the panel decided to adopt the NICE guideline.[74]

The panel decided to make a strong recommendation in favor of the intervention for the following reasons:

- The lack of a therapeutic standard for locally advanced and metastatic CSCC had made it impossible to conduct randomized clinical trials.
- In everyday clinical practice, there was currently no valid alternative therapy to the use of anti-PD-1 antibodies for the first-line treatment of locally advanced and metastatic CSCC.

Note: Cemiplimab is the only anti-PD-1 agent approved by the EMA for the treatment of patients with CSCC who cannot have surgery or radiotherapy with a curative intent.

Question 15: Should concomitant chemoradiation be recommended over exclusive radical radiation therapy in patients with non-resectable CSCC?

Recommendation: Concurrent chemoradiation may be considered as a first-line option for patients with unresectable CSCC.

Strength of recommendation: Conditional in favor

Overall quality of evidence: Very low

Motivation/comments on the benefit/risk balance: Only two studies evaluating the impact of concurrent chemoradiation in CSCC have been identified.[75,76] These retrospective studies had very limited sample sizes (12 and 11 patients treated in a curative setting), lacking a comparison arm, and including a mixed treatment approach with both platinum and cetuximab. Disease response rates ranged between 58% and 64%.[75,76] Acute side-effects reflected the well-known safety profiles of these drugs when used in combination with radiation therapy. Despite the absence of comparative data, considering the prognosis of these patients, the panel established that systemic treatment may be considered in this patient population. The desirable positive effects were deemed modest; the benefit/risk balance may favor treatment. The panel emphasized that the careful selection of patients for this treatment is crucial given the frailty conditions some patients with this disease may present, including age, comorbidities, or immunosuppression. See Supplementary Material (Question 14), available at https://doi.org/10.1016/j.esmoop.2024.103005, for EtD results, quality of evidence, and implications for future results.

Question 16: Should platinum-based chemotherapy be recommended over palliative care/best supportive care for patients with recurrent and/or metastatic CSCC who are not eligible for curative treatment?

Recommendation: Platinum-based chemotherapy may be considered over palliative care/best supportive care in patients with recurrent and/or metastatic CSCC who are not eligible for curative treatment.

Strength of recommendation: Conditional in favor

Overall quality of evidence: Very low

Motivation/comments on the benefit/risk balance: The study by Guthrie et al., published in 1990, assessed patients with mixed histology (BCC and SCC) in different settings (induction to surgery or radiotherapy and in palliative care), with a limited number of patients. In those not amenable to further treatment, a clinical response was observed in five out of eight patients treated with platinum-based chemotherapy.[77]

In the more recent study by Jarkowski et al., also retrospective and covering the period 2001-2011, a total of 25 patients with recurrent and/or metastatic disease were

studied.[78] The prevalent chemotherapy treatment included cisplatin or taxane, as well as the targeted anti-EGFR drug. The best responses were seen in combination therapy compared to monotherapy and in patients with locally advanced disease compared to metastatic disease. Patients who responded to systemic therapy had a significantly better prognosis.[78]

Note: It should be added that a study with cetuximab (anti-EGFR), not described in the current recommendations due to its lack of indication for use in Italy, achieved a response rate of 28% in a population not undergoing chemotherapy in a recurrent/metastatic setting.[79] See Supplementary Material (Question 15), available at https://doi.org/10.1016/j.esmoop.2024.103005, for EtD results, quality of evidence, and implications for future results.

Question 17: Should early integration of palliative care with oncological treatment be recommended in patients with advanced/metastatic CSCC over the 'solo practice model'?

Strength of recommendation: Strong in favor (if palliative care team available); weak in favor (if palliative care team unavailable)

Overall quality of evidence: Very low

Motivation/comments on the benefit/risk balance: The integrated care model for advanced/metastatic cancer patients, particularly the incorporation of early palliative care alongside active oncological treatment, has garnered significant attention in recent years. The integration of palliative care into the active treatment plans for advanced cancer patients has been a topic of interest since the early 2000s. Notably, the European Society for Medical Oncology (ESMO) initiated an accreditation program in 2003 to recognize oncology centers capable of ensuring the early integration of palliative care for symptomatic patients undergoing active oncological treatment. Over the past decade, various studies and expert opinions have consistently highlighted the benefits of this integrated approach on parameters related to the quality of life and symptom control.

A meta-analysis of key studies, including Tattersall et al. (2014), Temel et al. (2010), Temel et al. (2017), Zimmermann et al. (2014), Maltoni et al. (2016), and Groeneveld et al. (2017), assessed the impact of early and simultaneous palliative care on quality-of-life parameters, showing a small effect in quality of life and symptom intensity.[80-85] Zimmermann et al. (2014) trials included blinded participants, while the blinding of outcome assessment was unclear in five out of six studies. Allocation concealment was considered at high risk in Temel et al. (2010) and Zimmermann et al. (2014).[80,83] Downgrading of evidence was applied due to potential biases and imprecision.

The I^2 statistic was 67%, indicating moderate heterogeneity, and 92% for studies by Tattersall et al. (2014) and Temel et al. (2010), suggesting high heterogeneity.[80,81] The GRADE Handbook guided the decision to downgrade evidence for imprecision, as the 95% CI included 1, failing to exclude harm. The included studies used different scales for measuring outcomes, leading to a downgrade for indirectness.

The GRADE assessment underscores the need for cautious interpretation, given the very low certainty of evidence. While there is a suggestion of small positive effects on quality of life and symptom intensity, the impact on OS remains inconclusive. The meta-analysis highlights the challenges and variations in study methodologies, emphasizing the need for further research with robust design to enhance the certainty of evidence in this critical area of early palliative care integration with oncology models. See Supplementary Material (Question 17), available at https://doi.org/10.1016/j.esmoop.2024.103005, for EtD results, quality of evidence, and implications for future results.

FINAL CONSIDERATIONS

The management of patients with CSCC poses a clinical challenge, particularly when in its advanced stages, necessitating comprehensive and multidisciplinary care. Historically, a standard of care for advanced CSCC was elusive, leaving a substantial proportion of patients untreated due to concerns about low clinical efficacy and high risks of severe toxicities.[66] The advent of immunotherapy, specifically anti-PD-1 agents, has revolutionized the landscape of CSCC management.[67] Cemiplimab, as the first PD-1 inhibitor to gain regulatory approval for advanced CSCC, demonstrated remarkable efficacy with rapid and durable responses in >40% of patients, presenting a compelling case for its use in this challenging clinical scenario.[8]

Ongoing trials explore the potential of PD-1 inhibitors in adjuvant (NCT03969004, NCT03833167) and neoadjuvant (NCT04632433, NCT04808999, NCT04315701, NCT04428671) settings, aiming to establish them as the new standard of care. The encouraging results of these studies suggest a paradigm shift in the approach to high-risk and advanced CSCC, with anti-PD-1 agents poised to play a central role in reshaping treatment strategies. Neoadjuvant cemiplimab has been investigated in a phase II confirmatory study.[86,87] This multicenter, non-randomized trial focused on assessing cemiplimab as neoadjuvant therapy in patients with resectable stage II, III, or IV (M0) CSCC. Cemiplimab was administered for up to four doses before curative-intent surgery. The primary endpoint was a pathological complete response.[87] A total of 79 patients received neoadjuvant cemiplimab. The outcomes were striking, with a pathological complete response observed in 51% of patients on independent review. A pathological major response was noted in 13%, and an objective response on imaging was seen in 68% of patients.[87]

Neoadjuvant therapy with cemiplimab holds significant promise for patients with resectable CSCC, demonstrating a high rate of pathological complete response. This breakthrough represents a crucial advancement in the management of CSCC, offering a potential curative approach for a disease that lacked a clear standard of care in its advanced

stages. The study marked a critical milestone toward reshaping treatment paradigms in CSCC.

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REFERENCES

1. Green AC, Olsen CM. Cutaneous squamous cell carcinoma: an epidemiological review. *Br J Dermatol*. 2017;177:373-381.
2. AIOM and AIRTUM working group. I numeri del cancro in Italia. Available at https://www.aiom.it/wp-content/uploads/2018/10/2018_NumeriCancro-operatori.pdf. Accessed December 8, 2023.
3. Wilson A, Goltsman D, Nankervis J, Clark J, Gupta R, Ashford B. Defining the incidence of cutaneous squamous cell carcinoma in coastal NSW Australia. *Australas J Dermatol*. 2022;63:213-216.
4. Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma. *J Am Acad Dermatol*. 2018;78:237-247.
5. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. *J Am Acad Dermatol*. 2013;68:957-966.
6. De Vries E, Trakatelli M, Kalabalikis D, et al. Known and potential new risk factors for skin cancer in European populations: a multicentre case-control study: risk factors for skin cancer in European populations. *Br J Dermatol*. 2012;167:1-13.
7. Venables ZC, Autier P, Nijsten T, et al. Nationwide incidence of metastatic cutaneous squamous cell carcinoma in England. *JAMA Dermatol*. 2019;155:298.
8. Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Engl J Med*. 2018;379:341-351.
9. Maubec E, Boubaya M, Petrow P, et al. Phase II study of pembrolizumab as first-line, single-drug therapy for patients with unresectable cutaneous squamous cell carcinomas. *J Clin Oncol*. 2020;38:3051-3061.
10. Alonso-Coello P, Oxman AD, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: clinical practice guidelines. *Br Med J*. 2016;353:i2089.
11. Brouwers MC, Kerkvliet K, Spithoff K, AGREE Next Steps Consortium. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. *Br Med J*. 2016;352:i1152.
12. Wittlich M. Criteria for occupational health prevention for solar UVR exposed outdoor workers-prevalence, affected parties, and occupational disease. *Front Public Health*. 2021;9:772290.
13. Burnett ME, Wang SQ. Current sunscreen controversies: a critical review. *Photodermatol Photoimmunol Photomed*. 2011;27:58-67.
14. Farmer KC, Naylor MF. Sun exposure, sunscreens, and skin cancer prevention: a year-round concern. *Ann Pharmacother*. 1996;30:662-673.
15. Olsen CM, Wilson LF, Green AC, et al. Cancers in Australia attributable to exposure to solar ultraviolet radiation and prevented by regular sunscreen use. *Aust N Z J Public Health*. 2015;39:471-476.
16. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med*. 2003;348:1681-1691.
17. Cheng JY, Li F-Y, Ko CJ, Colegio OR. Cutaneous squamous cell carcinomas in solid organ transplant recipients compared with immunocompetent patients. *JAMA Dermatol*. 2018;154:60-66.
18. Wu JH, Cohen DN, Rady PL, Tyring SK. BRAF inhibitor-associated cutaneous squamous cell carcinoma: new mechanistic insight, emerging evidence for viral involvement and perspectives on clinical management. *Br J Dermatol*. 2017;177:914-923.
19. Sánchez G, Nova J, Rodriguez-Hernandez A, et al. Sun protection for preventing basal cell and squamous cell skin cancers. *Cochrane Database Syst Rev*. 2016;7:CD011161.
20. Green A, Williams G, Nèale R, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet*. 1999;354:723-729.
21. Sinz C, Tschandl P, Rosendahl C, et al. Accuracy of dermatoscopy for the diagnosis of nonpigmented cancers of the skin. *J Am Acad Dermatol*. 2017;77:1100-1109.
22. Lin MJ, Xie C, Pan Y, Jalilian C, Kelly JW. Dermoscopy improves diagnostic accuracy for clinically amelanotic nodules. *Australas J Dermatol*. 2019;60:45-49.
23. Argenziano G, Puig S, Zalaudek I, et al. Dermoscopy improves accuracy of primary care physicians to triage lesions suggestive of skin cancer. *J Clin Oncol*. 2006;24:1877-1882.
24. Koelink CJL, Vermeulen KM, Kollen BJ, et al. Diagnostic accuracy and cost-effectiveness of dermoscopy in primary care: a cluster randomized clinical trial. *J Eur Acad Dermatol Venereol*. 2014;28:1442-1449.
25. Bath-Hextall F, Leonardi-Bee J, Somchand N, Webster A, Delitt J, Perkins W. Interventions for preventing non-melanoma skin cancers in high-risk groups. *Cochrane Database Syst Rev*. 2007;2007:CD005414.
26. Chen AC, Martin AJ, Choy B, et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. *N Engl J Med*. 2015;373:1618-1626.
27. Bavinck JN, Tieben LM, Van der Woude FJ, et al. Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. *J Clin Oncol*. 1995;13:1933-1938.
28. Levine N, Moon TE, Cartmel B, et al. Trial of retinol and isotretinoin in skin cancer prevention: a randomized, double-blind, controlled trial. Southwest Skin Cancer Prevention Study Group. *Cancer Epidemiol Biomark Prev*. 1997;6:957-961.
29. Wright TI, Spencer JM, Flowers FP. Chemoprevention of nonmelanoma skin cancer. *J Am Acad Dermatol*. 2006;54:933-946.
30. Kadakia KC, Barton DL, Loprinzi CL, et al. Randomized controlled trial of acitretin versus placebo in patients at high-risk for basal cell or squamous cell carcinoma of the skin (North Central Cancer Treatment Group Study 969251). *Cancer*. 2012;118:2128-2137.
31. Clark LC, Combs GF, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *J Am Med Assoc*. 1996;276:1957-1963.

32. Greenberg ER, Baron JA, Stukel TA, et al. A clinical trial of beta carotene to prevent basal-cell and squamous-cell cancers of the skin. The Skin Cancer Prevention Study Group. *N Engl J Med*. 1990;323:789-795.
33. Elmets CA, Viner JL, Pentland AP, et al. Chemoprevention of nonmelanoma skin cancer with celecoxib: a randomized, double-blind, placebo-controlled trial. *J Natl Cancer Inst*. 2010;102:1835-1844.
34. Tangrea JA, Edwards BK, Taylor PR, et al. Long-term therapy with low-dose isotretinoin for prevention of basal cell carcinoma: a multicenter clinical trial. Isotretinoin-Basal Cell Carcinoma Study Group. *J Natl Cancer Inst*. 1992;84:328-332.
35. Peris K, Fargnoli MC. Conventional treatment of actinic keratosis: an overview. *Curr Probl Dermatol*. 2015;46:108-114.
36. Morton C, Horn M, Leman J, et al. Comparison of topical methyl aminolevulinate photodynamic therapy with cryotherapy or fluorouracil for treatment of squamous cell carcinoma in situ: results of a multicenter randomized trial. *Arch Dermatol*. 2006;142:729-735.
37. Salim A, Leman JA, McColl JH, Chapman R, Morton CA. Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease. *Br J Dermatol*. 2003;148:539-543.
38. Övermark M, Koskenmies S, Pitkänen S. A retrospective study of treatment of squamous cell carcinoma in situ. *Acta Derm Venereol*. 2016;96:64-67.
39. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. *J Am Acad Dermatol*. 1992;27:241-248.
40. Stratigos AJ, Garbe C, Dessinioti C, et al. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: part 2. Treatment. *Eur J Cancer*. 2020;128:83-102.
41. Breuninger H, Eigentler T, Bootz F, et al. Brief S2k guidelines—cutaneous squamous cell carcinoma. *J Dtsch Dermatol Ges*. 2013;11(suppl 3):37-45, 39-47.
42. Brantsch KD, Meisner C, Schönfisch B, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. *Lancet Oncol*. 2008;9:713-720.
43. Cherpelis BS, Marcusen C, Lang PG. Prognostic factors for metastasis in squamous cell carcinoma of the skin. *Dermatol Surg*. 2002;28:268-273.
44. Pugliano-Mauro M, Goldman G. Mohs surgery is effective for high-risk cutaneous squamous cell carcinoma. *Dermatol Surg*. 2010;36:1544-1553.
45. Vuyk HD, Lohuis PJ. Mohs micrographic surgery for facial skin cancer. *Clin Otolaryngol Allied Sci*. 2001;26:265-273.
46. Silapunt S, Peterson SR, Goldberg LH. Squamous cell carcinoma of the auricle and Mohs micrographic surgery. *Dermatol Surg*. 2005;31:1423-1427.
47. Baker NJ, Webb AA, Macpherson D. Surgical management of cutaneous squamous cell carcinoma of the head and neck. *Br J Oral Maxillofac Surg*. 2001;39:87-90.
48. Griffiths RW, Feeley K, Suvarna SK. Audit of clinical and histological prognostic factors in primary invasive squamous cell carcinoma of the skin: assessment in a minimum 5 year follow-up study after conventional excisional surgery. *Br J Plast Surg*. 2002;55:287-292.
49. Nemet AY, Deckel Y, Martin PA, et al. Management of periocular basal and squamous cell carcinoma: a series of 485 cases. *Am J Ophthalmol*. 2006;142:293-297.
50. Barysch MJ, Eggmann N, Beyeler M, Panizzon RG, Seifert B, Dummer R. Long-term recurrence rate of large and difficult to treat cutaneous squamous cell carcinomas after superficial radiotherapy. *Dermatol Basel Switz*. 2012;224:59-65.
51. Abbatucci JS, Boulier N, Laforge T, Lozier JC. Radiation therapy of skin carcinomas: results of a hypofractionated irradiation schedule in 675 cases followed more than 2 years. *Radiother Oncol*. 1989;14:113-119.
52. Werlinger KD, Upton G, Moore AY. Recurrence rates of primary nonmelanoma skin cancers treated by surgical excision compared to electrodesiccation-curettage in a private dermatological practice. *Dermatol Surg*. 2002;28:1138-1142; discussion 1142.
53. Nordin P, Stenquist B. Five-year results of curettage-cryosurgery for 100 consecutive auricular non-melanoma skin cancers. *J Laryngol Otol*. 2002;116:893-898.
54. Werner R N, Stockfleth E, Connolly S M, et al. Evidence- and consensus-based (S3) Guidelines for the Treatment of Actinic Keratosis - International League of Dermatological Societies in cooperation with the European Dermatology Forum - Short version. *J Eur Acad Dermatol Venereol*. 2015;29:2069-2079.
55. Stratigos A, Garbe C, Lebbe C, et al. Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. *Eur J Cancer*. 2015;51:1989-2007.
56. Lin C, Tripcony L, Keller J, Poulsen M, Dickie G. Cutaneous carcinoma of the head and neck with clinical features of perineural infiltration treated with radiotherapy. *Clin Oncol*. 2013;25:362-367.
57. Manyam BV, Garsa AA, Chin R, et al. A multi-institutional comparison of outcomes of immunosuppressed and immunocompetent patients treated with surgery and radiation therapy for cutaneous squamous cell carcinoma of the head and neck. *Cancer*. 2017;123:2054-2060.
58. Rosenthal DI, Mohamed ASR, Garden AS, et al. Final report of a prospective randomized trial to evaluate the dose-response relationship for postoperative radiation therapy and pathologic risk groups in patients with head and neck cancer. *Int J Radiat Oncol*. 2017;98:1002-1011.
59. Newman JG, Hall MA, Kurley SJ, et al. Adjuvant therapy for high-risk cutaneous squamous cell carcinoma: 10-year review. *Head Neck*. 2021;43:2822-2843.
60. Likhacheva A, Awan M, Barker CA, et al. Definitive and postoperative radiation therapy for basal and squamous cell cancers of the skin: executive summary of an American Society for Radiation Oncology clinical practice guideline. *Pract Radiat Oncol*. 2020;10:8-20.
61. Maruyama H, Tanaka R, Fujisawa Y, Nakamura Y, Ito S, Fujimoto M. Availability of sentinel lymph node biopsy for cutaneous squamous cell carcinoma. *J Dermatol*. 2017;44:431-437.
62. Brougham NDLS, Dennett ER, Cameron R, Tan ST. The incidence of metastasis from cutaneous squamous cell carcinoma and the impact of its risk factors. *J Surg Oncol*. 2012;106:811-815.
63. Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma: a 10-year, single-institution cohort study. *JAMA Dermatol*. 2013;149:541.
64. National Comprehensive Cancer Network. NCCN Guidelines Squamous Cell Skin Cancer. Version 1. 2024. https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed November 9, 2023.
65. Stratigos AJ, Garbe C, Dessinioti C, et al. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: part 1. Epidemiology, diagnostics and prevention. *Eur J Cancer*. 2020;128:60-82.
66. Stanganelli I, Spagnolo F, Argenziano G, et al. The multidisciplinary management of cutaneous squamous cell carcinoma: a comprehensive review and clinical recommendations by a panel of experts. *Cancers*. 2022;14:377.
67. Boutros A, Cecchi F, Tanda ET, et al. Immunotherapy for the treatment of cutaneous squamous cell carcinoma. *Front Oncol*. 2021;11:733917.
68. Kugel CH, Douglass SM, Webster MR, et al. Age correlates with response to anti-PD1, reflecting age-related differences in intratumoral effector and regulatory T-cell populations. *Clin Cancer Res*. 2018;24:5347-5356.
69. Grob J-J, Gonzalez R, Basset-Seguin N, et al. Pembrolizumab monotherapy for recurrent or metastatic cutaneous squamous cell carcinoma: a single-arm phase II trial (KEYNOTE-629). *J Clin Oncol*. 2020;38:2916-2925.
70. Baggi A, Quaglino P, Rubatto M, et al. Real world data of cemiplimab in locally advanced and metastatic cutaneous squamous cell carcinoma. *Eur J Cancer*. 2021;157:250-258.
71. Boutros A, Bruzzone M, Tanda ET, et al. Health-related quality of life in cancer patients treated with immune checkpoint inhibitors in randomised controlled trials: a systematic review and meta-analysis. *Eur J Cancer*. 2021;159:154-166.
72. Ruiz ES, Karia PS, Morgan FC, Schmults CD. The positive impact of radiologic imaging on high-stage cutaneous squamous cell carcinoma management. *J Am Acad Dermatol*. 2017;76:217-225.

73. Porceddu SV, Bressel M, Poulsen MG, et al. Postoperative concurrent chemoradiotherapy versus postoperative radiotherapy in high-risk cutaneous squamous cell carcinoma of the head and neck: the randomized phase III TROG 05.01 trial. *J Clin Oncol*. 2018;36:1275-1283.
74. NICE National Institute for Health and Care Excellence. Cemiplimab for treating advanced cutaneous squamous cell carcinoma.. 2022. https://www.nice.org.uk/guidance/ta802. Accessed April 16, 2024.
75. Lu SM, Lien WW. Concurrent radiotherapy with cetuximab or platinum-based chemotherapy for locally advanced cutaneous squamous cell carcinoma of the head and neck. *Am J Clin Oncol*. 2018;41:95-99.
76. Samstein RM, Ho AL, Lee NY, Barker CA. Locally advanced and unresectable cutaneous squamous cell carcinoma: outcomes of concurrent cetuximab and radiotherapy. *J Skin Cancer.* 2014;2014:284582.
77. Guthrie TH, Porubsky ES, Luxenberg MN, Shah KJ, Wurtz KL, Watson PR. Cisplatin-based chemotherapy in advanced basal and squamous cell carcinomas of the skin: results in 28 patients including 13 patients receiving multimodality therapy. *J Clin Oncol*. 1990;8:342-346.
78. Jarkowski A, Hare R, Loud P, et al. Systemic therapy in advanced cutaneous squamous cell carcinoma (CSCC): the Roswell Park experience and a review of the literature. *Am J Clin Oncol*. 2016;39:545-548.
79. Maubec E, Petrow P, Scheer-Senyarich I, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. *J Clin Oncol*. 2011;29:3419-3426.
80. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med*. 2010;363:733-742.
81. Tattersall MHN, Martin A, Devine R, et al. Early contact with palliative care services: a randomised trial in patients with newly detected incurable metastatic cancer. *J Palliat Care Med*. 2014;4:170.
82. Temel JS, Greer JA, El-Jawahri A, et al. Effects of early integrated palliative care in patients with lung and GI cancer: a randomized clinical trial. *J Clin Oncol*. 2017;35:834-841.
83. Zimmermann C, Swami N, Krzyzanowska M, et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet Lond Engl*. 2014;383:1721-1730.
84. Maltoni M, Scarpi E, Dall'Agata M, et al. Systematic versus on-demand early palliative care: a randomised clinical trial assessing quality of care and treatment aggressiveness near the end of life. *Eur J Cancer.* 2016;69:110-118.
85. Groeneveld EI, Cassel JB, Bausewein C, et al. Funding models in palliative care: lessons from international experience. *Palliat Med*. 2017;31:296-305.
86. Gross N, Ferrarotto R, Nagarajan P, et al. Phase II study of neoadjuvant cemiplimab prior to surgery in patients with stage III/IV (M0) cutaneous squamous cell carcinoma of the head and neck (CSCC-HN). *Ann Oncol*. 2019;30:v910.
87. Gross ND, Miller DM, Khushalani NI, et al. Neoadjuvant cemiplimab for stage II to IV cutaneous squamous-cell carcinoma. *N Engl J Med*. 2022;387:1557-1568.