e-ISSN 3050-8460
Journal of Dermatology Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Review Article

Diagnosis and Management of Squamous Cell Carcinoma: Interdisciplinary Consensus Statements of Jose R Reyes Memorial Medical Center: A Department of Health Tertiary Hospital in Manila, Philippines

Zharlah Gulmatico-Flores[1*], Raisa Celine R Rosete[1], Mobbydick G Tana[1], Agnes Espinoza-Thaebtharm[1], Ma Cricelda Rescober-Valencia[1], Konrad P Aguila[2], Austin James F Sy[2], Mary Ann Cruz-Ignacio[3], Melanie Rose H Garces-Chua[3], Veronica Vera Cruz[4], Reynaldo Jr Alvarez[4], Erwin D Palisoc[5], Anthony Christopher G Ortiz[5], Gerald C Sy[6], Jonalyn G Bagadiong[7], Bernadette Mayumi T Mortel[7], Katrina D Olitoquit[1], Melissa Rinne V See[1], Sharmaine H Lozano[1], Inna Blanca J Caimol[1], Karen Andrea D Cadacio[1], Rochelle Gabrielle G Galvez[1], Caryl Lyca Dematawaran[1]

[1]National Center for Dermatology, JRRMMC, Philippines
[2]Department of Otorhinolaryngology, Head and Neck Surgery, JRRMMC, Philippines
[3]Department of Internal Medicine, Section of Medical Oncology, JRRMMC, Philippines
[4]Department of Radiation Oncology, JRRMMC, Philippines
[5]Department of Ophthalmology, JRRMMC, Philippines
[6]Department of Surgery, JRRMMC, Philippines
[7]Department of Obstetrics and Gynecology, JRRMMC, Philippines
***Correspondence author:** Zharlah Gulmatico-Flores, MD, FPDS, National Center for Dermatology, JRRMMC, Philippines;
Email: zharlmd@gmail.com

Citation: Gulmatico-Flores Z, et al. Diagnosis and Management of Squamous Cell Carcinoma: Interdisciplinary Consensus Statements of Jose R Reyes Memorial Medical Center: A Department of Health Tertiary Hospital in Manila, Philippines. J Dermatol Res. 2026;7(2):1-14.

https://doi.org/10.46889/JDR.2026.7204

Received Date: 13-05-2026
Accepted Date: 08-06-2026
Published Date: 15-06-2026

Abstract

Squamous Cell Carcinoma (SCC) is the second most prevalent form of non-melanoma skin cancer. Along with other risk factors, such as genetic predisposition, chemical carcinogens, certain viruses and drugs, immunosuppression and chronic inflammation, Ultraviolet-B (UVB) radiation is the most significant etiologic factor in its developmental process. At the Jose R. Reyes Memorial Medical Center in Manila, Philippines, the departments of dermatology, otorhinolaryngology (head and neck surgery), medical oncology, radiation oncology, ophthalmology, plastic surgery and obstetrics and gynecology have developed consensus statements regarding the diagnosis and treatment of SCC patients.

The recommendations are summarized below:

1. Surgery is the preferred treatment for primary low-risk, high-risk and very high-risk SCCs with margins ranging from 4-10 mm, contingent upon the presence of tumor-related risk factors
2. Mohs micrographic surgery is recommended for high-risk SCC and lesions that are located in challenging anatomical sites
3. Radiation therapy is recommended for individuals who are non-surgical candidates and for those who decline surgery
4. For definitive treatment of advanced stages of SCC, a multi-disciplinary approach is advised. Although the metastatic rate of this condition is low, it is advisable to continue with follow-up and close monitoring for a period of up to two years, particularly in high-risk and locally advanced SCC.

Keywords: Squamous Cell Carcinoma; Inflammation; Skin Cancer

Guidelines Information

Specialists in Charge

This guideline for the management of Squamous Cell Carcinoma (SCC) was collaboratively authored by seven specialties at the Jose R. Reyes Memorial Medical Center (JRRMMC) in Manila. The specialties include dermatology, medical oncology, ophthalmology, Otorhinolaryngology - Head and Neck Surgery (ORL-HNS), plastic surgery, radiation oncology and gynecologic oncology. As the senior author, Dr. Zharlah Gulmatico-Flores was the responsible editor, while Dr. Raisa Celine R. Rosete, a fellow of dermatologic surgery was the coordinator of the guidelines.

Acknowledgement

The authors aim to create a national practice guideline that delineates the procedures for the diagnosis, treatment and monitoring of squamous cell carcinoma. However, it is crucial for users of these guidelines to acknowledge that the primary attending physician is responsible for the diagnosis, treatment and management of SCC patients. It is essential to recognize that the recommendations provided in this document are based on the most recent scientific knowledge at the time of publication and may be subject to future revisions.

Approach

Tentative consensus statements were developed by each department subsequent to a thorough literature review that encompassed the pathogenesis, risk factors, clinical characteristics, diagnostic approaches and treatment options for squamous cell carcinoma. Subsequently, the Delphi method was implemented to evaluate these statements over the course of two sessions during a virtual meeting. A consensus was deemed to have been achieved when a minimum average score of 5 was reached using a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree), where a score of 5 represented strong consensus.

Squamous Cell Carcinoma

Frequency

In recent years, there has been a rise in the prevalence of Squamous Cell Carcinoma (SCC). It is the second most prevalent nonmelanoma skin cancer, following basal cell carcinoma and accounts for 20% to 50% of skin cancers [2,3]. A comprehensive study on the incidence rates of SCC in both men and women in Australia, the United States and Germany demonstrated a variety of results. The estimated incidences per 100,000 person-years were as follows: 341 for men and 209 for women in Australia, 497 for men and 296 for women in the United States and 54 for men and 26 for women in Germany [4]. In the United Kingdom, the incidences of SCC are 77.3 and 34.1 per 100,000 person-years for men and women, respectively [5]. SCC incidences in Ireland reveal rates of 66.1 for men and 30.6 for women, in contrast to Norway, where the rates are 20 for men and 15 for women [6]. In Japan, the incidence of SCC is reported to be 51.6 for ages 80 and above [7].

Serquina, et al., conducted a study at the Jose R. Reyes Memorial Medical Center Department of Dermatology. The study documented 59 cases of Squamous Cell Carcinoma (SCC), which accounted for 27.31% of the 216 specimens retrieved from records spanning 2011 to 2020. The majority of patients (61 to 70 years) were female and the mean age of patients was 65.90 years, with a range of 33 to 87 years. An analysis of Mohs micrographic surgery cases conducted in the Philippines between 2003 and 2018 revealed that 10.6% (43 out of 404 cases) were diagnosed as SCC.

Pathogenesis

The most significant etiologic factor contributing to the development of squamous cell carcinoma is Ultraviolet-B (UVB) radiation. The occurrence of squamous cell carcinoma is positively correlated with occupational UV light exposure, as evidenced by consistent epidemiologic evidence [8,9]. Keratinocyte injury and DNA damage are the consequences of UVB exposure. Subsequently, repair mechanisms are facilitated by tumor suppressor genes, including p53. The preservation of genomic stability is significantly influenced by tumor suppressor genes. p53 regulates the expression of its target genes in response to numerous cellular stresses, thereby causing cell cycle arrest, apoptosis, senescence, DNA repair or metabolic changes [10,11]. In 54-95% of cases, the p53 sequence mutation is an early event in the pathogenesis of squamous cell carcinoma and is responsible for the significant genomic instability of these tumors [12-14]. Mutations are reported in both early lesions, such as actinic keratoses, squamous cell carcinoma in situ (7-48% of samples) and metastatic squamous cell carcinoma. The induction and accumulation of oncogenic mutations in epidermal keratinocytes are a consequence of the loss of p53 function, which subsequently facilitates the progression of squamous cell carcinoma.

Risk Factors

Exposure to physical and chemical carcinogens in the environment, genetic predisposition and immunosuppression are the primary risk factors associated with the development of Squamous Cell Carcinoma (SCC). Chronic inflammation, viral infection and drugs have also been associated with the development of SCC.

Ultraviolet Radiation

The most significant environmental risk factor for SCC is Ultraviolet Radiation (UVR). The International Agency for Research on Cancer (IARC) has classified ultraviolet radiation as a class I carcinogen, indicating that it is capable of initiating, promoting and progressing squamous carcinogenesis in the skin [15].

The preferential localization of SCC on sun-exposed and chronically photodamaged sites, as well as in sun-sensitive phenotypes, is indicative of a strong dose–response association with UVR exposure (both UVB and UVA) [16]. The formation of cyclobutane-pyrimidine dimers, which are responsible for the majority of the mutations in SCC, is directly damaged by UVR [17,18]. Approximately 90% of SCCs in humans exhibit mutations in the p53 tumor suppressor gene, a gene that is essential for the prevention of SCC carcinogenesis and progression [14].

Ultraviolet radiation also contributes to carcinogenesis by causing immunosuppressive and immunomodulatory effects. This encompasses the suppression of Langerhans cells in the epidermis, impaired antigen presentation in skin-draining lymph nodes and compromised tumor surveillance as a result of the proliferation of regulatory T cells that are specific to tumor antigens in UV-exposed skin [19].

Chemical Carcinogens

The development of SCC is associated with a variety of chemical exposures, including arsenic, polycyclic aromatic hydrocarbons (PAHs), nitrosamines and alkylating agents, in addition to UV radiation as a physical carcinogen. Arsenic has been historically employed in pesticides and is present in well waters in specific regions. In cases of chronic exposure, PAHs, which are present in tar, pitch and soot, are also associated with elevated SCC rates [20].

Genetic Predisposition

Environmental risk factors, particularly Ultraviolet Radiation (UVR), can be exacerbated by genetic factors. This is observed in individuals with albinism and those with light skin (skin photo types I and II). The skin's susceptibility to UV damage is increased, which is correlated with an elevated incidence of SCC, as a result of a lack of melanin, which serves as a natural defense against UVR due to its photoprotective mechanisms [21]. The risk of developing skin SCC is approximately 1000 times higher for individuals with albinism in sub-Saharan Africa than for the general population [22].

Additionally, the likelihood of developing squamous cell carcinoma is elevated by a number of genetic skin disorders. This is observed in conditions that are defined by inherited defects in DNA repair and genomic stability, including nucleotide excision repair genes XPA-G and XP-V in xeroderma pigmentosum, PTEN in Cowden syndrome, FANCA-N in Fanconi anemia, TP53 in Li-Fraumeni syndrome, RECQL4 in Rothmund-Thomson syndrome, WRN in Werner syndrome, telomere maintenance in dyskeratosis congenita and mammalian mismatch repair in Muir-Torre syndrome [18]. It is worth noting that individuals with xeroderma pigmentosum exhibit a more than a 10,000-fold increase in nonmelanoma skin cancer before the age of 20, with lesions primarily arising in UV-exposed areas [23,24].

Recessive Dystrophic Epidermolysis Bullosa (RDEB), which is caused by a mutation in the COL7A1 gene, is another condition that predisposes patients to the development of aggressive SCC. In its most severe form, RDEB presents a cumulative SCC risk that exceeds 90% by the age of 55, with approximately 80% of patients succumbing to metastatic complications within five years of their initial SCC diagnosis [23].

Immunosuppression

The risk of developing SCC is significantly elevated by immunosuppression, which can be either innate or acquired. Immunosuppression is identified as a risk factor for high tumor burden, metastatic disease and disease-specific death in SCC [25-28]. Solid-Organ Transplantation Recipients (SOTRs) are at an increased risk of developing skin SCC due to their long-term

immunosuppression. The risk of post-transplantation skin cancer is influenced by a variety of factors, including the type, duration and intensity of immunosuppressive therapy, the age at transplantation, cumulative UV exposure and skin type. In general, solid-organ transplant recipients are at a higher risk of developing SCC than hematopoietic stem cell transplant recipients [29-31]. Heart and lung transplant recipients, in particular, have a higher SCC risk than renal transplant recipients due to their older age and more aggressive immunosuppression [30].

Other forms of acquired immunosuppression, such as HIV/AIDS, also increase the risk of developing SCC as a result of progressive immune system impairment [32]. A study conducted by Nguyen, et al., demonstrated that cutaneous SCC can develop rapidly in HIV-positive patients, even at younger ages and is also associated with an increased risk of local recurrence and metastatic spread [33].

Immunosuppression in patients with chronic lymphocytic leukemia, which is defined by the absence of a competent cell-mediated and humoral immunity, also increases the risk of developing cutaneous squamous cell carcinoma, with a potential increase of 8 to 10 times [34].

Medications

Immunosuppressive and photosensitizing medications are among the medications that are linked to an elevated risk of developing SCC. Karagas, et al., conducted a case-control study that established the potential for the chronic use of other photosensitizing agents, including tetracyclines, fluoroquinolones and sulfonamides, to increase the risk of skin cancer, despite the well-established association between UVR-related skin cancers and psoralen and UVA therapy [35].

Immunosuppressives, such as azathioprine, which interferes with cellular DNA repair and upregulates the p53 oncogene, are also associated with the development of SCC [36]. Drugs that affect the cell cycle and are used to treat other cutaneous malignancies, such as BRAF-inhibitors vemurafenib and dabrafenib and hedgehog pathway inhibitor vismodegib, have a reported increased risk of SCC development [37].

Viral Infection

The oncogenic Human Papillomavirus (HPV) is known to be associated with squamous cell carcinoma, particularly HPV 16 and 18, which are considered to be more carcinogenic than other HPV types. HPV 16 and 18 are known to contain viral proteins E6 and E7, which are believed to function in a synergistic manner with UV-induced DNA damage by impairing the p53 tumor-suppressor function in keratinocytes [38]. In contrast, the skin's immune system may be temporarily suppressed by UV radiation, which allows HPV to evade the immune response [39].

Chronic Skin Inflammation and Injury

Approximately 20% of human cancers are attributable to chronic inflammatory conditions, including those that affect the skin and chronic inflammation plays a significant role in the progression of cancer across various organ systems. An increased risk of developing skin malignancies is associated with a number of chronic cutaneous inflammatory diseases. The following conditions are included in this list: atopic dermatitis, psoriasis, discoid lupus erythematosus, lichen planus, hidradenitis suppurativa, prurigo nodularis, lichen sclerosus, systemic sclerosis, morphea, chronic leg ulcers and dystrophic epidermolysis bullosa. The initiation, progression and eventual metastatic spread of cancer can be facilitated by the oncogenic transformation of epithelial cells, which is brought about by prolonged inflammation [40]. SCCs are susceptible to the development on injured skin, including cases of non-healing ulcers, burn scars and radiation dermatitis, in addition to chronically diseased skin. A prospective study was conducted at a burn surgery department in South Egypt, which examined 226 patients with chronic post-burn ulceration. The study revealed nineteen cases of Marjolin's ulcer [41].

Risk Stratification

The National Comprehensive Cancer Network (NCCN) guidelines for cutaneous squamous cell carcinoma were established in 2021 and they assign risk categories of low, high and very high respectively. This risk stratification was confirmed by a comprehensive retrospective study that included 12,684 primary tumors and 8,727 patients. The very high-risk group is at an elevated risk of both local recurrence and metastatic spread, while the high-risk group is susceptible to heightened local recurrence [42].

Baum, et al., proposed the Brigham and Women's Hospital staging system, which is another staging system that is employed to stratify cases of squamous cell carcinoma. This system is based on a single-institution cohort of approximately 1800 tumors. The absolute risk for Local Recurrence (LR) and Nodal Metastasis (NM) is correlated with the stratification of primary cutaneous Squamous Cell Carcinoma (cSCC) into low, intermediate and high risk [43].

The most recent SCC management guidelines recommend the use of both the NCCN risk stratification and BWH tumor classification system, as they offer specific and essential information to clinicians regarding the management and prognosis of SCC. In contrast, the BWH tumor classification is recommended for the evaluation of prognosis and clinical outcomes due to its superior prognostic accuracy, while the NCCN guidelines are recommended as a practical clinical guide for selecting different therapeutic options for each stage of SCC [44-47].

Based on clinical (location/size, clinical extent, primary versus recurrent lesion, immunosuppression, site of prior radiation therapy or chronic inflammatory process, rapidly growing tumor and neurologic symptoms) and pathologic parameters (degree of differentiation, histologic features, depth, perineural involvement, lymphatic or vascular involvement), the consensus group concurs that the most effective method for determining the therapeutic approach is to stratify SCCs as low, high or very high risk according to the National Comprehensive Cancer Network (NCCN) (Level of agreement: 5).

The consensus group also concurs that the most accurate method of predicting the outcome and prognosis of a suspected lesion, as well as the risk of local recurrence and nodal metastasis, is to stratify SCCs as low, intermediate and high risk based on the Brigham and Women's Hospital staging system. High tumor risk factors include a diameter of ≥2 cm, poorly differentiated histologic findings, perineural invasion of at least 0.1 mm, invasion beyond subcutaneous fat or bone invasion. Other factors, such as underlying immunosuppression in the case of chronic lymphocytic leukemia, may also contribute to this classification (Level of agreement: 5)

Clinical Characteristics

The clinical presentations of squamous cell carcinoma are characterized by their diversity, which is frequently contingent upon the histologic subtype and location of the tumor. Typically, they arise from precancerous lesions, such as actinic keratoses or Bowen disease and develop on sun-exposed areas.

These growths are frequently accompanied by secondary changes, such as ulcers, crusting and scaling and can range in color from skin-colored to red or erythematous lesions. They may occasionally exhibit visible blood vessels or telangiectasia and bleed. Some lesions may exhibit induration or subcutaneous spread, while others may be flat, nodular or plaque-like. The invasion of nearby nerves is indicated by symptoms such as pain or tenderness [44].

The clinical appearance of SCC may also vary based on the extent of invasiveness and the histologic grading (well differentiated to poorly differentiated).

Squamous Cell Carcinoma *In-Situ* (SCCIS) is typically characterized by a red, scaly patch or slightly raised plaque, which is often disregarded by patients. In contrast, invasive SCC typically exhibits persistent ulceration and may also exhibit distinct characteristics, including exophytic growth, papillomatous, papulonodular or patchy growth. The risk of metastasis may be elevated due to the greater propensity of these invasive variants to penetrate deeper layers of the skin. The clinical characteristics of SCC are further influenced by the degree of differentiation. SCC that is well-differentiated typically presents as scaly nodules or plaques, while SCC that is poorly differentiated tends to manifest as soft, ulcerated or bleeding lesions [45].

Diagnostic Modalities

The clinical presentation of cutaneous squamous cell carcinoma is the primary determinant of the initial diagnosis. This presentation takes into account the lesion's medical history, appearance and location.

While histopathology continues to be the primary method for diagnosing cutaneous SCC, newer techniques such as dermoscopy and Reflectance Confocal Microscopy (RCM) can enhance the diagnosis by enabling more precise identification and targeted biopsy selection [45].

Dermoscopic Examination

Dermoscopy, a noninvasive diagnostic method, allows for the assessment of the microstructures and colors of the epidermis, dermoepidermal junction and papillary dermis at a 10-fold magnification point. In comparison to visual inspection alone, this method improves the diagnostic precision of SCC [45].

Although dermoscopic features are present in a spectrum from actinic keratosis to SCC, the primary dermoscopic features of invasive squamous cell carcinoma are as follows: 1) keratin/scales, 2) blood spots, 3) white circles, 4) white structureless areas, 5) hairpin and linear-irregular vessels, 6) perivascular white halos and 7) ulceration [46].

Histopathological Diagnosis

Histologic evaluation should be conducted on any suspicious lesions that are identified during the clinical evaluation. Incisional, punch, shave or comprehensive excisional biopsies are among the numerous biopsy methods that are available, depending on the size, location and potential treatment options of the tumor. In cases where the diagnosis is uncertain, histologic examination may be warranted, particularly for tumors with limited or absent keratinization, using conventional hematoxylin and eosin stains, as well as additional immunohistochemical markers such as cytokeratins or molecular indicators [48,49].

In general, SCC is characterized by the presence of irregular clusters of epidermal cells that extend into the dermal layer. The proportion of abnormal squamous cells in the invading tumor clusters varies, but they consist of a combination of typical squamous cells and abnormal (anaplastic) squamous cells. Less differentiated tumors contain a greater number of abnormal squamous cells. Significant variations in cell size and shape, increased growth and coloring of the nuclei, the absence of cell connections, individual cell keratinization and the presence of abnormal mitotic figures are all indicative of the irregularity of squamous cells [49].

The path of keratinization is followed by the differentiation process in SCC. Horn pearls, which are distinctive structures composed of layers of squamous cells, frequently demonstrate this keratinization as they progress toward the center. The center typically exhibits incomplete keratinization, with the exception of occasional full keratinization. Keratohyalin granules are either sparse or absent within the horn pearls [49].

Reflectance Confocal Microscopy (RCM)

RCM is a noninvasive imaging technique that employs near-infrared laser light at 830 nm to achieve cellular-level resolution for *in-vivo* skin examination.

It is purported to have numerous benefits, including the ability to delineate the surgical margins of tumors and monitor therapeutic improvement for both invasive and noninvasive treatments. Additionally, it is not exclusively limited to the diagnosis of nonmelanoma skin cancers, such as SCC [45].

The spinous-granular layer exhibits an abnormal honeycomb pattern or disorganized pattern, 2) round nucleated cells are present within this layer and 3) round blood vessels pass through the dermal papillae perpendicular to the skin's surface are the primary characteristics of SCC as observed through RCM [46].

Recent studies that assessed the diagnostic capabilities of RCM image analysis, as conducted by skilled and expert readers, demonstrated sensitivity rates ranging from 80.0% to 93.3% and specificity rates ranging from 88.3% to 98.6% [46].

Nevertheless, the utilization of RCM is significantly restricted. Evaluating the thickest portions of the tumor is challenging due to the limited imaging depth of 200-300 μm, which corresponds to the papillary dermis in normal skin. This limitation is more apparent when assessing cases of SCC with prominent hyperkeratosis. Additionally, early recognition and differentiation of AK, in situ SCC and invasive SCC remains a diagnostic challenge [45]. The consensus group members do not routinely employ this and it is not accessible in the local hospital setting.

Further Imaging Investigations

The low general risk of nodal and distant metastases renders imaging studies for staging in cases of cutaneous SCC rarely necessary. However, in the event of invasive and/or aggressive SCC or essentially high-risk tumors, imaging techniques to assess

nodal metastases, such as computed tomography, positron emission computed tomography or ultrasonography, should be employed [45-47].

Additional imaging may be necessary to evaluate the deep structural involvement of the soft tissues, cartilage and bony invasion in cases of extensive localized disease. The depth of invasion can be mapped using Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), particularly in critical areas like the face and scalp [45-47].

Biopsy of the Sentinel Lymph Node

The function of Sentinel Lymph Node Biopsy (SLNB) in SCC remains uncertain. Although there are specific prognosticating factors, such as tumor size, thickness, angiolymphatic and/or perineural invasion, that may serve as potential predictors of sentinel lymph node positivity, their value is restricted by the small sample sizes [47].

Psychotherapy

Surgical Intervention

The Treatment of Choice (TOC) for primary low-risk, high-risk and very high-risk SCCs is surgery. Standard excision is used for low-risk tumors, while Mohs Micrographic Surgery (MMS) is used for high-risk and very high-risk tumors [48]. (Consensus level: 5)

The surgical margins that are recommended for standard excision are as follows: (Consensus level: 5)
Surgical margins of 4 to 6 mm are advised for primary, low-risk and well-demarcated SCC.
In 95% of cases, standard excision with 4-mm clinical margins resulted in complete removal of well-circumscribed, low-risk SCC. The assumed clinical tumor margins must encompass any observed peripheral rim of erythema around a lesion being treated as SCC [49,50].

Nevertheless, the EDF-EADO-EORTC consensus group, among others, recommends a minimum 5 mm clinical safety margin for low-risk SCC [51-53].

Surgical margins of 6 to 10 millimeters are permitted for certain primary, high-risk SCC cases.
The British Association for Dermatologists' guidelines recommend a minimum of a 6 mm margin for high-risk SCC and a minimum of a 10 mm margin for very-high-risk SCC, despite the fact that the majority of guidelines recommend broader safety margins for standard excision of high-risk SCC. In contrast, the European interdisciplinary guidelines recommend a clinical safety margin of 6 to 10 mm for high-risk SCC [53].

Although standard excision may be the primary therapeutic option for certain high-risk tumors, the primary clinician must exercise caution due to the absence of a comprehensive margin assessment prior to closure in standard excision [46,47]. Consequently, linear repair, skin graft or secondary intention healing are recommended while awaiting postoperative margin assessment. In instances where a more intricate repair necessitates substantial tissue arrangement, it is advisable to postpone closure until negative histologic margins are verified [46,47].

Mohs micrographic surgery is recommended for SCCs that are classified as high-risk and very high-risk. (Level of agreement: 5)
In cases of high-risk SCC, MMS exhibited lower recurrence rates when compared to standard excision and other non-MMS treatment modalities: 25.2% versus 41.7% for tumors larger than 2 cm, 32.6% versus 53.6% for poorly differentiated SCC and 0% versus 47% for neurotropic SCC [47].

Based on data from a prospective, multicenter Australian case series involving 1,263 SCC patients, the 5-year recurrence rate for SCC treated with MMS is as low as 2.6% in primary SCC and 5.9% in locally recurrent SCC patients. This series included a high proportion of high-risk tumors. These findings indicate that this technique achieves a high cure rate for high-risk SCCs [51].
Mohs micrographic surgery is recommended for the treatment of SCCs in challenging anatomic sites. (Level of agreement: 5)

Modalities That Do Not Involve Surgery

Although surgical methods are often the most effective and efficient method of achieving a complete cure, the decision to pursue

primary treatment with destructive modalities, radiation therapy, topical therapy or systemic medical therapy may be influenced by factors such as functional outcomes, cosmetic concerns and patient preferences, in order to achieve the best overall results.

Modalities That Are Destructive

Curette and Electrodessication (C and E)

Despite the scarcity of studies on C and E, it has the potential to be a highly effective treatment option for small, low-risk primary SCCs, with low recurrence rates. However, it may result in a poor cosmetic outcome and a prolonged healing time when contrasted with excision [53].

Cryosurgery

In patients with extensive field cancerization, cryosurgery may also be considered for low-risk lesions. The AAD guidelines indicate that it may be employed when effective therapies are contraindicated. The quality of evidence is low, but a systematic review reported lower recurrence rates in small lesions after cryosurgery [47,53,54].

Laser therapy

The utilization of Nd:YAG lasers in the treatment of cutaneous squamous cell carcinoma is scarcely documented.54

Photodynamic Therapy (PDT)

PDT entails the activation of photosensitizers, including Methyl Aminolevulinate (MAL) and Aminolevulinic Acid (ALA), followed by a specific incubation period during which the drug is absorbed and metabolized by cells to produce protoporphyrin IX.55 However, there is limited evidence supporting the use of PDT for advanced SCC. PDT may be employed as an adjuvant treatment in conjunction with other non-surgical modalities, such as curettage and surgery, for advanced SCC in high-risk patients, according to a limited number of reports. Nevertheless, the observed outcomes are inconsistent and therefore, current recommendations cannot be established [53].

Topical Modalities

5-Fluorouracil (5-FU) and Imiquimod

Imiquimod is a topical immunomodulator. One of its mechanisms is the stimulation of the cellular immune system, which results in the induction of numerous cytokines. Systemic symptoms, including fatigue and fever, were also reported. The use of this medication is restricted by adverse effects, including erosions, crust, erythema, ulcerations and edema [48].

5-FU is an anti-metabolite that is employed as an off-label treatment for SCCIS and SCC [58]. Certain studies indicate that 5-FU is effective in minimally invasive SCC [57]. However, its use is associated with significant erythema, erosions and crust that persist for a month or more, resulting in decreased patient compliance with treatment.

The current data does not recommend the use of these drugs for the treatment of SCC due to the limited number of reports that investigate their use [47].

Medical and Radiation Oncology

Although surgery is the primary treatment for advanced stages of SCC disease, a multidisciplinary approach is still recommended before definitive treatment. (Agreement: five).

Squamous cell carcinoma can be classified as either early-stage disease or advanced SCC. Advanced SCC is defined as SCCs that have a high risk of nodal involvement, positive nodal involvement or clinical or pathologic evidence of perineural spread [59].

Radiation therapy

Radiation therapy may be recommended for patients who are nonsurgical candidates or who decline surgery (Consensus: 5).

In situations where there are concerns regarding cosmetic outcomes, patient refusal or the inability to undergo surgery due to medical contraindications or technical considerations, radiation therapy may be employed as an alternative to primary surgical

intervention [59]. This may be due to the heterogeneous population of tumors, which includes early stage lesions, recurrent lesions after surgery and surgically or medically inoperable advanced lesions. Nevertheless, radiation is associated with good local control outcomes, particularly for early stage SCCs. Some reports indicate control rates as high as 95% with primary radiation, while others report rates of 80% or lower [59].
Adjuvant radiation therapy may be recommended in the following situations: 1) high-risk or very-high-risk tumors, 2) positive lymph node involvement, 3) clinical or pathologic evidence of perineural spread, 4) positive surgical margins after excision, particularly in anatomic locations that may preclude re-excision, 5) recurrent SCC in the context of margin-negative resection and 6) immunosuppressed patients. (Agreement: 5).

Post-operative radiation therapy is employed to mitigate the risk of recurrence in high-risk tumors, including high-risk primary sites, an increase in tumor thickness, desmoplastic growth, Perineural Invasion (PNI), recurrent tumors, positive surgical margins and immunosuppression, as determined by multiple series.

Brantsch, et al., discovered that the risk of locoregional recurrence is elevated by tumor thickness and desmoplastic growth pattern [61]. In cases where tumors are over 6mm thick in negative lymph node settings, adjuvant radiation should be considered. Furthermore, desmoplasia was independently linked to an elevated risk of local recurrence and these patients should also be assessed for adjuvant radiation.

PNI has also been linked to an elevated risk of locoregional recurrence in skin cancer. Patients with clinical symptoms from perineural involvement or involvement of named nerves should be treated as advanced disease. Adjuvant radiation should be considered for patients with less nerve involvement, particularly if the nerves involved have a diameter of >/= 0.1 mm or with microscopic extensive perineural involvement [59].

Adjuvant radiation should be considered for patients with positive surgical margins or recurrent cSCC following margin-negative resection. Re-resection is the primary treatment option for recurrent lesions or positive margins. Adjuvant radiation may be suggested if additional surgery is not feasible due to cosmetic or technical constraints [59].

Finally, it has been demonstrated in numerous series that immunosuppressed patients are at an elevated risk of locoregional recurrence and that adjuvant radiation is advantageous [59].

Conventional fractionated regimens, which are 1.8-2.0 Gy per fraction and deliver 60-70 Gy in 30-35 fractions and moderately hypofractionated regimens, which deliver 2.5-2.75 Gy per fraction and deliver 50-55 Gy in 20 fractions, have been thoroughly established [59].

The NCCN recommends a total biologic equivalent dose (BED10) of 70-93 Gy for conventional fractionation or 56-88 Gy for hypofractionation for primary tumor definitive radiation. For postoperative adjuvant radiation, the BED10 should be 60-79 Gy for conventional fractionation or 56-70 Gy for hypofractionation.60

Acute radiodermatitis, atrophy, hair loss, pigmentary changes, fibrosis, lymphedema and telangiectasias are among the adverse effects of radiotherapy. The incidence of these side effects is reduced by administering the dose in multiple small daily fractions. ten times

Medical Treatment
Chemotherapy is indicated when distant metastases are resistant to surgery and radiation. Nevertheless, there is a scarcity of data regarding the efficacy and standard regimens of these agents [47]. Cisplatin, Epidermal Growth Factor Inhibitors (EGFR) [cetuximab, panitumumab] and immune checkpoint blockers/anti-Programmed Death-1 (anti-PD1) [pembrolizumab] were the most frequently employed drugs.

Cisplatin
For more than 50 years, cisplatin has been the most extensively researched chemotherapeutic agent in SCC [69]. The standard dose for concurrent adjuvant chemotherapy is 100 mg/m^2 every three weeks. This led to superior local-regional control; however,

it was also accompanied by severe adverse effects, including fibrosis, cytopenias and nausea and vomiting [70,71]. The optimal dosage of to achieve effective local-regional control while minimizing adverse effects is still being investigated [69].

EGFR inhibitors (Cetuximab, Panitumumab)

Cetuximab is a chimeric monoclonal antibody that inhibits the EGFR, a protein that is highly expressed in epithelial tumors, including SCC. A phase II trial that assesses the safety and efficacy of single-agent cetuximab as a first-line treatment for unresectable SCC. The initial dose was 400 mg/m^2 and was administered as an IV infusion. Subsequently, infusions of 250 mg/m^2 were administered every week for one hour. At six weeks, a disease control rate of 69% and an overall response rate of 28% were observed. The average response time was 6.8 months. An acne-like rash is frequently present and may serve as a clinical indicator of response [72].

The EGFR is also inhibited by panitumumab, a human IgG2 monoclonal antibody. Panitumumab was also tested in a phase II trial as a single first-line agent in unresectable SCC. The dose was administered via IV infusion over a 60-minute period at a rate of 6 mg/kg. Until a maximum of 9 cycles was reached, a documented progressive disease or a dose-limiting toxicity was reached, subsequent doses were administered every 2 weeks. The overall response rate was 11%, while the disease control rate was 69%. The median duration of control was five months [73].

Immune checkpoint blockers/anti-Programmed Death-1 (anti-PD1) [pembrolizumab]

On June 24, 2020, the FDA approved pembrolizumab as a single agent for patients with recurrent or metastatic SCC who are not amenable to surgery and radiation. The KEYNOTE-629 trial was the basis for the approval. Until disease progression, unbearable toxicities or a maximum of 24 months, it was administered at a dose of 200 mg every 3 weeks. The disease control rate was 52.4% and the overall response rate was 34.3%. The median progression-free survival was 6.9 months and the median time to response was 1.5 months. Nevertheless, the median overall survival rate and median duration of response were not achieved. Pruritus, asthenia and fatigue were the most frequently observed adverse effects. One patient experienced treatment-related death as a result of cranial nerve neuropathy [74].

Prognosis

SCCs typically have a favorable prognosis and a high cure rate when detected early. Nevertheless, the prognosis for metastatic and locally advanced disease is generally bleak.

Metastasis

Metastasis from cutaneous SCC is low. Weinberg, et al., conducted a study that revealed an average rate of 3-9% of cases occurring one to two years following the initial diagnosis [62].

The regional lymph nodes (85%) are the most frequently affected sites of metastasis, with the cervical and parotid lymph nodes being the most common. The lung (21%), bone (18%), central nervous system (6%) and liver (4%) are the most frequently affected sites of distant metastasis. The highest risk of metastasis is associated with lesions located on the ear.

Adult patients exhibit a 56% 3-year disease-free survival rate, which is indicative of the poor prognosis of metastatic SCC.65

Recurrence

Recurrent SCCs are most frequently observed within two years of the initial treatment. Additionally, the risk of recurrence is elevated by the high-risk tumor factors.

SCCs that are treated with MMS have a reduced risk of recurrence in comparison to those that are treated with standard excision. The risk of recurrence for MMS was 3% with a median follow-up period of 4.9 years, as reported by Van Lee, et al., in a retrospective cohort study. This rate is three times lower than that of standard excision, which is 8% with a median follow-up period of 5-7 years [66].

Follow-up

The presence of regional spread and the risk of tumor recurrence should be the basis for follow-ups. Based on our previously

published consensus guidelines on basal cell carcinoma, we suggest the following follow-up schedules for patients with SCC, as there are no standardized follow-up guidelines [68].

Follow-up appointments may be scheduled at the following intervals for localized and low-risk SCCs: (1) one week, (2) one month, (3) three months and (4) six months. (Agreement 5).

A close follow-up schedule of every three months for the first two years is recommended for regional, advanced and high-risk SCC (Consensus five).

For tumors with regional metastases and advanced tumors, it is also recommended to conduct an ultrasound examination of the regional lymph node region every three months. (Agreement 5).

An estimated 30–50% of patients with a prior history of SCC are at risk of developing another SCC within five years, as well as new primary skin cancers (basal cell carcinoma, melanoma) [66]. Therefore, screening should be conducted on a minimum of an annual basis. Sun protection practices and self-skin examination should be implemented [47].

Conclusion

The majority of squamous cell carcinomas are low-risk tumors that exhibit an exceptional prognosis and treatment response when treated in their early stages. Recurrence rates of tumors treated with Mohs micrographic surgery have been decreased. The metastatic rate for this tumor is low, despite the fact that tumor-related factors increase the risk of metastasis and recurrence. A multidisciplinary treatment approach may be chosen by patients with advanced disease or contraindications to surgery. Sun protection practices must be implemented, as they are the primary etiologic factor that contributes to the development of the condition.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial or non-profit sectors.

Acknowledgement

The authors have no acknowledgments to declare.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Not Applicable.

Authors' Contributions

All authors contributed equally to this paper.

References

1. de Jong E, Lammerts MUPA, Genders RE, Bouwes Bavinck JN. Update of advanced cutaneous squamous cell carcinoma. J Eur Acad Dermatol Venereol. 2022;36 Suppl 1(Suppl 1):6-10.
2. Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: incidence, risk factors, diagnosis, and staging. J Am Acad Dermatol. 2018;78(2):237-47.

3. Nagarajan P, Asgari MM, Green AC, Guhan SM, Arron ST, Proby CM, et al. Keratinocyte carcinomas: Current concepts and future research priorities. Clin Cancer Res. 2019;25(8):2379-91.
4. Stang A, Khil L, Kajüter H, Pandeya N, Schmults CD, Ruiz ES, et al. Incidence and mortality for cutaneous squamous cell carcinoma: Comparison across three continents. J Eur Acad Dermatol Venereol. 2019;33 Suppl 8(Suppl 8):6-10.
5. Venables ZC, Autier P, Nijsten T, Wong KF, Langan SM, Rous B, et al. Nationwide incidence of metastatic cutaneous squamous cell carcinoma in England. JAMA Dermatol. 2019;155(3):298-306.
6. Stratigos AJ, Garbe C, Dessinioti C, Lebbe C, van Akkooi A, Bataille V, et al. European consensus-based interdisciplinary guideline for invasive cutaneous squamous cell carcinoma. Part 1: diagnostics and prevention-update 2023. Eur J Cancer. 2023;193:113251.
7. Umezono Y, Sato Y, Noto M, Yamada K, Noguchi N, Hasunuma N, et al. Incidence rate of cutaneous squamous cell carcinoma is rapidly increasing in Akita Prefecture: Urgent alert for super-aged society. J Dermatol. 2019;46(3):259-62.
8. Serquina BN, Gulmatico-Flores Z, Torres-Culala KM. Demographic and clinical profile of patients diagnosed histopathologically with basal cell carcinoma and squamous cell carcinoma at Jose R. Reyes Memorial Medical Center: A 10-year cross sectional study. Jose R. Reyes Memorial Medical Center. 2020.
9. Ciriaco-Tan CP, Luz KEH, Villaseñor LM, Rovira-Suetomi MVRM. Mohs micrographic surgery in the Philippines: A 15-year review. JAAD Int. 2021;3:61-2.
10. Lane DP. Cancer. p53, guardian of the genome. Nature. 1992;358:15-16.
11. Campos MA, Lopes JM, Soares P. The genetics of cutaneous squamous cell carcinogenesis. Eur J Dermatol. 2018;28:597-605.
12. Brash DE, Rudolph JA, Simon JA, Lin A, McKenna GJ, Baden HP, et al. A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. Proc Natl Acad Sci U S A. 1991;88:10124-8.
13. Ziegler A, Jonason AS, Leffell DJ, Simon JA, Sharma HW, Kimmelman J, et al. Sunburn and p53 in the onset of skin cancer. Nature. 1994;372:773-6.
14. Brash DE, Ziegler A, Jonason AS, Simon JA, Kunala S, Leffell DJ. Sunlight and sunburn in human skin cancer: p53, apoptosis and tumor promotion. J Investig Dermatol Symp Proc. 1996;1:136-42.
15. IARC Working group on the evaluation of carcinogenic risks to humans. Biological agents. IARC Monogr Eval Carcinog Risks Hum. 2012;100(Pt B):1-441.
16. Martinez JC, Otley CC, Stasko T, Euvrard S, Brown C, Schanbacher CF, et al. Defining the clinical course of metastatic skin cancer in organ transplant recipients: A multicenter collaborative study. Arch Dermatol. 2003;139(3):301-6.
17. de Gruijl FR, van Kranen HJ, Mullenders LH. UV-induced DNA damage, repair, mutations and oncogenic pathways in skin cancer. J Photochem Photobiol B. 2001;63(1-3):19-27.
18. Harwood CA, Proby CM, Inman GJ, Leigh IM. The promise of genomics and the development of targeted therapies for cutaneous squamous cell carcinoma. Acta Derm Venereol. 2016;96(1):3-16.
19. Welsh MM, Karagas MR, Kuriger JK, Houseman A, Spencer SK, Perry AE, et al. Genetic determinants of UV-susceptibility in non-melanoma skin cancer. PLoS One. 2011;6(7):e20019.
20. Yuspa SH. Cutaneous chemical carcinogenesis. J Am Acad Dermatol. 1986;15(5 Pt 1):1031-44.
21. Box NF, Duffy DL, Irving RE, Russell A, Chen W, Griffyths LR, et al. Melanocortin-1 receptor genotype is a risk factor for basal and squamous cell carcinoma. J Invest Dermatol. 2001;116(2):224-9.
22. Lekalakala PT, Khammissa RA, Kramer B, Ayo-Yusuf OA, Lemmer J, Feller L. Oculocutaneous albinism and squamous cell carcinoma of the skin of the head and neck in Sub-Saharan Africa. J Skin Cancer. 2015;2015:167847.
23. Fine JD, Johnson LB, Weiner M, Li KP, Suchindran C. Epidermolysis bullosa and the risk of life-threatening cancers: The National EB Registry experience, 1986-2006. J Am Acad Dermatol. 2009;60(2):203-11.
24. Bradford PT, Goldstein AM, Tamura D, Khan SG, Ueda T, Boyle J, et al. Cancer and neurologic degeneration in xeroderma pigmentosum: Long term follow-up characterises the role of DNA repair. J Med Genet. 2011;48(3):168-76.
25. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med. 2003;348(17):1681-91.
26. Harwood CA, Mesher D, McGregor JM, Mitchell L, Leedham-Green M, Raftery M, et al. A surveillance model for skin cancer in organ transplant recipients: A 22-year prospective study in an ethnically diverse population. Am J Transplant. 2013;13(1):119-29.
27. Thompson AK, Kelley BF, Prokop LJ, Murad MH, Baum CL. Risk factors for cutaneous squamous cell carcinoma recurrence, metastasis, and disease-specific death: A systematic review and meta-analysis. JAMA Dermatol. 2016;152(4):419-28.
28. Karia PS, Jambusaria-Pahlajani A, Harrington DP, Murphy GF, Qureshi AA, Schmults CD. Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital tumor staging for cutaneous squamous cell carcinoma. J Clin Oncol. 2014;32(4):327-34.
29. Garrett GL, Blanc PD, Boscardin J, Lloyd AA, Ahmed RL, Anthony T, et al. Incidence of and risk factors for skin cancer in organ transplant recipients in the United States. JAMA Dermatol. 2017;153(3):296-303.
30. O'Reilly Zwald F, Brown M. Skin cancer in solid organ transplant recipients: Advances in therapy and management: Part I. Epidemiology of skin cancer in solid organ transplant recipients. J Am Acad Dermatol. 2011;65(2):253-261.
31. Omland SH, Gniadecki R, Hædersdal M, Helweg-Larsen J, Omland LH. Skin cancer risk in hematopoietic stem-cell transplant recipients compared with background population and renal transplant recipients: A population-based cohort study. JAMA Dermatol.

2016;152(2):177-83.
32. Piketty C, Darragh TM, Da Costa M, Bruneval P, Heard I, Kazatchkine MD, et al. High prevalence of anal human papillomavirus infection and anal cancer precursors among HIV-infected persons in the absence of anal intercourse. Ann Intern Med. 2003;138(6):453-9.
33. Nguyen P, Vin-Christian K, Ming ME, Berger T. Aggressive squamous cell carcinomas in persons infected with the human immunodeficiency virus. Arch Dermatol. 2002;138(6):758-763.
34. Velez NF, Karia PS, Vartanov AR, Davids MS, Brown JR, Schmults CD. Association of advanced leukemic stage and skin cancer tumor stage with poor skin cancer outcomes in patients with chronic lymphocytic leukemia. JAMA Dermatol. 2014;150(3):280-287.
35. Karagas MR, Stukel TA, Umland V, Tsoukas MM, Mott LA, Sorensen HT, et al. Reported use of photosensitizing medications and basal cell and squamous cell carcinoma of the skin: Results of a population-based case-control study. J Invest Dermatol. 2007;127(12):2901-3.
36. Brem R, Li F, Montaner B, Reelfs O, Karran P. DNA breakage and cell cycle checkpoint abrogation induced by a therapeutic thiopurine and UVA radiation. Oncogene. 2010;29(27):3953-63.
37. Kwiek B, Schwartz RA. Keratoacanthoma (KA): An update and review. J Am Acad Dermatol. 2016;74(6):1220-33.
38. Chockalingam R, Downing C, Tyring SK. Cutaneous squamous cell carcinomas in organ transplant recipients. J Clin Med. 2015;4(6):1229-1239.
39. Wang J, Aldabagh B, Yu J, Arron ST. Role of human papillomavirus in cutaneous squamous cell carcinoma: a meta-analysis. J Am Acad Dermatol. 2014;70(4):621-629.
40. Ju T, Hernandez L, Mohsin N, Labib A, Frech F, Nouri K. Evaluation of risk in chronic cutaneous inflammatory conditions for malignant transformation. J Eur Acad Dermatol Venereol. 2023;37(2):231-242.
41. Mousa AK, Elshenawy AA, Maklad SM, Bebars SMM, Burezq HA, Sayed SE. Post-burn scar malignancy: 5-year management review and experience. Int Wound J. 2022;19(4):895-909.
42. Schmults CD, Blitzblau R, Aasi SZ, Alam M, Andersen JS, Baumann BC, et al. NCCN Guidelines® Insights: Squamous Cell Skin Cancer, Version 1.2022. J Natl Compr Canc Netw. 2021;19(12):1382-1394.
43. Baum CL, Wright AC, Martinez JC, Arpey CJ, Brewer JD, Roenigk RK, et al. A new evidence-based risk stratification system for cutaneous squamous cell carcinoma into low, intermediate, and high risk groups with implications for management. J Am Acad Dermatol. 2018;78(1):141-147.
44. Howell JY, Ramsey ML. Squamous Cell Skin Cancer. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024.
45. Combalia A, Carrera C. Squamous cell carcinoma: an update on diagnosis and treatment. Dermatol Pract Concept. 2020;10(3):e2020066.
46. Fania L, Didona D, Di Pietro FR, Verkhovskaia S, Morese R, Paolino G, et al. Cutaneous squamous cell carcinoma: from pathophysiology to novel therapeutic approaches. Biomedicines. 2021;9(2):171.
47. Kim JYS, Kozlow JH, Mittal B, Moyer J, Olenecki T, Rodgers P, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. J Am Acad Dermatol. 2018;78(3):560-578.
48. Kang S. Fitzpatrick's Dermatology. 9th Ed. New York: McGraw-Hill Education. 2019.
49. Elder DE. Lever's Histopathology of the Skin. 11th Ed. Philadelphia: Wolters Kluwer. 2014.
50. Nahhas AF, Scarbrough CA, Trotter S. A review of the global guidelines on surgical margins for nonmelanoma skin cancers. J Clin Aesthet Dermatol. 2017;10(4):37-46.
51. Maubec E. Update of the management of cutaneous squamous-cell carcinoma. Acta Derm Venereol. 2020;100(11):adv00143.
52. Keohane SG, Botting J, Budny PG, Dolan OM, Fife K, Harwood CA, et al. British Association of Dermatologists guidelines for the management of people with cutaneous squamous cell carcinoma 2020. Br J Dermatol. 2021;184(3):401-414.
53. Stratigos AJ, Garbe C, Dessinioti C, Lebbe C, Bataille V, Bastholt L, et al. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: Part 2. Treatment. Eur J Cancer. 2020;128:83-102.
54. Lansbury L, Bath-Hextall F, Perkins W, Stanton W, Leonardi-Bee J. Interventions for non-metastatic squamous cell carcinoma of the skin: systematic review and pooled analysis of observational studies. BMJ. 2013;347:f6153.
55. Kibbi N, Zhang Y, Leffell DJ, Christensen SR. Photodynamic therapy for cutaneous squamous cell carcinoma in situ: impact of anatomic location, tumor diameter, and incubation time on effectiveness. J Am Acad Dermatol. 2020;82(5):1124-130.
56. Hengge UR, Schaller J. Successful treatment of invasive squamous cell carcinoma using topical imiquimod—correction. Arch Dermatol. 2005;141(6):764.
57. Intralesional 5-fluorouracil for the treatment of cutaneous squamous cell carcinoma: A retrospective analysis. J Am Acad Dermatol. 2019;81(4):AB84.
58. Kim E, Parvathaneni U, Welliver MX. Radiation therapy in the management of cutaneous squamous cell carcinomas. In: Radiation Therapy for Sarcomas and Skin Cancers: A Practical Guide on Treatment Techniques. Switzerland: Springer. 2022;253-72.
59. Ruiz ES, Morgan FC, Zigler CM, Besaw RJ, Schmults CD. Analysis of regional and distant metastasis in cutaneous squamous cell carcinoma. JAMA Dermatol. 2020;156(10):1140-7.
60. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Squamous Cell Skin Cancer. Version 1.2024. Plymouth Meeting (PA): National Comprehensive Cancer Network. 2024.
61. Brantsch KD, Meisner C, Schönfisch B, Trilling B, Wehner-Caroli J, Röcken M, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: A prospective study. Cancer. 2008;113(7):1561-8.

62. Weinberg AS, Ogle CA, Shim EK. Metastatic cutaneous squamous cell carcinoma: an update. Dermatol Surg. 2007;33(8):885-899.
63. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis and deaths from disease in the United States. J Am Acad Dermatol. 2013;68(6):957-66.
64. Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma. J Invest Dermatol. 2013;133(9):2305-11.
65. Veness MJ. High-risk cutaneous squamous cell carcinoma of the head and neck. J Biomed Biotechnol. 2007;2007:80572.
66. van Lee CB, Roorda BM, Wakkee M, Voorham QJM, Mooyaart AL, de Vijlder HC, et al. Recurrence rates of cutaneous squamous cell carcinoma after Mohs micrographic surgery compared with standard excision: A retrospective cohort study. Br J Dermatol. 2019;181(2):338-43.
67. Ruiz ES, Karia PS, Besaw RJ, Schmults CD. Performance of the American Joint Committee on Cancer staging manual and the Brigham and Women's Hospital tumor classification system in cutaneous squamous cell carcinoma. JAMA Dermatol. 2019;155(7):819-25.
68. Stratigos AJ, Garbe C, Dessinioti C, Lebbe C, van Akkooi A, Bataille V, et al. European consensus-based interdisciplinary guideline for invasive cutaneous squamous cell carcinoma. Part 1: diagnostics and prevention-update 2023. Eur J Cancer. 2023;193:113251.
69. Pignon JP, le Maître A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomized trials and 17,346 patients. Radiother Oncol. 2009;92(1):4-14.
70. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med. 2004;350(19):1937-44.
71. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004;350(19):1945-52.
72. Maubec E, Petrow P, Scheer-Senyarich I, Duvillard P, Lacroix L, Gelly J, 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(25):3419-26.
73. Foote MC, McGrath M, Guminski A, Hughes BGM, Meakin J, Thomson D, et al. Phase II study of panitumumab in patients with incurable cutaneous squamous cell carcinoma. Ann Oncol. 2014;25(10):2047-52.
74. Grob JJ, Gonzalez R, Basset-Seguin N, Vornicova O, Schachter J, Joshi A, et al. Pembrolizumab monotherapy for recurrent or metastatic cutaneous squamous cell carcinoma: Results from the phase II KEYNOTE-629 study. J Clin Oncol. 2020;38(25):2916-25.

About the journal

ATHENAEUM SCIENTIFIC PUBLISHERS

Journal of Dermatology Research is an international, peer-reviewed, open-access journal published by Athenaeum Scientific Publishers. The journal publishes original research articles, case reports, editorials, reviews and commentaries relevant to its scope. It aims to disseminate high-quality scholarly work that contributes to research, clinical practice and academic knowledge in the field.

All submissions are evaluated through a structured peer-review process in accordance with established editorial and ethical standards. Manuscripts are submitted and processed through the journal's online submission system.

Manuscript submission: https://athenaeumpub.com/submit-manuscript/