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MAIN RISK FACTORS AND THERAPEUTIC INTERVENTIONS IN CUTANEOUS SQUAMOUS CELL CARCINOMA: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: The general objective of this study is to analyze the scientific production on cutaneous squamous cell carcinoma, identifying the main risk factors, diagnostic methods and treatment of this pathology. Methodology: This is a systematic review focused on understanding the essential aspects of cutaneous squamous cell carcinoma. The research was guided by the question: "What are the main risk factors for the development of cutaneous squamous cell carcinoma, as well as the therapeutic methods used in clinical practice?". To find answers, searches were performed in the PubMed database using five descriptors combined with the Boolean term "AND". This resulted in 106 articles, of which 14 were selected for analysis. Results: Non-melanoma skin cancers (NMSC), such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are highly prevalent, mainly due to exposure to UV radiation. Early detection and awareness of risk factors, such as sun exposure, are essential for prevention and management. The development of new therapies, including immunotherapies and targeted therapies, offers hope for improving treatment, especially in advanced cases of NMSC. Conclusion: Future research needs to further explore the molecular mechanisms underlying cSCC progression, as well as the

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long-term efficacy of new therapeutic approaches, in order to reduce mortality and improve patients' quality of life.

Keywords: Cutaneous Squamous Cell Carcinoma. Risk Factors. Diagnosis. Treatment.

INTRODUCTION

Non-melanoma skin cancer is the most common malignancy found in the world, with an increasing incidence rate of 3 to 8% per year since the 1960s. Basal cell carcinoma (75%) along with squamous cell carcinoma (25%) are the most important non-melanoma cancers affecting the skin. Cutaneous squamous cell carcinoma (cSCC) is the second most common carcinoma in Caucasians after basal cell carcinoma, affecting about one million people annually and contributing to 20% of all skin malignancies (Hyeraci et al., 2023) (Desai et al., 2023).

Squamous cell carcinoma can metastasize, usually to proximal lymph nodes, usually metastasizes locally within 1 to 2 years of diagnosis (Hyeraci et al., 2023) (Desai et al., 2023). It is often found in the head and neck region, as this area is exposed to sunlight and radiation more often than other areas of the body; therefore, initial spread is seen in the submandibular, sublingual, and ipsilateral intraparotid lymph nodes. This particular cancer has a metastatic range of 2.3% and 5.2% after considering follow-ups of 5 years or more, respectively (Desai et al., 2023).

Major risk factors for developing CCSC include chronic UV radiation, therapeutic UV light exposure, immunosuppression (especially in organ transplant recipients), exposure to carcinogenic chemicals, medications, smoking, chronic skin ulcerations, HPV infections, Fitzpatrick type I or II skin features (Damps et al., 2021). The incidence of NMSC cases is continuously increasing due to improved cancer screening processes, increasing elderly population, and increased exposure to ultraviolet radiation (UVR) as a consequence of ozone layer depletion. According to a report published in 2012, which estimates the incidence of NMSC in U.S. people, approximately 5.4 million cases of NMSC or keratincell carcinoma have been diagnosed; however, the exact epidemiology of NMSC is unknown because, in the US, NMSC is not included in cancer registries (Ansary et al., 2022).

Exposure to ultraviolet rays leads to the formation of pyrimidine dimer, which causes point mutations in the DNA, leading to the onset of tumor formation. Aggressive cSCC is characterized by a high recurrence rate requiring major surgical excisions, increased metastatic potential to regional lymph nodes, and a considerable mortality rate annually, the incidence of cSCC is about 200,000 to 300,000, and about 2,000 deaths occur every year in the United States (US). The incidence is 16 per 100,000 people in Central Europe, while the rate is 356 per 100,000 in sun-exposed white men in the southern U.S. It is mostly seen in men with an average age of 66 years. More than 2.1 million patients are treated every year for nonmelanoma skin cancer, according to Medicare data. The financial and economic burden of the cSCC is greater than 29 billion dollars. The tumor suppressor gene

p53 and oncogenic activity in the RAS pathway are all involved in tumor formation (Desai et al., 2023).

This systematic review article aims to compile and evaluate the existing scientific evidence on risk factors and management of cutaneous squamous cell carcinoma. The intention is to provide a comprehensive and up-to-date view, which not only synthesizes current knowledge about the condition, but also identifies gaps in research and directs future investigations and clinical practices. By offering an in-depth analysis of the evidence, this work aims to serve as a resource for health professionals, researchers, and academics, helping to optimize preventive and diagnostic approaches to cutaneous squamous cell carcinoma.

METHODOLOGY

This is a systematic review that seeks to understand the main aspects of cutaneous squamous cell carcinoma, as well as to demonstrate the main risk factors related to the development of the condition and also the therapeutic methods used to treat the condition, aiming to ensure a greater clinical elucidation of these pathologies. For the development of this research, a guiding question was elaborated through the PVO (population, variable and objective) strategy: "What are the main risk factors for the development of cutaneous squamous cell carcinoma, as well as the therapeutic methods used in clinical practice?"

The searches were carried out through searches in the PubMed Central (PMC) databases. 5 descriptors were used in combination with the Boolean term "AND": Squamous cell carcinoma, Risk factors, Skin neoplasms, History of skin cancer and Ultraviolet radiation. The search strategy used in the PMC database was: Squamous cell carcinoma AND Risk factors AND Skin neoplasms, Squamous cell carcinoma AND History of skin cancer and Squamous cell carcinoma AND Ultraviolet radiation. From this search, 106 articles were found, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes proposed for this research, in addition, review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 106 articles were found. After applying the inclusion and exclusion criteria, 19 articles were selected from the PubMed database, and a total of 14 studies were used to compose the collection.

RESULTS

Table 1 – contribution of the literature

Author	Contributions
Ansary et al., 2022	Detailed description of the risks of cSCC metastasis, information on perineural invasion and its histological definition, impact of UV radiation on the development of cSCC, mutations associated with the TP53 gene, and clinical characteristics related to sun exposure.
Catalano et al., 2024	Provision of data on the prevalence and mortality associated with cSCC, emphasizing the importance of early identification and appropriate treatment for locally advanced or metastatic cases.
Morandi et al., 2021	Discussion of perineural invasion, clinical impact, and proposal of multimodal treatment for cases with neural involvement, including strategies for therapeutic management.
Cozma et al., 2023	Comprehensive analysis of epidemiological characteristics of cSCC, patient- and tumor-related risk factors, details of staging and treatment strategies, including recommendations for resection margins, and use of Mohs microsurgery.
Lubov et al., 2021	Description of the areas commonly affected by cSCC, influences of sun exposure, and correlation between UV radiation dosage and types of skin cancer.
Choquet et al., 2020	Explanation of the different wavelengths of UV radiation, impact on cellular DNA, formation of pyrimidine dimers, and effects of UV radiation on carcinogenesis.
Sawada in Nakamura, 2021	Discussion of the role of the TP53 gene in cell regulation, response to DNA damage, and the importance of tumor suppressor protein p53 in the prevention of carcinogenesis.
Maubec, 2020	Presentation of the AJCC-8 tumor staging system, practical application in head and neck cSCCs, and limitation of usefulness in other areas, in addition to contributions to the understanding of tumor progression.
Roel et al., 2020	Discussion of treatment guidelines for cSCC, efficacy of surgical excision and Mohs microsurgery, and implications of resection margins on tumor recurrence and progression.
Newman et al., 2021	Analysis of the adverse effects of chemotherapy in the treatment of cSCC, limitations of efficacy, and detailed description of the potential adverse events and toxicities associated with chemotherapy treatments.
Lazar, Dinescu and Costache, 2020	Discussion of targeted treatments and immunotherapy in the management of cSCC, efficacy of EGFR inhibitors, impact of cetuximab, and development of novel immunotherapeutic approaches for aggressive cSCC.
Desai et al., 2023	Contributions on genetic and immunological risk factors for cSCC, increased incidence in immunocompromised patients, and impact of specific genetic conditions on the development and progression of cSCC.

Source: created by the author.

DISCUSSION

The main types of non-melanoma skin cancers (NMSCs) are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), which account for almost 99% of NMSC; the other types of NMSC include Merkel cell carcinoma, sebaceous gland carcinoma, apocrine adenocarcinoma, angiosarcoma, and dermatofibrosarcoma protuberans. At the time of diagnosis, most cSCCs are localized, resulting in favorable 5-year cure rates exceeding

90%. However, a subset of patients (3–7%) encounter locally advanced or metastatic cSCC, leading to substantial morbidity and mortality. The risk of metastasis ranges from 0.1% to 9.9%, carrying an associated mortality risk of 2.8% (Ansary et al., 2022) (Catalano et al., 2024).

A special mechanism of SCC spread is perineural invasion (PNI). Perineural invasion itself was first described in 1985 and was defined as neoplastic invasion along planes of least resistance within the connective tissue surrounding a nerve or lymphatic vessels in the epineurium and perineurium. Currently, the histological definition requires neoplastic cells "in close proximity to the nerve" with a circumferential involvement of at least one-third (33%), regardless of the nerve sheath layer in which the neoplastic cells are found. The heterogeneous group of squamous cell cancers has a variable rate of IBP ranging from 5.2% to 90%, with advanced stages showing the highest incidence of IBP regardless of their location. Histological IBP should be assessed using immunohistochemistry and is differentiated from clinical IBP, which is characterized by neurological symptoms such as numbness, motor impairment, or neuralgia. Clinical NIB represents a late stage of neoplastic invasion, but may be the first clinical indication of neural involvement in some cases. Especially in the face, IBP affecting branches of the cranial nerves can even result in neoplastic extension into the central nervous system, as cranial nerves enter the bony skull through the cranial foramina after only short strokes through the soft tissue. The invasive growth and high recurrence rate of these lesions have led to the suggestion of multimodal treatment (Morandi et al., 2021).

Squamous cell carcinomas are among the most frequent human malignancies and account for nearly 20% of all skin cancer-related deaths, characterized by accelerated and abnormal growth of squamous cells, originating from keratinocytes in the spinous layer of the keratinized stratified squamous epithelium. This origin makes it possible for SCC types to occur at the level of all organs and tissues that contain stratified squamous epithelium, such as skin, esophagus, oral and nasal cavity, salivary glands, lung, genitals, and urinary tract, and although rare, they are extremely fatal when they develop in the thyroid, prostate, scalp, and breast (Cozma et al., 2023). In the white population, almost 80% of squamous cell carcinomas develop mainly in areas chronically exposed to the sun; specifically, nearly half of a percentage of squamous cell carcinoma cases in Caucasians occur in the hands, head, and neck, implying that UVR is the most important carcinogen for squamous cell carcinoma. Other extrinsic risk factors unrelated to sunlight that contribute to SCC include exposure to radiation therapy and chemicals, usual factors, treatment with 8-methoxypsoralen (P) and ultraviolet light (UVA) (PUVA), and medications. Intrinsic risk

factors involved in the development of SCC include older age, skin pigmentation, history of immunosuppression, history of actinic keratosis (AK), chronic medical conditions, viral infections, chronic wounds, inherited conditions, and personal history of NMSC (Ansary et al., 2022).

As sun exposure is a major risk factor for SCCC, they commonly arise on the head and neck, usually on the ear, cheek, lip, and scalp (Lubov et al., 2021). The intensity and cumulative dose of UV radiation differentially affect the risk of SCC and cutaneous basal cell carcinoma (BCC). Intense, episodic sun exposure that causes severe sunburn increases the risk of BCC, while cumulative sun exposure increases the risk of SCC (Choquet et al., 2020). UV radiation from tanning beds also significantly increases the relative risk of SCC (RR; 1.67, 95% CI 1.29–2.17). UV radiation causes cell DNA mutation, resulting in accelerated cell growth, inactivating tumor suppressor genes, and tumor formation. Based on wavelength, UVR can be classified into three types: UVA (320–400 nm), UVB (280–320 nm), and UVC (100–280 nm). Among them, almost all UVC and about 90% of UVB are absorbed by the ozone layer. UVCs cannot have any impact on our skin (Choquet et al., 2020) (Ansary et al., 2022).

Of the three subtypes of UV radiation (A, B, C, distinguished by wavelength), only UV-A and UV-B are considered clinically relevant to the pathogenesis of skin cancer, because UV-C is absorbed entirely by the atmosphere. The daily dosage of UV-B is much lower than UV-A, however, UV-B is much more dangerous, because it is strongly absorbed by the DNA of the cell nucleus and proteins in the epidermis, thus exerting its effect on the genetic material of the epidermal keratinocytes, from which the cSCC originates. UV-B is also responsible for most sunburns. After stimulation by UV exposure, melanocytes in the basal layer of the epidermis act to absorb UV by undergoing melanogenesis, in which they produce the photoprotective pigment melanin that is also distributed to keratinocytes. As a result of this, the incidence of skin cancer is much lower in individuals with darker skin phenotypes, who have higher levels of photoprotective pigment However, protection is prone to failure in case of repeated exposure to intense UV radiation, so skin damage will appear, at first in the form of sunburn (Lazar; Dinescu; Costache, 2020).

The rest of the UVB radiation can reach the Earth's surface, irradiate the epidermal keratinocytes of the skin, and cause direct DNA damage; while UVA radiation has the longest wavelength and causes indirect DNA damage through oxidative stress pathways and by the formation of 8-oxoguanine, which results in GCÿTA transversion mutations during replication. The two main types of photoproducts are cyclobutane pyrimidine dimers and photoproducts produced by UVB and UVC irradiation and are responsible for DNA

photolesions, DNA mutation, and skin cancer. The most commonly mutated gene in SCC is TP53, which occurs in nearly 50–90% of cases and is UVR-induced. One mice –/– are over demonstrate that deficient irradiation is prone to developing SCC after UV reporting at p53. TP53 encodes the tumor suppressor protein p53, performs important functions as a transcription factor, and, under stress conditions, regulates cell cycle, apoptosis, senescence, and DNA repair. In response to an incident of DNA damage, such as UVR or radiation, the p53-p21Cip1 pathway is activated, inhibiting cyclin-dependent kinase (CDK), which initiates cell cycle arrest in the G1-S phase to enable the DNA damage response. Thus, p53 is known as a guardian of the genome in some cases. In other cases, when the DNA damage response is not initiated, the damaged cells are eliminated by p53-mediated apoptosis. Once the p53 gene mutation occurs, these cellular functions lose control and develop the tumor, promoting tumor growth, cell survival, and disruption of DNA repair (Ansary et al., 2022) (Sawada; Nakamura, 2021). Areas of human skin exposed to the sun, various photoproducts are activated by cyclobutane pyrimidine dimers (CPDs), and pyrimidine-pyrimidone causes CT or CC-TT mutation in the p53 gene, about half of these mutated cells die by apoptosis, and other mutated cells exandre, increase in size, and develop carcinogenesis. Generally, in most individuals, the sunlight exposure and p53 mutation event can occur early in life, which can lead to precancerous lesions, actinic keratosis, and ultimately develop into SCC later in life (Ansary et al., 2022).

Risk factors for aggressive cSCC include immunosuppression, continuous sun exposure associated with an outdoor occupation, Caucasian origin, male gender, changes in social trends, and age 65 years or older. It has been noted that the current incidence is expected to increase with increasing ozone depletion, an increase in the number of people receiving organ transplants, and an aging population. Certain genetic disorders are associated with high-risk cSCC. Xeroderma pigmentosum, oculocutaneous albinism, epidermodysplasia verruciformis, and dyskeratosis congenita are all linked to an increased risk of aggressive cSCC. Another genetic condition called recessive dystrophic epidermolysis bullosa, associated with aggressive or high-risk cSCC, shows the highest mortality (Desai et al., 2023).

Immunocompromised patients demonstrate a higher risk of developing aggressive cSCC along with a worse prognosis than immunocompetent patients. They show twice the risk of metastasis and 13% more risk than immunocompetent patients, which depends on the type of immunodeficiency. An increased incidence of aggressive and malignant cSCC of the head and neck region is seen in immunocompromised patients suffering from lymphoma or leukemia, or organ transplant recipients due to compromised cell-mediated

immunity. When compared to the general population, the prevalence of cSCC is 65 times higher among organ transplant recipients, with human papillomavirus being a significant risk factor. In addition, cSCC is recurrent, aggressive, and has a high mortality rate in individuals with small cell lymphocytic lymphoma and chronic lymphocytic leukemia (Desai et al., 2023).

The application of currently available staging systems helps to identify patients at high risk of recurrence. The American Joint Committee on Cancer staging 8th edition (AJCC-8) tumor staging items include tumor diameter, lymph node size, number of positive lymph nodes and their locations (ipsilateral, contralateral, bilateral), and extranodal extension. However, AJCC-8 is only relevant for head and neck cSCCs, which may limit its usefulness (Maubec, 2020).

The staging of cSCC is performed according to the criteria established by the AJCC 8th edition Staging Manual (American Joint Committee on Cancer, 2017) and the UICC 8th edition (Union for International Cancer Control, 2017). Stratification according to risk is performed according to characteristics related to the tumor or the patient. According to the EADO guide for diagnosis and treatment of cSCC, low-risk tumors are pT1 tumors (tumor < 2 cm in its largest dimension according to (AJCC8)) or tumors that do not have the risk factors established by EADO. High-risk tumors are those with at least one pT2 staging (tumor larger than 2 cm) (AJCC8) or those that are associated with EADO risk factors. However, the exact impact of each risk factor on recurrence is not known. Current treatment guidelines (AJCC 8th ed. classification, Brigham Women's Hospital BWH classification, NCCN guidelines, and EADO guidelines) attempt to systematize these risk factors in order to classify patients' disease stage, with subsequent impact on treatment choice. The risk factors related to patients are immunosuppression, the appearance of carcinoma in a radiotreated area or with chronic inflammation, and symptoms that indicate perineural invasion. Tumor-related risk factors are diameter greater than 2 cm, tumor location in a high-risk area, imprecise demarcated borders, rapid tumor growth, and recurrence. Radiological risk factors include bone invasion and perineural invasion. Histological risk factors include tumor thickness > 6 mm, poor differentiation, high-risk histological subtypes, perineural invasion, lymphatic/vascular invasion, and subcutaneous tissue invasion (Cozma et al., 2023).

The staging system of Brigham and Women's Hospital (BWH) is based on the presence of 4 risk factors, being tumor diameter greater than 2 cm, tumor invasion beyond subcutaneous fat (excluding bone invasion, which automatically elevates the tumor to T3), perineural invasion greater than 0.1 mm, and poorly differentiated tumor. The patient is

classified as follows: T1 when there are no risk factors, T2a presence of one risk factor, T2b of two to three risk factors, and T3 when there are more than four risk factors. The T3 stage of BWH accounts for only 5% of tumors, but 70% of lymph node metastases and 83% of disease-specific deaths (Maubec, 2020).

Regarding treatment, the main goal is complete removal of the tumor, along with maximum preservation of healthy surrounding tissues and good aesthetic results. Classic early surgical excision is the treatment of choice for localized stages, with a cure rate of >90% at five years. The treatment of choice in most countries is surgical excision with complete histological clearance at the peripheral and deep margins, Incomplete excision of cSCC has an increased risk of local recurrence, deep subclinical tumor progression, and metastasis (Roel et al., 2020).

According to the EDF-EADO-EORTC group, the limits of surgical resection are 5 mm margins for low-risk tumors and extended to 10 mm for high-risk tumors. Mohs microsurgery with margin control may be an option in high-risk patients and/or patients with special anatomical locations, given the greater curability associated with minimal recurrence rates, maximum tissue preservation, and good aesthetic outcomes. A percentage of 4-5% of patients with SCC progress to more advanced stages: locally advanced, respectively metastatic diseases (<5%) with locoregional or distant metastases; These stages require other therapeutic approaches, such as chemotherapy, radiation therapy, or, more recently. immunotherapy. The low incidence of metastatic forms makes these forms a therapeutic challenge; the management of these patients should be based on the medical decisions of a multidisciplinary team of dermatologists, surgeons, radiotherapists, and oncologists (Cozma et al., 2023).

Radiotherapy can be used as a therapeutic option for SCC in situ in patients over 60 years of age, with multiple lesions located on the lips, or those who refuse therapy but have a higher risk of recurrence than classic excision. It may also be an adjunctive therapy in patients with more advanced stages. For locally advanced SCC, radiotherapy may be used in case of perineural invasion or as an adjunctive method in case of positive post-excision margins. Side effects include mucositis/dermatitis; telangiectasia; hypodermic sclerosis; necrosis of soft tissue, cartilage and bone; decreased sensitivity; and skin carcinomas (Cozma et al., 2023).

Chemotherapy is a systemic approach that can be used in certain situations to treat oral or intravenous SCC administration of anticancer drugs (e.g., platinum-based drugs such as cisplatin and carboplatin; antimetabolites, such as 5-FU; and mitosis inhibitors). It can be combined with ART as adjunctive chemoradiation therapy (ACRT) after resection

without clear margins; however, this would likely be considered in the context of a clinical trial. For incurable situations, such as advanced cSCC that is inoperable or has been inadequately managed by surgery or RT, chemotherapy can be used as a palliative treatment. The use of chemotherapy in SCCCC has limitations due to the lack of efficacy and toxic effects it often has on healthy, rapidly dividing cells, including hair, weight loss, oral sores, nausea and vomiting, diarrhea, and fatigue. Other potential dose-limiting side effects or adverse events [AEs] include, but are not limited to, nephrotoxicity, hepatotoxicity, cardiotoxicity, and/or cachexia (Newman et al., 2021).

Significant progress in the treatment of SCCCC is represented by the introduction of targeted therapy drugs such as EGFR inhibitors. Overexpression of this growth factor receptor involved in RAS signaling is quite common in CCSC, mapping it as a promising target for molecular therapy. Cetuximab, an EGFR inhibitor, has been developed and tested in patients with high-risk SCCCC in clinical trials, with positive results. A good outcome was reported for patients with locally advanced or regional CCSC, whereas, for distant metastatic sites, it remained inefficient. Tyrosine kinase inhibitors have also been used to disrupt EGFR pathways in cases of SCCC. Clinical studies on gefetinib and imatinib have yielded slightly positive responses, with modest anti-tumour activity in recurrent or metastatic SCCC, but with limited adverse effects. Cetuximab has already been approved by the FDA for the treatment of SCCC, either as a stand-alone treatment or in combination with conventional therapies for greater efficiency. Radiotherapy has a synergistic effect with cetuximab, inducing apoptosis and blocking secondary repair mechanisms, and studies have shown that, in combination with chemotherapy, EGFR inhibitors are effective against metastatic squamous cell carcinoma (Lazar; Dinescu; Costache, 2020).

Cutaneous SCC harbors a heavy mutational burden caused by UV radiation, increasing the likelihood of response to immunotherapy, with promising results being reported in clinical studies for the use of checkpoint inhibitors in advanced cSCC. Recently, the human monoclonal antibody cemiplimab, which targets PD-1, was approved by the FDA for patients with locally advanced or metastatic cSCC, unsuitable for curative surgery or radiation therapy. Although efficient in ~50% of aggressive cases of cSCC, common adverse effects (rash, fatigue, diarrhea) as well as severe immune-mediated reactions such as pneumonitis, colitis, hepatitis, nephritis, have been reported, advising caution to be employed, especially for immunocompromised patients. Research is underway for further development of immunotherapy drugs, with the consensus that checkpoint inhibitors will play a large role in the treatment of cSCC in the future (Lazar; Dinescu; Costache, 2020).

CONCLUSION

Non-melanoma skin cancers, especially basal cell carcinoma (BCC) and squamous cell carcinoma (cSCC), pose a major public health challenge due to their high incidence, especially in terms of UV radiation exposure. Although most cSCCs present in localized stages, with cure rates greater than 90%, a small proportion of cases progress to locally advanced or metastatic forms, resulting in significant and higher morbidity. Long-term exposure to UV radiation remains the main modifiable risk factor, and preventive strategies such as sunscreen use and education about the risks of sun exposure are essential. In addition, accurate assessment of tumor staging, using systems such as AJCC and BWH, is crucial for identifying high-risk patients, helping to choose the most appropriate treatments and improve clinical outcomes.

New advances in treatment, including Mohs microsurgery, targeted therapies such as EGFR inhibitors, and immunotherapy with PD-1 inhibitors such as cemiplimab, have shown promising results in the management of advanced cases of cSCC. However, the high recurrence rate and complications associated with the management of recurrent cSCC highlight the importance of a multidisciplinary approach. Finally, there is a need for future research to further explore the molecular mechanisms underlying the progression of cSCC, as well as the long-term efficacy of new therapeutic approaches, in order to reduce mortality and improve patients' quality of life.

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