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Squamous Cell Carcinoma: From Diagnosis to Effective Treatment-A Comprehensive Guide

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Abstract **Review Article**

Squamous cell carcinoma (SCC) is the second most common malignant skin cancer, and its occurrence is on the rise globally. The main risk factors are cumulative sun exposure, immunosuppression, and inflammation. Early diagnosis and treatment are crucial to prevent metastasis and improve patient outcomes. Advanced diagnostic techniques, such as dermoscopy and reflectance confocal microscopy (RCM), have improved the accuracy of SCC diagnosis. Dermoscopy allows for better identification and targeted biopsy of suspicious areas, while RCM provides noninvasive and precise monitoring of treatment progress. The treatment of SCC has also advanced significantly in recent years. For patients with severe actinic damage and multiple in situ/low-risk SCC, cancer treatment has shown promising results. This approach involves the use of topical agents to target the tumor and the surrounding areas where cancer may develop. Additionally, novel therapies, such as epidermal growth factor receptor inhibitors and immune checkpoint inhibitors have been developed for locally advanced and metastatic SCC. In conclusion, the incidence of SCC has been increasing globally, and early diagnosis and treatment are crucial to prevent metastasis and improve patient outcomes. Advanced diagnostic techniques and treatment options have improved significantly in recent years.

Keywords: Squamous cell carcinoma, SCC, Skin Cancer, Diagnosis, Treatment.

1. INTRODUCTION

Squamous cell carcinoma (SCC) is the second most prevalent malignant skin tumour, behind basal cell carcinoma, and its occurrence is on the rise globally [1]. Cumulative sun exposure, particularly throughout childhood and adolescence, is the most significant factor in increasing the risk for SCC. Furthermore, in recent years, the role of immunosuppression, such as that caused by organ donation, has become more significant in the development of tumours [2]. Additionally, the occurrence of squamous cell carcinoma in regions of persistent inflammation should also be considered.

Squamous cell carcinoma (SCC) is responsible for the majority of cases of metastatic illness associated to nonmelanoma skin cancer. As a result, it is crucial to identify and treat SCC in its early stages to avoid the advancement of cancerous growth. While histopathology and surgical excision are currently considered the most reliable methods for diagnosing and treating SCC, the use of advanced diagnostic imaging techniques like dermoscopy and reflectance confocal microscopy (RCM) is improving the accuracy of diagnosis for these keratinizing neoplasms. These techniques enable better identification and targeted biopsy of suspicious areas, as well as noninvasive and precise monitoring of treatment progress. Furthermore, the treatment of cancerization in patients with severe actinic damage and multiple in situ/low-risk SCC, as well as the advancement of novel therapies like epidermal growth factor receptor inhibitors and immune checkpoint inhibitors for locally advanced and metastatic SCC, are significantly enhancing the management of the disease.

2. EPIDEMIOLOGY AND PATHOGENESIS:

SCC primarily affects older adults, with a median age at diagnosis of 66 years [3]. The incidence of SCC has been increasing, and it is predicted that this

trend will continue due to various factors, such as ageing population, increased UV exposure, and the use of immunosuppressive medications [3].

The primary risk factor for SCC is ultraviolet radiation (UVR) exposure, as it leads to genetic mutations in the TP53 tumour suppressor gene [6]. Other risk factors include immunosuppression, exposure to ionizing radiation, chemical carcinogens, and human papillomavirus (HPV) infection [3]. A study revealed that seven genes, including TP53, PIK3CA, CCND1, CDKN2A, SOX2, NOTCH 1, and FBXW7, are altered more frequently in SCC than in non-SCC, with KRAS alterations being less frequent in SCC [4].

3. DIAGNOSIS OF SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma (SCC) is a common type of skin cancer that typically manifests as a shallow ulcer with elevated margins, covered by a plaque, and is often found in sun-exposed areas [3]. This malignancy can present with various surface changes, including scaling, deep ulceration, crusting, and cutaneous horn [5]. However, a less common but noteworthy presentation is a pink cutaneous nodule without overlying surface changes [5].

In cases of head and neck SCC, regional metastasis may lead to enlarged and palpable submandibular or cervical lymph nodes [3]. Additionally, if SCC invades nearby peripheral nerves, patients may experience symptoms such as numbness, pain, and muscle weakness [7]. The diagnostic process involves a thorough clinical examination, dermoscopy, and a skin biopsy for histopathological confirmation [7]. Furthermore, imaging modalities, including computed tomography (CT) and magnetic resonance imaging (MRI), play a crucial role in evaluating soft tissue or bony invasion and detecting lymph node metastasis [3].

The initial step in diagnosing SCC is a comprehensive skin examination conducted by a healthcare professional, followed by a biopsy of the suspicious lesion [8]. A biopsy entails the removal of a small portion of the lesion for histopathological examination, which remains the gold standard for SCC diagnosis [5]. Histopathological features indicative of SCC includes the presence of atypical squamous cells, keratin pearls, and invasion into the dermis. Notably, the depth of invasion and the presence of perineural invasion are crucial prognostic factors for SCC [5].

To further assess the extent of the disease, imaging modalities such as CT, MRI, or positron emission tomography (PET) may be employed [9]. These techniques aid in evaluating local invasion and detecting distant metastasis. CT scans provide detailed images of the anatomy and help assess the involvement of adjacent structures, while MRI is particularly useful for visualizing soft tissues and evaluating bony invasion. PET scans, on the other hand, can detect metabolic activity, aiding in identifying areas of increased cell proliferation and potential metastasis.

The multidisciplinary approach to SCC diagnosis ensures a comprehensive evaluation of the disease, combining clinical examination, histopathology, and imaging studies. Early detection and accurate staging are crucial for determining the appropriate treatment strategy. Once diagnosed, treatment options for SCC may include surgical excision, radiation therapy, and, in advanced cases, systemic therapies such as chemotherapy or targeted agents [10].

4. CLINICAL PRESENTATION

The presumed diagnosis of SCC relies on their interpretation of clinical facts, such as the visual characteristics, anatomical location, and patient-reported medical history. The most common way that SCC in situ appears clinically is as a red and scaly patch or a slightly raised area that patients may not notice. In contrast, invasive SCC is commonly ulcerated and may have a patchy, nodular, papillomatous, or exophytic appearance.

While histopathology is still considered the most reliable method for diagnosing SCC, some noninvasive optical technologies like dermoscopy and RCM have been used lately to improve the accuracy of clinical diagnosis and to acquire a real-time characterisation of the tumor [11].

Dermoscopy is a noninvasive diagnostic technique that enables the examination of colours and microstructures of the epidermis, dermo-epidermal junction, and papillary dermis at a magnification of 10 times. This technique enhances the accuracy of diagnosing SCC compared to visual inspection without any assistance. While there are similarities in the dermoscopic characteristics of actinic keratosis (AK), in situ SCC (Bowen disease), and micro-invasive SCC, there are also distinct markers that may aid in the diagnosis of SCC and its subsequent treatment [12].

Surgical Treatment

The gold standard for surgical removal of tissue is by excision, which encompasses both conventional and Mohs surgery [13]. Conventional excision should guarantee thorough removal, which necessitates include a margin of skin that seems normal clinically around the tumour and the surrounding redness. Prior to surgery, clinical margins may be evaluated using imaging methods such as dermoscopy, RCM, HFUS, or OCT. These approaches can reduce the occurrence of partial excision and impacted margins. The NCCN recommendations suggest using clinical margins of 4-6 mm for the routine excision of low-risk SCC (*Treatment by cancer type*, no date). However, for high-risk SCC,

SCC in immunocompromised individuals, or SCC in particular sites such as the head and neck, where preserving tissue is crucial, Mohs surgery [14]. The American Academy of Dermatology, the American College of Mohs Surgery, the American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery have collaborated to revise the criteria for the proper use of Mohs surgery [14].

Non-Surgical Treatment:

Squamous cell carcinoma with a low risk of complications. Other non-surgical local methods may be explored if surgical intervention is not possible or chosen [15]. For cases of in situ or low-risk squamous cell carcinoma (SCC), the physician has several treatment options to choose from. These include photodynamic therapy, which involves a two-step process. First, a photosensitizer such as 5-aminolevulinic acid or methylaminolevulinate is topically applied. Then, the affected area is exposed to light irradiation for a period of one to several hours using a blue, red, or broadband light source. Another option is topical therapy with imiquimod, which is available in concentrations of 3.75% to 5%. Lastly, 5-fluorouracil can also be used as a topical treatment. These treatment methods not only target the tumor directly, but also have an impact on the surrounding area where cancer may develop if administered across a wider region. In some situations when surgery is not possible, not recommended, or not desired by the patient, noninvasive ablative methods may be considered as an alternative. The methods include laser ablation using CO2 and erbium, electrocoagulation, and cryosurgery. Nevertheless, because to the absence of precise control over histological margins using these methods, the recurrence rate of SCC is elevated [16]. In some circumstances when alternative treatments are not recommended or not feasible, primary local radiation therapy might be used [17].

High-risk squamous cell carcinoma (SCC) and the presence of metastatic disease Surgically removing high-risk SCC is usually recommended, ideally using the Mohs method. However, in cases of primary SCC with perineural invasion or a high risk of regional or distant metastases, adjuvant radiation therapy to the tumor site after surgery may be explored. Treatment for locally progressed and metastatic SCC is determined by the scope of the illness. If there is involvement of lymph nodes, it is necessary to undertake dissection whenever feasible, and it is important to consider adjuvant radiotherapy with or without concomitant systemic treatment [15]. Patients with advanced, unresectable SCC have shown positive response to systemic therapy such as capecitabine or epidermal growth factor receptor inhibitors (cetuximab, panitumumab) [18]. Due to the significant number of mutations in SCC, the presence of lymphocytes infiltrating the tumor, and the expression of programmed death ligand 1 (PD-L1), there is a potential benefit in using immune checkpoint inhibitors like Pembrolizumab to treat SCC [19]. The US Food and medication Administration authorized the first anti-PD1 medication, Cemiplimab, in September 2018. The European Medicines Agency also approved it in July 2019. This therapy has shown positive responses in around 50% of patients with advanced or metastatic SCC.

5. DISCUSSION

The incidence of squamous cell carcinoma (SCC), the second most common malignant skin cancer, has been increasing globally [3]. Cumulative sun exposure, immunosuppression, and inflammation are significant risk factors for SCC development [3, 4, 8]. Early diagnosis and treatment of SCC are crucial to prevent metastasis and improve patient outcomes [7].

Advanced diagnostic imaging techniques, such as dermoscopy and reflectance confocal microscopy (RCM), have improved the accuracy of SCC diagnosis [7, 12]. Dermoscopy allows for better identification and targeted biopsy of suspicious areas, while RCM provides noninvasive and precise monitoring of treatment progress [12]. A study found that dermoscopy significantly improved the diagnostic accuracy of SCC, with a sensitivity of 96.7% and a specificity of 87.2% [12]. Similarly, RCM has been shown to improve the diagnostic accuracy of SCC, with a sensitivity of 91.7% and a specificity of 82.6% [7].

The treatment of SCC has also advanced significantly in recent years. For patients with severe actinic damage and multiple in situ/low-risk SCC, cancerization treatment has shown promising results [20]. This approach involves the use of topical agents, such as 5-fluorouracil, Imiquimod, or photodynamic therapy, to target the tumor and the surrounding area where cancer may develop [20].

Additionally, novel therapies, such as epidermal growth factor receptor inhibitors and immune checkpoint inhibitors, have been developed for locally advanced and metastatic SCC [21]. A study found that the immune checkpoint inhibitor, Cemiplimab, showed a response rate of 47% in patients with advanced or metastatic cutaneous SCC [21]. Similarly, The epidermal growth factor receptor inhibitor, Cetuximab, showed a response rate of 26% in patients with locally advanced or metastatic SCC [21].

6. CONCLUSION

In conclusion, the incidence of SCC has been increasing globally, and early diagnosis and treatment are crucial to prevent metastasis and improve patient outcomes. Advanced diagnostic imaging techniques, such as dermoscopy and RCM, have improved the accuracy of SCC diagnosis. Treatment options for SCC have also advanced significantly in recent years, with the development of cancerization treatment for patients with

severe actinic damage and multiple in situ/low-risk SCC and novel therapies, such as epidermal growth factor receptor inhibitors and immune checkpoint inhibitors, for locally advanced and metastatic SCC.

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