

REVIEW ARTICLE

Update of advanced cutaneous squamous cell carcinoma

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Abstract The incidence of cutaneous squamous cell carcinoma (cSCC) is rapidly increasing. A growing part of this patient group is formed by immunocompromised patients, for example organ-transplant recipients (OTR). Although over 90% of the cSCC show a relatively harmless clinical behaviour, there is also a chance of developing advanced cSCC and metastases. Locally advanced cSCC are defined as cSCC that have locally advanced progression and are no longer amenable to surgery or radiation therapy. Better understanding of the clinical behaviour of cSCC is essential to discriminate between low- and high-risk cSCC. Staging systems are important and have recently been improved. Genetic characterisation of SCC will likely become an important tool to help distinguish low and high-risk cSCC with an increased potential to metastasise in the near future. Available treatments for high-risk and advanced cSCC include surgery, radiotherapy, chemotherapy and targeted therapy with epidermal growth factor receptors inhibitors. Anti-PD-1 antibodies show promising results with response rates of up to 50% in both locally advanced and metastatic cSCC but, in its present form, is not suitable for OTR.

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Introduction

Cutaneous squamous cell carcinomas (cSCC) are keratinocyte carcinomas, originating from the keratinocytes located in the epidermis or adnexal structures. They account for approximately 20% of all cutaneous malignancies. Although exact cumulative incidences are hard to estimate, a rising trend in cSCC is documented worldwide for decades.¹

Risk factors for cSCC are increasing age, male gender, exposure to ultraviolet radiation (UVR), infection with β -human papillomaviruses (HPV), smoking, genetic factors (fair skin, genetic syndromes) and immunosuppression. In the context of organ transplantation, the immunosuppressive agents azathioprine and cyclosporin and the antifungal drug voriconazole are associated with an increased risk of cSCC.²

Although more than 90% of the cSCC display a relatively harmless behaviour, there is also a group of patients who develop advanced cSCC.³ Advanced cSCC include locally advanced and/or metastatic cSCC. Locally advanced cSCC are defined as cSCC that have locally advanced progression (tumours that are large or have penetrated deep into underlying tissues, muscles or nerves) and are no longer amenable to surgery or radiation therapy. Metastatic cSCC are tumours that have spread beyond the original location to adjacent skin, lymph nodes or other organs.⁴

Better understanding of the clinical course of cSCC is essential to identify those cSCC that are prone to aggressive growth and/or metastatic behaviour. The immune system plays an important role in the development of cSCC. Organ transplant recipients (OTR) have a 60–100 times increased risk to develop cSCC compared to the age and sex matched immunocompetent population.⁵ The number of immunocompromised patients worldwide is rising due to an increase in the number of organ transplantations but also the number of patients with inflammatory bowel disease and rheumatoid arthritis who are treated with immunosuppressive drugs for prolonged periods increases over time.^{6,7}

Staging systems for cSCC are important and have been recently improved.⁸ Genetic characterisation of cSCC with an increased potential to metastasise will possibly become an important tool to help us diagnosing cSCC with a poor prognosis in the near future.⁹

The relatively poor prognosis of locally advanced and metastatic cSCC emphasises the need for novel therapeutic strategies in this group. PD-1 inhibitors show promising results but may not be useful for cSCC in OTR, because of the increased risk of transplant rejection.

This review will give an update on the epidemiology, risk factors, staging systems and current treatment options of advanced

cSCC. Management of advanced cSCC in the immunocompromised population receives extra focus in this review.

Epidemiology and patient related risk factors associated with local recurrence and metastases

The risk of cSCC metastases varies between 0.1% and 9.9% in the immunocompetent population, with a 2.8% chance of dying because of this disease.¹⁰ Most cSCC represent low-risk cSCC. However, high-risk cSCC may have a metastatic rate of up to 37%.¹¹ Approximately 90% of cSCC metastases appear within 2 years after the initial diagnosis.¹² More than two-third of the patients suffering from cSCC metastases die because of locally invasive cSCC or nodal metastases, rather than distant organ metastases.¹³ Thompson *et al.*¹⁴ published an excellent study regarding tumour related risk factors for recurrence, metastases and disease-specific death and a summary is displayed in Table 1.

It is expected that the risk factors for metastases are similar in OTR and the immunocompetent population, yet immunosuppressed patients with cSCC could have worse outcomes.¹⁵ In one study, the metastatic rate of cSCC is estimated at 13% in the presence of immunosuppression¹⁶; however, a recent meta-analysis showed a pooled metastasis risk estimate of 7.3%.¹⁷ Another study related the high metastatic rate of cSCC in OTR to the higher amount of local recurrences in OTR compared to immunocompetent patients.¹⁸

Better understanding of pathogenesis of high-risk cSCC

The influence of the immune system on the development of cSCC and cSCC metastases is still underreported and merits more attention.

In immunocompetent patients, the immune system is able to recognise antigens related to viral infections, as well as tumour antigens. This is called immune surveillance. Immunocompromised patients, for example OTR have an impaired immune surveillance due to their life-long immunosuppressive medication, which is needed to retain the transplanted organ, but thereby facilitating the survival and proliferation of atypical cells. The cSCC have a high mutational load with on average 50 mutations per megabase pair DNA.¹⁹ This is even more than the

average mutational load in malignant melanoma,²⁰ which should be sufficient to lead to frequent formation of neoantigens that can be recognised by T lymphocytes.²¹ cSCC are, therefore, highly immunogenic tumours, which makes immunocompromised patients, especially vulnerable for developing cSCC.²² An important defence line consists of elimination of altered cells by innate and adaptive arms of the immune system.²³ Antigens are secreted by tumour cells, will be expressed on the cell membrane and recognised by antigen presenting cells (APC). T lymphocytes and natural killer (NK) cells, among others, are then activated to help eliminate the tumour cells. The human leukocyte antigen (HLA) system has an important role in the recognition of antigens. HLA class I can be found on all cells in the human body. Its function is to present antigens to the CD8 positive T lymphocytes and to make connections with NK cells. HLA class II are expressed on APCs (dendritic cells, macrophages, B cells and CD4 positive T lymphocytes). HLA class III has involvements within the complement system and cytokine formation. When a T lymphocyte recognises the peptide presented by the HLA antigen in the tumour cell, co-receptors act as activators and inhibitors of the immune response (Fig. 1). Programmed cell death 1 protein (PD-1) and Cytotoxic T-Lymphocyte Antigen 4 (CTLA4) are inhibitory receptors and known as immune checkpoint receptors. PD-1 is expressed on the surface of T cells, B cells, natural killer cells, dendritic cells and monocytes.

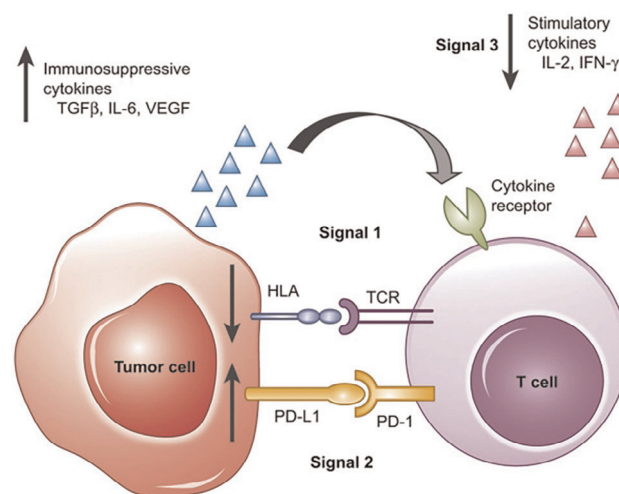


Figure 1 Immune surveillance. Reproduced from Moy *et al.*⁴⁶ with permission from Elsevier. T-cell activation requires three simultaneous signals in order to carry out its anti-tumour effects. Signal 1 comprises the T-cell receptor – HLA interaction, with presentation of antigens from the tumour cell. Signal 2 is a summation of costimulatory and coinhibitory signals. These signals must occur in the presence of Signal 3, made up of immune-activating cytokines, such as IL-2 or IFN- γ . Programmed cell death 1 protein (PD-1) is an inhibitory receptor. Immune evasion can occur at any of these signals (black arrows), impairing the immune system from effectively eradicating malignant cells.

Table 1 Risk factors for recurrence or metastasis of cutaneous squamous cell carcinoma, adjusted from Thompson *et al.*¹⁴

Risk factors
Breslow thickness >2 mm
Invasion beyond subcutaneous fat
Perineural invasion
Diameter >20 mm
Poor differentiation
Immunosuppression
Location on the lip, ear or temple

UVR plays a key role in cSCC carcinogenesis by inducing DNA mutations and escaping from immune surveillance.²⁴ DNA mutations caused by UVR in skin cancers include inactivation of tumour suppressor genes (p53, CDKN2A and PTCH) or activation of proto-oncogenes (Ras). These genes are regulators of the cell cycle and when altered are able to induce tumorigenic effects. The accumulation of mutations ultimately involves various signalling pathways, which mediate epidermal growth factor receptor (EGFR) overexpression. These pathways include RAS-RAF-MEK-MAPK, PLC-gamma/PKC, and PI3K/AKT/mTOR and when altered, they can trigger increased proliferation, migration, survival, resistance to apoptosis and altered differentiation.²⁵

UVR has also important effects on immune function and causes alterations of the cutaneous cell mediated immunity.²³ A decrease of function of the Langerhans cells, cytotoxic and helper T lymphocytes as they are depleted and may have undergone changes in morphology, and an simultaneous increase of UV-induced regulatory T cells lead to alterations in favour of both the development of skin tumours and a higher risk of metastasis. UV-mediated immunosuppression can be both local and systemic by secretion of immunosuppressive cytokines.²³ For example azathioprine and voriconazole are both photosensitive agents and as such can induce tumorigenic effects.

Chronic inflammation can also trigger certain molecular and cellular networks that have a role in the initiation and progression of cSCC, as well as tumour angiogenesis and metastasis.²⁶

Infection with β HPV is thought to play a role in the initiation stage of cSCC carcinogenesis, although the opinions on this subject are controversial.²⁷ There is evidence that the processes of

DNA repair and UVR-induced apoptosis are less effective in β HPV infected cells, which leads to accumulation of DNA damage with actinic keratoses, Bowen's disease and cSCC as the final end result. β HPV most likely does not play a role in the maintenance of the malignant phenotype or in the development of advanced stages of cSCC.²⁸

Better identification of high-risk cSCC

The significant morbidity and mortality of patients with advanced cSCC highlights the urgent need for early identification of high-risk cSCC.

Multiple tumour classification systems have been developed in which various criteria are determined that carry a higher risk of locoregional or distant metastases. Commonly used classification systems are the American Joint Committee on Cancer (AJCC) tumour classification system, the Union for International Cancer Control (UICC) classification system and the Brigham and Women's Hospital (BWH) Tumour Classification System. Differences between the systems are displayed in table 2. In January 2018, the eighth edition of the AJCC (AJCC8) came into force.⁸ Important changes compared to the seventh edition (AJCC7) were the following: SCC of the vermilion lip were categorised under cSCC instead of oral SCC. Risk factors for T1 to upstage to T2 were removed. Instead, risk factors as tumour invasion of >6 mm (instead of >4 mm) and/or invasion beyond the subcutaneous fat, and perineural invasion was defined as tumour cells in the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in calibre, were introduced to upstage a T1 or T2 tumour to T3. Well-known risk factors such as differentiation grade, angioinvasion and a location

Table 2 Changes between the American Joint Committee on Cancer (AJCC8), Union for International Cancer Control (UICC8) and Brigham and Women's Hospital (BWH) classification systems.^{30,36}

AJCC8	UICC8	BWH	
T1	≤2 cm in greatest diameter	T1	0 High-risk factors§
T2	>2–4 cm in greatest diameter	T2	T2a 1 High-risk factors T2b 2–3 High-risk factors
T3	Tumour >4 cm in greatest diameter or minor bone invasion or perineural invasion or deep invasion†	T3	T3 ≥4 High-risk factors
T4a	Tumour with gross cortical bone and/or marrow invasion	T4a	Tumour with gross cortical bone and/or marrow invasion
T4b	Tumour with skull bone invasion and/or skull base foramen involvement	T4b	Tumour with skull bone invasion and/or skull base foramen involvement

†Deep invasion defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumour), perineural invasion defined as tumour cells in the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in calibre or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.

‡Deep invasion defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumour); perineural invasion for T3 classification is defined as clinical or radiographic involvement of named nerves without foramen or skull base invasion or transgression.

§BWH high-risk factors include tumour diameter ≥2 cm, poorly differentiated histology, perineural invasion of nerve(s) 0.1 mm in calibre or tumour invasion beyond subcutaneous fat (excluding bone invasion, which upgrades tumour to BWH stage T3).

on the ear or lip do not contribute to the tumour, nodes, metastasis classification anymore. Recurrent cSCC and immunosuppression are often mentioned as risk factors for metastases; however, they are not yet incorporated in these staging systems.

The positive predictive value of the AJCC8 for a poor outcome remains only 17%^{8,29,30} as the majority of cSCC designated 'high-risk' do not develop advanced disease, and does not allow accurate prediction of which cSCC will progress to locoregional spread or disease-specific death.^{8,31,32} An alternative staging system from BWH performs better, but the positive predictive value for a poor outcome is still only 24%–38%.^{8,30}

Staging systems for locally advanced cSCC have not been extensively studied. In staging systems for melanoma and Merkel cell carcinoma, it is known that in-transit metastasis has prognostic value; however, this is not yet incorporated in cSCC staging. A recent study compared the outcome of patients with cSCC in-transit metastases with T3N0 tumours, T4 tumours with bone invasion, lymph node metastases and distant metastases. cSCC patients with in-transit metastases experienced outcomes similar to locally advanced non-metastatic cSCC patients.³³

Besides these clinical and histological characteristics, better understanding of the genomic alterations and the mechanisms of immune evasion that drive locally advanced and metastatic cSCC is urgently needed to provide more accurate predictive algorithms. Recently, a study was published in which a gene expression profile was developed and validated for predicting high-risk cSCC, showing a positive predictive value of 60% in the highest risk group.⁹ Large-scale studies investigating genetic risk factors for cSCC metastases in OTR have not yet been performed.

Currently, lymph node palpation, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) are frequently used methods for detection of metastasis. Recent studies state that in patients with high-risk cSCC, in the cases of absence of clinically palpable lymphadenopathy and negative imaging, it would be reasonable to consider sentinel lymph node biopsy; however, convincing evidence is still lacking.^{34,35}

Better treatment and prevention

Management of cSCC is important, especially in patients suffering from multiple cSCC. Surgery remains the golden standard for low-risk cSCC. The European consensus group suggests 6–10 mm clinical safety margins for cSCC with high-risk factors.³⁶

The great advantage of Mohs' over traditional surgical excision is that 100% of the surgical margins can be evaluated, resulting in lower recurrence rates (3% vs. 8% during a follow-up period of 5 years, respectively).³⁷ However, it should be mentioned that no randomised controlled trials comparing Mohs' and standard surgical excision have been performed. One study found a 52% tissue-sparing effect for Mohs' vs. standard surgical

excision.³⁸ When it is not possible to perform a re-excision in case of narrow margins, adjuvant radiotherapy can be considered. Curettage and electrodesiccation is a safe therapy for OTR suffering from multiple T1 cSCC (well differentiated tumours on low-risk locations) with a cure rate of around 95%.³⁹

Locally advanced and metastatic cSCC require other treatments that need to be evaluated by a multidisciplinary team. Available treatment options include chemotherapy (such as cisplatin), targeted therapy with EGFR inhibitors (i.e. cetuximab) and anti-PD-1 antibodies (cemiplimab, pembrolizumab, nivolumab). Cemiplimab is the first systemic treatment approved by FDA and EMA for advanced and metastatic cSCC.⁴⁰ Anti-PD-1 antibodies show promising results with response rates of up to 50% in both locally advanced and metastatic cSCC,⁴¹ with emerging evidence of durable responses.⁴² The side effect profile of anti-PD-1 antibodies appears to be favourable compared to chemotherapy. PD-1 inhibitors may not be useful for cSCC in OTR, because of the high chance of transplant rejection.⁴³

Education for prevention and early detection of cSCC is a corner stone for all OTR. The use of sun-protective clothing, hats and sunscreens should be promoted. Prescription of systemic retinoids, nicotinamide and field treatments for actinic keratoses such as 5-fluorouracil should be discussed for high-risk patients.

Animal studies with an HPV vaccine have shown a protective effect against the development of cSCC in HPV infected animals, but an effective vaccine to protect against actinic keratoses and cSCC in human beings is currently not available.⁴⁴

Reliable identification of the highest risk cSCC by gene expression profile could allow clinicians in the future to deploy more aggressive surgery and/or adjuvant radiotherapy for these tumours, thus reducing metastatic risk.^{9,45}

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