

## Review

**Squamous cell carcinoma of the skin: epidemiology, classification, management, and novel trends**

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**Abstract**

Squamous cell carcinoma (SCC) is the second most common non-melanoma skin cancer. It originates from epidermal keratinocytes or adnexal structures (such as eccrine glands or pilosebaceous units). We describe the salient features of cutaneous SCC. We also review novel classification schemes proposed during the last decade which attempt to stratify SCC lesions based on prognosis. Biopsy leads to definitive diagnosis. Treatment includes surgical excision; Mohs micrographic surgery produces excellent cure rates and spares the maximal amount of tissue. Other modalities include electrodessication and curettage, cryosurgery, radiotherapy, topical medications, photodynamic therapy, and systemic therapy. Management and follow-up depend on the risk stratification of individual lesions.

**Introduction**

Traditionally, skin cancers have been divided into two major groups: melanoma, and non-melanoma skin cancer (NMSC). Squamous cell carcinoma (SCC) is the second most common skin cancer in individuals of White European ethnicity and is preceded in frequency by basal cell carcinoma (BCC). Squamous cell carcinoma is estimated to have a lifetime incidence of 7–11% in the USA, whereas that of BCC is 28–33%.<sup>1</sup> Other NMSCs include cutaneous lymphoma, Kaposi's sarcoma, Merkel cell carcinoma, and other sarcomas. Together, these account for <1% of NMSCs. This article reviews the salient features of cutaneous SCC, investigates novel trends in its classification, and discusses the diagnostic considerations of these new guidelines.

**Epidemiology**

The average age of onset of cutaneous SCC in the USA is the mid-sixth decade of life.<sup>2</sup> Individuals may be as young as 20–30 years of age in regions such as Australia, Florida, New Zealand, and southern California. The dis-

ease has a predilection for males, but the incidence of SCC originating on the legs is greater in females. Factors that increase the risk for SCC include Fitzpatrick skin types I and II (usually White individuals), outdoor occupations (farming, construction work), and exposure to human papillomavirus (HPV) types 16, 18, and 31.<sup>3</sup>

Exposure to ultraviolet (UV) radiation and sunlight is the greatest risk factor, as illustrated in studies showing a direct correlation between psoralen and UVA (PUVA) exposure and the incidence of SCC. For example, in patients treated with PUVA for psoriasis, exposure to more than 350 PUVA treatments greatly increased the risk for SCC, and exposure to fewer than 150 PUVA treatments also had a modest effect.<sup>4</sup> In this study, the relative risk for developing SCC in patients with 350–450 PUVA treatments compared with <50 treatments was 6.01.<sup>4</sup> Treatment with PUVA increases the risk for SCC by two mechanisms, which refer to, respectively, its mutagenic effects and its immunosuppressive effects. Patients who develop SCC as a result of PUVA often carry C→T or CC→TT transitions at dipyrimidine sites of the p53 gene. Recent studies show that there are 18 Ha-ras missense or nonsense mutations in this gene locus.<sup>5</sup>

Overall, SCC is uncommon in dark-skinned individuals, but it is the most common cutaneous cancer in African-Americans. In such individuals, the cancer usually occurs in areas that are not sun-exposed.<sup>6</sup> Darkly pigmented skin possesses greater amounts of melanin in the epidermis, which protects against the carcinogenic effects of UV light. As a result, sun exposure is a less common etiology. As in the overall population, SCC in darker skin is often preceded by the development of actinic keratosis (AK).

Some chronic medical conditions increase the likelihood of developing SCC. The incidence of SCC in transplant patients is much higher than that in the general population: in Australia, 70% of transplant recipients develop SCC within 20 years of the transplant.<sup>7</sup> Multiple reasons for this have been postulated. The possession of certain human leukocyte antigen (HLA) and glutathione S-transferase polymorphisms may play a role in SCC development after transplant. Genetics, coupled with infection with HPV types 16, 18, and 31 and exposure to UV radiation, may result in increased oncogenesis. In addition, the use of prophylactic immunosuppressive agents in patients who undergo transplant increases the risk for developing SCC. In transplant patients SCC tends to grow more rapidly and results in higher mortality.<sup>8</sup>

Some inherited skin conditions are associated with a high risk for SCC development. Albinism, a congenital defect in melanin formation, is one example.<sup>9</sup> Xeroderma pigmentosum (XP), a rare autosomal recessive disease, reduces the ability of the skin to repair damage to DNA caused by sun exposure. Xeroderma pigmentosum is caused by a deficiency in DNA nucleotide excision or post-replication repair. Individuals with this disorder develop severe skin damage with minimal sun exposure that manifests in diffuse erythema, bullae, blisters, and eventual xerosis and scaling. As a result, patients with XP have a tendency to develop skin cancers at an early age. The median age of onset of NMSCs in individuals with XP is eight years.<sup>10</sup> Patients aged <20 years have a >1000-fold increased risk for developing SCC.<sup>10,11</sup>

## Clinical presentation

The clinical presentation of SCC is extremely variable and depends on the location and subtype. This section will explain the clinical presentations of precursors to SCC, as well as common SCC subtypes.

Actinic keratosis is a cutaneous lesion that is ubiquitously regarded as premalignant: one in every 1000 AK lesions progresses to SCC.<sup>12</sup> It appears as scaly, flesh-colored, pink or brown papules or plaques, often with an erythematous base. Lesions of AK usually measure several millimeters in diameter. Actinic cheilitis (AC) is another precancerous lesion that may progress to infiltrative SCC.

It usually originates on the lower lip. It presents as an atrophic white papule or plaque that usually becomes fissured, eroded, or ulcerated. One study found SCC to coexist with AC in 17% of cases.<sup>13</sup> Patients are usually males and have a mean age of 53 years. Smoking and outdoor activities are risk factors for the development of actinic cheilitis. Keratoacanthoma, which may be regarded as a subtype of SCC, also commonly originates on the vermillion border of the lower lip, as well as in areas with hair follicles. This lesion has a predilection for White men in their 60s. Keratoacanthoma is further described in Pathogenesis.

Squamous cell carcinoma usually develops on sun-exposed skin (Figs. 1 and 2). Approximately 55% of all



**Figure 1** Two biopsy-proven lesions of squamous cell carcinoma on the dorsum of the right hand of this patient were galvanized by chronic sun exposure



**Figure 2** An example of an exophytic, ulcerated squamous cell carcinoma on the extensor surface of the arm



**Figure 3** An example of a verrucous, exophytic and ulcerated squamous cell carcinoma on the lower lip

cutaneous SCC occurs on the head and neck and frequently involves the extensor surfaces of the hands and forearms (18%). Other common sites include the legs (13%), shoulders and back (4%), upper extremities (3%), and other regions (7%) (Figs. 1 and 2).<sup>14</sup> However, SCC can occur in any location, including the lips (Fig. 3), anus, and genitals.

Bowen's disease (SCC *in situ*) usually presents as an erythematous, well-demarcated, scaly plaque. These lesions can also appear as flesh-colored, pigmented, poorly demarcated, and flat (as a patch). Erythroplasia of Queyrat (SCC *in situ* of the penis) is usually described as a velvety red lesion; scale is not a notable feature of this subtype. Although most patients with SCC *in situ* are asymptomatic, symptoms such as bleeding, weeping, pain, and tenderness may be noted, especially with larger lesions.

Classically, patients with invasive SCC present with a persistent ulcer (Fig. 2) or non-healing wound. An SCC that arises from a burn wound is known as a Marjolin ulcer, an occurrence that was first described by Jean-Nicolas Marjolin in 1828. The most frequent site of occurrence is the lower extremity. Patients present with induration, elevation, ulceration, and weeping at the site of a pre-existing scar or ulcer. These lesions have a high rate of metastases; one study reported that 32% of patients presenting with Marjolin ulcers had lymph node metastasis at the time of diagnosis.<sup>15</sup> Distant metastasis to the lungs, liver, bone, and brain accounted for 27% of cases.<sup>15</sup> Marjolin ulcer behaves aggressively and has a propensity for local recurrence and lymph node metastases.<sup>16</sup> The average period of latency is 35 years.<sup>17</sup> Therefore, its diagnosis requires a high index of clinical suspicion.

The presenting symptoms and clinical presentation of invasive SCC are location-specific and highly variable. For example, SCC of the conjunctiva presents with irritation and/or chronic conjunctivitis and usually develops as a result of chronic contact lens use. These patients may notice an enlarging conjunctival mass.<sup>18</sup> An SCC of the eyelid may be associated with ocular symptoms such as decreased vision, diplopia, proptosis, and ocular surface irritation. Numbness, tingling, and muscle weakness may reflect underlying perineural involvement; it is important to elicit this finding because it adversely influences prognosis.<sup>19</sup>

Squamous cell carcinoma that is induced by HPV most commonly manifests as a new or enlarging warty growth on the penis, vulva, or perianal or periungual region. Patients often present with a history of warts that have been refractory to various treatment modalities in the past. A history of previously documented genital HPV infection is usually elicited. The location of papillary SCC determines the symptoms.<sup>20</sup> Lesions may range in size from <1.0 to >5.0 cm. The etiology of HPV-induced SCC is described in more detail in Pathogenesis.

In addition, the clinical appearance of SCC is largely influenced by the level of differentiation of the lesion. Well-differentiated SCC classically presents as thick, scaly papules and plaques. By contrast, poorly differentiated SCC is often soft, non-scaly, ulcerated, or hemorrhagic.

## Pathogenesis

Squamous cell carcinoma originates from epidermal keratinocytes and adnexal structures (such as eccrine glands or pilosebaceous units). It commonly arises from AK. Patients with AK have an estimated 6–10% lifetime risk for developing SCC. The classification of AK is controversial. Although many clinicians consider this a pre-cancerous lesion, Bernard Ackerman postulates that AK is a form of SCC *in situ*.<sup>21</sup> Different variants of AK have been identified, including hypertrophic, atrophic, acantholytic, pigmented, proliferative, and Bowenoid subtypes. In general, proliferative AK is associated with more aggressive biological behavior, such as higher malignant potential, lateral growth, invasive histological features, and resistance to treatment.<sup>22</sup>

Squamous cell carcinoma can develop even if the subject's history of sun exposure occurred decades before the development of the skin lesion.<sup>23</sup> It is the most frequent cutaneous cancer to arise within a previous scar. This is especially true in Japan, where 32–44% of SCC arises from scars (as opposed to 1.9–2.5% in other countries). This difference is likely to reflect the facts that non-scar SCC is more common in countries with predominantly light-skinned populations and that UV-induced SCC is



**Figure 4** An example of the keratoacanthoma subtype of squamous cell carcinoma on the chest.

relatively less common in countries with dark-skinned individuals.<sup>24</sup>

Keratoacanthoma is another cutaneous neoplasm that appears very similar to a conventional SCC lesion (Fig. 4). Controversy exists about whether or not this lesion is a separate entity or a subtype of SCC. Those who consider it a separate entity believe it to be a benign lesion, whereas others characterize it as a low-grade SCC. The etiologies of keratoacanthoma are similar to those of SCC and refer to UV irradiation, HPV exposure, immunodeficiency, and DNA repair anomalies.<sup>25</sup> Keratoacanthoma has also been consistently reported to arise from surgical scars, skin grafts, trauma, and laser resurfacing.<sup>26</sup> Numerous keratoacanthomas can be found in Ferguson-Smith syndrome, Grzybowski syndrome, Muir-Torre syndrome, and Witten-Zak syndrome.<sup>27</sup>

The role of HPV in the formation of cutaneous SCC has been studied by many groups. Human papillomavirus is a non-enveloped DNA virus that infects humans, mammals, birds, and reptiles. The virus replicates in the nuclei of keratinocytes and depends on keratinocyte differentiation to complete its life cycle.<sup>28</sup> Low-risk HPV DNA exists in an episome separate from the host DNA, whereas high-risk (carcinogenic) HPV integrates into the host genome.<sup>29</sup> The beta ( $\beta$ ) subtype of HPV has the strongest association with cutaneous SCC.<sup>30,31</sup> HPV type 1 is more common in benign lesions, whereas HPV 2 is more common in SCC. Furthermore, sun exposure promotes HPV infection and the formation of SCC.<sup>32</sup> Ultraviolet light may increase the rate of HPV infection through its destructive and immunosuppressive effects. One group showed there to be higher rates of HPV infection in patients treated with PUVA and narrowband UVB.<sup>33</sup> Immunocompromised individuals have a high risk for acquiring HPV and subsequent malignant transforma-

tion because the adaptive immune system (functional T cell response) is integral to fighting HPV infection.<sup>34</sup> In immunocompromised patients, the most common HPV subtypes are 5, 20, 23, and 24.<sup>35</sup> In a study of 60 skin biopsies of SCC in immunocompetent patients, mucosal type HPV DNA was detected in 30% of samples, and HPV 18 was found to be the most common subtype, followed by types 6 and 11.<sup>36</sup> However, many studies show no correlation between HPV and SCC in immunocompetent patients.<sup>37,38</sup> As a result, the role of HPV in SCC still requires much investigation.

### Diagnosis and differential diagnosis

The definitive diagnosis of cutaneous SCC is ascertained through biopsy of the lesion and examination with histopathology. Most lesions that clinically appear benign do not require a biopsy; preventative treatment and observation usually suffice.

The differential diagnosis of AK includes Bowen's disease, chronic cutaneous lupus erythematosus, seborrheic keratosis (SK), superficial BCC, and verruca plana.<sup>3</sup> Erythematous AK resembles benign lichenoid keratosis, irritated SK, psoriasis, and seborrheic dermatitis. Hypertrophic AK more closely resembles discoid lupus erythematosus, keratoacanthoma, porokeratosis, SCC, and verruca vulgaris. Pigmented AK may mimic flat SK, lentigo maligna, and solar lentigo. The differential diagnosis of AC includes chapped lips, lichen planus, angular cheilitis, and other types of cheilitis.<sup>39</sup>

The differential diagnosis of Bowen's disease (SCC *in situ*) includes most dermatoses that may present as well-circumscribed erythematous plaques, including AK, amelanotic melanoma, condyloma acuminatum, nummular eczema, Paget's disease, psoriasis, SK, superficial BCC, verruca vulgaris, and verruca plana. The differential diagnosis of invasive SCC includes any persistent nodule, plaque, or ulcer, especially those that occur on sun-damaged skin, prior irradiated regions, old burns, scars, and on the lips and genitals. The differential diagnosis of keratoacanthoma includes hypertrophic AK, SCC, and verruca vulgaris.<sup>3</sup>

### Novel classification schemes

The pathological profile of cutaneous SCC has been well established for many years, although its classification and how its prognosis should be stratified remain subject to a great deal of controversy. The Broder grading system, mitotic index, and lymphocytic infiltrate are commonly utilized but not proven to affect prognosis.<sup>40</sup> Broder originally proposed this grading system in 1932; it divides SCC into four categories based on histological grade.



Grade I is composed of well-differentiated tumors, in which 75–100% of squamous cells are differentiated. Grade II is composed of moderately differentiated tumors in which 50–75% of cells are differentiated. Grade III is composed of poorly differentiated tumors in which only 25–50% of cells are differentiated. Grade IV is an anaplastic tumor in which 0–25% of cells are differentiated. In addition to Broders system, SCC can be histologically categorized by Clark level. The Clark level refers to the depth of tumor penetration. Level I lesions are *in situ* cancers that are confined to the epidermis. Level II lesions invade the papillary dermis. Level III lesions encompass the entire papillary dermis but do not invade the reticular dermis. Level IV lesions invade the reticular dermis. Level V lesions extend to the hypodermis.

One group has proposed a classification scheme that loosely organizes SCC subtypes into three separate categories.<sup>41</sup> The first represents sun-induced superficial lesions, including those of AK, Bowen's disease (SCC *in situ*), and Bowenoid papulosis. The second category represents subtypes that emerge from the invasive progression of the aforementioned lesions, including invasive SCC, clear-cell SCC, spindle cell (sarcomatoid) SCC, and SCC with single-cell infiltrates. The third category is composed of highly uncommon SCC variants that have no direct correlation to sun exposure or actinic precursors, including *de novo* SCC, lymphoepithelioma-like carcinoma of the skin, and verrucous carcinoma.<sup>41</sup>

In 2000, the National Comprehensive Cancer Network (NCCN) divided SCC into high risk and low risk groups based on the likelihood of recurrence and metastasis.<sup>42</sup> According to the NCCN, any one of the factors listed in Table 1 place SCC in the high-risk category.<sup>42</sup> Subsequent management – especially with non-surgical modalities – depends on this classification (see Treatment modalities).

The tumor–node–metastasis (TNM) staging system for the classification of cutaneous SCC has existed for many years but has not been shown to have significant prognostic value. In 2002, O'Brien *et al.* proposed the P/N staging system, which takes parotid and lymph node metastases into account.<sup>43</sup> In this system, stages P<sub>0</sub> to P<sub>3</sub> denote clinical disease in the parotid gland: P<sub>0</sub> refers to no disease; P<sub>1</sub> refers to a metastatic parotid node of ≤3.0 cm in diameter; P<sub>2</sub> refers to a node of >3.0 cm but ≤6.0 cm in diameter; and P<sub>3</sub> refers to a node of >6.0 cm or involvement of the facial nerve or skull base. Stages N<sub>0</sub> to N<sub>2</sub> refer to neck disease: N<sub>0</sub> refers to no disease; N<sub>1</sub> refers to a single lymph node measuring ≤3.0 cm in diameter; and N<sub>2</sub> refers to a single node of >3.0 cm in diameter or multiple nodes. Increasing P stage and advanced neck disease are associated with decreased survival.<sup>44</sup> In an international trial of 322 patients with

**Table 1** Factors determined by the National Comprehensive Cancer Network (NCCN) as defining cutaneous squamous cell carcinoma as subject to high risk for recurrence<sup>a</sup>

Clinical risk factors for recurrence	
Size and location of lesion <sup>b</sup>	≥20 mm on area L ≥10 mm on area M ≥6 mm on area H
Poorly defined borders	
Recurrent tumor	
Tumor in an immunosuppressed patient	
Tumor at a site of prior radiation treatment or chronic inflammatory process	
Rapidly growing tumor	
Neurological symptoms: pain, paresthesia, paralysis	
Pathological risk factors for recurrence	
Moderately or poorly differentiated	
Adenoid (acantholytic), adenosquamous (showing mucin production) or desmoplastic subtypes	
Clark level IV or V	
Modified Breslow thickness ≥4 mm	
Perineural involvement	
Vascular involvement	

<sup>a</sup>Adapted from Miller (2000)<sup>42</sup>. Any one of the following factors is sufficient for the high risk category.

<sup>b</sup>Area H: mask areas of face, which are at High risk for recurrence (central face, eyelids, eyebrows, periorbital area, nose, lips [both cutaneous and vermillion], chin, mandible, preauricular and postauricular regions, temple), ears, genitalia, hands and feet.

Area M: Middle risk for recurrence: cheeks, forehead, neck, scalp.

Area L: Low risk for recurrence: trunk, extremities.

metastatic SCC, stages P<sub>3</sub>, N<sub>1</sub>, and N<sub>2</sub> were independently associated with reduced survival.<sup>45</sup>

Another group developed the N<sub>1</sub>S<sub>3</sub> system in an attempt to simplify the P/N system while maintaining the prognostic significance of parotid metastasis.<sup>46</sup> N<sub>1</sub>S<sub>3</sub> is divided into three stages: Stage I refers to a single node measuring ≤3.0 cm. Stage II refers to a single node measuring >3.0 cm or multiple nodes of ≤3.0 cm. Stage III refers to multiple nodes of >3.0 cm. This group found this system to have prognostic significance in 215 patients with metastatic SCC.<sup>46</sup>

The ITEM prognostic system utilizes four factors that are determined after the surgical excision of SCC: Immunosuppression; Treatment; Extranodal spread; and Margin.<sup>47</sup> Patients are stratified into low-, medium-, and high-risk groups. In the 250 patients studied by the developers of this classification scheme, 5-year mortality rates in patients with high-, moderate- and low-risk ITEM scores were 56, 24, and 6%, respectively.<sup>47</sup> Although the ITEM score is a powerful prognostic indicator, it is

**Table 2** The 2011 American Joint Committee on Cancer guidelines for staging of cutaneous squamous cell carcinoma<sup>a</sup>

Stage	T	N	M
0	<i>In situ</i>	N0 <sup>b</sup>	M0 <sup>c</sup>
I	T1 <sup>d</sup>	N0	M0
II	T2 <sup>e</sup>	N0	M0
III	T3 <sup>f</sup>	N0 or N1 <sup>g</sup>	M0
	T1 or T2	N1	M0
IV	T1, T2 or T3	N2 <sup>h</sup>	M0
	Any T	N3 <sup>i</sup>	M0
	T4 <sup>j</sup>	Any N	M0
	Any T	Any N	M1 <sup>k</sup>

<sup>a</sup>Adapted from Farasat *et al.* (2011)<sup>48</sup>.<sup>b</sup>No lymph node metastases.<sup>c</sup>No distant metastases.<sup>d</sup>Tumor ≤2.0 cm in greatest diameter with fewer than two high-risk features.<sup>e</sup>Tumor >2.0 cm with one or fewer high-risk features OR tumor of 2.0 cm with two or more high-risk features.<sup>f</sup>Tumor invading maxilla, mandible, orbit, or temporal bone.<sup>g</sup>Metastasis in single ipsilateral lymph node ≤3.0 cm in greatest diameter.<sup>h</sup>(i) Single ipsilateral lymph node metastasis >3.0 cm but ≤6.0 cm in diameter; (ii) multiple ipsilateral lymph node metastases ≤6.0 cm; and (iii) bilateral or contralateral metastases, all ≤6.0 cm.<sup>i</sup>Any lymph node metastasis >6.0 cm.<sup>j</sup>Perineural invasion OR axial/appendicular skeletal invasion.<sup>k</sup>Distant metastasis present.

disadvantaged by the fact that the cutaneous lesion must be excised before the patient can be risk-stratified.

In 2011, the 7th edition of the American Joint Committee on Cancer (AJCC) staging system represented a reorganized version of the TNM staging system of cutaneous SCC.<sup>48</sup> For the prior 20 years, SCC had been staged similarly to other NMSCs. Because of the increasing incidence of SCC, a new scheme was formulated specifically for the tumor (T) characteristics of TNM staging (Table 2). Higher stages are given to tumors of >2.0 cm in diameter with two or more high-risk features. High-risk features in this system are Breslow's thickness, a Clark level higher than IV, perineural invasion, bony invasion, and location on the ear or lip.<sup>48</sup>

In 2012, another group used regression analysis to compose another classification system for metastatic SCC that delineated lesions as being of high risk versus low risk.<sup>49</sup> They identified the absolute risk factors for metastasis (factors with the most predictive value) as poor differentiation, perineural involvement, and lymphovascular invasion. Relative risk factors were identified as lesion size of ≥2.0 cm, moderate differentiation, and Clark level

V thickness. A high-risk lesion has either one absolute risk factor or all three relative risk factors. An intermediate-risk lesion has only two of the three relative risk factors and no absolute risk factor. A low-risk lesion has only one or none of the relative risk factors.<sup>49</sup>

The prognosis of cutaneous SCC has also been investigated on a molecular level. One study found that increased expression of the podoplanin tumor marker correlates with lower survival rates.<sup>40</sup> This study denounced prior findings that human epidermal receptor (HER) and E-cadherin positivity may be linked with prognosis.

### Treatment modalities

For clinically well-defined, low-risk tumors of <2.0 cm in diameter, surgical excision with a minimum margin of 4.0 mm around the tumor border is appropriate and would be expected to completely remove the primary tumor mass in 95% of cases.<sup>50</sup> Tumors of >2.0 cm in diameter – stage T2 or higher – should be removed with margins of ≥6.0 mm. These include tumors with high-risk features such as: moderate, poor, or lack of differentiation; subcutaneous tissue involvement; and location on the ear, eyelid, lip, scalp or nose. Microscopic metastases may be found with high-risk primary cutaneous SCC. In this circumstance, a wide surgical margin extending well beyond the primary tumor may be indicated.<sup>50</sup> Advanced cases involving lymph nodes (N1 or greater) may require extensive resection, dissection, or even amputation. These events are often accompanied by high morbidity and mortality.<sup>40</sup>

Mohs micrographic surgery (MMS) is reported to achieve better cure rates than standard excision.<sup>50,51</sup> Indications for MMS include: (i) lesions located on the scalp, nose, ear, eye, lip, hand or nail unit; (ii) aggressive histological subtypes of SCC; (iii) ill-defined tumors or tumors of >2.0 cm at any location; and (iv) recurrent cancer at any location. In one study of patients with SCC complicated by perineural invasion, 5-year overall survival in patients treated by MMS was 86%, whereas that in patients with SCC treated by standard resection was 76%.<sup>52</sup>

Another study found that only 3.1% of SCCs of the ear recur after MMS, whereas 10.9% recur after standard excision.<sup>53</sup> Recurrence rates of SCC on the lip treated by MMS or standard excision were 5.8 and 18.7%, respectively. Recurrence rates of SCC with perineural invasion treated by MMS or standard excision were 0 and 47%, respectively. Recurrence rates of SCCs of >2.0 cm treated by MMS or standard excision were 25.2 and 41.7%, respectively. Recurrence rates of poorly differentiated SCCs treated by MMS or standard excision were 32.6 and 53.6%, respectively.<sup>53</sup> Another study showed that

MMS should be considered even for SCC *in situ* (rather than locally destructive therapies such as cautery and electrodesiccation) because 31% of these lesions are eventually found to have invasive components on histopathology.<sup>54</sup> Furthermore, the treatment of recurrent SCC by MMS is far superior to that by standard excision; only 10% of recurrent lesions treated by MMS recur, whereas 23.3% of those treated with wide excision recur.<sup>53</sup> A disadvantage of MMS is that it usually cannot capture micrometastases. For this reason, when treating high-risk tumors, some Mohs surgeons will excise a further surgical margin after the surgical specimen has been histologically confirmed as clearing the primary tumor mass. In addition, MMS is time-consuming and costly. It is estimated that MMS procedures performed in the USA in 2013 will have cost more than US\$2 billion.<sup>55</sup> It is imperative that MMS is used only for tumors that meet the aforementioned indications.

Several case series suggest that well-differentiated, slow-growing tumors of <1.0 cm in diameter can be removed by electrodesiccation and curettage (ED&C).<sup>56–58</sup> Curettage can also be used to debulk the tumor prior to MMS. One group of authors reviewed two studies of the efficacy of ED&C compared with that of standard excision of low-risk SCC.<sup>59</sup> The first study showed no significant difference in cure rates between ED&C (14 of 14 patients successfully cleared) and excision (15 of 16 patients successfully cleared) ( $P = 0.1711$ ). The second study found ED&C to be much more efficacious than placebo (106 of 106 patients successfully cleared by ED&C;  $P = 0.0091$ ).<sup>59</sup> However, ED&C cannot be used for recurrent or high-risk SCC.<sup>60</sup>

Good short-term cure rates have been reported for small histologically confirmed SCCs treated with cryosurgery by experienced surgeons.<sup>61,62</sup> However, cryosurgery is not appropriate for locally recurrent disease or high-risk tumors. The most common technique involves the spraying of liquid nitrogen onto the lesion in two freeze–thaw cycles. Cryotherapy utilized on SCC of the extremities resulted in an 88% cure rate, with follow-up of 1–8 years.<sup>63</sup> In the treatment of Bowen's disease, cryotherapy has proven inferior to surgery and phototherapy (relative risk of 1.17 comparing phototherapy with cryotherapy) and achieved no statistically significant difference in tumor clearance and 1-year recurrence in comparison with topical 5-fluorouracil (5-FU) in a study of 127 patients.<sup>64</sup>

Radiotherapy can be used in cases of recurrence, perineural invasion, and in the context of positive margins after excision. The NCCN recommends radiotherapy for low-risk lesions in area H (excluding the hands, feet, and genitals) in patients aged >55 years (Table 1). Radiotherapy should only be used in high-risk lesions if they measure

<1.5 cm in diameter and are located in area H or <2.0 cm in diameter and are located in area M (Table 1) and cannot be used for verrucous carcinoma.<sup>42</sup> Radiotherapy is beneficial in regions that are difficult to close, which may benefit more from direct radiotherapy; these include the lower eyelid, the inner canthus of the eye, the lip, the tip of the nose, and the ear.<sup>65</sup> However, radiation usually produces pallor and telangiectases in the treated skin, and the scar from standard excision may be more acceptable for some patients. For SCC of the eyelid, a study using a median dose of 60.0 Gy resulted in 5-year rates of local relapse-free survival of 71.8%, nodal relapse-free survival of 77.5%, distant metastasis-free survival of 90.6%, and overall relapse-free survival of 58.0%.<sup>66</sup> Another group utilized 6-MeV and 8-MeV electron beam radiotherapy (EBRT) for SCC of the lip and achieved their best outcomes in patients with lesions of 1.5 cm in diameter.<sup>67</sup> Furthermore, data on 217 patients showed that the addition of local adjuvant radiotherapy improved 5-year relapse-free survival from 51% after surgery alone to 92% after adjuvant radiotherapy.<sup>68</sup> The total radiotherapy dose used in SCC of the subungual region is approximately 62 Gy over six weeks; this dose results in no recurrence.<sup>69</sup> By contrast, SCCs on the back of the hand, the abdominal wall, and the lower limb are better treated with excision. In addition, SCC involving cartilage should not be irradiated because of the risk for necrosis.

Photodynamic therapy (PDT) has also proven to be an effective modality for SCC, as well as for other NMSCs. Methyl aminolevulinate PDT (MAL-PDT) offers a 70–90% lifetime cure rate for NMSC, thus making it invaluable when surgical excision is not feasible.<sup>70</sup> With this technique, MAL 160 mg/g cream is applied three hours prior to light-emitting diode (LED) illumination at a wavelength of about 630 nm and intensity of 37 J/cm<sup>2</sup>. This treatment is administered every week for approximately three months.<sup>71</sup> Many other variations of this technique exist. Although one retrospective chart review found MAL-PDT to be reliable only for Bowen's disease,<sup>72</sup> another retrospective study showed that MAL-PDT had resolved nearly all instances of invasive SCC in patients who were poor candidates for surgery.<sup>73</sup> We recommend that the use of MAL-PDT be limited to well-differentiated lesions of Bowen's disease and microinvasive SCC.

Locally applied treatments that are occasionally utilized but for which sufficient evidence is lacking include topical imiquimod, intralesional interferon- $\alpha$  (IFN- $\alpha$ ), and topical 5-FU. In one study, nine of 15 Bowen's disease lesions were cleared by imiquimod, whereas placebo failed to clear any of 16 lesions. There were no recurrences at 12 months, but two of the 15 patients developed invasive SCC at 18 months.<sup>64</sup> Another study compared outcomes

in invasive SCC in patients treated with surgery alone with those in patients treated with surgery followed by adjuvant intralesional IFN- $\alpha$ . The results showed no significant difference (hazard ratio: 1.08, 95% confidence interval [CI] 0.43–2.72).<sup>74</sup> Topical 5-FU applied twice daily for six months was shown to clear 70% of facial SCCs in 10 patients with XP.<sup>75</sup> Unfortunately, four patients had biopsy-proven progression of invasive SCC.<sup>75</sup> Another group used iontophoresis (direct electrical current) to enhance the penetration of topical 5-FU into the deeper dermis in 26 patients with Bowen's disease.<sup>76</sup> Patients received eight treatments over four weeks. Only one patient failed therapy.<sup>76</sup> Treatment with 5-FU is an acceptable strategy in Bowen's disease, but the outcomes in invasive SCC dissuade its use.

The role of systemic chemotherapy with cytotoxic agents in SCC is still unclear. Most data suggest that chemotherapy is best for local lesions that are not amenable to surgery. For metastatic disease, cisplatin, 5-FU, doxorubicin, bleomycin, or combinations of these have been most efficacious but are not well established.<sup>77</sup>

The NCCN stratifies recommendations for the treatment of SCC based on its low- versus high-risk categorization (Table 1). Low-risk lesions in non-hair-bearing areas can be treated with cautery and electrodesiccation (C&E). However, if the subcutis is reached during this procedure, surgical excision is recommended. If low-risk lesions can be excised with 6-mm margins and repaired primarily, standard surgical excision is advised; otherwise, MMS is considered the best strategy. If the patient is aged >55 years and has lesions in areas M or H excluding the feet, hands, and genitalia, radiotherapy may suffice. Photodynamic therapy is also an option for low-risk lesions. For high-risk lesions, standard excision is best used for SCCs measuring >2.0 cm in diameter in area L which can be excised with 1.0-cm margins and closed primarily. Otherwise, MMS is the preferred excisional technique. If positive margins remain after the completion of MMS, adjuvant radiation may be used. Radiation therapy alone may be used for high-risk lesions if the patient is aged >55 years, is not diagnosed with verrucous carcinoma, and has lesions in area H measuring <1.5 cm in diameter or in area M measuring <2.0 cm in diameter.<sup>42</sup> Patients with high-risk SCC should be followed up for at least two years and for up to five years; 75% of recurrences and metastases are detected within two years, and 95% are detected within five years.<sup>53,78</sup>

## Metastatic disease

Incidences of local recurrence, regional metastases, distant metastases, and disease-specific death caused by cutaneous SCC have been reported as 5, 5, 1, and 1%, respectively.<sup>79</sup>

Many risk factors that increase the likelihood of metastasis have been identified. These include immunosuppression (which increases the likelihood of metastasis to 13–20%), a longer average duration of the primary lesion (8 months for metastatic SCC vs. 5 months for non-metastatic SCC), median tumor diameter (2.0 cm vs. 1.0 cm), moderate and poor differentiation (12–32% likelihood), perineural invasion (40–47% likelihood), lymphovascular invasion (40% likelihood), incomplete primary excision, and local recurrence (25–62%).<sup>80</sup> The largest study to date was conducted in 2008 and included 615 patients who developed metastases; the most important risk factors were tumor thickness of >2.0 mm, tumor size of >2.0 cm, location on the ear, and immunosuppression.<sup>80</sup> The 2012 study that suggested a new classification scheme for SCC determined that the absolute risk factors for metastasis (factors with the most predictive value) were poor differentiation, perineural invasion, and lymphovascular invasion.<sup>49</sup> A tumor size of  $\geq 2.0$  cm, moderate differentiation, and Clark level V thickness were determined to be relative risk factors for metastasis.<sup>49</sup> The most common site of lymph node metastasis is the parotid gland (especially the parotid tail, external jugular lymph node junction, and upper cervical nodes).<sup>46</sup>

## Follow-up and prognosis

In most patients with cutaneous SCC, prognoses are good and cure rates exceed 95% with complete excision of the primary tumor.<sup>46</sup> However, the likelihood of metastasis increases with the aforementioned risk factors. According to the NCCN, palpable regional lymph nodes detected in a total-body skin examination should be assessed with fine needle aspiration (FNA). If results are negative, an open biopsy with frozen section should be undertaken. If either FNA or open biopsy yield positive results, a regional lymph node dissection should take place. If more than one positive lymph node is found, or if one lymph node measuring >3.0 cm is found, adjuvant radiotherapy must be administered.<sup>42</sup>

As the parotid gland is the most common site of metastasis, palpable intraparotid SCC requires a superficial parotidectomy with adjuvant radiation.<sup>42</sup> Based on a study of 295 neck dissections, the Sydney Head and Neck Cancer Institute makes the following recommendations for cutaneous SCC metastasizing to the neck: metastases to lymph nodes of the neck but sparing the parotid from any primary site should be treated with a comprehensive neck dissection followed by adjuvant radiotherapy to both the neck and parotid gland.<sup>46</sup> The management of metastases to the parotid that spare the lymph nodes varies: (i) if the primary SCC lesion was on the anterior scalp or external ear, parotidectomy with sentinel lymph node biopsy followed by adjuvant radiotherapy to the



parotid is required; (ii) if the primary lesion was on the posterior scalp or neck, adjuvant radiotherapy must also include the neck; and (iii) if the primary lesion was located elsewhere, a parotidectomy with complete neck dissection is required. For SCC metastases to both the parotid and neck, parotidectomy, complete neck dissection, and radiotherapy to the parotid and neck are required.<sup>46</sup>

## Conclusions

Squamous cell carcinoma is the second most common type of NMSC. Commonly affected individuals include elderly people, those with UV light exposure, those with light skin types, immunosuppressed subjects, and people with inherited skin conditions. Squamous cell carcinoma has many clinical manifestations that depend on location and subtype. Lesions associated with SCC include AK, AC, and keratoacanthoma; controversy exists about whether AK and keratoacanthoma are forms of SCC *in situ*. Squamous cell carcinoma may manifest as Bowen's disease, Marjolin ulcer, HPV-induced SCC, and other entities. The etiology commonly includes exposure to sunlight, AK, HPV, prior scars or burns, and persistent ulcers. The differential diagnosis of SCC refers to any persistent nodule, plaque, or ulcer; biopsy leads to definitive diagnoses whenever there is doubt. Many classification schemes have been proposed to stratify prognosis; these include subtype-based protocols, the 2000 NCCN scheme,<sup>42</sup> the 2002 P/N system,<sup>43</sup> the N1S3 system,<sup>46</sup> the ITEM prognostic score,<sup>47</sup> and the TNM staging system, last modified in 2011 by the AJCC.<sup>48</sup> Treatment includes surgical excision, MMS, ED&C, cryotherapy, radiotherapy, PDT, the application of topical agents, and systemic chemotherapy. The choice of treatment and follow-up depend on associated risk factors. Factors affecting the metastatic potential of SCC include tumor location, size, duration, depth, differentiation and subtype, and immunosuppression and recurrence.

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