Skin Cancer: Back to Basics

Squamous Cell Carcinoma

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ABSTRACT: There are more than a million cases of cutaneous squamous cell carcinoma that occur annually, with incidences increasing over the past 30 years. This common skin cancer has a variety of risk factors, with ultraviolet radiation and increasing age being two of the greatest known associated risks. This article is a review of the epidemiology and other risk factors of this common skin cancer and is also an update on its pathophysiology and treatment.

DEFINITION
Cutaneous squamous cell carcinoma (cSCC) is a malignant epithelial neoplasm and is the second most common form of skin cancer, after basal cell carcinoma (BCC). It frequently develops on sun-exposed areas, related to the ultraviolet radiation (UVR) absorption within the DNA of cutaneous keratinocytes, causing mutation and subsequent malignant transformation. It has greater potential to be life-threatening compared with BCC because of a greater propensity to metastasize via the lymphatic system, or hematogenous spread (Chung, 2016). Atypia of the keratinocytes associated with cSCC originates within the epidermal layer of the skin and extends beyond the dermoepidermal junction, into the dermis. cSCC is most likely to appear on the forehead, face, ears, vermilion border of the lower lip, scalp, neck, and dorsum of the hands. Types of cSCC include acantholytic, spindle cell, verrucous, Bowen, cSCC in situ (cSCCis), and pseudovascular (Saldanha et al., 2003).

Influences that affect the potential for metastatic involvement include the size of the tumor, the site of the tumor, involvement peripherally, recurrence of the tumor, precipitating factors such as chronic arsenic ingestion, and immunosuppression of the patient (Bos & Teunissen, 2009; Kossard et al., 2006). Actinic keratosis (AK) is a lesion with well-defined aggregates of abnormal keratinocytes. Invasive cSCC shares genetic tumor markers with AKs, and nearly all cSCC contains changes of AK histologically. Some consider AKs precursors to cSCC. The percentage of AKs that may progress to invasive cSCC versus those that might spontaneously regress has been poorly defined, however.

Another difference between BCC and cSCC is that cSCC incidence increases more rapidly with age than does BCC incidence (Apalla et al., 2017).

EPIDEMIOLOGY AND RISK FACTORS
Cancer has been on the rise for the past 30 years, with a nearly 200% increase over such time. The exact cause is unknown but may be related to better skin cancer detection, increased sun exposure, and/or longer life spans. There are more than one million cases of cSCC diagnosed each year. There is a greater risk among men to develop cSCC. Like BCC, those with advanced age have a greater risk for cSCC. Like BCC, those with advanced age have a greater risk for cSCC (“Skin Cancer Facts and Statistics,” 2020).

Cancer has an even greater association with cumulative UVR dose than does BCC. Transplant recipients are at a 100-fold risk of developing a cSCC compared with their immunocompetent counterparts and are likely to develop a greater number of lesions with a greater risk for recurrence (Bos & Teunissen, 2009). Long-term, high-dose exposure to psoralens combined with Ultraviolet A (PUVA) is consistently observed to increase the risk of cSCC. This may be observed in those treated with PUVA for psoriasis or other skin disorders. Skin infections, such as human papilloma virus (HPV), have also been associated with skin cancers arising from keratinocyte transformation. Individuals with suppressed immune systems, such as untreated HIV, may develop rapidly growing cSCC at a younger than typical age. Such tumors have an increased risk for metastasis or recurrence (“Basal and Squamous Cell Skin Cancer Risk Factors,” 2019). Tumor thickness is a prognostic variable, with those tumors less than 2 mm in depth rarely metastasizing and those greater than 5 mm having a rate of metastasis around 20% (Jennings & Schmults, 2010).
ETIOLOGY

UVR is considered the predominant risk factor for cSCC, having a linear correlation between incidence and UVR exposure. UVR-induced skin cancers in mice are almost exclusively cSCCs rather than BCCs. More evidence supporting UVR as a cause of skin cancer is the associated 30-fold increase in nonmelanoma skin cancer (NMSC), most of which are cSCCs, seen in those who have received PUVA for psoriasis (Kossard et al., 2006).

Personal History of AK

AK is considered a potential precursor to cSCC, with some studies even identifying them as “early cSCC in situ” (“in situ”: Latin term, meaning the tumor is localized to where it originated; Vargo, 2003). AKs affect more than 58 million individuals in the United States (Chung, 2016). AKs are an atypical proliferation developing from mutated keratinocytes. They arise from the basal layer of the epidermis (Chung, 2016).

The morphology of atypical cells in both AK and cSCC is identical. As well, cellular changes in both AK and cSCC reveal similar patterns, including the same mutation in the tumor suppressor gene p53 (Berner, 2005; Roewert-Huber et al., 2007). Approximately 63% of cSCCs show transformation from AK (Chung, 2016). The risk of progression to cSCC seems to be minimal, and to date, there is insufficient evidence to contribute a specific rate of transformation of AK to cSCC. Risk for progression, even in small percentages, provides rationale for treating AKs when they arise. There is some evidence that regression of AK may occur, especially when sun exposure is decreased (Werner et al., 2013). However, rates of regression are also undetermined.

Scars and Skin Disease

cSCC has also been associated with scar, in particular, those from thermal injuries. Chronic ulcers and other chronic inflammatory diseases such as lupus, hidradenitis suppurativa, lichen planus, lichen sclerosis, and osteomyelitis have shown an increased risk for development of cSCC (Grossman & Lefell, 2007).

Immunosuppression

Immunosuppression has also been shown to contribute to the development of cSCC, even more so than the development of BCC. These are primarily on sun-exposed sites. There are currently more than 170,000 solid-organ transplant recipients (SOTRs) living in the United States. Research has shown up to an 18-fold increase in cSCC in renal transplant patients. These tended to appear 3–7 years after the onset of their long-term immunosuppressive drug therapies, most frequently including corticosteroids, azathioprine, or cyclosporine (Greenberg & Zwald, 2011).

The considerable acceleration of cSCC incidence in SOTRs is such that the diagnosis of a first cSCC has been shown to be predictive of multiple subsequent NMSCs within 5 years. In addition to the increased incidence of cSCC, the tumors displayed a more aggressive phenotype in SOTRs than in the general population, with more rapid growth, local recurrence in 13.4% of SOTRs, and a metastatic rate of approximately 8% (Grossman & Lefell, 2007).

The cutaneous malignancies most frequently diagnosed in SOTRs are BCC and cSCC, accounting for a combined 90%–95% of the total cases, in multiple reported cohorts. Although the incidence of both tumor types is increased in SOTRs, the rate of cSCC is disproportionately higher. cSCC occurs at a rate of between 65 and 250 times that of the general population (Greenberg & Zwald, 2011).

Other immunosuppression contributes to an individual’s risk for developing cSCC. In particular, individuals who are immunosuppressed secondary to HIV infection have an increased risk of developing an NMSC, such as cSCC, and are at a 3 or greater times risk than that of the general population. cSCC that arises in the setting of immunosuppression typically involves a more aggressive course, increasing the rates of recurrence, metastasis, or death. Immunosuppression is also diminished in individuals with diseases such as chronic lymphocytic leukemia or other lymphoproliferative disorders, increasing the risk of cSCC with a more aggressive course.

HPV

HPV infection shows a role in cSCC. HPV types have been classified as either high or low risk. The highest risk types appear to include HPV 16, 18, 31, 33, and 8. HPV types 5 and 8 have been associated with cSCC in the setting of epidermodysplasia verruciformis and in some solid-organ transplant patients. Epidermodysplasia verruciformis shows an autosomal recessive inheritance and is quite rare (Liu et al., 2018). HPV 16 has been identified in cSCC tumors of both the genital and periungual cSCC, suggesting the possibility of genital–digital spread (Bouvard et al., 2009; Greenberg & Zwald, 2011; Grossman & Lefell, 2007).

Genetic Predisposition

Individuals with xeroderma pigmentosum (XP; Figure 1) and epidermolysis bullosa (EB) show an increased risk for developing cSCC because of genetic susceptibility. XP is a rare autosomal-recessive disorder. It is characterized by extreme photosensitivity, pigmentedary changes, premature skin aging, and development of malignant tumors such as cSCC, malignant melanoma, BCC, and fibrosarcoma. Malignancies may occur as early as the age of 4–5 years and are more prevalent in sun-exposed areas.
These tumors arise because of a cellular hypersensitivity to UVR and an inability to repair DNA after UVR damage. EB is a group of inherited bullous disorders characterized by blister formation in response to mechanical trauma. Blistering can range from mild to severe, posing a significant threat to life from infection and sepsis. The most severe variants of EB have a very high mortality rate, with the Herlitz type of EB showing an 87% mortality rate during infancy. cSCC occurs specifically in individuals with recessively inherited type of EB. These cSCCs are aggressive, will commonly metastasize, and may cause death in individuals who have survived childhood and reached the ages of 15–35 years. XP and EB are fairly uncommon examples of genetic predisposition to cSCC (Vargo, 2003).

Environmental Carcinogens
Like BCC, exposure to arsenic is a well-established cause of cSCC. The sources of arsenic that may continue to place individuals at risk are contaminated well water and some traditional Chinese medicines. Other carcinogens that have been associated with cSCC include polycyclic aromatic hydrocarbons seen in tar-based products as well as insecticides, herbicides, smoking tobacco, and alcohol (Bos & Teunissen, 2009). Ionizing radiation has a strong association with cSCC but appears to be more associated with those who are likely to burn from UVR (Grossman & Lefell, 2007; Wong et al., 1998).

CLASSIFICATION

cSCC can be classified by its depth of invasion within the levels of the skin. Prognosis is dependent on factors including locations, size, depth, differentiation, and previous treatment of the tumor. A cSCC is one that invades only the epidermis of the skin and is considered early-stage cSCC. This is also referred to as superficial cSCC or Bowen’s disease. A cSCC that extends into the dermis is considered an invasive cSCC. cSCC may invade all surrounding structures including adipose tissue, muscle, nerves, and bone. If it invades the lymphatic or vascular systems, it is considered metastatic. Certain types of cSCC are considered more invasive, with a higher likelihood to metastasize. These include types such as desmoplastic SCC, clear cell SCC, or spindle cell SCC (Yanofsky et al., 2011).

Staging of cSCC is based on factors including size of tumor (T), lymph node involvement (N), and metastasis (M).

Staging of the tumor is as follows (per American Joint Committee on Cancer and Brigham and Women’s Hospital guidelines):

- **Tumor (T)**
  - Tis: in situ
  - T1: <2 cm
  - T2: ≥2 cm and <4 cm
  - T3: ≥4 cm, minor bone erosion or perineural invasion
  - T4: cortical bone/marrow (Ta), skull/skull base invasion (T4a), beyond subcutaneous fat (T4b)

- **Regional lymph nodes (N)**
  - Nx: Regional lymph nodes cannot be assessed
  - N0: No regional lymph node metastasis
  - N1: Single ipsilateral lymph node metastases ≤ 3 cm in greatest dimension
  - N2a: Metastasis in a single ipsilateral lymph node and >3 cm, but ≤6 cm in greatest dimension
  - N2b: Metastasis in multiple ipsilateral lymph nodes and ≤6 cm in greatest dimension
  - N2c: Metastasis in bilateral or contralateral lymph nodes and ≤6 cm in greatest dimension
  - N3: Metastasis in a lymph node and >6 cm in greatest dimension

Staging of distant metastasis is as follows:

- **Distant metastasis (M)**
  - Mx: Distant metastasis cannot be assessed
M0: No distant metastasis  
M1: Distant metastasis  

Stage groups are as follows (Najjar, 2020):

### PATHOPHYSIOLOGY

There are several factors associated with the development of cSCC. Genes within complex networks and molecular pathways have shown a role in the pathogenesis of cSCC. Genes include tumor protein 53, cyclin-dependent kinase inhibitor 2A, NOTCH1 and NOTCH2, epidermal growth factor receptor (EGFR), and telomerase reverse transcriptase. Pathways include rat sarcoma (RAS), rapidly accelerating fibrosarcoma, mitogen-extracellular activated protein kinase, extracellular-signal-regulated kinase, mechanistic target of rapamycin, phosphoinositide 3-kinase, and protein kinase.

### RAS

RAS defects are one of the most commonly identified genetic alterations associated with human cancer. RAS is the term coined for the studies performed with rat sarcoma leading to the identification of the defects involved. RAS genetic mutations play a role in unintended, upregulated cell proliferation, including that seen with cSCC. H-RAS is a member of the RAS family specifically associated with cSCC. H-RAS mutations have been implicated in up to 46% of cSCCs. There is also evidence that supports its association with the cSCC precursor AK. It does appear that RAS mutation alone is not the probable cause of cSCC, especially because it has been shown to also induce cell-cycle arrest (Di Nardo et al., 2020; Roewert-Huber et al., 2007).

### CDK2NA

CDK2NA of a chromosome typically mediates tumor suppression. Mutation affects the downstream activity on the p53 tumor suppressing pathway and has been identified in up to 42% of sporadic cSCCs. Complete loss of CDK2NA has been identified in AK lesions 21% of the time and in cSCC lesions 46% of the time. This would indicate aberrations associated with CDK2NA are important factors in the malignant changes of cSCC and its precursor lesion, AK (Puizina-Ivic et al., 2108).

### p53 Pathway

The development of cSCC from normal keratinocytes begins with DNA mutations and instability of the genes. Gene expression is altered and leads to loss of cell growth control. There is subsequent penetration of the basement membrane, followed by invasion of surrounding tissues. The keratinocytes become resistant to apoptosis or the immune system’s attempts to halt growth. Keratinocytes that have UVR-induced DNA damage are termed “sunburn cells.” The result of these damaged keratinocytes is the up-regulation of p53, a tumor suppressor protein. This delays the cell cycle progression until DNA damage can be repaired or initiates apoptosis. If the function of p53 is impaired, apoptosis resistance can occur, increasing proliferation, and a cSCC may develop. Mutations in the p53 gene are a common finding in cSCC. p53 mutations were found in up to 75% of AK and cSCCis lesions. The p53-apoptosis pathway may be disabled in keratinocytes infected with oncogene-type HPV (Puizina-Ivic et al., 2108).

Other apoptotic regulatory proteins have been associated with cSCC, in particular, the Bcl-2 and Bcl-2-associated X proteins. Bcl-2 is an apoptotic inhibitor (keeps cells living), which, in the instance of low expression, can lead to low-risk cSCC. However, higher-risk cSCC can be seen in the cases of cSCC with decreased expression of the proapoptotic Bcl-2-associated X (typically initiates cell death). Dysregulation of the apoptotic regulators appears to have a clear role in cSCC (Puizina-Ivic et al., 2108; South et al., 2014).

### Notch

Studies have confirmed that notch receptor mutation is a major tumor suppressor mechanism in cutaneous cSCC, specifically NOTCH1, as a tumor suppressor important for HRAS-driven skin carcinogenesis (South et al., 2014).  

### EGFR

EGFR has shown that it may be a marker of prognosis in cSCC. Over expression of EGFR has been shown to be one of two independent variables (along with poor grade differentiation) associated with lymph node metastasis and tumor progression in cSCC (Cañueto et al., 2017).

### Genetic Alteration

Most studies of cSCC have been performed on cSCC of the head, neck, and oral cavity. Chromosomal deletions most commonly occur in Chromosomes 3, 9, 11, and 17. The regions that are most commonly identified include those sites on the genes where p53 and INK4A are located. Some such deletions have been found even on those younger than 40 years old. The full potential of identifying
these genetic markers is not yet clear, neither is it certain whether prognosis can be determined with such indicators (Tannapfel & Weber, 2001).

**MULTISYSTEM EFFECTS**

cSCC has the potential, when aggressive or left untreated, to metastasize. These cSCC tumors have been known to infiltrate to surrounding bone, muscle, and salivary glands, especially in those tumors that are recurrent. cSCC may also metastasize to regional lymph nodes or parotid glands. This is more common in SOTRs and those with lymphoma, leukemia, or other immunosuppressive status. In these patients, prognosis may be poor, with the uncommon potential for distant metastatic involvement, such as the brain, liver, or lungs.

**CLINICAL MANIFESTATIONS**

cSCC most commonly presents as an erythematous papule or plaque, often with hyperkeratosis. They may be crusted, have an indurated border, or have shallow ulceration. The lesion of cSCC may begin as a scaling, mildly erythematous thin papule. It may also develop a cutaneous horn (a firm, horn-like protuberance). Periungual cSCC may mimic a verruca (wart) and be misdiagnosed for years. A Marjolin ulcer is an uncommon, deep ulceration, seen in a very aggressive type of cSCC. They develop at a sight of previous burn scars. These types of cSCC have a higher rate of metastasis than typical cSCC (Yanofsky et al., 2011).

**TREATMENT**

Treatment of cSCC is based largely on the assessment of risk for progression, metastasis, or recurrence. Treatment methods recommended for cSCC are very similar to those of BCC, with few exceptions. Ablative methods such as electrodessication and curettage, liquid nitrogen cryotherapy, carbon dioxide laser, and photodynamic therapy are common choices for superficial cSCC. However, they do not allow for histological margin assessment. These methods are not recommended for invasive cSCC.

Surgical excision remains the treatment of choice for most cSCCs, especially invasive types. The recommended margins are 4–6 mm for low-risk primary cSCC to the depth of mid-subcutaneous adipose (Work et al., 2018). Mohs micrographic surgery is indicated for primary and recurrent cSCC on all areas of the face, genitalia, hands, neck, feet, nail units, ankles, areola, and pretilial, whether or not immunosuppressed (Ad Hoc Task Force et al., 2012). Mohs micrographic surgery is also recommended for all high-risk cSCC, recurrent cSCC tumors, those with poorly defined clinical margins, immunosuppressed individuals, >2-cm tumors, previously irradiated sites, cosmetically and functionally sensitive areas where skin sparing is indicated, and deeply infiltrative tumors (Najjar, 2020).

Radiation is appropriate for treatment of superficial tumors and some moderate-risk lesions that are not recurrent. It may be a good option for those where surgery is a poor option. Radiation is also an important adjuvant to surgery when there is persisting microscopic involvement perineurally. Radiation is considered contraindicated with verrucous carcinoma in which there is an associated low rate of anaplastic transformation.

When aggressive cSCC tumors do not respond to conventional therapies, oral 5-fluorouracil can be used for its chemotherapeutic properties (Najjar, 2020). Interferon, retinoids, and beta carotene have also been used with variable results. These treatment modalities have mostly been replaced by checkpoint inhibitors, which are discussed in the following paragraph.

Recently, head and neck cSCCs that have metastasized or cannot be treated with surgery are being treated with immunotherapy, specifically checkpoint inhibitors. This is also considered “targeted therapy.” Checkpoints are utilized by the body to inhibit the immune system’s response and prevent it from attacking healthy cells. Because cancer cells hijack these checkpoints, the goal becomes inhibiting the checkpoints so that cancer cells can no longer prevent the immune system from activating. Checkpoints that these inhibitors will affect include those of the programmed cell death (PD-1/PD-L1) and CTLA-4 pathways. Thus, such medications work by encouraging the immune system to respond to the cancer cells and block the PD-1 pathway to keep the cancer cells from hiding from the immune system (Lyford-Pike et al., 2013; Seiwert et al., 2016). Examples of immune checkpoint inhibitors include ipilimumab, nivolumab, and pembrolizumab (Jia et al., 2018; Stevenson et al., 2017).

**IMPLICATIONS FOR PEDIATRIC, PREGNANT, AND GERIATRIC POPULATIONS**

As with BCC, cSCC should be treated on a case-by-case basis, considering that those who are pregnant or elderly may have a lowered immune system and have more rapid growth of a lesion. As well, considerations regarding health status, desired outcome, quality of life, and patient preference must be considered.

**GOLD STANDARD DIAGNOSTIC TESTS**

Clinical assessment and histological examination is the gold standard for diagnostic testing for cSCC. Any suspicious lesion should be sent for histopathological review, for definitive diagnosis.

Workup for possible metastatic involvement with sentinel lymph node biopsy may be performed for those with cSCC-associated lymphadenopathy (Fahradyan et al., 2017). There is little evidence that sentinel lymph node dissection improves patient outcomes in metastatic cSCC but is considered appropriate for staging. Magnetic resonance imaging, computed tomography, or positron emission
tomography-computed tomography scans may also be performed if metastasis is suspected.

KEY CONCEPTS

The following are key concepts of this study:

1. cSCC is an NMSC that invades locally with a greater potential for metastasis compared with BCC.
2. cSCC has been increasing for the past 30 years, which is likely because of the increased sun exposure and an aging population.
3. Immunosuppression, scars, HPV, environment carcinogens, and history of AK contribute to the development of cSCC.
4. Genetic mutations in RAS, CDK2NA, and p53 pathways have been implicated in the development of cSCC.
5. cSCC commonly presents as erythematous papules and plaques, typically with hyperkeratosis, or is crusted. They may also have an indurated border or ulceration.
6. Surgical excision remains the treatment of choice for most cSCC. Other treatments may be considered and should be based on risk for progression, metastasis, or recurrence.

REFERENCES


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