



# A Review of Cutaneous Squamous Cell Carcinoma Epidemiology, Diagnosis, and Management

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## Abstract

**Context:** Cutaneous squamous cell carcinoma (CSCC) is the second most common type of skin cancer and its incidence continues to rise worldwide. While the majority of CSCCs have excellent prognosis, a subset have the propensity to cause poor outcomes.

**Evidence Acquisition:** A thorough Pubmed search was done and a collection of CSCC-relevant articles were selected based on the expert opinion.

**Results:** A number of high-risk factors have been identified including perineural invasion (PNI), desmoplastic growth pattern, poor differentiation, high risk location and large diameter. Various staging systems have been developed based on these high-risk factors. Radiologic imaging is important for high-stage tumors and is likely associated with more aggressive management.

**Conclusions:** Although surgical management is the gold standard, newer therapies such as programmed cell death protein-1 (PD-1) inhibitors show promise for locally advanced or metastatic disease. Despite advances in treatment, early diagnosis and prevention of CSCC is still the most important measure to ensure good outcomes.

**Keywords:** Review, Squamous Cell Carcinoma, Skin

## 1. Context

Cutaneous squamous cell carcinoma (CSCC) is the second most common form of skin cancer. While the majority of CSCC have excellent prognosis, a subset of tumors has the propensity to cause poor outcomes. Although CSCCs are not captured in cancer registries, recent epidemiologic studies have documented a rise in the incidence of CSCC worldwide, which highlights the potential public health impact of this disease (1). The subsequent article reviews current epidemiology, diagnosis and management of invasive primary CSCC.

## 2. Evidence Acquisition

A thorough Pubmed search was done and a collection of CSCC-relevant articles were selected based on the expert opinion. The most updated data regarding the epidemiology, diagnosis and treatment of CSCC were extracted and summarized.

## 3. Results

### 3.1. Incidence

The incidence of CSCC is increasing worldwide (2); however, the global age-adjusted incidence varies according to latitude with a doubling in incidence with each 8 to 10° decrease in latitude (3). Information regarding the incidence of CSCC is primarily derived from North America, Europe and Australia. The age-adjusted incidence of CSCC ranges from less than 10/100,000 person-years in Scandinavian countries to 387/100,000 person-years in Australia (4).

There is limited data on the incidence rate of CSCC in the Middle East and African continent. In Northern Jordan, the age-adjusted incidence was 14.24/100,000 in males and 4.18/100,000 in females between 1997 and 2001. Notably, during the study period, the incidence of CSCC decreased in females and increased in males (5). Although there are no population-based incidence studies in Saudi Arabia, CSCC is the second most common type of skin cancer after basal cell carcinoma (BCC) with an estimated incidence of 18% (17 out of 94) to 42% (57 out of 137) of all skin cancers (6-8).

Similar to worldwide trends, skin cancer is the most prevalent cancer in Iran; however, the incidence is not well

documented. A recent review of the Iranian cancer registry between 2003 and 2008 documented an increase in incidence of skin cancer, which was primarily attributed to CSCC. The standardized incidence rate (SIR) of skin cancer increased from 10.05 and 13.89 in 2003 to 15.57 and 22.62 in 2008 in women and men, respectively. In addition, the percentage of CSCC among all registered skin cancers increased from 12% and 20% in 2003 to 14% and 22% in 2008 in women and men, respectively (9).

### 3.2. Risk Factors

#### 3.2.1. Ultraviolet Radiation

Ultraviolet (UV) radiation exposure is the most common cause of CSCC (10). UV radiation induces deoxyribonucleic acid (DNA) damage in several genes. Mutations have been identified in the p53 tumor suppressor gene, which plays a role in DNA repair mechanisms, in half of CSCCs (11-13). CSCC formation is linked to cumulative chronic UV radiation, either from natural or artificial resources (14). In a meta-analysis, Schmitt et al. showed a two-fold increase in the risk of CSCC in individuals who had occupational exposure to UV radiation (15). Similarly, another meta-analysis showed a 67% increased risk of CSCC in individuals who had ever used tanning beds compared to those who had never used indoor tanning beds (16). Finally, a 30-year cohort demonstrated a great increase in the risk of CSCC in patients who had been exposed to more than 350 psoralen and ultraviolet A (PUVA) treatments (350-450 vs 50 treatments, incidence rate ratio [IRR] = 6.01, 95% confidence interval [CI] = 4.41-8.20) (17).

#### 3.2.2. Ionizing Radiation

Ionizing radiation therapy has been shown to induce CSCC formation. The most important risk factor is the total accumulated dose and this is inversely correlated to the latency period for CSCC development (18).

#### 3.2.3. Immunosuppression

CSCC is the most common cancer in organ transplant recipients (OTR) with a 65 to 250 times greater frequency compared to general population (19) and CSCCs tend to act more aggressive in OTRs (20). The increased incidence of CSCCs is tied to immunosuppressive medications, including calcineurin inhibitors (cyclosporine and tacrolimus), azathioprine, mycophenolic acid (mycophenolate mofetil and mycophenolate sodium), and prednisone (21). Recent studies have shown inhibitors of mTOR (mechanistic target of rapamycin, such as sirolimus and everolimus), to be protective against CSCC formation (22-25). Some studies suggest an increase in mortality in OTRs on mTOR inhibitors; however, mortality is more likely related to

higher doses of the medication (25). In addition, a recent retrospective study failed to show a decrease in CSCC in OTRs on sirolimus; however, the study did not include information on sirolimus dosage or concomitant exposure to other immunosuppressive medications, which could explain the contradictory findings to prior evidence (26).

#### 3.2.4. Chronic Inflammation

CSCC can arise on chronically inflamed skin, such as in chronic ulcers, burns, scars, skin areas overlying osteomyelitis, sinus tracts and inflammatory dermatoses (27). The interval between skin injury and the development of CSCC varies from 6 weeks (28) to 60 years (29). Only 1% of skin cancers arise from chronically inflamed skin, but 95% of the tumors are CSCC (27).

#### 3.2.5. Arsenic Exposure

Chronic exposure to arsenic, either occupational or from contaminated drinking water, increases the risk of CSCC. One study found a 2 to 4-fold increase in the incidence of CSCC in individuals exposed to well water with an arsenic level above 0.64 mg/L (30). Individuals with a toenail arsenic concentration > 97th percentile have a 2-fold increase in the risk of CSCC compared to those with low to moderate levels of arsenic exposure (31).

#### 3.2.6. Human Papilloma Virus (HPV)

Although HPV has been isolated in some CSCCs, no mechanism of carcinogenesis has been identified to explain the association. While some studies have reported an increased risk of CSCC in immunocompetent individuals with HPV infection (32-34), other studies have failed to show a relationship between HPV and CSCC risk (35-37) with the exception of anogenital CSCC (38).

#### 3.2.7. Polycyclic Hydrocarbons

Multiple studies have shown that individuals who are exposed to tar, pitch, asphalt, creosote and chimney soot are at increased risk of CSCC formation, especially scrotal CSCCs (39-41).

#### 3.2.8. Genetic Disorders

A number of genetic disorders carrying an increased risk of CSCCs include xeroderma pigmentosa, albinism, epidermolysis bullosa, epidermolysis verruciformis, Ferguson-Smith disease, Rothmund-Thomson syndrome, Bloom Syndrome, Fanconi anemia, dyskeratosis congenita, and Werner syndrome (42).

### 3.2.9. Smoking

The role of smoking as a risk factor for CSCC is somewhat unclear. While a large cohort study in Sweden found no association between smoking and the risk of CSCC after 30 years of follow-up (former and current smokers vs. never smokers: IRR = 0.95 (95% CI, 0.77 - 1.18) and 0.97 (95% CI, 0.80 - 1.17), respectively) (43), a systematic review identified a 52% increase in odds of CSCCs in smokers compared to nonsmokers (odds ratio [OR]=1.52; 95% CI, 1.15 - 2.01) (44).

### 3.3. Risk Factors Associated with Poor Outcomes

Since only a minority of CSCCs develop poor outcomes, accurate identification of high-risk tumors is important for providing appropriate management to this subset of patients. Prior studies have identified a number of risk factors associated with high-risk CSCC.

### 3.4. Perineural Invasion

Perineural invasion (PNI) is associated with an increased risk of tumor recurrence, lymph node metastasis, distant metastasis, and death (45, 46). Tumors with PNI of large caliber nerves have a worse prognosis than those that invade small caliber nerves (47). PNI is classified as histological if only diagnosed incidentally on pathology and clinical if the patient has sensory or motor neurologic symptoms. MRI is the most sensitive imaging modality for identifying PNI, but tends to only identify large caliber nerve invasion. Adjuvant radiation therapy is recommended for large caliber PNI, but patients with multifocal PNI may also benefit (48).

### 3.5. Desmoplastic or Sclerosing Growth Pattern

Desmoplastic growth pattern is an independent risk factor for local recurrence (49). Desmoplastic CSCCs have 10 and 6 times increased risk of local recurrence and metastasis, respectively, compared to other types of CSCCs (50).

### 3.6. Tumor Diameter

The American joint committee on cancer (AJCC) and the Union for International Cancer Control (UICC) 7th editions incorporated the cutpoint of tumor diameter of 2 cm into the staging systems (51, 52); however, the AJCC and UICC 8th edition will use both 2 cm and 4 cm diameters as cutpoints for staging (53, 54). It is important to recognize that the diameter is continuous, but most studies have evaluated it as a dichotomous variable. In studies that have evaluated the diameter as a continuous variable, larger tumors had a higher risk for recurrence and metastasis (55).

### 3.7. Location

Tumor locations associated with poor outcomes include ear, cheek, lip, temple, and anogenital area (55-57). However, not all studies have shown location to be an independent risk factor for poor outcomes. The AJCC and UICC staging systems include lip and ear as high-risk sites (52-55).

### 3.8. Thickness/Depth

Tumor depth has been measured by either tissue level (Clark's level) or millimeter depth (Breslow depth) (58, 59). The majority of studies evaluating depth based on tissue level found invasion beyond subcutaneous fat to be associated with poor outcomes. Studies examining millimeter depth have shown the threshold for poor outcomes is anywhere between 2 and 6 mm (49).

### 3.9. Histologic Differentiation

CSCCs are histologically characterized by the degree of differentiation as well differentiated, moderately differentiated, or poorly differentiated/undifferentiated. Several studies have shown that poorly differentiated tumors have an increased risk of poor outcomes (46, 55, 60).

### 3.10. CSCC Staging

#### 3.10.1. Current Staging

A separate (T)-based tumor staging system for non-melanoma skin cancer (NMSC) was first introduced by AJCC and UICC in 2010 in their 7th editions (51, 52). Recently, revised staging systems have been introduced in the 8th edition of the AJCC manual. The AJCC 8th edition initially opted to not include a CSCC staging system; however, a CSCC staging system has been included in head and neck tumors chapter. Although this system does not directly apply to non-head and neck CSCCs, it will likely be utilized for all CSCC tumors until a separate CSCC staging system is introduced in future editions of AJCC CSCC staging systems. The AJCC 8th edition stages the tumor based on diameter, depth of invasion, and presence of perineural invasion (53). Table 1 summarizes the different staging systems.

#### 3.10.2. Alternate T Staging Systems

Peat et al. performed a retrospective case-control study of 78 metastatic and 92 non-metastatic head and neck CSCCs. Risk factors were classified as absolute and relative based on multivariate analysis. The absolute risk factors included poor differentiation and PNI/lymphovascular invasion. The relative risk factors included moderate differentiation, diameter  $\geq$  20 mm, and Clark level 5. Tumors were risk stratified into low, intermediate, and high

risk based on the number of absolute and relative risk factors. Based on their cohort, 37% of the high-risk, 5% of the intermediate-risk, and 0.3% of the low-risk tumors metastasized. One limitation to the Peat system is that it was developed based solely on risk factors for metastasis (60).

The Brigham and women's hospital (BWH) staging system is based on a 10-year retrospective cohort study of more than 1800 primary CSCC tumors. The BWH staging system considers the following high-risk factors: PNI of nerves  $\geq 0.1$  mm, depth of invasion beyond the subcutaneous fat, diameter  $> 2$  cm, and poorly differentiated histology. Tumors are staged based on the number of high-risk factors (Table 1). The BWH staging system offers improved homogeneity and monotonicity compared to the AJCC and UICC 7th staging systems with the majority of poor outcomes occurring in BWH stage T2b and T3 (61). Comparative studies between the BWH and AJCC and UICC 8th editions have not been published.

### 3.10.3. Evaluation of High-Stage CSCC

Although the majority of CSCC do not require additional diagnostic studies, high-stage tumors should be considered for additional imaging and diagnostic evaluation at the time of diagnosis.

### 3.11. Radiology

There are minimal recommendations on which CSCC tumors should be subject to radiologic imaging. The national comprehensive cancer network (NCCN) guidelines for CSCC recommend imaging of tumors with suspicion of extensive disease, defined as deep structural involvement, perineural disease, or deep soft tissue involvement. The guidelines also specify that magnetic resonance imaging (MRI) is the most useful for evaluating PNI, but does not make recommendations for other imaging modalities (62). Studies evaluating imaging of CSCC tumors with PNI found lower rates of local recurrence and survival in imaging-negative patients (63, 64). A recent retrospective study of 108 high-stage tumors (BWH T2b/T3) based on the BWH staging system found that of the 46% of patients who underwent imaging, management was altered in 33%. Interestingly, the group that did not undergo imaging had higher risk of nodal metastasis (nonimaging: 30%, imaging: 13%,  $P=0.041$ ), which was attributed to more aggressive management with adjuvant radiotherapy in the imaging group (65). Based on the results of this study, the authors recommend routine imaging of tumors stage BWH T2b and T3.

### 3.12. Sentinel Lymph Node Biopsy (SLNB)

There is limited data on the role of SLNB for CSCC. Although the current literature provides conflicting evi-

dence, one limitation has been selection of appropriate cases for SLNB due to the limitations of the AJCC and UICC staging systems.

A recent meta-analysis concluded that most positive SLNBs occur in CSCC tumors with a diameter greater than 2 cm. The majority of positive SLNBs were AJCC T2 stage tumors (13 out of 116 SLNBs; 11.2%) and BWH stage T2b tumors (5 out of 17 SLNBs; 29.4%) while no AJCC or BWH stage T1 and only 6 out of 85 (7.1%) BWH stage T2a tumors had a positive SLN. Although more data is needed, the rate of positive SLNB in BWH stage T2b tumors far exceeds the 10% rate threshold for SLNB in malignant melanoma (66). A recent systematic review reported the rate of positive SLNB in CSCC patients as 13.9% (32 out of 231 patients) with a false negative rate of 4.6% (10 out of 215 patients). When SLNB results were compared to positron emission tomographic (PET) computed tomographic (CT), SLNB had a higher sensitivity in detecting lymph node metastasis. Results regarding the prognostic importance of SLNB in CSCC patients are conflicting. Takahashi et al. reported the 3-year survival of patients with negative and positive sentinel lymph nodes as 100% and 20.8%, respectively (67). However, Krediet et al. showed a high rate of false negative SLNBs (35%; 6 out of 17 patients), which decreases the sensitivity and prognostic value of SLNB. In this cohort, 6 patients with negative sentinel lymph nodes developed distant metastasis during the 24 months follow up period (68).

### 3.13. Treatment

Although squamous cell carcinoma in situ can be managed with various modalities, including electrodesiccation and curettage, topical therapy, cryotherapy, and photodynamic therapy, these treatments are not appropriate for invasive CSCC (69). The discussion on management will focus on treatment of invasive CSCC.

### 3.14. Surgical Excision

Surgical excision is the gold standard for treatment of invasive CSCC. For low-risk tumors, excision with a 4-mm margin is recommended, whereas, margins of at least 6 mm are recommended for high-risk tumors (70). In a recent systematic review of 12 observational studies, the rate of local recurrence following surgical removal of invasive CSCCs in 1,144 patients ranged from 0 to 15% with a pooled average rate of 5.4% (69). Mohs micrographic surgery (MMS) is the preferred treatment modality for high-stage tumors or tumors arising in locations where tissue sparing is important for cosmetic and functional outcomes. A prospective study of 480 primary CSCCs found positive margins following standard excision in a 6.3% of tumors

removed with a 2 - 5 mm margin (71). On the other hand, a systematic review of 2,133 MMS-treated CSCCs at any sites of the body revealed a pooled cure rate of 97.4% (95%CI, 96.2% - 98.3%) and an only 3% (95%CI, 2.2% - 3.9%) local recurrence rate among 1,572 MMS-treated tumors (69). When MMS is not available, high-stage tumors should be managed with surgical excision with complete circumferential margin evaluation (72).

### 3.15. Primary Radiation Therapy

Primary radiation therapy is another therapeutic option for small well-defined primary CSCC, but should be reserved for patients who are not surgical candidates (73). A systematic review of 761 patients who underwent primary radiation for CSCCs found a local recurrence rate of 6.4% (95% CI, 3.0 - 11.0%) and death from disease of 9.1% (95% CI, 1.4% - 22.8%) (69).

### 3.16. Adjuvant Radiation Therapy

Adjuvant radiation should be considered following surgical excision of high-stage tumors with certain risk factors. Radiation is currently recommended for CSCC cases with large caliber nerve invasion (> 0.1 mm nerve diameter), cases with uncertain or positive surgical margins, or as a salvage treatment for cases not treated with surgery or those with in-transit metastasis. Treatment outcomes are optimized when radiation is performed as adjuvant rather than salvage therapy (48).

### 3.17. Programmed Cell Death Protein 1 Inhibitors

Recent preclinical studies found programmed cell death protein 1 (PD-1) overexpression in keratinocytes to be associated with accelerated SCC development (74). Immunotherapeutic agents blocking PD-1/PD-1L1 (PD-1 ligand 1) pathway are currently undergoing phase II studies in patients with locally advanced or metastatic CSCC. There are a few case reports of patients with CSCC successfully treated with pembrolizumab and nivolumab (75, 76). Chang et al. reported a case of unresectable CSCC with brain metastasis that dramatically improved on pembrolizumab after 2 treatment cycles and remained progression-free after 6 cycles of treatment (75). Sura et al. reported four patients with advanced unresectable or metastatic CSCC who were treated with PD-1/PD-1L1 pathway inhibitors. Two of the reported cases had stabilization of the disease or partial response on PD-1 inhibitor (76). PD-1/PD-1L1 inhibitors are a promising treatment option for advanced CSCC.

### 3.18. Chemoprevention

Non-steroidal anti-inflammatory drugs (NSAID) block production of pro-inflammatory mediators such as prostaglandins and leukotrienes by blocking cyclooxygenase enzymes. Mediators such as prostaglandin E2, a product of cyclooxygenase-2 enzyme, have been shown to increase when skin cells are damaged by UV radiation (77). Apart from the anti-inflammatory effects of NSAIDs, they are anti-neoplastic by inducing apoptosis and inhibiting angiogenesis. Although their protective role against CSCC has been shown in vitro and in animal models, the utility of NSAIDs for chemoprophylaxis in humans is not well defined (78, 79). A systematic review and meta-analysis found that non-aspirin NSAIDs significantly reduced the risk of CSCC (relative risk [RR] = 0.85; 95% CI 0.78 to 0.94) and there was a trend toward significance for aspirin users (RR = 0.88; 95% CI, 0.75 to 1.03). These findings suggest that non-aspirin NSAIDs may play a role in chemoprophylaxis for CSCC (77).

Nicotinamide, the amide form of vitamin B3, has been shown to be effective for chemoprophylaxis for NMSC. Nicotinamide, a precursor of nicotinamide adenine dinucleotide (NAD+) which is an important coenzyme in ATP production, enhances the energy-dependent process of DNA repair, a crucial step in preventing tumorigenesis in UV-irradiated cells (80). A phase III randomized controlled trial (RCT) of nicotinamide 500 mg twice a day compared to placebo found a 23% reduction in the rate of new NMSC development in the nicotinamide group compared to placebo group (P = 0.02). In addition, the risk of new CSCC development in nicotinamide group was reduced by 30% (P = 0.05) during a 12-month period (81). A phase II RCT comparing the same dose of nicotinamide to placebo in renal transplant recipients showed a trend toward significance in the reduction of NMSC formation (35% relative difference, P = 0.36). One caveat is that cessation of nicotinamide led to loss of the chemoprophylaxis effects of the vitamin (82). Nicotinamide is an over-the-counter vitamin widely available in the united states and many other countries. The low cost of this supplement and its proven safety, has made it a suitable option for chemoprevention of NMSC (81).

Acitretin is a systemic retinoid that has been used for chemoprevention of NMSC for many years. Studies have shown mixed results in the risk reduction associated with acitretin. An RCT of 70 healthy patients with a history of NMSC found a 59% decrease odds of new NMSC in a 2-year period (acitretin: 54%, control: 74%; P = 0.13), although this did not meet statistical significance (83). A systemic review of 3 RCTs of acitretin in solid organ transplant recipients (SOTR) noted less CSCC development in patients receiving acitretin (84). In the authors' experience, acitretin

**Table 1.** Summary of the AJCC, UICC, and BWH Tumor (T) Staging Systems

Stage	Definition
<b>AJCC 7th Edition</b>	
T1	Tumor $\leq$ 2 cm in greatest dimension with less than two high-risk <sup>a</sup> factors
T2	Tumors > 2 cm in greatest dimension with two or more high-risk <sup>a</sup> factors
T3	Tumor with invasion of orbit, or of maxilla, mandible, or temporal bone
T4	Tumor with invasion of other bones or direct perineural invasion of skull base
<b>AJCC 8th Edition</b>	
T1	T < 2cm in greatest dimension
T2	Tumor $\geq$ 2 cm, but < 4 cm in greatest dimension
T3	Tumor $\geq$ 4 cm in greatest dimension or minor bone erosion or perineural invasion or deep invasion <sup>b</sup>
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull bone invasion and/or skull base foramen involvement
<b>UICC 7th Edition</b>	
T1	Tumor $\leq$ 2 cm
T2	Tumor > 2 cm
T3	Tumor with invasion of deep structures (e.g., muscle, cartilage, bone [excluding axial skeleton], orbit)
T4	Tumor with invasion of axial skeleton or direct perineural invasion of skull base
<b>UICC 8th Edition</b>	
T1	Tumor $\leq$ 2cm
T2	Tumor 2 to 4 cm
T3	Tumor > 4 cm
T4a	Tumor with gross cortical bone / marrow invasion
T4b	Tumor with skull base or axial skeleton invasion including foraminal involvement and/or vertebral foramen involvement to the epidural space
<b>BWH</b>	
T1	0 high-risk factors <sup>c</sup>
T2a	1 high-risk factor <sup>c</sup>
T2b	2 - 3 high risk factors <sup>c</sup>
T3	$\geq$ 4 high-risk factors <sup>c</sup>

<sup>a</sup>High-risk factors include: > 2 mm thickness, Clark level  $\geq$  IV, perineural invasion, primary site ear, primary site non-hair-bearing (vermillion) lip, or poorly differentiated histology.

<sup>b</sup>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 tumor), perineural invasion for T3 classification defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.

<sup>c</sup>BWH high-risk factors include tumor diameter  $\geq$  2 cm, poorly differentiated histology, perineural invasion  $\geq$  0.1 mm, or tumor invasion beyond fat (excluding bone invasion which automatically upgrades tumor to BWH stage T3).

is started at 10 mg every other day and increased monthly with a goal of 20 mg daily. Slowly increasing the dose reduces the incidence of acute side effects. In addition, the slow taper can help identify a tolerable dose for patients who develop side effects on higher doses of acitretin. Fasting lipid profile, metabolic panel, and complete blood count should be checked prior to initiating acitretin and then after 4 - 8 weeks on therapy. Once at goal dose, the laboratory values should be monitored every 3 months (85).

Capecitabine is a prodrug of 5-fluorouracil used for chemoprevention of CSCC. Endrizzi et al. found a 68% reduction ( $P < 0.005$ ) in CSCC formation in SOTRs during treatment with low-dose oral capecitabine compared to pre-capecitabine treatment (86).

#### 4. Conclusions

The incidence of CSCC continues to rise worldwide. While most invasive tumors can be cured with surgical excision alone, identification of high-risk tumors is essential since a subset of CSCC do go on to develop poor outcomes. The role of radiology and adjuvant therapy is evolving; however, high-stage tumors likely benefit from radiologic studies as this allows for early identification of advanced local or regional disease and more aggressive therapy. Ongoing studies of PD-1 inhibitors are promising for locally advanced and metastatic disease. Yet, despite advances in treatment, early diagnosis and prevention of CSCC is important to ensure good outcomes.

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#### Footnotes

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