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REVIEW ARTICLE

# Cutaneous Squamous Cell Carcinoma: A Review of High-Risk and Metastatic Disease

**Kyle A. Burton[1] · Kurt A. Ashack[2] · Amor Khachemoune[3,4]**

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**Abstract** Non-melanoma skin cancer represents one-third of all malignancies and its incidence is expected to rise until the year 2040. Cutaneous squamous cell carcinoma (cSCC) represents 20 % of all non-melanoma skin cancer and is a deadly threat owing to its ability to metastasize to any organ in the body. Therefore, a better understanding of cSCC is essential to strengthen preventative measures and curable treatment options. Currently, research demonstrates that cSCC is diagnosed at a rate of 15–35 per 100,000 people and is expected to increase 2–4 % per year. With respect to metastatic cSCC, this disease is more common in men; people over the age of 75 years; and inhabitants of the south and mid-west USA. In 2010, the American Joint Committee on Cancer updated the Cancer Staging Manual's primary tumor designation to now include high-risk factors; however, factors such as immunosuppression and tumor recurrence were not included. Other staging systems such as Brigham and Women's Hospital have allowed for increased stratification of cSCC. High-risk cSCC is defined as a cSCC that is staged as N0, extends beyond basement membrane, and has high-risk features associated with subclinical metastasis. High-risk features are depth of invasion (>2 mm), poor histological differentiation, high-risk anatomic location (face, ear, pre/post auricular, genitalia, hands, and feet), perineural involvement, recurrence, multiple cSCC tumors, and immunosuppression. Epidermal growth factor receptor and nuclear active IκB kinase (IKK) expression are also predictive of metastatic capabilities. Clinically, the initial lesions of a cSCC tumor can present as a painless plaque-like or verrucous tumor that can ultimately progress to being large, necrotic, and infected. Tumors can also present with paresthesias or lymphadenopathy depending on the location involved. With respect to prognosis, metastatic cSCC is lethal, with several large studies demonstrating a mortality rate of >70 %. Therefore, treatment of metastatic cSCC is difficult and depends on the location involved and extent of metastasis. Treatment options include surgery, radiation therapy, chemotherapy, and any combination of the above. Surgery alone can be used for metastatic cSCC treatment, but is not as effective as surgery in conjunction with radiation therapy. Radiation therapy has some success as a monotherapy in low-risk or cosmetically sensitive areas such as the external ear, eyelid or nose. According to the 2013 National Comprehensive Cancer Network Guidelines, cisplatin as a single agent or combined with 5-fluorouracil hold the strongest support for the treatment of metastatic cSCC; however, the supporting evidence is inconsistent and a curative chemotherapeutic approach is still lacking. Epidermal growth factor receptor inhibitors are a newer class of agents being used in metastatic cSCC and hold some promise as a therapy for this disease. Other areas of interest in finding curative treatments for metastatic cSCC include p53, hypermethylation of specific genes, chromatin remodeling genes, and the RAS/RTK/PI3K pathway. This review addresses the epidemiology, staging, risk factors,

K. A. Burton and K. A. Ashack are co-first authors.

✉ Amor Khachemoune
amorkh@gmail.com

[1] University of Central Florida College of Medicine, Orlando, FL, USA

[2] Michigan State University College of Human Medicine, Grand Rapids, MI, USA

[3] Veterans Affairs Medical Center Brooklyn, 800 Poly Place, Brooklyn, NY 11209, USA

[4] Department of Dermatology, SUNY Downstate, Brooklyn, NY, USA

clinical presentation, management, and new trends in the treatment of high-risk and metastatic cSCC.

**Key Points**

With the incidence of cutaneous squamous cell carcinoma (cSCC) continuing to rise, more focus should be placed on cSCC and its curative therapeutic options, especially because of its ability to metastasize and cause devastating outcomes.

With a lack of effective life-saving treatments for metastatic cSCC, further investigations of associated biochemical pathways and genetic sequences as well as therapies targeted at these pathways are necessary as they may hold promise for future treatments of metastatic cSCC.

Clinicians should have a high index of suspicion in high-risk patient populations to achieve favorable patient outcomes.

## 1 Introduction

### *Key Points*

- Non-melanoma skin cancer is a common malignancy and represents one-third of all malignancies.
- Cutaneous squamous cell carcinoma contributes to 20 % of skin cancer deaths and its ability to metastasize makes preventative measures and curable treatment options a priority.

Non-melanoma skin cancer (NMSC) is one of the most common malignancies diagnosed by clinicians today and represents one-third of all malignancies [1]. The majority of NMSC develop as a result of the mutagenic effects of excessive sun exposure, and the incidence of this group of skin cancers is expected to continue to increase until the year 2040 [2]. Therefore, a better understanding of the composites of the disease is necessary.

Though many entities can be placed under the term NMSC, the most common cancers that make up NMSC are basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC). These two cancers roughly account for 80 and 20 %, respectively [3, 4] with <1 % of NMSC consisting of other cancers [5]. While cSCC represents about only 20 % of NMSC, it poses a threat with its ability to metastasize. Additionally, the literature also demonstrates that 20 % of skin cancer deaths are attributable to cSCC [2]. Oppositely, cutaneous BCC is a locally destructive cancer that rarely results in death or metastasis [6].

For these reasons, an understanding of the complexity of cSCC and its ability to metastasize is vital. This up-to-date review provides this understanding by describing metastatic cSCC in terms of its epidemiology, staging, risk factors, clinical presentation, review studies, treatment, and new trends. MEDLINE, PubMed, and Cochrane databases were searched up to March 2016 for relevant articles. Search terms included the terms: "cutaneous", "cSCC", "NMSC", "metastatic", "high-risk", "staging", "histology", "treatment", and "new trends".

## 2 Epidemiology

### *Key Points*

- Research has shown cutaneous squamous cell carcinoma to be diagnosed at a rate of 15–35 per 100,000 people with an expected increase of 2–4 % per year.
- Metastatic cutaneous squamous cell carcinoma is more common in men; people over the age of 75 years; and inhabitants of south and mid-west USA.

One of the most recent studies looking at the incidence of NMSC in USA found that there was approximately 5.4 million NMSC, with 3.3 million people being treated for the condition in 2012 [7]. Another study by Guy et al. demonstrated a statistically significant ($p < 0.001$) increase in NMSC in patients aged 65 years and older between 2002–2006 and 2007–2011 [8]. Specifically for cSCC, one study estimates a diagnosis rate of 15–35 per 100,000 people, with an average increase of 2–4 % per year [9]. This makes it the second most common skin cancer behind BCC, which has a reported incidence of 100 per 100,000 inhabitants in USA and Europe, with an increasing incidence of 5 % per year [9]. The rate of metastatic spread between these two types of skin cancers is also markedly different. Metastatic cSCC has an annual incidence of approximately 4 %, while metastatic BCC is rarely diagnosed, with roughly 300 cases ever being reported in literature [10, 11].

Although there are limited epidemiological data on metastatic NMSC owing to its omission from most US cancer registries, some studies have helped to fill the gap. One study looked at 43 cases of metastatic NMSC in USA, finding that metastatic disease was more common in people who were men (85 %), over the age of 75 years (42 %), and who lived in south (35 %) or midwest (35 %) USA [5]. For metastatic cSCC, a 2012 study consisting of 603 patients found that people diagnosed with metastatic cSCC were more commonly male (85.4 %) and around 70 years

of age [12]. Additionally, the literature demonstrated lower rates of head and neck metastasis in northern hemispheres as compared with the southern hemisphere (i.e., Australia and New Zealand). The proximity to the equator and the fair skinned Anglo-Celtic population of the southern hemisphere are possible reasons for this difference [13].

With respect to non-metastatic cSCC, a similarity exists with the limited data describing metastatic cSCC. Currently, states in southwestern USA are reported to have cSCC annual rates as high as 290/100,000, while states in northeastern USA have rates of 45/100,100 [14, 15]. These figures align with reports showing an increasing incidence of NMSC for countries that lie closer to the equator [16]. Non-metastatic cSCC is also more commonly diagnosed in the seventh decade of life and in people with fair skin, similar to the patient population presenting with metastatic disease [17].

## 3 Staging

***Key Points***

- In 2010, the American Joint Committee on Cancer updated the Cancer Staging Manual's primary tumor designation to now include high-risk factors; however, factors such as immunosuppression and tumor recurrence were not included.
- Other staging systems such as Brigham and Women's Hospital have allowed for increased stratification of cutaneous squamous cell carcinoma.
- Updates were also made to the regional lymph node designation, which now considers number of nodes involved, the dimensions of nodes involved, and whether the metastatic spread is ipsilateral or contralateral.

The prognosis of cSCC and its high-risk variants can be stratified according to current staging systems. In 2010, the American Joint Committee on Cancer (AJCC) published the seventh edition of the *Cancer Staging Manual* [18, 19]. This Tumor, Nodes, and Metastases staging system made several updates with respect to the previous edition. Some of the greatest changes were made to the tumor stage (T) (Table 1). For example, high-risk factors were now included for stratification in this category. These high-risk factors included tumor depth greater than 2 mm, Clark level of IV or more, perineural involvement, primary site located on the ear or non-hair-bearing lip, and poorly differentiated tumor [18].

Despite this update, concern still exists with the staging systems failure to include other important risk factors. One recent study evaluated the difference between the AJCC and the National Comprehensive Cancer Network (NCCN) guidelines, finding discordance in classifications of high-risk cSCC. This was attributed to the exclusion of host factors in the AJCC such as immunosuppression and tumor recurrence [20]. Many believe that these factors should be considered in the development of a new staging system as they confer an increased metastatic risk [21].

Some reports have also questioned the preciseness of the AJCC staging guidelines and have proposed alternative staging systems. In 2013, a study of 256 patients with high-risk primary cSCC was conducted to evaluate the ability of the AJCC guidelines to stratify poor outcomes (nodal metastasis and/or death). It found that only four cases resulting in poor outcomes met AJCC criteria for stage T3 or T4, with most poor outcome patients being clustered within the T2 stage [22].

In an effort to improve stratification of tumors and patient outcomes, an alternative system was created that separated the T2 stage into two separate groups (T2a and T2b) based on the number of risk factors present (Table 2) [22]. These risk factors included a tumor diameter of 2 cm or greater, poorly differentiated, perineural invasion of 1 mm or greater, and tumor invasion beyond fat (excluding bone invasion, which would upgrade the tumor to stage T3). This alternative system, later renamed as the Brigham and Women's (BWH) tumor (T) staging system, had the goal of placing a larger number of the poor outcome patients in the higher T stages (Table 2) [23]. Jambusaria-Pahlajani et al. validated this study twice showing similar results with the high risk T2b and T3 categories containing fewer patients within the cohort, but a majority of these patients had adverse outcomes [22, 23].

Other updates in the new AJCC guidelines included increased stratification of the regional lymph node (N) designation (Table 3). The guidelines now consider the number of nodes involved, the dimensions of nodes involved, and whether the metastatic spread is ipsilateral vs. contralateral [18]. Other studies have also highlighted the importance of the number of nodes involved, as well as the size of nodes in the prognosis of cSCC [24, 25] (Table 4). These new improvements may lead to increased utility and use of the sentinel lymph node biopsy as a staging tool for high-risk cSCC. This procedure can lead to increased diagnosis of occult or subclinical nodal spread leading to earlier treatment, ultimately improving the prognosis [26, 27]. Other modalities such as positron emission tomography/computed tomography (PET/CT) scans do exist that can help in the management of high-risk cSCC, but further studies are needed in this area based on a recent review [28]. One study also showed that PET/CT scans are less sensitive than the sentinel lymph node biopsy. The study found 3 of the 41 patients showing negative PET/CT scans for metastasis having positive sentinel lymph node biopsies [29].

Despite these improvements in the AJCC nodal staging system, some reports continue to find inherent faults. In one prospective study of 603 patients with metastatic

**Table 1** American Joint Committee on Cancer (AJCC) tumor staging system [19]

| Designation | Description |
|---|---|
| T1 | Tumor ≤2 cm in greatest dimension with fewer than two high-risk features |
| T2 | Tumor >2 cm in dimension or tumor any size with two or more high-risk features |
| T3 | Tumor with invasion of the maxilla, mandible, orbit, or temporal bone |
| T4 | Tumor with invasion of skeleton or (axial or appendicular) or perineural invasion of skull base |

High-risk features includes >2 mm thickness, Clark level of IV or greater, perineural invasion, primary site ear, primary site non-hair-bearing lip, poorly differentiated or undifferentiated

**Table 2** Brigham and Women's Hospital (BWH) tumor staging system [22]

| Designation | Description |
|---|---|
| T1 | 0 high-risk factors |
| T2a | 1 high-risk factor |
| T2b | 2–3 high-risk factors |
| T3 | 4 or more high-risk factors or bone invasion |

High-risk factors include tumor diameter of ≥2 cm, poorly differentiated, perineural invasion of ≥1 mm, tumor invasion beyond fat (excluding bone invasion, which would upgrade tumor to stage T3)

cSCC, the N1S3 nodal staging system was compared with the seventh edition of the AJCC nodal staging system. This study found that in the new AJCC guidelines, the N2a and N2c increased complexity without any benefit. It was also found that survival did not consistently decrease with an increase in nodal stage group, which is a key goal in cancer staging systems [30]. Additional faults in this staging system include a lack of information regarding micrometastasis or extracapsular nodal extension, which can help to determine prognosis [18].

Last, there were no changes made to the metastasis (M) designation in the AJCC guidelines despite changes to the T and N classification. Tumors were either considered M0 or M1, indicating no metastasis or distant metastasis respectively [18].

## 4 Risk Factors

### *Key Points*

- High-risk cutaneous squamous cell carcinoma is defined as cutaneous squamous cell carcinoma that is staged as N0, extends beyond basement membrane, and has high-risk features associated with sub-clinical metastasis.

Risk factors associated with an increased metastatic rate of cSCC are thoroughly discussed in the literature. If a cSCC lesion has any of these risk factors, it is deemed a high-risk cSCC, and carries the ability to metastasize at a rate of up to 37 % [31]. However, it is also important to mention that tumors having two or more high-risk features are classified as higher stage tumors and that there is variation in the AJCC and BWH staging systems on what constitutes high-risk features (Tables 1, 2). The current definition of a high-risk cSCC is a cSCC that is clinically staged as N0 (no metastasis to the nodes), extends beyond the basement membrane, and has an increased risk of subclinical metastasis [32]. Factors enhancing the metastatic potential include depth of invasion, histologic features, location, horizontal size, perineural involvement, tumor recurrence, incomplete excision, multiple tumors, patient characteristics, and genetic/molecular markers.

### 4.1 Depth of Invasion

#### *Key Points*

- Cutaneous squamous cell carcinoma with greater tumor depths are more likely to metastasize than those with less depth of invasion.
- Tumor depth of 2 mm or less is of minimal if any metastatic potential.

As the Breslow's depth is important for prognosis of melanoma, the depth of a cSCC tumor is equally important with respect to defining metastatic potential, and thus prognosis [33]. Brantsch et al. go as far as to state that

**Table 3** American Joint Committee on Cancer (AJCC) nodal staging system [19]

| Designation | Description |
|---|---|
| N1 | Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension |
| N2a | Metastasis in a single ipsilateral lymph node, >3 cm but not >6 cm |
| N2b | Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension |
| N2c | Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension |
| N3 | Metastasis in a lymph node >6 cm in dimension |

**Table 4** Alternative staging systems

| Staging | Number of patients | Results |
|---|---|---|
| N1S3 [24] | | |
| I (single lymph node measuring ≤3 cm) | 102 | N1S3 staging system has a statistically significant predictive capacity for DSS and overall survival |
| II (single lymph node >3 cm or multiple lymph nodes ≤3 cm) | 99 | |
| III (multiple lymph nodes >3 cm) | 66 | |
| O'Brien et al. [25] | | |
| P (parotid involvement) | | There was no statistically significant relationship between survival and P stage |
| P1 (lymph node up to 3 cm) | 43 | |
| P2 (lymph node >3 cm up to 6 cm or multiple nodes) | 35 | |
| P3 (lymph node more than 6 cm or disease involving facial nerve or skull base) | 9 | |
| N (neck involvement) | | The N2 stage had a statistically significant effect on survival when separated from the N1 stage |
| N0 (no clinical neck disease) | 66 | |
| N1 (single ipsilateral node up to 3 cm) | 11 | |
| N2 (single node more than 3 cm or multiple neck nodes or contralateral nodes) | 10 | |

*DSS* disease-specific survival

tumor thickness in NMSC in general provides better prognostic data than current Tumor, Nodes, and Metastases staging [34]. Another more recent systematic review of cSCC metastatic risk factors identifies tumor depth as being the risk factor associated with the highest risk ratio of local recurrence and metastasis [35]. Regardless, there is an abundance of evidence demonstrating that cSCC tumors with greater thickness are more likely to metastasize than those with less depth of invasion [36–38]. Thus, tumor thickness in cSCC provides important prognostic data and can indicate initiation of prophylactic measures (nodal dissection, radiation therapy (RT) or close observation with magnetic resonance imaging or CT scan) [33, 39].

Though there is a uniform goal in evaluating the association between tumor thickness and metastatic potential, there are several differing recommendations of thresholds for tumor metastasis. Current reported thresholds range from 3 to 6 mm [36, 37, 40, 41]. One study also highlighted that tumor thickness in relation to metastatic potential can be further divided into different subcategories. Brantsch et al. reported cSCC metastatic potential as three subcategories: no detectable risk (≤2.0 mm), low-risk (2.1–6.0 mm), and high-risk for metastasis (>6.0 mm) [34]. A similar classification was described by Breuninger et al. with a 0 % rate if ≤2 mm, 4.5 % rate if between 2 and 6 mm, and a 15 % rate of metastatic spread if tumor thickness was >6 mm [39]. Despite differing thresholds for metastasis, most agree that cSCC <2 mm are of minimal to no metastatic potential [34, 38, 39]. Last, it is also important to note that the BWH T staging system does not specify an exact Breslow depth, rather they found that invasion beyond subcutaneous fat to be the best prognostic risk factor in one validation study [22].

### 4.2 Histology

***Key Points***

- Tumors classified as desmoplastic, acantholytic, and de novo can have a higher risk of metastasis in cutaneous squamous cell carcinoma.
- Histologic features are important prognostic factors, with less differentiated tumors indicating a worse prognosis.

Though less important than tumor thickness and location, pathologic features of cSCC have been demonstrated as prognostic features of the disease with respect to disease recurrence and metastasis [13, 33]. Histologic subtype ('acantholytic', 'spindle', 'verrucous', 'cSCC with single cell infiltrates', and 'desmoplastic') of the tumor is important in evaluating metastatic potential as different subtypes present more aggressively than others [42]. Cassarino et al. stratified subtypes of cSCC using the histological features of tumors. The cSCC subtypes with the highest risk of metastasis were desmoplastic, acantholytic, and de novo tumors (tumors not arising within a precursor lesion) [43, 44]. In fact, one review published in 2015 found that desmoplastic tumors, tumors with nests and strands encircled by an extreme desmoplastic response, had a rate of metastasis ranging from 21.4 to 44.4 % [45].

Spindle cell (sarcomatoid) cSCC is another rare variant of cSCC that is characterized by prominent spindle cells and decreased keratinization. This tumor often arises in areas of strong sun exposure, but can be especially aggressive in patients having prior RT [46]. cSCC associated with single cell infiltrates is also thought to be a more aggressive subtype owing to the delay in diagnosis from the difficulty in identifying patterns of atypical single cell infiltration [46, 47].

On the other end of the spectrum, there are several cSCC subtypes that behave less aggressively. Verrucous

carcinoma, a variant of cSCC, is thought also to be relatively indolent [46]. One report stated that verrucous carcinomas should be categorized as low-malignancy neoplasms [48]. Second, tumors originating within actinic keratoses (AK) also have a lower risk of metastatic spread; however, certain histological variants of AK such as hypertrophic and proliferative AK have been associated with a more aggressive biological behavior [46, 49]. Despite the many studies on histologic sub-types there is a limitation of the current studies with respect to specific histologic sub-types and their stratification to factors such as immune status of the patient, tumor location, and age.

Histologic grading or differentiation is another important factor associated with aggressive cSCC tumors and in evaluating prognosis [50]. Histologic grading of cSCC was first described by Broders [51] consisting of four grades ranging from Grade I (one-fourth of tumor is undifferentiated) to Grade IV (cells do not have a tendency to differentiate within the tumor). This histopathologic grading is still the standard as outlined by the AJCC [33].

In terms of prognosis, the less differentiated the tumor, the worse the prognosis and cure rate [13, 38]. Friedman et al. [52] supported this theory by describing 63 cases of cSCC, finding that higher graded tumors, Grade II (percentage of undifferentiated and differentiated epithelium are equal within the growth) and III (undifferentiated epithelium forms three-fourths of skin cancer), were more likely to be associated with recurrence and death to the patient. Another recent study also found that poorly differentiated or undifferentiated tumors are more likely to have nodal metastasis than moderately or highly differentiated tumors. In fact, half of the patients in the study who had metastasis had a poorly differentiated tumor [53].

Despite a large percentage of metastatic cSCC being related tumors that are highly undifferentiated, well-differentiated-type tumors (Grade I) should not be ignored. This is supported by two different studies demonstrating that at least half of all metastatic cSCC were well-differentiated tumors [54, 55]. Additionally, a more recent study by Pastuszek et al. observing 68 patients with primary lip squamous cell carcinoma, found that half of metastatic cSCC tumors were moderately to well differentiated with zero poorly differentiated tumors having nodal metastasis [36]. Thus, the prognostic information provided by histological features of cSCC is not always reliable, but can still play a role when considering preventative measures.

### 4.3 Location

#### *Key Points*

- Anatomic location of cutaneous squamous cell carcinoma can play an important role in prognosis.
- The face, ear, pre/post auricular, genitalia, hands, and feet are all locations associated with a higher risk of metastasis.

The primary location of the tumor is of great importance when defining high-risk lesions. Early reports defining which anatomical location pose a higher risk for metastatic disease were largely based on studies containing low patient numbers and did not correct for other factors such as depth of invasion [56]. In 1989, Dinehart and Pollack published one of the earliest studies correlating tumor location with risk level, finding that tumors of the temple, dorsa of the hands, and the lips carried a higher risk of metastasis [54].

Today, several more recent studies have clarified certain locations as independent risk factors for metastasis. The largest prospective study to date assessed 615 patients with cSCC, finding that a primary tumor on the ear was a statistically significant risk factor for metastasis ($p = 0.004$) [34]. Another large study examined pathology records of over 9000 excised cSCC in a 10-year period and found that the cheek, lip, ear, and retro auricular areas were significant and independent risk factors for metastasis [56]. Locations such as the ear and lower vermillion lip are considered high risk, possibly owing to the proximity near lymphovascular structures and thinness of the skin [57]. Tumors involving the eyelid and periocular region have also been found to act more aggressively and have a higher rate of lymph node and neural invasion. This is attributed to the location of these tumors, more specifically the proximity of these tumors to the facial, supraorbital, and infraorbital nerves [58].

These studies, in addition to many others, have led to the stratification by anatomic location and associated risk level for metastasis by the NCCN. For example, high-risk locations are the 'mask areas' of the face, chin, mandible, ear, pre/post auricular area, genitalia, hands, and feet. Areas of medium risk are the cheeks, forehead, scalp, neck, and pretibial. Last, areas of lowest risk are tumors of the trunk and extremities [59].

### 4.4 Horizontal Size

#### *Key Points*

- Horizontal tumor size >2 cm indicates a greater ability for tumor metastasis.

The horizontal size of the tumor, taken as the lesion's greatest dimension, is another clinical feature taken into consideration when determining the metastatic risk of cSCC. The AJCC defines a cSCC as a higher-risk lesion when its diameter grows beyond 2 cm. In fact, the tumor stage in the AJCC cancer guidelines changes

from T1 to T2 when its diameter expands beyond 2 cm [60]. One study assessing 615 patients using multivariate analysis found horizontal size to be an independent risk factor for metastatic disease. In this study, 26 patients developed metastasis in which eight had a tumor diameter <2 cm, 12 had a lesion of 2–5 cm, and six had lesions >5 cm in diameter [34]. Other much earlier studies have also seen a similar positive correlation between the size of the primary lesion and the risk of metastatic spread [61, 62].

### 4.5 Perineural and Lymphovascular Involvement

***Key Points***

- Perineural involvement is an important risk factor to consider in cutaneous squamous cell carcinoma as it can alter staging.
- Perineural involvement can present clinically, but many times it is found microscopically.
- Lymphovascular invasion, while rare, has been noted in several studies to be related to increased risk of metastasis.

Perineural involvement is another important component to consider in assessing the metastatic potential of a cSCC. In fact, perineural invasion is one of the high-risk factors that can alter staging in both the AJCC and BWH tumor staging systems [19, 22]. Perineural involvement can be diagnosed clinically; however, it is more common that patients present without clinical symptoms and are instead diagnosed by microscopic identification of nerve involvement [63].

In 2015, one prospective study of patients with high-risk cSCC assessed with sentinel node biopsy found that perineural invasion was a significant predictor of metastasis ($p = 0.05$) [31]. A more recent systematic review including 36 studies evaluating 23,421 cSCC identified perineural invasion as a statistically significant risk factor for recurrence (risk ratio, 4.30; 95 % confidence interval [CI] 2.80–6.60), metastasis (risk ratio, 2.95; 95 % CI, 2.31–3.75), and disease-specific death (risk ratio, 4.06; 95 % CI 3.10–5.32) [35].

Last, lymphovascular involvement has been found in multiple studies to be a poor prognostic factor in cSCC. Moore et al. found a 7.54 increase in risk of metastatic spread if this was present, while another study in 2012 by Brougham et al. found a hazard ratio of 8.03 (3.88–16.2; $p < 0.0001$) using a univariate analysis [56, 64]. While this is usually a rare finding it should indicate additional work-up and treatment when present.

### 4.6 Tumor Recurrence, Incomplete Excision, and Multiple Tumors

***Key Points***

- Recurrent tumors are more biologically aggressive and have reported metastatic rates as high as 30 %.
- Multiple tumors can also have an effect on recurrence and outcomes.

Tumor recurrence and incomplete primary excision are other risk factors increasing the risk of cSCC metastasis [32, 65, 66]. In terms of recurrence, studies have shown these to be biologically more aggressive tumors with metastatic rates of up to 25–30 % [61, 67]. One study identified 25 patients with recurrent tumors and found 48 % of them to have metastatic disease [62]. In addition, one study demonstrated that recurrent cSCC are often larger, more likely to have perinerual or lymphovascular invasion, and more commonly extend below into the subcutaneous tissue than non-recurrent tumors [68].

Incomplete primary excision of the tumor can also promote the development of recurrence and ultimately metastasis. One study looking at positive margins in surgically excised cSCC found recurrence in up to 50 % of patients [69]. Last, it is also important to consider the number of tumors when determining the prognosis of a cSCC. One 10-year study showed that patients with multiple cSCC were more likely to have recurrence, worse outcomes, and higher tumor stage than patients with just one cSCC [70].

### 4.7 Patient Characteristics

***Key Points***

- Patients with immunosuppression, receiving organ transplants, or with chronic wounds are all at a higher risk than the normal population of developing cutaneous squamous cell carcinoma with increased metastatic potential.

Patient characteristics such as immunosuppression also play an important role in the prognosis of cSCC [71]. For example, a study of patients with chronic lymphocytic leukemia found that patients had an 18 % metastatic rate 5 years after undergoing Mohs surgery for removal of a primary cSCC [72]. Velez et al. also found that the main prognostic factor in this population was tumor stage. Patients with low tumor stages (BWH stages T1 and T2a) had similar prognoses to the general population as opposed to chronic lymphocytic leukemia patients with high tumor stages (BWH stages T2b and T3) who had a metastatic rate

of 29 % [73]. Organ transplant recipients (OTR) also have a poor prognosis in association with cSCC, with a metastatic rate around 7–8 %, much larger than the 0.5–5 % rate in the general population [74, 75].

Additionally, one study assessing cSCC in OTR, specifically renal transplant patients, found that these patients had more aggressive cSCC than their immunocompetent counterparts [76]. Variation in the risk of metastasis based on the type of transplant is also demonstrated in the literature; with heart transplant patients exhibiting high-risk cSCC tumors more often than other transplant types [77].

While immunosuppression is one common finding in patients predisposed to high-risk cSCC, there are also pre-malignant dermatoses that subject patients to a higher risk of metastatic disease. For example, patients with discoid lupus erythematosus-related cSCC tend to have higher rates of metastasis compared with non-discoid lupus erythematosus lesions. The mechanism behind this was thought to arise from chronic inflammation, scarring, and actinic damage occurring in these lesions [78]. Lesions exposed to such conditions have metastatic rates as high as 10–30 % [79]. One study found that the risk of metastasis with these chronically damaged and inflamed lesions was associated with a decrease in the E-cadherin level, allowing the atypical keratinocytes to spread more easily along the epidermis and into the dermis [80].

### 4.8 Genetic Factors/Molecular Markers

#### *Key Points*

- Epidermal growth factor receptor has been associated with a high incidence of metastatic cutaneous squamous cell carcinoma.
- Nuclear active IκB kinase (IKK) can also be predictive of metastatic capabilities.

With the advances in technology today, scientists have found associations of many more molecular and genetic risk factors with an increased risk of cSCC metastasis. Recently, Toll et al. found that mesenchymal vimentin was a better indicator of metastatic risk compared with the membranous E-cadherin. In fact, within the study vimentin-positive tumors were significantly associated with recurrence ($p < 0.008$) and disease-related death ($p < 0.002$) [81]. Epidermal growth factor receptor (EGFR) may also be associated with a high incidence of metastatic disease. One report noted an overexpression of EGFR in 79 % of patients with cSCC followed by metastatic spread. However, the marker was found in only 36 % of patients who had a primary without metastasis [82].

There is also evidence that elevated levels of nuclear active IKK can be predictive of the capacity of cSCC to metastasize. The study found mean P-IKK grading to be 1.962 for metastatic tumors while non-metastatic tumors had a value of 1.078 ($p < 0.001$) [11]. Other markers possibly associated with high-risk cSCC are the loss of p16 and the amplifications of CKS1B [32]. While the study of these novel markers and genetic alterations is just in its early beginning, advancements such as these will have the possibility to change management in this disease.

## 5 Clinical Presentation

#### *Key Points*

- Initial lesions of cutaneous squamous cell carcinoma can present as a painless plaque-like or verrucous tumor that can ultimately progress to being large, necrotic, and infected.

While it is important to understand the end-clinical features of metastatic cSCC, it is first essential to appreciate the clinical features of the primary tumor. High-risk and aggressive cSCC more commonly arise in the older patient presenting with lesions often found on the head, neck, and/or upper limbs [61]. The initial lesion of cSCC can have a variety of presentations. At first, the lesion is often painless and can be ulcerated, plaque like, or verrucous in nature [83].

The tumor can often stem from and be found within a background of pre-malignant lesions such as AK, actinic cheilitis, and bowenoid papulosis, with AK being the most common [84–86]. Lichen sclerosus of the genitals has also been found to have malignant potential for transformation to cSCC, despite having a low metastatic rate in some studies. The rate of lichen sclerosus patients developing cSCC of the genitals has been found to be 4–7 % in women and as high as 50 % in men [87–91].

While AK is the most common pre-malignant lesion for cSCC, only 1 in 1000 progress to cSCC [92]. It is also important to note that one recent study found only 13 % of cSCC of the lower extremities to arise from AKs. This is uncommon as most lesions in other areas often are associated with these pre-malignant lesions [93].

High-risk tumors that have the propensity to metastasize can progress to large necrotizing masses that can be infected and malodorous [83]. Other signs of advanced tumors stem from perineural invasion. Patients that have perineural invasion can present with facial paresthesia, facial nerve palsies, or formication. Thus, it is important to conduct a thorough sensory and motor exam if this is suspected [94, 95].

As the tumor progresses, metastatic findings can be evident on clinical exam with lymphadenopathy. The area of lymphadenopathy can vary depending on whether the

primary tumor is located on the head/neck area, trunk/extremities, or genitals.

### 5.1 Tumors of the Head and Neck

***Key Points***

- Tumors of the head and neck can present with facial paresthesias; lymphadenopathy commonly presents within the parotid gland, posterior triangle, submandibular, and submental areas.

The regional lymphatic nodes in the parotid gland have been the area most commonly involved with metastatic cSCC of the head and neck, and the route of metastasis is usually via lymphatic drainage [96]. The nodes located in the parotid gland drain some of the more common locations that cSCC can be found in such as the temple, forehead, anterior scalp, and pinna [2]. The nodes that are involved in the parotid are usually found within the superficial lobe [56]. Lymphadenopathy can also be present in the posterior triangle for occipital scalp lesions and the submandibular or submental area for primary tumors of the lower lip [2, 94, 97].

### 5.2 Tumors of the Trunk and Extremities

***Key Points***

- Tumors of the extremities can have signs of lymphadenopathy in the axillary or inguinal regions.

When a primary cSCC does not arise from the head and neck, other areas of lymphatic involvement can be appreciated on examination. For example, metastatic tumors of the trunk and extremities can at times involve the axillary and inguinal lymph nodes [98]. One study that evaluated 232 patients with metastatic cSCC found nine cases of axillary spread and eight cases of inguinal lymph node metastasis [56]. For the latter clinical presentation of inguinal lymphadenopathy, it is also important to consider anogenital cSCC in the differential, as this is a common site of metastasis. Other reports have also mentioned important sites of spread from primary cSCC of the extremities such as lymph nodes in popliteal and epitrochlear region [99].

Despite the fact that cSCC most commonly metastasizes via the lymphatic system or hematogenously to regional nodes, there have also been a small percentage of patients with distant spread to a variety of organ systems. One report has shown the incidence of this occurring to be 1 % [100]. The route of spread in these cases most often occurs through hematogenous dissemination. In 15 % of cases, this process can bypass the lymph nodes [101, 102]. Distant cutaneous metastatic spread from a primary cSCC is one example of this, and it often presents with painless nodules or erythematous macules [103].

Other cases reported in the literature highlight the many ways cSCC can present when distant metastasis occurs. One case highlighted a patient with metastatic cSCC spreading to bone, ultimately resulting in hypercalcemia and renal failure [104]. Another case in 2014 reported a patient presenting with a small bowel obstruction owing to the metastatic spread of a 2 × 2 cm cSCC located on the palm of his hand [105]. Cardiopulmonary collapse from right ventricular inflow tract obstruction owing to a metastatic cSCC has also been reported [106].

## 6 Review of Studies of Metastatic cSCC with Emphasis on Recurrence and Mortality

***Key Points***

- All studies unanimously found a poor prognosis associated with distant metastasis of cutaneous squamous cell carcinoma, each reporting a mortality rate of >70 %.
- Of the studies reporting recurrence rates of distant metastatic cutaneous squamous cell carcinoma, recurrence rates ranged from 15 to 28 %.

There have been multiple studies over the past several decades studying metastatic cSCC (Table 5) [12, 107–110]. These studies mostly consisted of moderate to large populations of patients with metastatic cSCC, distant or regional. They have assessed recurrence, mortality, and response to treatment such as surgery or surgery combined with RT [12, 107–109]. Of note, a majority of the studies involved cSCC of the head and neck and there are limited studies evaluating metastatic cSCC elsewhere.

In 2013, a large study reviewing 603 patients with metastatic cSCC found that 89 % of patients with distant metastasis ($n = 35$) died of their disease, much higher than those with regional metastasis [12]. An earlier published review of 695 cases of cSCC conducted by Joseph et al. found a 70.6 % mortality rate in the 34 cases of metastatic cSCC with almost half of these deaths due to inoperable or regional recurrence of disease without evidence of distant metastasis [107]. Similarly, Oddone et al. found that of 250 patients regional metastatic disease of the head and neck, 70 developed recurrent regional disease with 73 % dying from their disease [108]. Poor outcomes were also associated with immunosuppression and involvement of the surgical margin [108].

In 2005, Veness et al. conducted one of the largest studies of metastatic cSCC and reported patterns of recurrence, outcome, and predictors for survival after treatment in 167 patients [109]. They reported a 28 % recurrence rate following treatment and found a worse prognosis associated with multiple node involvement and

**Table 5** Studies of metastatic cSCC with emphasis on recurrence and mortality

| Population | Number of patients with metastasis[a] | Distant metastasis | Deaths from cSCC | Number of patients with recurrence | References |
|---|---|---|---|---|---|
| Patients treated for metastatic cSCC (Sydney, Australia) | 603 | 35 (6 %) | 92 (15 %) | Not reported | Brunner et al. [12] |
| 695 patients with primary cSCC of the trunk and limbs treated from 1977 to 1987 (Concord, New South Wales) | 34 | 1 (3 %) | 24 (71 %) | Not reported | Joseph et al. [104] |
| Patients with metastatic cSCC to lymph nodes of the head and neck treated from 1980 to 2005 (Sydney, Australia) | 250 | 9 (4 %)[b] | 51/70 (73 %) with recurrence[c] | 70 (28 %) | Oddone et al. [105] |
| Patients with metastatic cSCC to the parotid and/or cervical nodes treated from 1980 to 2002 (Sydney, Australia) | 167 | 10 (6 %) | Not reported[d] | 47 (28 %) | Veness et al. [106] |
| Patients with metastatic cSCC to lymph nodes of the head and neck treated with curative intent from 1980 to 2005 (Sydney, Australia) | 266 | Not reported | Not reported | 40 (15 %) | Veness et al. [107] |

*cSCC* cutaneous squamous cell carcinoma

[a] Regional and distant metastases included

[b] Only reported for recurrences

[c] Reported 5-year survival rate of 78 %

[d] Reported 5-year disease-free survival rate of 58 %

single-modality treatment (surgery alone) [109]. A second study conducted by Veness et al. in 2006 of 266 patients with metastatic cSCC lymph node disease of the head and neck found disease recurrence following treatment in 15 % of cases, slightly less than the other study [110].

Together, these studies reveal the poor prognosis associated with distant metastasis and also recurrence. Thus, clinical efforts should be made to address patients with these factors in addition to having other poorly associated outcome factors.

## 7 Treatment

### *Key Points*

- Treatment for metastatic cutaneous squamous cell carcinoma depends on the location involved and extent of metastasis.
- Treatment options include surgery, radiation therapy, chemotherapy, and any combination of the above.

The approach for treatment of metastatic cSCC depends on whether or not there is regional involvement of lymph nodes, distant metastasis, or inoperable metastatic disease [57]. Immune suppression, especially in OTR, should also be taken into consideration [33]. Therapeutic options consist of surgery, RT, or chemotherapy. Current recommendation for the management of regional spread is surgical excision with consideration of adjuvant RT (Fig. 1).

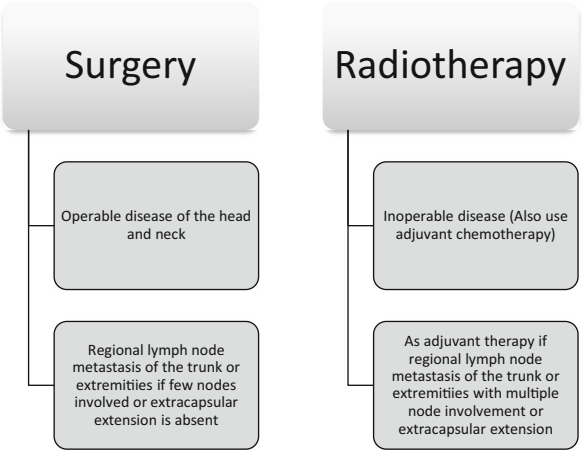


**Fig. 1** 2013 National Comprehensive Cancer Network guidelines for loco-regional metastasis of squamous cell carcinoma [120]

Conversely, first-line treatment for distant metastasis should be chemotherapy [42, 57]. Emphasis of treatment will be on metastatic cSCC, but all therapeutic approaches are outlined in detail below.

### 7.1 Surgery and Radiation Therapy

#### *Key Points*

- Surgery alone can be used for metastatic cutaneous squamous cell carcinoma treatment, but is not as

effective as surgery in conjunction with radiation therapy.
- Radiation therapy has some success as a monotherapy in low risk areas or cosmetically sensitive areas such as the external ear, eyelid or nose.

Metastatic disease proves to be more difficult without ideal treatment guidelines, and aside from chemotherapy, other treatment modalities consist of surgery and RT [42, 111]. Surgery and RT together yield the greatest results with a 5-year disease specific survival rate of 70–75 % [17].

Surgery may be performed in patients with metastasis when tumor characteristics (size, location, and number) allow for complete removal at or near the primary tumor site [42]. However, superior results are achieved when adjunct RT is used with surgery as demonstrated by Veness et al. in their treatment of 167 patients over a 20-year period [109]. In this study, patients treated with the combination of RT and surgery experienced less disease recurrence (20 vs. 43 %) and achieved a more favorable 5-year disease-free survival rate (73 vs. 54 %) compared with those treated with only surgery [109].

Other examples of the success of combination RT and surgery have been demonstrated in treating metastatic cSCC of the parotid gland [112–114]. One of the earliest studies conducted at the University of Florida found 20 patients with metastatic cSCC whose first evidence of metastasis was that of a pre-auricular mass. This 11-year study found that surgery followed by irradiation of the parotid gland was the most effective treatment for this area of metastasis [115]. Additionally, newer studies are evaluating the efficacy of RT vs. chemoradiotherapy in patients with cSCC, such as the Trans-Tasman Radiation Oncology Group (TROG). TROG is currently conducting a phase III clinical trial evaluating the difference, if any, in time to loco-regional relapse compared with patients treated with post-operative concurrent chemoradiotherapy as compared with RT alone in patients with high-risk cSCC of the head and neck.

Though RT should be discussed as an adjuvant therapy, especially in the case of locally advanced or metastatic cSCC where recurrence rate is high, it can also be used as a monotherapy [42, 116]. Specifically, RT can be used as an alternative to surgery in the case of small cSCC in low-risk areas. Consideration of radiation monotherapy should also occur in areas where cosmetic results are of importance, such as the external ear, eyelid, or nose [116]. Another reason to use radiation as a primary treatment is for inoperable cSCC such as in the cavernous sinus or with perineural invasion [42, 116–118].

Although positive advancements have been made with surgery, RT, and chemotherapy in the treatment of metastatic cSCC, a curative method with strong data and good results remains underdeveloped.

### 7.2 Current Chemotherapy Approach

***Key Points***

- According to the 2013 National Comprehensive Cancer Network guidelines, cisplatin either as a single agent or combined with 5-fluorouracil hold the strongest support for treatment of metastatic cutaneous squamous cell carcinoma; however, the supporting evidence is weak and inconsistent.
- Polychemotherapeutic approaches are often more effective than single-agent chemotherapy. However, this is an observation with little supporting data owing to a lack of comparative studies.
- Chemotherapy in combination with other treatment options tends to be reserved for severe disease or a palliative approach. A curative chemotherapeutic approach is still lacking.

Originally a palliative adjunct for patients with advanced or metastatic cSCC, chemotherapy now plays a curative role in combination with other treatment modalities for this disease [111]. Although chemotherapeutic success in treatment of metastatic cSCC exists in the literature, it lacks a standardized regimen and robust data outside of head and neck cSCC [33, 42]. While a curative approach can be taken, it should remain clear that data are insufficient to support a curative claim, and recurrence rates are high. Therefore, a curative vs. palliative approach is a decision that should be made on a case-by-case basis [42, 57]. Current chemotherapeutic agents used in advanced or metastatic disease are as follows: platin derivates (i.e., cisplatin or carboplatin), 5-fluorouracil (5-FU), bleomycin, methotrexate, adriamycin, taxanes, gemcitabine, or ifosfomide alone or in combination [42, 119–122]. Current NCCN guidelines suggest cisplatin either alone or in conjunction with 5-FU, but state that supporting data are weak and inconsistent and that newer options should be considered [123]. Similarly, Breuninger et al. recommend a polychemotherapeutic approach with cisplatin and 5-FU being first-line treatment for metastatic cSCC (Table 6) [42, 57]. Reported response rates (complete and partial) with the proposed polychemotherapeutic approach are up to 80 %, much higher than 60 % reported with 5-FU alone (Table 7) [57].

Additionally, partial success of chemotherapy occurs when used in conjunction with RT or followed by surgical interventions [33, 123, 124]. When used with other treatment modalities, chemotherapy achieves the primary goal of reducing tumor size allowing for more effective surgical or RT [38]. Especially when followed by surgical treatment, the use of chemotherapy has been shown to improve disease-free survival [124].

**Table 6** Breuninger et al. [8] chemotherapeutic approach to metastatic cSCC

| Designation | Chemotherapeutic agents |
|---|---|
| First line | Cisplatin + 5-FU (or oral analog) |
| Diminished patient condition | 5-FU (or oral analog) monotherapy |
| If no response to 5-FU monotherapy | Cetuximab, gefitinib, and erlotinib may also be used |

*cSCC* cutaneous squamous cell carcinoma, *5-FU* 5-fluorouracil

**Table 7** Prospective studies of chemotherapeutic agents for the treatment of advanced or metastatic cSCC (adapted from Stratigos et al. [40])

| Number of patients | Treatment | Response | References |
|---|---|---|---|
| 14 | Oral 5-FU 175 mg/m$^2$ for 3 weeks every 5 weeks | 2 PR (14.3 %) | Cartei et al. [116] |
| | | 7 SD (50 %) | |
| 14/13 evaluable | Cisplatin bolus injection | 4 CR (30 %) | Sadek et al. [117] |
| | 5-FU and bleomycin continuous 5-day infusion | 7 PR (54 %) | |
| | | 2 SD (16 %) | |
| 12 | Cisplatin and doxorubicin ($n = 7$) | 4 CR (33 %) | Guthrie et al. [118] |
| | Neoadjuvant to surgery or radiation ($n = 5$) | 3 PR (25 %) | |
| 7 | Cisplatin and 5-FU every 21 days | 3 CR (43 %) | Khansur et al. [119] |
| | | 3 PR (43 %) | |
| | | 1 SD (14 %) | |

*CR* complete response, *cSCC* cutaneous squamous cell carcinoma, *PR* partial response, *SD* stable disease

Chemotherapy as a monotherapy has also been evaluated with several studies reporting success of chemotherapeutics with respect to cure and/or progression of disease. Cartei et al. administered oral 5-FU (capecitabine) for 3 weeks, every 5 weeks to 14 patients with aggressive cSCC tumors and achieved some success with 14.3 % partially responding and 50 % remaining stable in terms of disease progression [119]. In another study, Sadek et al. achieved some success administering combination chemotherapy consisting of a bolus injection of cisplatin followed by 5-day continuous infusion of 5-FU and bleomycin. Of 13 evaluated patients, 30 % had a complete response (CR), 54 % a partial response (PR), and 16 % remained stable in terms of disease progression [120]. Guthrie et al. and Khansur et al. demonstrated similar results with use of cisplatin and doxorubicin as adjunct therapy to surgery or radiation [121] and 5-FU every 21 day [122], respectively. However, despite any success, these studies are limited in that they lack confirmatory follow-up studies, and are subject to publication bias [42].

Aside from 5-FU or cisplatin, a combination of 13-cis-retinoic Acid and interferon alpha-2a can also be used in patients with advanced inoperable cSCC. In a phase II trial, Lippman et al. observed a 68 % (19/28) response rate with the use of oral 13-cis-retinoic Acid (1 mg/kg per day) and subcutaneous recombinant human interferon alpha-2a (3 million units per day) for at least 2 months. However, greater responses were recorded for advanced local and regional disease, whereas patients with distant metastasis experienced only a 25 % response rate (2/8) with only one patient completely responding to therapy [125].

When chemotherapy and other treatment methods fail in patients with advanced or metastatic cSCC, their uses convert from curative to palliative [111]. This modality is usually reserved for patients with metastatic disease with the goal of palliation and prolongation of life as outlined by the 2001 NCCN guidelines [111]. At this stage, chemotherapy can be more beneficial than supportive treatments alone with an approximate addition of 10 weeks to the 4- to 6-month median survival [111, 126, 127].

### 7.3 Management of Immune-Suppressed Patients

#### *Key Points*

- Immune-suppressed patients and organ transplant recipients represent a vulnerable population with respect to their increased risk for cutaneous squamous cell carcinoma metastasis.
- Minimizing the risks for the development of cutaneous squamous cell carcinoma and metastasis is very important for these patients. Calcineurin inhibitors may be of benefit, whereas antifungals such as voriconazole should be avoided. Human papillomavirus remains a controversial topic in terms of any association with cutaneous squamous cell carcinoma risk.

- Though treatment is similar to patients who are immunocompetent, physicians should consider the poor prognosis in this patient population when considering the therapeutic options.

Special consideration should be given to the management of OTR and immune-suppressed patients owing to their increased incidence of cSCC and 3 % increase in metastatic risk [75, 128]. The first priority in treating immunosuppressed patients is to minimize the risk of developing cSCC. For example, Ayache et al. demonstrated in a 2007 study that long-term calcineurin inhibitor monotherapy is a safe and beneficial immunosuppressive minimization strategy for cSCC in select patients as compared with bi- and tri-therapy (incidence of 15.9/1000 patients/year for monotherapy vs. 26.2 for bi- or tri therapy ($p = 0.07$)) [129].

Another consideration to minimize the risk of cSCC in immunosuppressed patients is human papillomavirus infection. To date, multiple human papillomavirus subtypes have been suggested as an integral etiologic role along with ultraviolet radiation and genetic predisposition. However, the association is controversial and more robust data proving a direct link between the two are needed [75, 130].

Antifungal therapy is also an area of concern in the immunosuppressed patient population. Several anecdotal case reports have indicated an association between antifungals, specifically voriconazole, with an increased risk of cSCC development [131–133]. This association is further enhanced by Singer et al. who demonstrated a 2.6-fold increased risk for cSCC with patients receiving voriconazole 200 mg twice daily (hazard ratio 2.62, 95 % CI 1.21–5.65; $p = 0.014$) [134]. Additionally, a retrospective review of eight immunocompromised patients taking voriconazole, conducted by Cowen et al., observed 51 cSCC among the eight patients over a median of 46.5 months, raising suspicion for a causal link between the two [135]. With these data in mind, voriconzaole should be avoided to reduce the risk of cSCC in OTR and immune-suppressed patients.

In terms of high-risk cSCC among OTR and immunosuppressed patients, treatment options consist of evaluation of metastatic potential, early aggressive surgical therapy (Mohs micrographic surgery), reduction of immunosuppression, treatment with systemic retinoids, and consideration of adjuvant RT for the operative site and draining lymph nodes [128, 136, 137]. If any risk factors for metastasis are present, adjuvant therapy in the form of nodal dissection or RT should be considered [136].

Management of metastatic cSCC in this patient population is difficult due to the lack of a standard of care in OTR and the poor prognosis in this patient population [111, 138]. Current options, in addition to stopping immune suppression therapy, consist of therapeutic lymphadenectomy if regional lymph node involvement, adjuvant RT, adjuvant chemotherapy, and EGFR inhibitors [128, 136]. Regardless of these options, palliative and newer investigational agents offer the greatest opportunity for innovation in OTR and immune-suppressed patients experiencing regionally advanced and metastatic cSCC [111].

## 8 New Trends

### *Key Points*

- Epidermal growth factor receptor inhibitors are a newer class of agents being used in metastatic cutaneous squamous cell carcinoma and hold some promise as therapy for this disease.
- Other areas of interest in finding curative treatments for metastatic cutaneous squamous cell carcinoma include p53, hypermethylation of specific genes, chromatin remodeling genes, and the RAS/RTK/PI3K pathway.

One area of promise with regard to treatment for metastatic cSCC consists of targeted therapies, with a focus on EGFR inhibitors [42, 111, 139]. Overexpression of EGFR has been observed in cSCC and is associated with a worse prognosis [42, 140]. Thus, researchers have targeted this receptor with hopes of a potential cure for patients with aggressive and/or metastatic cSCC [42].

EGFR inhibitors, either as monoclonal antibodies (mAb) (cetuximab and panitumumab) or small molecule kinase inhibitors (erlotinib, gefitinib, and dasatinib), have been approved for the treatment of head and neck cSCCs with some documented success [42, 57, 139]. Initially, the chimeric mAb Cetuximab demonstrated encouraging results in the treatment of cSCC [141]. Currently, there are several phase I and II controlled trials evaluating the effects of these targeted therapies in patients with aggressive, recurrent, or metastatic disease [141–145].

In 2012, Lewis et al. conducted a prospective phase II trial with 23 patients receiving two cycles of gefitinib prior to surgery and/or radiotherapy, followed by 3 months of gefitinib maintenance therapy. Of the 23 patients, four experienced a CR, six PR, and five experienced stable disease [142]. In a 15-patient, non-randomized, single-arm, phase I clinical trial evaluating erlotinib with postoperative radiotherapy, Heath et al. observed a 2-year overall survival rate of 65 % and a disease-free survival rate of 60 % [143]. Kalapurakal et al. performed a retrospective study of four patients receiving weekly cetuximab for recurrent cSCC and found that three patients had a CR to therapy

whereas the fourth patient only partially responded to therapy [144].

In 2011, Maubec et al. conducted a phase II uncontrolled trial administering cetuximab weekly to 36 patients with locally advanced, unresectable cSCC or metastatic cSCC with document progression. The best overall response rate observed was 28 % (95 % CI, 14–45), with two patients obtaining a CR to therapy and eight achieving a PR [141]. Another phase II trial conducted by Foote et al. looked at the use of pantimumab as a single agent chemotherapy in 16 patients with locally advanced, metastatic, or recurrent cSCC not suitable for curative local therapy. Fifteen patients had loco-regional advanced disease or recurrent disease, with an overall response rate of 31 % (3/16 PR, 2/16 CR), with 6 of 16 achieving stable disease. Progression-free survival was 8 months and overall survival was 11 months. Ten patients died, six were alive with one having no evidence of disease at the time of evaluation [145]. Though these treatment regimens achieve some success, they can only be considered as second-line treatment following failure of mono- or polychemotherapeutic agents until further data are shown [42, 123].

Another therapeutic approach to locally unresectable and metastatic cSCC is the new class of immune checkpoint antibodies that target programmed cell death protein 1, such as nivolumab and pembrolizumab; however, data on their effectiveness are scarce. Borradori et al. described four heavily pretreated patients with advanced unresectable or metastatic cSCC treated with anti-PD1 antibodies (two with pembrolizumab and two with nivolumab). Two patients experienced a PR to their disease and two observed stabilization of their disease, with progression-free survival being >4 months in all four patients. One patient died from complications of their disease and the other three we not evaluable after 6 months [146].

Other areas of increased attention are targeting the p53 gene. This mutation can be present in up to 70 % of head and neck cSCC [111]. Expression of p53 has also been linked with enhanced EGFR gene amplification and worse prognosis [140]. Thus, clinical trials focusing on this genetic marker may be of substantial benefit in the near future and hold promise for tyrosine kinase inhibitors such as erlotinib [139, 140].

A more recent area of focus involves epigenetics of primary tumors of patients developing regional or metastatic disease. In a small subset of 46 patients with cSCC, Darr et al. found that metastatic cSCC tumors more commonly contained hypermethylated regions on two different genes (FRZB and TrkB) [147]. Therefore, hypermethylation of these two sequences could be useful as future biomarkers of tumors with aggressive features and metastatic potential and drive preventative measures in patients with these specific findings [147].

Similarly, Li et al. performed genomic analyses on metastatic cSCC and found mutations in the RAS/RTK/PI3K pathway and chromatin remodeling genes to be prevalent [148]. Thus, therapeutic agents in trials targeting these specific kinases could also be promising for patients with metastatic cSCC in the near future. However, until clinical trials occur, the use of agents targeting this pathway should be judicious if at all.

## 9 Conclusions

With a rising incidence of NMSC, more focus should be placed on cSCC because of its ability to metastasize and cause devastating outcomes. Thus, clinicians should have a high index of suspicion in high-risk patient populations, such as the immunosuppressed, and treat aggressively in areas associated with higher rates of metastasis or larger depths of invasion to achieve favorable patient outcomes. Although the literature is rich with data describing high-risk patients, tumor characteristics, tumor markers, and staging, clinicians and scientists continue to unveil more information regarding metastatic cSCC.

Prevention and identification of associated risk factors is of utmost importance in metastatic cSCC because of a lack of effective life-saving treatments. However, further investigations of associated biochemical pathways and genetic sequences as well as therapies targeted at these pathways are necessary as they may hold promise for future treatments of metastatic cSCC.

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