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HEAD & NECK: NON-MELANOMA SKIN CANCER OF THE HEAD AND NECK (J MOYER, SECTION EDITOR)

High-Risk Cutaneous Squamous Cell Carcinoma

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Abstract

Purpose of Review The aim of this report is to review the literature on patients diagnosed with a "high-risk" cutaneous squamous cell carcinoma (cSCC), defined as the subset (5–10%) of cSCC patients at increased risk of developing predominantly local and/or regional recurrence and, to a lesser extent, distant metastasis.

Recent Findings There are no universally accepted criteria for defining or managing patients with a high-risk cSCC. We reviewed the literature and examined risk stratification, management strategies, and promising future directions. A new staging system, from the Brigham and Women's Hospital, has provided important data on high-risk cSCC patients, highlighting the increasing risks associated with the interaction of a number of high-risk independent variables a patient has.

Summary Only a minority of cSCC patients can be considered as high risk for developing recurrence and potentially dying from cSCC. Most patients are cured following local treatment, usually surgery. It is the high-risk patients that need to be identified and managed appropriately, often requiring multimodality treatment.

Keywords High risk · Nodal metastases · Radiotherapy · Squamous cell carcinoma

Introduction

Cutaneous squamous cell carcinoma (cSCC) is one of the most common cancers worldwide, and the majority of patients have an excellent prognosis. However, a minority (< 5%) will develop nodal metastases and ~ 1–3% will die from cSCC, predominantly due to loco-regional recurrence [1–3]. While relatively rare, due to the high incidence of cSCC, the absolute burden is significant, with an estimated 5–12,000 cases of nodal metastases and up to 9000 deaths in the USA annually [2].

This current review will examine the so-called high-risk cSCC subgroup—defined as patients at increased risk of developing local and/or regional (i.e., locoregional) recurrence and distant metastasis. To date, there are no widely accepted criteria for defining or managing these patients, and we therefore examine risk stratification, management strategies, and promising future directions.

This article is part of the Topical Collection on *HEAD & NECK: Non-melanoma Skin Cancer of the Head and Neck*

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Epidemiology and Etiology

The incidence of cSCC varies markedly with ethnicity and latitude, from ~ 200/100,000 person years in the Northern United Kingdom (UK) to 2448/100,000 person years in Australia (with world's highest incidence of skin cancer) [4]. Treatment costs, which are often underestimated as cSCC, noting also that there is no statutory requirement for non-melanoma skin cancers (NMSC) to be reported to most cancer registries, ranging from 46 million pounds/year (UK) [5] through to 500–700 million AUD annually in Australia [6].

cSCC are more common in white males, and the incidence rises with increasing age, typically seen in > 60–70 year olds. The majority (75–80%) of primary cSCC will develop on the sun exposed head and neck (HN), especially the scalp, midface, and lower lip. Geographical trends map the intersection between the risk factors of fair skin along with high ultraviolet light (UV) exposure, such as in Queensland in Northern Australia. This long-observed clinical observation is underpinned by recent genomic studies documenting an

association between variation in skin pigment genes and cSCC development [7]. Outdoor occupational cumulative sun exposure also strongly contributes to cSCC risk [8].

An important risk factor is immunosuppression which includes organ transplant recipients (OTRs), patients with HIV-AIDS, non-Hodgkin lymphoma, and chronic lymphocytic leukemia (CLL), as well as patients treated with immunomodulating drugs such as for rheumatoid arthritis. For example, rates in OTRs are 65–250 times higher than the general population [9]. The type of immunosuppression used may be important: mTOR inhibitors (such as sirolimus) and mycophenolate mofetil are associated with a decreased risk of developing posttransplant NMSC, compared with other types of immunosuppressive drugs [10]. Other risk factors include rare genetic syndromes such as xeroderma pigmentosum, artificial UV exposure (recreational or iatrogenic), chemical exposures such as pesticides and herbicides, arsenic, ionizing radiation and polycyclic aromatic hydrocarbons [11]. Other more contentious risk factors include diet (omega-3 polyunsaturated fatty acids), alcohol, smoking, hormonal factors, and physical exercise/obesity although these factors are difficult to separate from UV exposure.

Precursor Lesions and Natural History

cSCC most commonly arise in the sun-damaged skin (although can rarely arise from previous burns, scars, or chronic infection). Patients with large numbers of actinic keratoses (AK) are at increased risk of cSCC, although the percentage and rate of progression are not well understood [12]. The natural history of untreated cSCC is local invasion, including perineural invasion (PNI), the development of nodal metastases via the lymphatic system, and less commonly visceral metastases via hematogenous spread. There is a wide range of reported incidence of metastases developing, depending on risk factors but generally reported to be between 2 and 9%. One large retrospective study of patients followed for 4 years reported local recurrence developing in 5%, nodal metastases in 4% and death from cSCC in only 2% [13]. However, another large series from a single UK population (on the Isle of Wight) reported lower rates—2.7% recurred and 1.2% metastasized—and advocated that time allocated to clinical follow-up be better spent on the education of patients self-detecting symptoms of recurrence [14].

Prognostic Stratification

"High-Risk" Features

The majority of patients diagnosed with cSCC (usually thin 1–2 mm and small < 1.5 cm cSCC) will have an excellent prognosis following appropriate treatment; however, risk stratification is essential to identify those relatively uncommon cSCC which are at increased risk of loco-regional (most common) or distant (relatively rare) relapse. Accurately identifying and validating clincopathological features associated with high risk is difficult, in part, because quality cancer registry data are not routinely collected. Multiple factors have, however, been identified in multivariate analyses as independent risk factors from institutional studies (mainly observational cohort studies), albeit varying between studies (Table 1).

Tumor diameter, the maximum clinical diameter of a lesion, is strongly associated with biologically aggressive disease. Size >2 cm is associated with a 5.6-fold higher risk of local recurrence, 7-fold higher risk of nodal recurrence, and 15.9-fold higher risk of death from cSCC [13]. A prospective study confirmed this increased risk, albeit at a lower level [15••]. Tumor thickness, in addition to size, is also important, with one large prospective study ($n = 615$) documenting risk of metastases being 0% in tumors < 2 mm but 16% in those > 6 mm [15••], supported by a study of the role of sentinel lymph node biopsy (SLNB), in which metastases were identified only in patients with tumors > 4 mm thick [16••]. Due to loss of granular layer in cSCC, it is recommended that millimeter depth be measured from the granular layer of adjacent normal skin to the base of the tumor for consistent documentation [17]. Tissue level of invasion also increases the risk of metastases as tumor progresses from dermis to subcutaneous adipose tissue, with invasion beyond subcutaneous fat one of the highest risk factors for metastases in a recent meta-analysis [18•].

The location of the cSCC may confer a higher risk with lesions that drain to the parotid gland (i.e., ear, temple, forehead, cheek) at increased risk. The parotid gland is the "metastatic nodal basin" of the HN, and the majority of patients developing nodal metastases will do so to the parotid gland ± cervical nodes. Patients will rarely ever present with distant metastases as an isolated site of relapse, which more often occur after initial treatment for regional metastases. The lip is often nominated as a high-risk subsite although lymphatic drainage is to the upper (levels I/II) neck and not to the parotid gland.

The finding of PNI occurs in 5–10% of patients and portends to an increased risk of recurrence, especially with spread along the 3rd (trigeminal) or 7th (facial) cranial nerves and occasionally beyond the skull base. Both the development of nodal and distant metastases are also reported to be increased in the setting of PNI. Despite this, isolated small caliber PNI (nerves < 0.1 mm) confined to the tumor carries low risk in the absence of other high-risk factors, while multifocal (i.e., extensive) PNI of nerves ≥ 0.1 mm in diameter and extending beyond the tumor carries an elevated risk of poor outcomes (increasing if other risk factors are present). The optimal

Table 1 High-risk features in staging systems

NCCN Guidelines (2017)	8th edition AJCC (2017)	BWH staging system (2014)
Diameter dependent on area; Area L ≥ 20 mm Area M ≥ 10 mm Area H[a]	Diameter ≥ 2 cm (deemed T2) Location on ear, cheek, temple or lip	Diameter ≥ 2 cm
	Bone or skull base invasion	
Recurrent tumor		
Poorly defined border		
Immunosuppression		
Site of prior RT or chronic inflammation		
Thickness ≥ 2 mm or Clark level IV, V	Thickness ≥ 6 mm or beyond subcutaneous fat (Clark level V)	Invasion beyond subcutaneous fat
Poorly differentiated	Poorly differentiated	Poorly differentiated
Perineural or lymphovascular invasion	Perineural invasion (≥ 0.1 mm caliber or nerve invasion beyond the dermis or named nerves)	Perineural invasion ≥ 0.1 mm caliber[b]
Rapidly growing		
Neurological symptoms		
High-risk subtype		

[a] Area H = "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, and feet. Area M = cheeks, forehead, scalp, neck, and pretibia. Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles)

[b] PNI of any caliber is a risk factor in J-P system, but only PNI ≥ 0.1 mm is a risk factor in BWH system

management of patients with PNI is unclear, but in select cases, both surgery (including skull base surgery) and radiotherapy play an important role [19•].

cSCC are immunogenic tumors (unlike basal cell carcinoma), and multiple studies have identified immunosuppressed patients at much higher risk of both developing cSCC and metastases with poorer outcomes despite appropriate treatment [20–22]. In a study of 34 immunosuppressed patients (CLL), all with primary cSCC and all excised with most receiving adjuvant radiotherapy (positive margins), 2-year local recurrence rate was 15% with regional recurrence in 36%, and 33% dying, from cSCC [23]. Other high-risk features that may contribute to a patients risk include the following: poorly defined clinical borders, histopathological grade or differentiation, desmoplasia, rapid growth, and especially recurrent tumors.

Most patients with a high-risk cSCC will have more than one individual high-risk variable, and several studies have found that with an increasing number of high-risk features, so is the risk of recurrence, especially nodal [16••, 24].

Current AJCC Staging System (8th Edition)

Due to the wide variety of clinical outcomes from cSCC, several international staging systems have been developed, including the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC). As in other sites, tumors are classified on the basis of primary lesion size and the presence or absence of nodal metastases and distant metastases. In the AJCC system [17], size is the main risk criterion for the primary tumor, with tumors < 2 cm being classified as T1 and those ≥ 2 cm being T2. T3 tumors include those ≥ 4 cm, or with minor bone erosion, PNI, or deep invasion (beyond the subcutaneous fat or > 6 mm as measured from the granular layer of adjacent normal epidermis to tumor base). T4 tumors are rare and include gross cortical bone/marrow, skull base invasion, and/or skull base foramen invasion. Nodal stage takes into account size, laterality, and number, with a focus on the presence of extranodal extension, in keeping with the staging of mucosal HN SCC [25]. However, the system has been criticized in a recent analysis of its predictive value with no difference in outcome observed between pN1, pN2, and pN3 categories [26].

Current UICC Staging System (8th Edition)

The UICC system is similar to the AJCC system [27]. Tumor classification is based on the diameter of the primary (with 2 cm the cut-point between T1 and T2), while T3 tumors are > 4 cm, minor bone erosion, PNI, or deep invasion (beyond subcutaneous fat). T4 tumors are those with gross cortical bone/marrow invasion (T4a) or axial skeleton invasion including foraminal involvement (T4b). The nodal classification is based on size (3 cm) and number.

Alternative Staging Systems

The AJCC/UICC staging systems have limitations. Firstly, they are based more on consensus opinion (due to the paucity of large multicenter or prospective studies). Secondly, while the systems are designed to have parallels with other tumor types in the mucosal HN, the majority of poor outcomes in cSCC occur in patients with early stage tumors (T1/2), as T3/T4 tumors are uncommon [28••, 29••]. This has led to the development of other systems including the Brigham and Women's Hospital system (BWH) [28••, 29••]. Jambusaria-Pahlajani et al. performed a retrospective cohort study of 257 cSCC and identified four independent risk factors on multivariate analysis. One point was given for the presence of each variable: size ≥ 2 cm, poorly differentiated tumor, PNI, or invasion beyond adipose tissue, to divide tumors into four stages—T1 (0 high-risk factors), T2a (1 high-risk factor), T2b (2–3 high-risk factors), and T3 (all four). The majority of tumors (95%) were categorized as T1/T2a, with only small numbers (1–3%) developing nodal metastases, while those patients with a T2b/T3 cSCC (6% in total) experienced the majority of nodal metastases and cancer deaths (Table 2).

A cohort of 1818 primary clinically node negative cSCC (in $n = 974$ patients) from the BWH was analyzed to validate the previous findings, with the refinement that PNI needed to be ≥ 0.1 mm caliber to be considered as high-risk. The BWH system was compared to the AJCC/UICC systems and demonstrated greater homogeneity, distinctiveness, and sequentially higher risk of recurrence or death with each alternative T stage. Of note, in the BWH system, location of the cSCC or immunosuppression was not found to be significant predicators with missing data on whether lesions were recurrent (and therefore not analyzed) [29••].

The BWH system again also better stratified $n = 106$ immunosuppressed (58% OTR) patients than the AJCC/UICC systems in a recent large single institution study. In this study, the risk of local recurrence for BWH T1 vs T2a was 11.4 vs 20.3% and risk of nodal metastases similarly increasing with T stage [30]. Despite all patients being immunosuppressed, only 17% of cSCC were ≥ 20 mm in diameter with 18% T2a or T2b/T3 (1.2%). In keeping with immunocompetent patients, the majority of recurrences (90%) arose in low T stage (T1/T2a) patients.

Molecular Markers and Future Directions

The multitude of clinicopathological high-risk factors reported and the difficulty in predicting an individual patient's risk (many patients developing metastases would be considered low-risk) have led to interest in molecular markers. Tests which are predictive of which cSCC may recur, either loco-regionally or distantly, would be clinically useful. Studies are relatively sparse compared with other tumor types; however, emerging results suggest diagnostic and therapeutic potential.

Genetic Mutations and Epigenetic Changes

cSCC have an extremely high mutation rate due to UV damage, some 5-fold greater than lung cancer [31], and greater than any other human cancer except BCC. However, there is also a high level of mutations (indeed, at a rate similar to many cancers) in clinically normal, sun-damaged skin, suggesting a high tolerance of keratinocytes to somatic mutations. The high background rate makes it difficult to develop diagnostic tests to differentiate high-risk cSCC from those with a more benign clinical course. Nevertheless, several studies [32–35] have shown both mutations specific to aggressive cSCC and that the burden of these mutations is higher as disease progresses. These particularly involve mutations in key tumor suppressor genes such as TP53, CDKN2A, and NOTCH, as well as activating mutations in pro-proliferative RAS-RAF and PI3K-AKT pathways [32]. Several studies have found mutations in the "druggable targets" BRAF, FGFR3, PIK3CA, and EGFR, with similarities to lung and HNSCC [32,35]. While data are preliminary at this stage, progression to locally invasive and metastatic cSCC is also likely to involve epigenetic changes such as global promoter hypomethylation (a feature of cSCC in OTR) [36] and alterations in methylation and histone profiles [37, 38]. There have also been described alterations in microRNAs and long non-coding RNAs, but the clinical significance remains uncertain.

Immune Surveillance

The immune microenvironment associated with cSCC comprises dynamic forces driving tumor suppression and tumor

Table 2 Brigham and Women's Hospital system

Stage	Number of high-risk factors (HR)[a]	Percent of patients in series	Percent of nodal metastases
T1	0 High-risk factors	77%	< 1%
T2a	1 High-risk factor	18%	3%
T2b	2–3 High-risk factors	5%	21%
T3	All 4 high-risk factors or bone invasion	< 1%	67%

[a] HR including size > 2 cm, depth beyond subcutaneous fat, poorly differentiated histology, PNI (only ≥ 0.1 mm)

promotion. cSCC have significantly decreased numbers of antigen-presenting cells such as myeloid dendritic cells (mDCs). Furthermore, these mDCs appear to be impaired functionally, with an inability to stimulate an appropriate T cell response [39]. In addition, regulatory T cells (Tregs) are present in the immune infiltrate of cutaneous SCC and contribute to ineffective antitumor immune responses [40]. Increased ratio of Tregs to cytotoxic CD8 T cells has been described in tumors, and especially in transplant-associated cSCC [41]. Emerging data shows that expression of the immunosuppressive tumor cell antigen programmed cell death ligand 1 (PD-1) correlates with nodal metastasis in cSCC of the HN [42•], and with disease-free survival [43•], suggesting a relationship between tumor immune escape and patient outcome. In addition, many studies are suggesting a relationship between high mutational burden (such as occurs in cSCC) and response to immunotherapy [44]—encouraging for future therapies.

Management

Workup and Staging

Patient history should focus on previous UV exposure, previous (radiation) treatment, immunosuppression, and signs and symptoms suggestive of PNI (such as cranial nerve palsy, formication). Physical examination should include a full skin and regional lymph node examination. Although uncommon at presentation, clinically or radiologically suspicious nodes should be biopsied via a fine needle aspiration biopsy.

There has been little evidence on the clinical utility of radiological imaging for prognostic staging. However, a retrospective review suggested a benefit for patients with BWH stage T2b or greater, with management changed in 33%, including a change in surgical approach (bone resection, lymphadenectomy, parotidectomy, dural excision, or nerve resection), or the addition of adjuvant radiotherapy [45].

Patients considered high risk for nodal relapse may be recommended surveillance scans in conjunction with clinical examination. These may range from simple ultrasound scanning to MRI and PET scans. There is currently no consensus on the benefit of imaging in this setting, and the cost and inconvenience of putting patients through these must be considered.

Role of SLNB

Patients developing clinical nodal metastases are at risk of death and therefore identifying patients with subclinical nodal metastases has the potential to improve outcome. Several meta-analyses of SLNB for cSCC have a reported positive lymph node metastasis rate ranging from 12 to 44% depending on criteria used, and a false negative rate of approximately 5% [46, 47]. Most of these studies were small case series and failed to accurately define important clinicopathological variables that warranted the SLNB being performed. The largest prospective study to date in cSCC was in 57 Australian patients with all having at least one predefined high-risk feature, such as size > 2 cm, poorly differentiated, locally recurrent, or the presence of PNI. The mean tumor diameter was 25 mm, depth of invasion 9.2 mm, and PNI in 39%. In total, 12% had subclinical nodal metastasis at the time of SLNB and proceeded to regional treatment. Importantly, local recurrence occurred in 14%, despite appropriate local treatment, and 11% died from cSCC, but notably the majority of cancer deaths occurred in the SLNB-negative group. As with the BWH study patients, the odds ratio for predicating a positive SLNB increased with the number of high-risk features present [16••].

The clinical impact of identifying subclinical nodal metastases on outcome has not been proven, although from first principles, there are likely to be benefits, as the patients' greatest risk is loco-regional recurrence rather than distant metastases [48••]. Currently, the optimal patient that may benefit from SLNB remains unclear and investigational, with an increasing number of high-risk factors associated with a higher rate of positivity [49]. Using the BWH stage to guide management, some authors recommend consideration of SLNB in BWH T2b/T3 and T2a tumors > 2 cm [50•].

Elective Nodal Treatment

The role of elective nodal treatment, be it surgery or radiotherapy, remains unclear noting that even with proven high-risk cSCC (BWH T2b), or using data from the Australian SLNB study, that most patients (75–85%) will not harbor subclinical nodal metastases. As such, the majority of patients will undergo needless, potentially morbid, extra treatment for unclear survival benefit.

Treatment—Primary

Local Therapy: Surgery or Definitive Radiotherapy

By definition, excision and synoptic specimen reporting are required to accurately define a high-risk cSCC. Biopsies alone may fail to identify PNI or accurately define grade or depth of invasion. Most patients therefore should be considered for surgery, with radiotherapy (definitive or adjuvant), an accepted option in select cases [51]. Irrespective of modality of primary treatment, patients are at greatest risk of recurrence within the first 12 months following treatment, so close clinical surveillance is required, particularly if immunosuppressed.

Surgery Achieving clear margins is the aim of any surgery, while taking form and function into consideration. The advantages of surgery include margin assessment, obtaining pathological data, and is usually a "one-step" procedure. The disadvantages include the invasive nature of surgery, may require hospitalization and general anesthetic for complex reconstruction, re-operation if margin positive, and may be disfiguring in functional or cosmetic sensitive areas (lip, eyelid, nose). High-risk cSCC are especially suitable for Moh's micrographic surgery (MMS), where 100% of the margin is examined microscopically and mapped, with positive margins re-excised in stages until clear. MMS usually achieves a negative margin, high cure rate, and minimizes normal tissue removal but is expensive and requires clinician expertise. In a large Australian MMS series ($n = 1263$), local recurrence rate was < 4% despite many being high-risk cases, including 40% that were recurrent cSCC. Adjuvant radiotherapy was only indicated in 3.6% of patients with the main indication PNI (82% of adjuvant cases) [52]. Alternatives to MMS usually involve wide local excision noting that unlike MMS, only a limited assessment is made of the margin status.

Radiotherapy Radiotherapy is reserved where surgery is considered not feasible (patient unfit, technically difficult to obtain margin clearance, patient refusal, anticoagulation problems, or significant co-morbidities), or where surgery would result in unacceptable toxicity (such as loss of function lips/eyelids, large tissue deficit, multiple lesions). As an example, radiotherapy to cSCC of the lower lip is highly efficacious with excellent maintenance of oral function and high rates of control and an alternative if complex flap reconstruction is being considered [53].

If radiotherapy is utilized, the field margin (analogous to an excision margin in surgery) is determined, in part, by the size of lesion. Khan and colleagues [54] reported on microscopic cSCC extension post resection and subsequently made recommendations for radiotherapy field margins of 11 mm for cSCC < 2 cm and 14 mm for > 2 cm, with consideration for larger margins for poorly differentiated/large (> 3 cm) cSCC, or in the setting of PNI.

Multiple dose and fractionation schedules have been prescribed, from 64 Gy in 32 fractions to 50 Gy in 20 fractions or 45 Gy in 15 fractions. More hyperfractionated (long course) regimens are preferred for younger patients to minimize late effects. For older patients or those of poor performance status, hypofractionated (short course) radiotherapy is both effective and convenient [55].

Adjuvant Radiotherapy to Primary Site

Despite equipoise among clinicians on the role of adjuvant radiotherapy in high-risk cSCC [56], there is evidence that adjuvant radiotherapy can decrease the risk of local and/or regional recurrence. In cases where margins are clear, cure rates are generally high, with risk of local recurrence in the order of < 5% in a review of 2449 cases [57]. In general, it is recommended in cases with clinical or extensive PNI [19•], recurrent [50•] tumor, or where excision to achieve clear margins is not technically possible [58]. Margin status is a well-documented risk for developing local relapse; however, there is limited published evidence on the benefit of the addition of local adj RTx in reducing local recurrence in this setting. Kyrgidis et al. documented the outcome of 315 patients with HN and extremity cSCC with patients undergoing adjuvant radiotherapy after local excision at significantly lower risk of developing recurrence (HR 0.08, 95% CI 0.03–0.26, p value < 0.001) [59]. In an Australian study ($n = 217$ T1/T2 lip cSCC), the addition of local adjuvant radiotherapy in the setting of a close/positive margin significantly improved relapse-free survival ($p = 0.008$). Fifty-seven percent of surgery patients with a close/positive margin relapsed compared with only 9% who received adjuvant radiotherapy [53].

The addition of adjuvant radiotherapy for "high-risk" features such as immunosuppression [20], tumor size ≥ 2 cm, poor differentiation, or a close margin also likely to improve loco-regional control [19•,51,53] and should be individualized after discussion in a multidisciplinary setting.

Treatment—Nodal Metastases

Patients with cSCC metastatic to regional lymph nodes, especially of the HN, should be referred to a multidisciplinary cancer service. Only a minority (20%) present with a concomitant primary cSCC and nodal metastases with the reminder presenting as a relapse event postprimary cSCC treatment usually within 12 months of treatment of the primary, but can present up to 3–4 years later [60••]. In approximately 25% of cases no cutaneous "index lesion" is found. The HN is the most common site to develop nodal metastases, with axilla and groin being relatively uncommon [61]. The parotid and its associated lymph nodes are the commonest sites for metastatic nodes [62], in approximately two thirds of cases, with the remaining one third developing to other cervical (levels I-IV) nodal metastases without parotid involvement.

Multimodal Management

Patients with confirmed nodal metastases should undergo regional dissection. In most cases this should be followed by adjuvant radiotherapy [63], although it may be omitted in the immunocompetent patient with a single involved node < 3 cm, with no extracapsular spread and clear margins [64]. Survival is improved with the addition of adjuvant radiotherapy, with a 28-year retrospective analysis showing that radiotherapy more than halved the risk of recurrence (from 55 to 23%) [65]. Dose delivered is typically 60 Gy in 30 fractions, often delivered

using intensity-modulated radiotherapy or volumetric arc therapy in order to spare nearby normal organs.

While only presented in abstract form, a recent multicenter phase 3 trial showed no significant clinical benefit to the addition of weekly concurrent chemotherapy (carboplatinum) to adjuvant radiotherapy for high-risk patients following nodal dissection [66••]. Despite aggressive multimodality therapy, patients with immunosuppression have an inferior outcome [20]. In a large Australian series of patients with metastatic nodal cSCC, four independent variables were identified to develop a predictive model referred to as the ITEM score (immunosuppression, treatment, extranodal spread, and margin status). Patients that were immunosuppressed with the addition of other high-risk variables had a 56% chance of dying from cSCC [67•].

Future Directions

Treatment options for patients with recurrent or metastatic cSCC remain limited. In addition to cytotoxic chemotherapy, with low response rates, several agents are under investigation. The most studied has been inhibition of epidermal growth factor receptor (EGFR), with either monoclonal antibodies or tyrosine kinase inhibitors, and trials in both the neoadjuvant and recurrent/metastatic settings are underway. Furthermore, genomic profiling of advanced and metastatic cSCC reveal that nearly 90% of patients had clinically relevant genomic alterations that are "targetable" with available anticancer drugs or in registered clinical trials [68].

In keeping with the tumoral immunosuppressive microenvironment described above, immunotherapy with checkpoint inhibitors is showing great promise. For example, a phase III trial in recurrent or metastatic (mucosal) SCC after platinum chemotherapy showed a significant survival benefit [69]. Excitingly, a response rate of 52% (higher than many other subsites) was noted in a phase I study of a PD-1 inhibitor [70]. It is possible that future studies may identify a clinical role for these agents.

Conclusions

Only a minority of cSCC patients can be considered as high-risk for developing recurrence and potentially dying from cSCC. Most patients are cured following local treatment, usually surgery. It is these high-risk patients that need to be identified and managed appropriately, often requiring multimodality treatment. The addition of adjuvant locoregional radiotherapy may reduce the risk of recurrence in select patients. Further data is required on the role of SLNB and the benefits of systemic agents.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent All reported studies with human subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Tseros EA, Gebski V, Morgan GJ, Veness MJ. Prognostic significance of lymph node ratio in metastatic cutaneous squamous cell carcinoma of the head and neck. Ann Surg Oncol. 2016;23:1693–8.
2. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. J Am Acad Dermatol. 2013;68:957–66.
3. Eigentler TK, Leiter U, Häfner H-M, Garbe C, Röcken M, Breuninger H. Survival of patients with cutaneous squamous cell carcinoma: results of a prospective cohort study. J Investig Dermatol. 2017;137:2309–15.
4. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol. 2012;166:1069–80.
5. Vallejo-Torres L, Morris S, Kinge JM, Poirier V, Verne J. Measuring current and future cost of skin cancer in England. J Public Health (Oxf). 2014;36:140–8.
6. Perera E, Gnaneswaran N, Staines C, Win AK, Sinclair R. Incidence and prevalence of non-melanoma skin cancer in Australia: a systematic review. Aust J Dermatol. 2015;56:258–67.
7. Chahal HS, Lin Y, Ransohoff KJ, Hinds DA, Wu W, Dai H-J, et al. Genome-wide association study identifies novel susceptibility loci for cutaneous squamous cell carcinoma. Nat Commun. 2016;7:12048.
8. Schmitt J, Haufe E, Trautmann F, Schulze H-J, Elsner P, Drexler H, et al. Is UV-exposure acquired at work the most important risk factor for cutaneous squamous cell carcinoma? Results of the population-based case-control study FB-181. Br J Dermatol. 2018;178:462–72.
9. Madeleine MM, Patel NS, Plasmeijer EI, Engels EA, Bouwes Bavinck JN, Toland AE, et al. Epidemiology of keratinocyte carcinomas after organ transplantation. Br J Dermatol. 2017;177:1208–16.
10. Chockalingam R, Downing C, Tyring S. Cutaneous squamous cell carcinomas in organ transplant recipients. J Clin Med. 2015;4:1229–39.
11. Green AC, Olsen CM. Cutaneous squamous cell carcinoma: an epidemiological review. Br J Dermatol. 2017;177:373–81.
12. Werner RN, Sammain A, Erdmann R, Hartmann V, Stockfleth E, Nast A. The natural history of actinic keratosis: a systematic review. Br J Dermatol. 2013;169:502–18.

13. Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma. JAMA Dermatol. 2013;149:541–7.
14. Nelson TG, Ashton RE. Low incidence of metastasis and recurrence from cutaneous squamous cell carcinoma found in a UK population: do we need to adjust our thinking on this rare but potentially fatal event? J Surg Oncol. 2017;116:783–8.
15.•• Brantsch KD, Meisner C, Schönfisch B, Trilling B, Wehner-Caroli J, Röcken M, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol. 2008;9:713–20. **Large prospective study examining high-risk features.**
16.•• Gore SM, Shaw D, Martin RCW, Kelder W, Roth K, Uren R, et al. Prospective study of sentinel node biopsy for high-risk cutaneous squamous cell carcinoma of the head and neck. Head Neck. 2016;38(Suppl 1):E884–9. **The first and largest prospective study of SLNB in high-risk SCC patients indicating that local recurrence is a similar concern along with regional metastases.**
17. Amin MB, Edge SB, Greene FL, et al. AJCC Cancer Staging Man 8th ed. New York: Springer; 2017.
18.• Thompson AK, Kelley BF, Prokop LJ, Murad MH, Baum CL. Risk factors for cutaneous squamous cell carcinoma recurrence, metastasis, and disease-specific death: a systematic review and meta-analysis. JAMA Dermatol. 2016;152:419–28. **Large meta-analysis examining high-risk features.**
19.• Gupta A, Veness M, De'Ambrosis B, Selva D, Huilgol SC. Management of squamous cell and basal cell carcinomas of the head and neck with perineural invasion. Aust J Dermatol. 2016;57:3–13. **Review article with suggested management pathways following the finding of perineural invasion.**
20. Manyam BV, Garsa AA, Chin R-I, Reddy CA, Gastman B, Thorstad W, et al. A multi-institutional comparison of outcomes of immunosuppressed and immunocompetent patients treated with surgery and radiation therapy for cutaneous squamous cell carcinoma of the head and neck. Cancer. 2017;123:2054–60.
21. Zavos G, Karidis NP, Tsourouflis G, Bokos J, Diles K, Sotirchos G, et al. Nonmelanoma skin cancer after renal transplantation: a single-center experience in 1736 transplantations. Int J Dermatol. 2011;50:1496–500.
22. Lott DDG, Manz R, Koch C, Lorenz RRR. Aggressive behavior of nonmelanotic skin cancers in solid organ transplant recipients. Transplantation. 2010;90:683–7.
23. Tomaszewski JM, Gavriel H, Link E, Boodhun S, Sizeland A, Corry J. Aggressive behavior of cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia. Laryngoscope. 2014;124:2043–8.
24. Ch'ng S, Clark JR, Brunner M, Palme CE, Morgan GJ, Veness MJ. Relevance of the primary lesion in the prognosis of metastatic cutaneous squamous cell carcinoma. Head Neck. 2013;35:190–4.
25. Lydiatt WM, Patel SG, O'Sullivan B, Brandwein MS, Ridge JA, Migliacci JC, et al. Head and neck cancers-major changes in the American joint committee on cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67:122–37.
26. Liu J, Ebrahimi A, Low T-HH, Gao K, Palme CE, Sydney C, et al. Predictive value of the 8th edition American Joint Commission Cancer (AJCC) nodal staging system for patients with cutaneous squamous cell carcinoma of the head and neck. J Surg Oncol. 2018;117:765–72.
27. Brierley J, Gospodarowicz MK, Wittekind C, editors. TNM classification of malignant tumours. 2016.
28.•• Jambusaria-Pahlajani A, Kanetsky PA, Karia PS, Hwang W-T, Gelfand JM, Whalen FM, et al. Evaluation of AJCC Tumor Staging for Cutaneous Squamous Cell Carcinoma and a Proposed Alternative Tumor Staging System. JAMA Dermat. 2013;149:402. **Define the now commonly used "BWH" criteria in the alternate staging system.**
29.•• Karia PS, Jambusaria-Pahlajani A, Harrington DP, Murphy GF, Qureshi AA, Schmults CD. Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital Tumor Staging for Cutaneous Squamous Cell Carcinoma. J Clin Oncol. 2014;32:327–34. **Define the now commonly used "BWH" criteria in the alternate staging system.**
30. Gonzalez JL, Cunningham K, Silverman R, Madan E, Nguyen BM. Comparison of the American joint committee on Cancer seventh edition and Brigham and Women s hospital cutaneous squamous cell carcinoma tumor staging in immunosuppressed patients. Dermatol Surg. 2017;43:784–91.
31. Durinck S, Ho C, Wang NJ, Liao W, Jakkula LR, Collisson EA, et al. Temporal dissection of tumorigenesis in primary cancers. Cancer Discov. 2011;1:137–43.
32. Li YY, Hanna GJ, Laga AC, Haddad RI, Lorch JH, Hammerman PS. Genomic analysis of metastatic cutaneous squamous cell carcinoma. Clin Cancer Res. 2015;21:1447–56.
33. Pickering CR, Zhou JH, Lee JJ, Drummond JA, Peng SA, Saade RE, et al. Mutational landscape of aggressive cutaneous squamous cell carcinoma. Clin Cancer Res. 2014;20:6582–92.
34. Yilmaz AS, Ozer HG, Gillespie JL, Allain DC, Bernhardt MN, Furlan KC, et al. Differential mutation frequencies in metastatic cutaneous squamous cell carcinomas versus primary tumors. Cancer. 2017;123:1184–93.
35. Zilberg C, Weicai Lee M, Yu B, Ashford B, Kraitsek S, Ranson M, et al. Analysis of clinically relevant somatic mutations in high-risk head and neck cutaneous squamous cell carcinoma. Mod Pathol 2018;31:275–87.
36. Laing ME, Cummins R, O'Grady A, O'Kelly P, Kay EW, Murphy GM. Aberrant DNA methylation associated with MTHFR C677T genetic polymorphism in cutaneous squamous cell carcinoma in renal transplant patients. Br J Dermatol. 2010;163:345–52.
37. Darr OA, Colacino JA, Tang AL, McHugh JB, Bellile EL, Bradford CR, et al. Epigenetic alterations in metastatic cutaneous carcinoma. Head Neck. 2015;37:994–1001.
38. Nandakumar V, Vaid M, Tollefsbol TO, Katiyar SK. Aberrant DNA hypermethylation patterns lead to transcriptional silencing of tumor suppressor genes in UVB-exposed skin and UVB-induced skin tumors of mice. Carcinogenesis. 2011;32:597–604.
39. Bluth MJ, Zaba LC, Moussai D, Suárez-Fariñas M, Kaporis H, Fan L, et al. Myeloid dendritic cells from human cutaneous squamous cell carcinoma are poor stimulators of T-cell proliferation. J Investig Dermatol. 2009;129:2451–62.
40. Lai C, August S, Behar R, Polak M, Ardern-Jones M, Theaker J, et al. Characteristics of immunosuppressive regulatory T cells in cutaneous squamous cell carcinomas and role in metastasis. Lancet (Lond, Engl). 2015;385(Suppl 1):S59.
41. Zhang S, Fujita H, Mitsui H, Yanofsky VR, Fuentes-Duculan J, Pettersen JS, et al. Increased Tc22 and Treg/CD8 ratio contribute to aggressive growth of transplant associated squamous cell carcinoma. Toland AE, editor. PLoS One. 2013;8:e62154.
42.• García-Pedrero JM, Martínez-Camblor P, Diaz-Coto S, Munguia-Calzada P, Vallina-Alvarez A, Vazquez-Lopez F, et al. Tumor programmed cell death ligand 1 expression correlates with nodal metastasis in patients with cutaneous squamous cell carcinoma of the head and neck. J Am Acad Dermatol. 2017;77:527–33. **Are the first to examine markers of response to checkpoint inhibitors in high-risk SCC.**
43.• Roper E, Lum T, Palme CE, Ashford B, Ch'ng S, Ranson M, et al. PD-L1 expression predicts longer disease free survival in high risk head and neck cutaneous squamous cell carcinoma. Pathology. 2017;49:499–505. **Are the first to examine markers of response to checkpoint inhibitors in high-risk SCC.**

44. Goodman AM, Kato S, Bazhenova L, Patel SP, Frampton GM, Miller V, et al. Tumor mutational burden as an independent predictor of response to immunotherapy in diverse cancers. Mol Cancer Ther. 2017;16:2598–2608.
45. Ruiz ES, Karia PS, Morgan FC, Schmults CD. The positive impact of radiologic imaging on high-stage cutaneous squamous cell carcinoma management. J Am Acad Dermatol. 2017;76:217–25.
46. Ahadiat O, Higgins S, Sutton A, Ly A, Wysong A. SLNB in cutaneous SCC: a review of the current state of literature and the direction for the future. J Surg Oncol. 2017;116:344–50.
47. Navarrete-Dechent C, Veness MJ, Droppelmann N, Uribe P. High-risk cutaneous squamous cell carcinoma and the emerging role of sentinel lymph node biopsy: a literature review. J Am Acad Dermatol. 2015;73:127–37.
48.•• Veness MJ, Morgan GJ, Palme CE, Gebski V. Surgery and adjuvant radiotherapy in patients with cutaneous head and neck squamous cell carcinoma metastatic to lymph nodes: combined treatment should be considered best practice. Laryngoscope. 2005;115:870–5. **Important data that indicate a benefit to the addition of radiotherapy to surgery for high-risk cases following nodal surgery.**
49. Schmitt AR, Brewer JD, Bordeaux JS, Baum CL. Staging for cutaneous squamous cell carcinoma as a predictor of sentinel lymph node biopsy results. JAMA Dermatol. 2014;150:19–24.
50.• Baum CL, Wright AC, Martinez J-C, Arpey CJ, Brewer JD, Roenigk RK, et al. A new evidence-based risk stratification system for cutaneous squamous cell carcinoma into low, intermediate, and high risk groups with implications for management. J Am Acad Dermatol. 2018;78:141–7.. **Practical guidelines for management of high-risk SCC.**
51. Thanh Pham T, Cross S, Gebski V, Veness MJ. Squamous cell carcinoma of the lip in Australian patients: definitive radiotherapy is an efficacious option to surgery in select patients. Dermatol Surg. 2015;41:219–25.
52. Leibovitch I, Huilgol SC, Selva D, Hill D, Richards S, Paver R. Cutaneous squamous cell carcinoma treated with Mohs micrographic surgery in Australia I. Experience over 10 years. J Am Acad Dermatol. 2005;53:253–60.
53. Najim M, Cross S, Gebski V, Palme CE, Morgan GJ, Veness MJ. Early-stage squamous cell carcinoma of the lip: the Australian experience and the benefits of radiotherapy in improving outcome in high-risk patients after resection. Head Neck. 2013;35:1426–30.
54. Khan L, Choo R, Breen D, Assaad D, Fialkov J, Antonyshyn O, et al. Recommendations for CTV margins in radiotherapy planning for non melanoma skin cancer. Radiother Oncol. 2012;104:263–6.
55. Veness M. Hypofractionated radiotherapy in older patients with non-melanoma skin cancer: less is better. Aust J Dermatol. 2017.
56. Jambusaria-Pahlajani A, Hess SD, Katz KA, Berg D, Schmults CD. Uncertainty in the perioperative management of high-risk cutaneous squamous cell carcinoma among Mohs surgeons. Arch Dermatol. 2010;146:1225–31.
57. Jambusaria-Pahlajani A, Miller CJ, Quon H, Smith N, Klein RQ, Schmults CD. Surgical monotherapy versus surgery plus adjuvant radiotherapy in high-risk cutaneous squamous cell carcinoma: a systematic review of outcomes. Dermatol Surg. 2009;35:574–85.
58. Babington S, Veness MJ, Cakir B, Gebski VJ, Morgan GJ. Squamous cell carcinoma of the lip: is there a role for adjuvant radiotherapy in improving local control following incomplete or inadequate excision? ANZ J Surg. 2003;73:621–5.
59. Kyrgidis A, Tzellos TG, Kechagias N, Patrikidou A, Xirou P, Kitikidou K, et al. Cutaneous squamous cell carcinoma (SCC) of the head and neck: risk factors of overall and recurrence-free survival. Eur J Cancer. 2010;46:1563–72.
60.•• Veness MJ, Porceddu S, Palme CE, Morgan GJ. Cutaneous head and neck squamous cell carcinoma metastatic to parotid and cervical lymph nodes. Head Neck. 2007;29:621–31. **Large Australian instituional series and analysis of high-risk features associated with metastatic nodal SCC.**
61. Goh A, Howle J, Hughes M, Veness MJ. Managing patients with cutaneous squamous cell carcinoma metastatic to the axilla or groin lymph nodes. Aust J Dermatol. 2010;51:113–7.
62. O'Brien CJ. The parotid gland as a metastatic basin for cutaneous cancer. Arch Otolaryngol Head Neck Surg. 2005;131:551–5.
63. Porceddu SV, Veness MJ, Guminski A. Nonmelanoma cutaneous head and neck cancer and Merkel cell carcinoma: current concepts, advances, and controversies. J Clin Oncol. 2015;33:3338–45.
64. Ebrahimi A, Clark JR, Lorincz BB, Milross CG, Veness MJ. Metastatic head and neck cutaneous squamous cell carcinoma: defining a low-risk patient. Head Neck. 2012;34:365–70.
65. Wang JT, Palme CE, Morgan GJ, Gebski V, Wang AY, Veness MJ. Predictors of outcome in patients with metastatic cutaneous head and neck squamous cell carcinoma involving cervical lymph nodes: improved survival with the addition of adjuvant radiotherapy. Head Neck. 2012;34:1524–8.
66.•• Porceddu SV, Poulsen M, Bressel M, Stoneley A, Veness M, Kenny LM, et al. Post-operative concurrent chemo-radiotherapy versus post-operative radiotherapy in high-risk cutaneous squamous cell carcinoma of the head and neck: a randomized phase III trial (Trans Tasman Radiation Oncology Group 05.01 Trial; POST study). J. Clin Oncol Am Soc Clin Oncol. 2017;35:6008. **Outcome of a phase 3 trial, rare in this area.**
67.• Oddone N, Morgan GJ, Palme CE, Perera L, Shannon J, Wong E, et al. Metastatic cutaneous squamous cell carcinoma or the head and neck. Cancer. 2009;115:1883–91. **Predictive model that highlights the poor outcome of immunosuppressed patients developing metastatic cutaneous nodal SCC.**
68. Al-Rohil RN, Tarasen AJ, Carlson JA, Wang K, Johnson A, Yelensky R, et al. Evaluation of 122 advanced-stage cutaneous squamous cell carcinomas by comprehensive genomic profiling opens the door for new routes to targeted therapies. Cancer. 2016;122:249–57.
69. Ferris RL, Blumenschein G, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016;375:1856–67.
70. Papadopoulos KP, Owonikoko TK, Johnson ML, Brana I, Gil-Martin M, Perez RP, et al. REGN2810: a fully human anti-PD-1 monoclonal antibody, for patients with unresectable locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC)—initial safety and efficacy from expansion cohorts (ECs) of phase I study. J Clin Oncol Am Soc Clin Oncol. 2017;35:9503.