INVITED REVIEW

High-risk Cutaneous Squamous Cell Carcinoma

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ABSTRACT

Cutaneous squamous cell carcinoma (cSCC) is the second most common nonmelanoma skin cancer worldwide. Cutaneous squamous cell carcinoma can potentially be treated fully with minimal morbidity when detected early; however, certain subtypes of cSCC have been shown to confer a poorer prognosis for patients. In these high-risk tumors, increased incidence of recurrence, as well as metastasis to local lymph nodes and distant sites, is seen as a result of certain patient characteristics and pathological features. While guidelines regarding the management of high-risk cSCC have been produced, no clear consensus management or prognostic algorithms exist. In this review, we discuss current definitions of high-risk cSCC, recommendations regarding the management of cSCC, and current guidelines.

Keywords: Clinical guidelines, High-risk, Oncology, Squamous cell carcinoma.

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INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most common nonmelanoma skin cancer worldwide.[1,2] Risk factors including ultraviolet radiation, fair skin, chronic wounds/scar, ionizing radiation, and certain genetic conditions are well established.[1] Meanwhile, other factors including human papillomavirus infection have more recently been implicated in certain cases, e.g., in immunosuppressed patients.[3] The role of a number of genes including *TP53, HRAS, EGFR, CDKN2A,* and others has also been investigated.[4]

Cutaneous squamous cell carcinoma can potentially be treated fully with minimal morbidity when detected at an early stage; however, certain subtypes of cSCC have been shown to confer a poorer prognosis for patients.[5,6] In these "high-risk" tumors, increased incidence of

recurrence (>5%), as well as metastasis to local lymph nodes and distant sites, is seen as a result of certain patient characteristics and pathological features.[5,7]

While the American Joint Committee on Cancer (AJCC) and the National Comprehensive Cancer Network (NCCN) have produced staging systems for cSCC, no clear consensus management or prognostic algorithms exist.[8-10] In this review, we discuss current definitions of high-risk cSCC, recommendations regarding the management of these cases, and current guidelines.

HIGH-RISK FEATURES IN cSCC

Defining High-risk Features

Identifying the small subgroup of cSCCs associated with poor prognosis represents a significant challenge. A number of staging systems, including the AJCC, Union for International Cancer Control, NCCN, and Brigham and Women's Hospital staging systems, are available for cSCC.[10-12] Both the AJCC and NCCN staging systems define high-risk features of cSCC; however, a number of differences exist between the two (Tables 1 and 2).[10,12] Notable disparities between the two systems include the exclusion of clinical risk factors, such as recurrence and immunosuppression from AJCC guidelines. Furthermore, AJCC guidelines do not include incomplete excision or lymphovascular invasion as a pathological features denoting high-risk status. In the latest eighth edition of AJCC guidelines, a separate staging for cSCC located in the head and neck has been introduced.[13]

Area H refers to areas at high risk for recurrence, including mask areas of the face (central face, eyelids, eyebrows, periorbital area, nose, lips, chin, ears, genitalia, hands, and feet). Area M refers to middle-risk areas for recurrence, including cheeks, forehead, neck, and scalp. Area L refers to low-risk areas for recurrence, including the trunk and extremities.

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Table 1: American joint committee on cancer guideline "high-risk" features

Depth
– Breslow's thickness ≥2 mm
– Clark level ≥IV
Location
– Ear
– Hair-bearing lip
Poor histological differentiation
Perineural invasion

Table 2: National comprehensive cancer network guideline "high-risk" features

History and presentation:
Location
 – ≥20 mm on area L
 – ≥10 mm on area M
 – ≥6 mm on area H
Poorly defined borders
Site of prior radiotherapy or chronic inflammatory process
Immunosuppression
Recurrent tumor
Rapidly growing tumor
Neurological symptoms
Pathology
Moderate or poor histological differentiation
Adenoid, adenosquamous, desmoplastic, metaplastic subtypes
Depth
 – Modified Breslow thickness ≥4 mm
 – Clark levels IV or V
Perineural, lymphatic, or vascular invasion

Adapted from the 2016 NCCN Guidelines.[10] The presence of one of the above factors signifies high risk; Area H refers to areas at high risk for recurrence, including mask areas of the face (central face, eyelids, eyebrows, periorbital area, nose, lips, chin, ears, genitalia, hands, and feet). Area M refers to middle-risk areas for recurrence, including cheeks, forehead, neck, and scalp. Area L refers to low-risk areas for recurrence, including the trunk and extremities.

Variations in high-risk features between the two systems may lead to differing classification of the same tumor. For example, Chu et al[14] found when retrospectively applying each staging system to 269 cases of cSCC that NCCN categorized 87% as high risk, while the AJCC conferred a T2, high-risk classification in only 13.9% of cases, with most of these based on size ≥2 cm alone. The inclusion of patient characteristics appeared to lead to a higher proportion of high-risk cases when using NCCN guidelines. The finding of the Brigham and Women's group that a cohort of T2 cSCC could be divided into two groups with distinct prognosis, with the amalgamation of the T3 and T4 stages into a single group, led to the development of a separate tumor staging system for cSCC.[11,15]

Understanding the differences between these staging systems and the relative merits of each is required for clinicians when interpreting definitions of high-risk cSCC.

High-risk Pathological Features

Consensus regarding the high-risk features of cSCC may guide clinicians in decision-making and may improve prognostic information available for patients. We will now explore in more detail the evidence behind each of the commonly described high-risk features of cSCC.

Tumor size, as a pathological high-risk feature of cSCC, is measured as the maximum diameter of the tumor at excision. Diameter ≥2 cm is associated with an increased likelihood of metastasis.[5,16] The large systematic review and meta-analysis of Thompson et al[17] including 17,248 patients highlighted tumor size ≥2 cm as a factor associated with local recurrence and metastasis of cSCC [relative risk (RR) 9.64; 95% confidence interval (CI), 1.30–71.52]. Tumor size ≥2 cm is shown to independently predict recurrence and metastasis in multivariate analysis.[5] Meanwhile, tumor size ≥2 cm of the lip or ear has been described by Row et al[18] as approximately twice as likely to locally recur (15.2 *vs* 7.4%) and three times as likely to metastasize (30.3 *vs* 9.1%).

Depth of invasion, or tumor thickness, independently predicts both metastasis and local recurrence and should be measured to the granular layer, to the deepest point of invasion. Both the AJCC and NCCN guidelines include depth of ≥2 mm or Clark level ≥IV as a high-risk factor.[10,12] One large retrospective study of 594 cSCCs found no metastases in the 233 tumors <2 mm thick over a median 5.3-year follow-up; 4.7% (13) of the tumors >2 mm but <5 mm were shown to metastasize, while 20% (18) of the 89 tumors >5 mm did so.[19] The prospective study of Brantsch et al[5] including 653 patients showed no metastases in patients with cSCC <2 mm thickness, but 4% in tumor thickness 2.1 mm to 6.0 mm and 16% in tumor thickness >6 mm.

Recurrence of cSCC can be considered an independent high-risk feature of this disease. When compared with primary cSCC, recurrence of tumor at a previous site may be associated with increased size, greater patterns of invasion (lymphovascular and perineural), and nodal spread.[20-22] Metastasis rates of 32 to 45% have been highlighted in reviews of recurrent cSCCs of the pinna and lip.[18]

As highlighted, tumor recurrence has, to date, been omitted as a high-risk feature from the AJCC guideline for cSCC, potentially meaning that these tumors are not appropriately upstaged.[12] Proposals to designate these cases with the letter "r" when recording tumor characteristics have been supported by a number of authors.[14,23]

Poor histological differentiation has been associated with increased metastasis rates and mortality. Moderate and poor differentiation is included as a high-risk pathological feature in both NCCN and AJCC guidelines.[10,12] Brinkman et al[24] previously highlighted metastasis-free survival and overall survival at 5 years are increased in the well-differentiated tumors, when compared with moderately and poorly differentiated lesions, at 70, 51, and 26% respectively.[24]

Specific histopathological subtypes are also identified as high-risk features in NCCN guidelines, including acantholytic, adenosquamous, desmoplastic, and basosquamous subtypes.[25-31] Invasive Bowen's disease has

also been highlighted as a poorly recognized pathology which portends poor outcomes.[32] Desmoplastic tumors, in particular, have been shown to carry higher risk of metastasis, with Breuninger et al highlighting 6 times more metastases and 10 times more recurrences where desmoplastic subtypes were identified in a sample of 509 patients with cSCC.[19] To date, these histological details have not been included in AJCC guidelines.

Perineural and lymphovascular invasion have both been highlighted as risk factors for nodal spread of disease in cSCC.[7,16,17,33] In perineural invasion (PNI), spread of tumor along nerve sheath connective tissue surrounding the fascicles leads to neurological symptoms and pain, which signal spread of disease.[34] The presence of PNI has been shown to independently predict local recurrence and metastasis in a number of studies, including Thompson's meta-analysis (RR 2.95; 95% CI 2.31–3.75).[17,34,35] The association with large-caliber nerves, location on the head and neck, and tumor size, however, have been disputed by some authors.[36] Similarly, invasion of vascular and lymphatic structures increases the risk of disease spread.[5,17] Lymphovascular invasion has been recorded as an independent predictor of lymph node metastasis (odds ratio 7.54, p<0.0001).[7] While both AJCC and NCCN guidelines highlight PNI as a high-risk feature, lymphovascular invasion is included only in the NCCN system.

Particular anatomic sites, including the lips, cheeks, forehead, ears, periauricular area, and scalp, have been highlighted as high-risk regions for local recurrence or metastatic spread of cSCC, in particular to parotid and cervical nodes.[10,18,37-39] In a series of 152 patients with parotid and cervical nodal metastasis, primary tumor sites were cheek (21.7%), periauricular area (20.4%), temple (15.8%), and forehead (15.8%).[39] The AJCC guidelines classify only the hair-bearing lip and ears as high-risk regions for cSCC.[12] Meanwhile, NCCN guidelines designate the entire head and neck region as high risk.[10] Notably, recent meta-analysis has found no independent predicted association between cSCC of the lips and ears with recurrence, in contrast with previous studies.[17,40]

Immunosuppression is associated with higher rates of cSCC.[41,42] Solid organ transplant recipients, such as renal transplant patients, demonstrate a 100-fold increased risk for invasive cSCC compared with the general population.[41] Patients transplanted at an older age with a prior history of sun damage or with longer duration or greater intensity of immunosuppression may be at greater risk of developing cSCC.[43] Immunosuppression with azathioprine or calcineurin inhibitors is closely associated.[41,44] Unlike the NCCN guideline, the AJCC does not include immunosuppression as a high-risk feature of patients presenting with cSCC.[10,12]

Incomplete excision of surgical margins is not currently recognized as a high-risk feature of cSCC.[10,12] Rates of incomplete excision range from 5 to 17.6%, with a particular association with high-risk areas of the head and neck.[45-49] Positive findings on reexcision of incompletely excised cSCC have been associated with a 10-fold increased risk of recurrence when compared with negative reexcision margins in a 5-year prospective study from Bovill et al.[49]

MANAGEMENT OF HIGH-RISK cSCC

Parotid Metastases

In 2002, O'Brien et al[50] proposed a staging system to further stratify patients diagnosed with parotid or cervical metastases from cSCC in the head and neck (Table 3). The staging system was based on a prospective study of 87 patients with metastatic cSCC.[50] P2 and P3 categories in their model were independently associated with decreased disease control in the parotid region.[50] Meanwhile, N2 designation for the neck was associated with reduced survival.[50]

Later studies led to the development of the N1S3 system, which allowed further staging based on the number and size of any involved nodes in the parotid or neck.[51] The N1S3 classification demonstrated superior patient stratification when compared with the AJCC TNM staging at later review.[51]

RADIOLOGY

The presence of high-risk features during clinical evaluation should alert surgeons to the potential for nodal involvement in the neck. Ultrasound may be used as an initial investigation, with additional screening with computed tomography (CT) or magnetic resonance imaging (MRI) or positron emission tomography (PET)-CT as required on a case-by-case basis. While MRI may

Table 3: O'Brien P/N staging system

Parotid	
P1	Metastatic node ≤3 cm diameter
P2	Metastatic node ≥3 and ≤6 cm diameter or multiple parotid node
P3	Metastatic node >6 cm diameter or disease involving cranial nerve VII or skull base
Neck	
N0	No clinical neck disease
N1	Single ipsilateral neck node ≤3 cm diameter
N2	Single node >3 cm diameter or multiple neck nodes or contralateral nodes
N1S3 system:	
I) single lymph node ≤3 cm	
II) multiple lymph nodes or single lymph node ≥3 cm	
III) multiple nodes diameter >3 cm	

be recommended in patients with neurological involvement suggestive of PNI, no clear guidelines are currently in place.[52]

SURGERY

Conventional Surgical Excision

Radial excision of margins of 4 mm in low-risk and 6 mm in high-risk cSCC provides oncologic clearance rates of 95%.[53,54] European consensus recommendations of 10 mm in high-risk disease have also been proposed.[55] Caution should be applied to ensure that the deep excision margin extends to the hypodermis, macroscopically deep to tumor, as the majority of positive margins occur at the deep margin.[48,55] Where possible neural structures, for example, perichondrium or periostium, should not be disturbed.[48] Neck dissection should be performed in cases of cervical nodal involvement, with priority given to dissection of levels I and II, where the majority of metastases occur.[56]

Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy (SLNB) has been well investigated as a means to confirm the presence of subclinical nodal metastasis in melanoma and breast cancer.[57-59] Its role in the management of cSCC of the head and neck remains opaque.[60] In the case of melanoma, while sensitivity of 87.5 to 89.2% has been reported in meta-analysis and prospective trials respectively, data supporting its effect on survival outcomes are lacking.[59]

Limited studies exist to suggest a clear role for SLNB in cSCC. One review of 173 patients with high-risk cSCC undergoing SLNB highlighted 79% sensitivity and 100% specificity, with negative predictive value of 96%.[61] Further systematic reviews have suggested the putative role for SLNB in cSCC may be limited to T2 lesions >2 cm diameter lesion only.[62] Traditionally, the complex drainage pattern of the neck and relatively small nodal size in the neck has led authors to suggest that the procedure is impractical in cSCC.[63] Further investigation with larger cohorts is required to further guide surgeons.

Elective Neck Dissection

The use of elective neck dissection in the clinically N0 neck to reveal occult nodal metastases has been reported.[64-67] To date, however, no prospective study has demonstrated a survival benefit where elective neck dissection is added to management of high-risk cSCC of the head and neck in the N0 setting.[67] Studies report rates of occult nodal metastasis of 10 to 60%.[50,68]

The Wong and Morton[65] decision analysis tree for the use of elective neck dissection in the high-risk cSCC with an N0 neck was introduced in 2014. The tool attempts to establish the relative utility of elective neck dissection *vs* elective nodal irradiation *vs* surveillance. The decision tree provides a useful framework, but data to support its use are not robust.

Prophylactic Parotidectomy

The propensity of high-risk cSCC of the head and neck to metastasize to the parotid gland is well established. Veness et al[69] have reported 266 cases of metastatic cSCC, with 162 (61%) involving the parotid gland. On this basis, authors have suggested parotidectomy in cases of T3 or T4 lesions with high-risk features.[69] Kadakia et al[70] have retrospectively reported 104 patients following elective parotidectomy for high-risk cSCC of the ear >2 cm (without preoperative nodal metastases on radiology).[70] In total, 39 (37.5%) demonstrated metastatic cSCC in parotidectomy specimens.[70] Despite these reports, further studies are required to clarify the precise role of elective parotidectomy for high-risk cSCC.

Mohs Microsurgery

Mohs microsurgery (MMS) offers a tissue-sparing procedure for cSCC occurring in cosmetically sensitive areas, such as the eye, ear, nose, and lip.[71-73] Tissue is excised and examined intraoperatively as frozen section to confirm clear margins and limit unnecessary further resection.[71,72] The systematic review of Lansbury et al[74] reports pooled estimate of local recurrence during variable follow-up periods after MMS from 10 studies was 3.0% (2.2 to 3.9%), which was nonsignificantly lower than the pooled average local recurrence of 5.4% (2.5–9.1%) after standard surgical excision (12 studies), and 6.4% (3.0–11.0%) after external radiotherapy (7 studies).[74] When considered alongside the additional resource burden of the technique, some critics suggest little benefit is offered by MMS, with MMS procedures in the United States costing over $2 billion in 2013.[75]

Radiotherapy

Radiotherapy (RT) may be proposed as adjuvant treatment for high-risk cSCC or as a nonsurgical primary treatment in select candidates. Primary RT has been reported to offer similar cure rates to primary surgery for smaller, low-risk cSCC, but may also be considered in elderly patients or those with significant comorbidities.[76,77] Adjuvant RT is proposed for advanced primary lesions (T3, T4), in the setting of recurrence and in node-positive disease.[35,78] Radiotherapy should also be considered in the setting of incomplete excision margins or where PNI is recorded.[36] It is not clear which patient subgroups would benefit most from adjuvant RT. One

study of 217 patients with SCC lip highlighted 5-year relapse-free survival of 92%, *vs* 51% after surgery alone.[79] The evidence for adjuvant RT is not supported by randomized trials, however, but rather based on retrospective series, which is acknowledged by NCCN guidelines.[10]

Chemotherapy

No gold standard chemotherapeutic regimen exists for advanced cSCC, due to the typically limited response of available agents.[80,81] Relatively nonselective, platinum-based therapies, most commonly with cisplatin with or without 5-fluorouracil, remain the most common chemotherapeutic treatment.[80] Adjuvant systemic treatment in the form of chemotherapy is typically offered where cSCC lesions have metastasized or have advanced locally beyond a point where surgical resection is possible. Experimental trial of cisplatin in combination with bleomycin and 5-fluorouracil to produce tumor regression permitting surgery has been reported in 11 patients.[82] Results from randomized trials comparing chemotherapy *vs* adjuvant RT alone in high-risk cSCC are awaited. Further prospective clinical trials are also required to clarify the role of chemotherapy in high-risk cSCC.

Novel Treatments

A number of novel treatments in the setting of cutaneous malignancy, including cSCC, have emerged in recent years. Electronic brachytherapy (EBT) allows application of a localized radiation dose through an electrically generated X-ray source on the skin surface.[83] By allowing for a reduced dosage scatter and small penumbra, EBT can deliver a relatively high dose of treatment in a 2 to 3 minutes period.[83,84] Bhatnagar et al[85] reported their experience of 171 nonmelanoma skin lesions, including 70 SCCs, treated with 40 Gy dosage (5 Gy twice a week), with 100% control at 1-year follow-up.[85] Limitations of the treatment include its complications, such as rash dermatitis, pruritus, hypopigmentation, and others, as well as limitations in its use for patients with collagen vascular disease, uncontrolled diabetes mellitus, and certain other conditions.[85]

Targeted therapies and forms of immunotherapy utilize the overexpression of epidermal growth factor receptor (EGFR) in the setting of cSCC to disrupt cell proliferation.[86-88] These novel treatments, which include monoclonal antibodies, such as cetuximab, can offer an overall disease control rate of 69%, as seen in a phase II trial using cetuximab in the setting of metastatic cSCC.[88] A further stage III randomized trial adding cetuximab to cisplatin significantly improved treatment response when compared with placebo (26.3 *vs* 9.8%; p=0.29).[89] The promising human immunoglobulin G-2 monoclonal antibody against EGFR, panitumumab, demonstrated a 31% response rate in a phase II study of 16 patients with recurrent or metastatic SCC.[90] In a larger phase III with 51 patients, however, only a 4% response was recorded. To date, only cetuximab has been granted FDA approval.

The use of immunotherapies, such as programmed cell death protein 1 inhibitors (e.g., nivolumab and pembrolizumab) and the cytolytic T-lymphocyte-associated antigen 4 inhibitors (e.g., ipilimumab), has also been investigated.[91-93] Early data from the use of these treatments in other malignancies, such as melanoma and SCC of the head and neck suggest that potential response may be seen in cSCC in future.[94]

CONCLUSION

A high-risk cSCC is a tumor with additional cytological, histopathological, and clinical implications which portend to a worse prognosis. Cutaneous SCC remains a common condition, with an increasing incidence, which is curable if detected and treated at an early stage. Surgical excision with adequate margins, either with MMS or conventional wide radial excision, remains the mainstay of treatment. Controversy exists regarding the role of SLNB, prophylactic parotidectomy, and elective neck dissection in the treatment algorithm. Consensus regarding definitions of high-risk features of cSCC may help guide clinicians in their decision-making and allow clearer prognostic information to be delivered to the patient. Novel therapies, including EBT, immunotherapy, and targeted therapies, may offer an alternative to adjuvant RT and traditional platinum-based chemotherapy where used. It is essential that all clinicians dealing with cSCC have an understanding of the high-risk features. Significant further large, prospective clinical trials will facilitate better understanding of this varied pathology.

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