

Advances in the management of cutaneous squamous cell carcinoma

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F1000Prime Reports 2014, 6:70 (doi:10.12703/P6-70)

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Abstract

Cutaneous squamous cell carcinoma is one of the most common non-melanoma skin cancers worldwide. While most cutaneous squamous cell carcinomas are easily managed, there is a high-risk subset of tumors that can cause severe morbidity and mortality. Tumor characteristics as well as patient characteristics contribute to the classification of cutaneous squamous cell carcinomas as low-risk vs. high-risk. Advances in the treatment of cutaneous squamous cell carcinomas largely relate to the management of this high-risk subset. Surgical and non-surgical management options, including newer targeted molecular therapies, will be discussed here. Larger, multicenter studies are needed to determine the exact significance of individual risk factors with respect to aggressive clinical behavior and the risks of metastasis and death, as well as the role of surgical and adjuvant therapies in patients with high-risk cutaneous squamous cell carcinomas.

Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most common non-melanoma skin cancer (NMSC) worldwide. While most of these lesions can be successfully managed with excision, there is a subset of lesions that metastasize, leading to severe morbidity and mortality. While small, the number of cSCCs that metastasize has been compared to the metastatic rate of renal and oropharyngeal carcinomas, as well as melanoma [1]. Given the relative ease of treating most cSCCs, most advances in treatment and the focus of our review relate to the management of the small but serious subset of high-risk cSCCs with metastatic potential.

Identification of high-risk cSCC

Given the variability of cSCC behavior, early identification of those cSCCs that are high-risk for recurrence and metastasis is important, so that appropriate management can be initiated. Significant literature has attempted to characterize high-risk features and their correlation with poor outcomes, but no consensus exists regarding how to define high-risk cSCC. The National Comprehensive

Cancer Network (NCCN) and the American Joint Committee on Cancer (AJCC) have distinct criteria to determine whether a lesion is high-risk, but no data supporting one definition over the other have been validated. As a result, classification of high-risk cancers is essentially up to the discretion of the clinician, taking into consideration the patient, the history, and the characteristics of the lesion. Factors that suggest that a lesion is more likely to demonstrate high-risk clinical behavior are discussed below.

Tumor factors

Multiple outcome studies have demonstrated that cSCCs with the following characteristics have a greater risk of metastasis: tumor recurrence, diameter greater than or equal to 2 cm, location on the ear, vermilion lip, "mask areas" of the face, hands, feet, genitalia or in embryonic fusion planes, thickness greater than 2 mm, poorly differentiated histology, or invasion of the subcutaneous tissue or structures such as perineural, vascular, or lymphatic tissue [1-6]. Recent evidence has shown that specifically named nerve involvement or involvement of

nerves greater than 0.1 mm in diameter is specifically associated with a poor prognosis [3].

Host factors

Immunosuppression

It is well documented that immunosuppressed patients are at greater risk of developing cSCC than the general population. While cSCCs make up 20% and basal cell carcinomas make up 80% of NMSCs in immunocompetent patients, the statistics are reversed in the immunosuppressed population [7]. Patients who have undergone solid organ transplantation have a 65 to 250-fold increased incidence of developing cSCC [8-10], and that risk positively correlates with higher doses of immunosuppression. These cancers are more aggressive, with an increased risk of local and distant metastases [11]. Recurrence and mortality rates are also higher in patients who are immunosuppressed (5%) than those who are immunocompetent (1%) [12,13]. Heart transplant recipients are at the highest risk of developing aggressive or metastatic cSCC followed by renal, lung, and liver recipients [12]. Patients who suffer from hematologic malignancies and myelodysplastic syndromes are also at greater risk for developing cSCC, with chronic lymphocytic leukemia and small lymphocytic lymphoma associated with the highest risk [12,14,15]. Lastly, patients with autoimmune or chronic inflammatory disorders, such as inflammatory bowel disease and rheumatoid arthritis (on chronic immunosuppressants), as well as patients with HIV, are at greater risk of cSCC development [16-19].

Chronic wounds

In addition to chronically immunosuppressed patients, patients with a history of UV light or radiation therapy or those who suffer from chronic skin injuries, such as wounds, ulcers, or burns, are at increased risk of developing aggressive or metastatic cSCC [12, 20-23]. Included in this category are patients with a genetic predisposition to skin injury, many of whom suffer from genodermatoses, including epidermolysis bullosa, xeroderma pigmentosum, epidermodysplasia verruciformis, oculocutaneous albinism, and congenital dyskeratosis [12,24].

We classify tumors as high-risk when they possess at least two or three high-risk features on initial evaluation. We also recommend defining a more specific category of very high-risk cSCC for tumors that demonstrate lymphovascular, perineural, periorbital, parotid, cartilaginous or bony invasion, or if they develop in-transit, regional, or distant metastasis [25].

Work up

Staging is the most critical step when determining the best way to treat high-risk cSCC. While the AJCC and the

International Union Against Cancer (UICC) have created staging systems based on expert consensus, neither one accurately determines prognosis. Validation and comparative studies of the AJCC and UICC staging systems executed by a group at Brigham and Women’s Hospital (BWH) found that the bulk of poor outcomes (i.e. nodal metastasis, disease-specific death) occurred in the AJCC T2 tumors and that the T3 and T4 stages of the two systems were indistinct [4,26]. The group proposed an alternative staging system that divided the AJCC T2 stage into two groups (T2a and T2b) based on risk (Table 1) and were able to show that 72% of nodal metastases and 83% of disease-specific deaths occurred in the T2b group. This alternative system, though not yet widely accepted and an area of developing knowledge, appears to more accurately correlate prognosis with staging as it relates to four risk factors, each of which is an independent prognostic predictor. These high-risk factors include diameter greater than or equal to 2 cm, tumor invasion beyond fat, perineural invasion greater than or equal to 0.1 mm, and poorly differentiated histology [4]. A study comparing the three staging systems demonstrated that the alternative staging system provides improved distinctiveness, homogeneity, and monotonicity compared to the AJCC and UICC staging systems [4].

CSCC has an estimated 3.7–5.4% risk of nodal metastasis and an estimated disease-specific death rate of 1.5–2.1% [4]. Of those cSCCs that metastasize, 80% involve regional lymph nodes [5,25,27]. CSCCs can also metastasize to distant sites including the lungs, liver, brain, bones, and other cutaneous locations [27,28]. The risk factors most often associated with metastasis include perineural invasion, recurrence after treatment, size greater than 2 cm, and poorly differentiated histology [6,29].

Table 1. Brigham and women’s hospital alternative staging system [4]

Stage	Criteria
T1	0 high-risk factors
T2a	1 high-risk factor
T2b	2-3 high-risk factors
T3	≥4 high-risk factors OR bone invasion

High-risk factors:

- Tumor diameter ≥2 cm
- Poorly differentiated histology
- Perineural invasion ≥0.1 mm
- Tumor invasion beyond fat (excludes bone invasion)

Radiologic imaging

The role of radiologic imaging has not been established in the diagnosis or staging of cSCC. However, if involvement of lymph nodes is not clinically evident (but highly

suspected) in lesions that possess features of very high-risk cSCC, radiologic imaging modalities [including ultrasound, computerised tomography (CT) scan, magnetic resonance imaging (MRI), and positron emission tomography (PET)/CT] may be considered in order to confirm negative lymph nodes and assist in preoperative planning [30,31]. A recent survey of surgeons using Mohs micrographic surgery (MMS) demonstrated that perineural invasion and in-transit metastasis were top factors in the consideration of obtaining nodal imaging [32]. In the few studies of imaging in cSCC that exist, the sensitivities and specificities of different imaging modalities are variable [30]. Of the surgeons that participated in the study, 54% preferred CT scan, 36% MRI, and 15% PET scan to evaluate their patients with high risk cSCC [31,32].

Role of nodal biopsy

Given that an estimated 80% of metastatic cSCCs involve lymph nodes, examining sentinel lymph nodes for early detection of metastasis in the hopes of reducing disease-related morbidity and mortality could be beneficial. A recent study to evaluate which stages of the AJCC and BWH alternative staging systems were associated with positive sentinel lymph node biopsy (SLNB) findings in non-anogenital cSCC found that positive SNLBs were more likely in T2 lesions of both staging systems, with a greater risk in lesions larger than 2 cm [27]. However, the rate of positive SNLB was statistically higher in T2b lesions than T2a lesions of the BWH system, suggesting that the BWH system appears more precise in delineating which high-risk lesions would warrant SNLB [27]. Other studies have shown excellent negative predictive values for SLNB for cSCCs ranging from 95.2 to 100% and suggest that SLNB may be of value to rule out nodal metastases [33]. Research continues to be conducted in order to validate the routine use of SLNB in cSCC but very high-risk patients may benefit from undergoing this procedure.

Management

Surgical options

Excisional surgery

Surgical excision is often the treatment of choice for cSCC, as it is an outpatient procedure, has shorter healing times, allows for histologic examination of tissue, and offers cure rates as high as 95% for selected primary cSCC [34]. Typically, a margin of normal skin is removed at the time of tumor removal, which varies depending on the severity of the lesion, with a recommended 4-6 mm margin of normal skin for low-risk cSCC and 6-10 mm for high-risk cSCC [6,35,36]. Excised tissue specimens should be sent to a pathologist for careful margin examination to ensure complete tumor removal. Clear data are lacking regarding the appropriate margins of normal skin to remove for tumors with multiple high-risk features.

National guidelines require a minimum 10 mm margin of normal skin. We recommend considering wider margins of at least 15 mm for lesions with multiple high-risk characteristics or that are considered very high-risk, to ensure complete tumor clearance. Margins this wide, of course, are only feasible for limited areas of the body that have enough tissue laxity to accommodate such large defects. As a result, high-risk tumors should be treated by MMS instead of standard surgical excision to allow for confirmed removal of tumor without the need for prophylactically wide margins of normal skin.

Mohs micrographic surgery

MMS is a surgical technique that provides detailed microscopic visualization of the tissue removed for accurate identification of positive tumor margins, to provide a greater guarantee of complete tumor clearance. As surgical excision with negative margins is associated with significantly lower recurrence rates than those with unknown or positive margins, MMS is the gold standard for the surgical removal of high-risk cSCC [37,38]. MMS offers cure rates of 97% for primary cSCC and 94% for recurrent cSCCs [21,37]. Recent studies have shown that MMS is highly effective in treating high-risk cSCCs and preventing local recurrence [39,40]. Extensive tumors may warrant a multidisciplinary team to achieve complete clearance in the event of bony invasion, tracking along major nerves, parotid gland involvement, or in-transit metastasis.

Nonsurgical options

Radiation therapy

Given its non-invasive nature, radiation therapy has been used as a non-surgical primary treatment option for high-risk cSCC. It has a wide range of cure rates, with lower rates for aggressive cSCC types (Table 2). Radiation therapy has demonstrated outcomes comparable to surgery for tumors on the lip and eyelid [41,42]. It necessitates an intensive treatment schedule involving weeks of commitment and does not allow for histologic confirmation of tumor margins. Additionally, there are side effects of radiation therapy that some patients may not tolerate, including malaise, nausea, induced erythema, telangiectasia, or hypopigmentation, epidermal atrophy, soft-tissue necrosis, and radiation-induced malignancy [43]. Therefore, radiation therapy is probably best suited for patients

Table 2. Cure rates of cSCC with radiation therapy [45,66-69]

Tumor characteristic	Cure rate with radiation therapy
Size <1.0 cm low-risk, non-aggressive	97.8%
Size 1.0-3.0 cm	80-90%
Incidental perineural invasion	80%
> 3.0 cm or recurrent tumors	50-88%
Locally advanced	55%

who are poor surgical candidates, who have tumors in locations that are inoperable, or whose reconstruction would cause cosmetic or functional drawbacks [43]. Otherwise, radiation therapy alone is used most frequently as salvage or palliative therapy in tumors that have failed to respond to other treatment options [44].

Adjuvant therapy options

Adjuvant treatment in the management of high-risk cSCC is advisable given the risk of recurrence, metastasis, and disease-specific death associated with it. While there are multiple possible options for therapy adjuvant to surgery, there is minimal consensus regarding the best perioperative management of high-risk cSCC [32].

Adjuvant radiation therapy

Adjuvant radiation therapy is used in areas with an increased likelihood of residual disease. Postoperative radiation therapy is typically indicated when tumor margins are positive, when there are multiple recurrences, and when there is perineural invasion, or involvement of the bones or nerves [45]. However, there is little consensus regarding which patients benefit from adjuvant radiation therapy, as the data available are limited [32]. We agree with the NCCN recommendations that adjuvant radiation therapy should be considered for patients with symptomatic perineural invasion of large-caliber nerves [6]. We also recommend adjuvant radiation for patients with uncertain tumor clearance or bone involvement.

Targeted molecular therapies

Increased expression of epidermal growth factor receptor (EGFR) in cSCC has been repeatedly noted to exert significant effects upon cellular proliferation, progression, and survival [46,47]. As a result, therapies aimed at inhibiting EGFR have been studied. These therapies consist of monoclonal antibodies such as cetuximab and panitumumab, or small molecule tyrosine kinase inhibitors such as erlotinib and gefitinib [48]. Cetuximab is a monoclonal antibody that binds to the extracellular component of the receptor, blocking EGFR and downstream signaling pathways that lead to cell proliferation and survival. The US Food and Drug Administration (FDA) approved cetuximab for treatment of head and neck SCC in 2006 [7]. Cetuximab has since been used in the treatment of advanced cSCC in an off-label fashion. There have been few clinical trials determining the role of cetuximab in cSCC treatment. One phase II prospective clinical trial examining 31 patients with surgically unresectable or metastatic cSCC showed that cetuximab was beneficial, with a 69% disease control rate and 28% response rate [49]. A study looking at cetuximab in an adjuvant role with surgery demonstrated improved outcomes in patients with very high-risk cSCC [25]. Patients who develop an acne-like

rash with cetuximab treatment have better therapeutic responses with sustained progression-free survival [49]. Few case reports exist in the literature suggesting a positive role of panitumumab in cSCC [48,50]. A phase I study of erlotinib used with radiation therapy in patients with advanced cSCC was also conducted and suggested positive results [51].

Very recent studies have also looked at the role of S100 proteins A8 and A9 in cSCC, suggesting a possible therapeutic role for these proteins normally found in neutrophils, monocytes, and macrophages [52]. Further, larger studies using these molecular therapies are required in order to establish a definitive role in the treatment of cSCC.

Chemotherapy

Chemotherapy is typically used in locally advanced or metastatic cSCC. Multiple chemotherapy agents have been used, including methotrexate, bleomycin, doxorubicin, and cisplatin, alone or in combination with 5-fluorouracil [53]. While there are no reports of the benefit of using chemotherapy as an adjuvant to surgery, chemoprophylaxis for the prevention of new cSCC with retinoids and capecitabine is useful, as discussed below.

Special considerations in the management of high-risk patients

Field cancerization therapy

Field cancerization in skin refers to a bed of genetically altered tissue secondary to carcinogenic insults, within which malignancies may be scattered [54]. In other words, a carcinogenic insult affects a large surface area, creating a bed of actinically damaged skin in which tumors may be present or develop. In these circumstances, surgeons must be careful to excise only biopsy-proven cancerous lesions to avoid removing excess tissue. Once these have been addressed, attention must also be directed at treating the larger surface of actinically-damaged skin.

Multiple modalities exist to address actinically damaged skin in patients with field cancerization. Medications including 5-fluorouracil 5%, imiquimod 5%, diclofenac 3%, chemical peels, and ingenol mebutate are effective at treating large areas of actinic damage with only topical applications [55]. Photodynamic therapy, a modality that utilizes a photosensitizer such as methyl aminolevulinic acid (MAL) or aminolevulinic acid (ALA), a light source, and reactive oxygen species, has been used to treat and prevent actinic damage as well. Multiple studies have demonstrated the utility of photodynamic therapy in field cancerization [56]. We recommend using photodynamic therapy in conjunction with topical regimens in order to maximize clearance. We recommend two cycles

of photodynamic therapy two weeks apart followed by a 6 to 8 week holiday. Photodynamic therapy every 4 to 8 weeks has also been demonstrated as an effective preventive measure in patients with field cancerization who are immunosuppressed [57].

Oral therapies with retinoids and capecitabine have also been used for field cancerization therapy. Oral retinoids have been shown to reduce the incidence and burden of actinic keratosis and cSCC [58,59]. Although there are no guidelines, experts recommend the use of oral retinoids for chemoprevention in patients with innumerable actinic keratoses, numerous (5-10) NMSCs yearly, NMSCs that develop at an accelerated frequency, multiple NMSCs in high-risk areas, eruptive keratoacanthomas, and high-risk or metastatic NMSC [60]. While both isotretinoin and acitretin are effective chemopreventive agents, we recommend acitretin due to its lower cost, ease of prescribing, and literature support of its use in high-risk and organ transplant patients [58]. Patients who are prescribed oral retinoids should receive baseline evaluations of complete blood counts, basic metabolic and lipid panels as well as liver function tests, with monthly follow-up of mucocutaneous side effects, liver function tests, creatinine levels, and a lipid panel [60].

Capecitabine, an oral precursor of 5-fluorouracil, has been used as chemoprophylaxis in patients with diffuse field cancerization, though it is recommended for use only after patients have failed to respond to oral retinoids, given its more significant adverse event profile [61-63]. A study involving organ transplant patients demonstrated that capecitabine was associated with a 0.33 and 2.45 decrease in event occurrence rates of cSCC and actinic keratosis per month, respectively [64]. Before initiating treatment, patients should be evaluated for any dihydropyrimidine dehydrogenase deficiencies, as the enzyme plays a critical role in 5-fluorouracil metabolism [65].

Follow up

The NCCN recommendations for follow up of patients with high-risk cSCC are detailed in Table 3. Patients with high-risk cSCC have a greater risk of developing recurrence, lymph node or distant metastasis, or another high-risk tumor [28]. Of the lesions at risk, 70-80% will locally recur or metastasize within the first 2 years and 95% within the first 5 years of the initial cSCC diagnosis [21]. Between 30 and 50% of patients will develop a second skin cancer within 5 years [53]. Thus, close follow up is critical. A multidisciplinary team approach involving cutaneous, medical and radiation oncologists, Mohs and oncologic surgeons, and dermatopathologists should be considered for very high-risk patients to optimize follow up and disease-free survival.

Table 3. The National Comprehensive Cancer Network (NCCN) recommendations for patient follow up [6]

Patient	Follow up
High-risk cSCC	<ul style="list-style-type: none"> • Full skin exam and lymph node exam every 3-6 months for first 2 years • Every 6-12 months for next 3 years • Annually after 5 years
High-risk cSCC with regional disease	<ul style="list-style-type: none"> • Full skin exam and lymph node exam every 1-3 months for first year • Every 2-4 months for the next year • Every 4-6 months until the fifth year • Every 6-12 months for patient's lifetime

Conclusion

Management of high-risk cSCC is complex, and a multi-disciplinary approach is often required for this serious problem. Lack of large outcome studies assessing risk factors have left significant holes in the stratification and prognosis of disease, thus leading to inconsistent definitions and treatment recommendations. Precise tumor staging and clear risk stratification are needed for effective management of patients with cSCC. We have attempted to present a comprehensive and current expert opinion on high-risk cSCC management options. There is an as yet unmet need for larger, longitudinal multicenter studies to best determine the role of each risk factor, the risks of metastasis and death, and the effectiveness of surgical treatment and adjuvant therapies in patients with high-risk cSCC.

Abbreviations

AJCC, American Joint Committee on Cancer; BWH, Brigham and Women's Hospital; cSCC, cutaneous squamous cell carcinoma; CT, computerised tomography; EGFR, epidermal growth factor receptor; MRI, magnetic resonance imaging; MMS, Mohs micrographic surgery; NCCN, National Comprehensive Cancer Network; NMSC, non-melanoma skin cancer; PET, positron emission tomography; SNLB, sentinel lymph node biopsy; UICC, International Union Against Cancer.











Disclosures

The authors declare that they have no disclosures.

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