

Review Article

High-Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck

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Nonmelanoma skin cancers (squamous cell and basal cell carcinomas) occur at an epidemic rate in many countries with the worldwide incidence increasing. The sun-exposed head and neck are the most frequent sites for these cancers to arise and in most patients diagnosed with a cutaneous squamous cell carcinoma, local treatment is usually curative. However, a subset is diagnosed with a high-risk cutaneous squamous cell carcinoma. High-risk factors include size (> 2 cm), thickness/depth of invasion (> 4 mm), recurrent lesions, the presence of perineural invasion, location near the parotid gland, and immunosuppression. These patients have a higher risk (> 10–20%) of developing metastases to regional lymph nodes (often parotid nodes), and in some cases also of experiencing local morbidity (perineural invasion), based on unfavourable primary lesion and patient factors. Despite treatment, many patients developing metastatic cutaneous squamous cell carcinoma experience mortality and morbidity usually as a consequence of uncontrolled metastatic nodal disease. It is therefore important that clinicians treating nonmelanoma skin cancers have an understanding and awareness of these high-risk patients. The aim of this article is to discuss the factors that define a high-risk patient and to present some of the issues pertinent to their management.

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1. INTRODUCTION

Nonmelanoma skin cancers (NMSC) are a major public health concern in Australia [1] and around the world and although most patients are cured, a minority will die of cutaneous SCC (cSCC), usually in the setting of metastases to regional lymph nodes of the head and neck (HN) [2]. Most lesions (80–90%) develop on the sun-exposed HN in older Caucasian males with the overall incidence of patients with a cSCC developing metastases to regional lymph nodes reported as low (<5%) [3].

The majority of patients treated in the community with a small (<2 cm), thin (<4 mm), and previously untreated cSCC will not develop nodal metastases and can be classified as low-risk. However, the incidence of nodal metastases in patients referred to a tertiary referral hospital is often much higher (10–20%) secondary to patients having high-risk factors [4–6]. Patients with high-risk cSCC have a higher risk of developing metastases to regional lymph nodes based on both unfavorable primary lesion and also patient factors (Table 1).

The definition of a patient with a high-risk cSCC is often underappreciated by clinicians and is not well documented

in the literature. The current TNM (tumor, node, metastases) staging system for cSCC does not incorporate important prognostic factors (discussed below) such as thickness/depth of invasion when assigning T stage [7]. Size alone (e.g., T1 ≤ 2 cm) is the main criterion used. With emerging data on high-risk cSCC and the risk associated with other factors there is a need to investigate an improved and more prognostic staging system. Similarly, pathology reports often lack important data such as thickness/depth of invasion, grade or the presence of perineural and lymphovascular invasion. As well, factors such as lesion location and the patient's immune state are also important to note. In a recent comprehensive review Cassarino et al. [6] attempted to classify histological subtypes of cSCC based on the metastatic potential they exhibit. High-risk (>10% risk) subtypes included de novo cSCC and cSCC arising in association with predisposing factors (e.g., immunosuppression, burn scars).

Despite some limitations, patients with high risk cSCC can be identified and clinicians should be aware so that appropriate management can be recommended. The aim of this article is to discuss those factors that make a patient diagnosed with a cSCC at higher risk of developing metastases.

TABLE 1: High-risk factors (patients often have multiple high-risk factors present).

	Factor
(1)	Large size (>2 cm).
(2)	Thick or deeply invasive lesion (>4 mm).
(3)	Incomplete excision (<4 mm).
(4)	Recurrent setting.
(5)	High-grade or desmoplastic lesion.
(6)	Presence of perineural invasion.
(7)	Presence of lymphovascular invasion.
(8)	Located near the parotid gland (ear, temple, forehead, ant. scalp).
(9)	Immunosuppressed state (e.g., transplant recipient).

2. LESION SIZE

Lesion size is reported as an important predictor for developing nodal metastases. However size alone is probably a weak independent predictor although many studies report a threshold size of approximately 2 cm beyond which patients have an increasing propensity to metastases to nodes. In a series of 200 patients with cSCC, 12.5% developed metastatic cSCC with the authors reporting a significant difference in the rate of nodal metastases from various primary sites of the HN using a 2 cm threshold size (13% versus 68%; $P = .004$) [4]. In a large review Rowe et al. [8] reported the incidence of metastases was 30% for cSCC >2 cm versus 9% for cSCC <2 cm. Mullen et al. [9] identified tumor size >2 cm as an independent predictor on univariate analysis for recurrence or death, although size did not remain a significant predictor on multivariate analysis. In a study of patients with metastatic cSCC to HN nodes, the authors compared the data to nonmetastatic historical controls and found a difference in the number of patients with cSCC >2 cm (19% non-metastatic versus 81% metastatic) [10]. Moore et al. [5] reported median lesion size as highly significant (3 cm versus 2 cm; $P = .0002$) in a study of 40 patients with metastatic cSCC when compared to 153 cSCC patients without metastases. Veness et al. [11] reported median size of cSCC of only 1.5 cm with only 30% of patients having a cSCC >2 cm in a large study of 266 patients with metastatic nodal cSCC of the HN. This latter study would suggest that other factors (i.e., tumor thickness, site, etc.) are also likely to contribute to the risk of developing metastases. Of note, 20–30% of patients may not have an identifiable nearby high-risk index lesion in the setting of nodal metastases. However, most patients invariably will have had a past history of NMSC treated in the HN.

3. THICKNESS/DEPTH OF INVASION

Thickness (or depth of invasion) is an important predictor of metastases. Depth of invasion >4 mm is associated with an increasing risk. In a study of patients with lower lip SCC, there was a significant difference in mean depth of invasion in node negative patients compared with those developing

nodal metastases (4.2 mm versus 11.2 mm; $P < .001$) [12]. In another study of patients with metastatic cSCC of the HN only 17% with a lesion <4 mm metastasised compared with 83% with lesions >4 mm [9].

Patients with lesions <4 mm thick have a low incidence of nodal metastases. A large study of 550 patients with 594 cSCC (including 149 lip SCC) documented a 4% rate of nodal metastases with only 7 patients (2.9%) with a tumour ≤ 5 mm thick developing metastases compared with 14 (17.5%) patients with a tumour >5 mm thick. Of note, no patient with a superficial cSCC (<2 mm thick) developed metastases [13].

Clark levels are also prognostic with one study reporting patients with metastatic cSCC significantly ($P = .0001$) more likely to have cSCC invading beyond Clark level III compared to those without metastases [4]. In a large review of prognostic factors in patients with cSCC, those with a tumor <4 mm or Clark levels I–III had a metastatic rate of 6.7% compared to 45.7% in those with a tumor >4 mm or Clark level IV–V [8].

4. INCOMPLETE EXCISION/RECURRENCE

Up to 50% of patients with a positive margin with a cSCC will locally recur with a subsequent increased risk of developing nodal metastases [14]. In a study of patients with lip SCC, those with recurrent lip SCC experienced a significant difference in nodal metastases compared with those not developing local recurrence (15% versus 2%; $P < .0001$) [15]. In a large review of the literature, patients experienced a 32% and 45% incidence of nodal metastases in the setting of recurrent lip SCC and ear SCC, respectively [8].

There is no consensus in regards to the definition of an acceptable surgical margin in cSCC. In a series of patients undergoing intraoperative frozen section analysis to achieve a minimum of a 3 mm surgical margin, only 3% recurred with a median follow up of 5.1 years [16]. Another study of patients with cSCC <2 cm in diameter found that with a 4 mm excision margin 95% had negative excision margins. With lesions >2 cm a 6 mm margin would achieve a 95% rate of negative excision margins [17]. The authors subsequently recommended 6 mm margins with high-grade tumours or those located in high-risk areas. In concordance with these findings in another study of 150 excised NMSC (25% cSCC) a 4 mm surgical margin resulted in clearance in 97% of cases compared with a 2 mm excision margin achieving this in only 78% of cases [18]. In one study of metastatic cSCC to HN nodes 51% of patients developing nodal metastases had a recurrent primary lesion [19]. Therefore a recommendation of observation in patients with an inadequately excised cSCC (<4 mm) must be considered very carefully in light of the increased risk of metastatic nodal disease in the recurrent setting. Further surgery or adjuvant radiotherapy should be recommended.

5. DIFFERENTIATION

Poorly differentiated cSCC are more likely to be associated with the development of regional metastases. In a study of

571 patients with cSCC, there was a significant difference in the rate of metastases for high-grade lesions compared to other grades (17% versus 4%; $P = .004$) [20]. The incidence of poorly differentiated lesions in one series of patients with metastatic cSCC was significantly increased in patients developing metastases (44% versus 5%; $P < .01$) [4]. There are also data that desmoplastic SCC, an aggressive histological variant of SCC, possesses a high propensity to regional metastases especially with increasing tumor thickness. Using Broder's classification, over a quarter of patients (27%) in one study with a desmoplastic SCC were assigned as grade IV differentiation compared to only 11% with a nondesmoplastic cSCC [13].

6. PERINEURAL INVASION

Perineural invasion (PNI) occurs in ~5% of patients with cSCC and is usually an incidental finding but is reported to be associated with a higher incidence of nodal metastases compared to patients without PNI. In a large study from MD Anderson, Texas, there was a significant increase in both regional (35% versus 15%; $P < .0005$) and distant metastases (15% versus 3.3%; $P < .0005$) for patients diagnosed with PNI compared to those without [20]. In a large study of 135 patients with PNI and treated with radiotherapy +/- surgery, half of all failures in patients with microscopic PNI were in regional nodes, prompting the authors to recommend elective nodal treatment in patients with PNI [21]. A study comparing prognostic features of patients with metastatic and nonmetastatic lip SCC also reported a highly significant difference in the presence of PNI (41% versus 5%; $P < .0001$) [22].

It should also be noted that PNI may also lead to significant morbidity and mortality from the involvement of cranial nerves (usually facial or trigeminal) leading to skull base/intracranial spread. The optimal treatment of patients with PNI remains unclear although wide field radiotherapy is an important modality in many patients. Patients diagnosed even with focal PNI, especially if located in the peri-orbital region, should be recommended appropriate treatment. The finding of PNI away from the actual tumor mass, and often extending to excision margins, indicates progressive perineural spread and a need for further treatment. Recent data from the University of Florida suggests patients with asymptomatic microscopic (incidental) PNI have a significantly better outcome compared to patients presenting with clinically or radiologically positive PNI (local control at 5 years 87% versus 55%; $P = .0006$) [21, 23].

7. SITE

Patients with cSCC located within the lymphatic drainage of the parotid gland (on or around the external ear, temple, forehead, anterior scalp) or lower lip are associated with a higher incidence of metastases. The scalp is often a site for high-risk cSCC and, in particular, patients can develop satellite or in-transit metastases which carry a poor prognosis [24]. Most patients developing metastatic nodal cSCC of the HN do so to the parotid and/or upper cervical

nodes [24, 25]. There are advocates of elective nodal dissection in select high-risk patients with lesions located on the ear/preauricular region [26, 27] and lip [28]. Accurately predicting patients that may develop nodal relapse is difficult, however, clinicians should consider patients with recurrent SCC that are >4 mm thick and in the vicinity of the parotid gland (ear, lateral scalp, forehead, temple, cheek) at higher risk of developing parotid nodal metastases. It is these patients that should be considered as candidates for the elective treatment of parotid nodes. Depending on the type of treatment to the primary cutaneous lesion, elective nodal treatment may entail either a superficial parotidectomy, or alternatively, radiotherapy to the parotid gland.

8. IMMUNOSUPPRESSION

Immunosuppression, particularly in the setting of an organ transplantation recipient (OTR), often leads to significant morbidity from NMSC, usually cSCC. A subset of cSCC in OTR is aggressive in nature with rapid growth and the development of regional and distant metastases. In an Australian study of 619 cardiothoracic transplant recipients, 26 developed an aggressive NMSC with most diagnosed with a poorly differentiated cSCC [29]. Death occurred in 13 of the 26 with 10 patients dying from systemic disease. Martinez et al. [30] reported the outcome of 60 OTR all with metastatic skin cancer (85% cSCC) noting that 27% of patients had an unknown index lesion. In this study median primary lesion size was 12 mm and median depth of invasion was 3.2 mm. Three-year disease specific survival was only 56%. This would suggest a smaller lesion size and lesser depth of invasion associated with the development of metastatic cSCC and a significantly worse outcome compared with immunocompetent (IC) patients. In another study comparing IC and OTR patients a significant proportion of OTR had thick (>5 mm) tumors and exhibited early dermal invasion compared with IC patients [31]. Of note, patients immunosuppressed as a consequence of chronic lymphocytic leukemia (CLL) also have a similar increased risk of cutaneous SCC and poor outcome from developing metastases [32]. In many cases, the level of immunosuppression cannot be markedly reduced. The basic tenets of obtaining adequate surgical margins and examining for PNI are especially applicable to this group of patients. Adjuvant radiotherapy to incompletely excised cSCC, or those with PNI, should be strongly considered. Close liaison with a transplant physician is also important.

9. LYMPHOVASCULAR INVASION

Recent evidence suggests that the presence of lymphovascular invasion may increase the risk of developing nodal metastases. Moore et al. [5] documented lymphovascular invasion as an independent predictor of nodal metastases on multivariate analysis (OR 7.54; $P < .00001$). In this study 40% of patients with nodal metastases had lymphovascular invasion compared with only 8% of node negative patients. Other studies of high-risk cSCC also report the presence of lymphovascular invasion although fail to find any significant impact on outcome [2-4].

TABLE 2: Indications for radiotherapy in high-risk cutaneous squamous cell carcinoma. DXR: deep energy photons (orthovoltage); Gy: Gray; RTx: radiotherapy; SXR: superficial energy electrons; Sx: surgery; #: daily fraction of radiotherapy; ¶: surgery would compromise function and/or cosmesis.

Setting	Indication	Dose/fractionation/technique
Adjuvant local RTx	Inadequate excision and re-excision not possible [¶]	50–55 Gy in 20–25#s using SXR/DXR or low-energy electrons with bolus and 1.5–2 cm margins
Adjuvant nodal RTx (post node dissection)	Multiple metastatic nodes and/or extranodal spread	55–60 Gy in 25–30#s using megavoltage photons
Elective nodal RTx (elective Sx also an option)	Multiple high-risk features and proximity to parotid gland	50 Gy in 25#s using moderate-energy electrons or megavoltage photons
RTx to neural pathway (include brainstem in select patients)	Perineural invasion in high-risk location (e.g., periorbit or parotid gland)	50–55 Gy in 25–30#s using multifield megavoltage photons (hyperfractionation may be considered)
Dermal metastases (usually scalp-based)	All patients: definitive or adjuvant RTx	55–60 Gy in 25–30#s using a wide field technique (4–5 cm margins) (consider whole scalp RTx in some patients)

The consequences of cSCC in dermal lymphatic vessels, which is uncommonly reported, is unclear but may increase a patient's risk of relapse and may explain the phenomenon of in-transit metastases [33]. Patients that develop in-transit metastases are best treated with wide field high-dose radiotherapy encompassing the sites of gross disease plus generous 4–5 cm margins to treat potential subclinical dermal lymphatic spread.

10. GUIDELINES AND RECOMMENDATIONS

The National Comprehensive Cancer Network (NCCN) has created an algorithm to aid clinicians [34]. While not entirely evidenced-based, the authors consider patients with tumors ≥ 4 mm thick, Clark level IV–V, moderate to poor differentiation, PNI present and recurrent as high-risk and recommend wide excision (10 mm margins if achievable) and adjuvant radiotherapy if warranted. No specific recommendation is made on the elective treatment of regional nodes in high-risk patients. The British Association of Dermatologists recently published guidelines for managing a patient with cSCC [35]. Patients were considered at greater risk of local recurrence and developing metastases based on six variables: site (lip, ear, non-sun-exposed sites), size (>2 cm), depth (>4 mm or Clark level V), grade (poorly differentiated), host immunosuppression (immunosuppressed), and presentation (recurrent). The guidelines did not support electively treating lymph nodes because of insufficient evidence. The American Academy of Dermatologists also recommended patients with selected recurrent cSCC and those with increased biological aggressiveness to undergo Moh's micrographic surgery [36]. No recommendation was made on electively treating lymph nodes in high-risk patients. The International Transplant-Skin Cancer Collaboration (ITSCC) recently published guidelines for man-

aging OTR with cSCC [37]. All features considered high-risk in non-OTR patients were also deemed high-risk in OTR patients although the authors considered a much lower size threshold (>0.6 cm for "mask" facial area and >1 cm for cheek, forehead, scalp). Moh's micrographic surgery was recommended or alternatively wide local excision with 6–10 mm margins.

Clinicians managing patients with high-risk cSCC need to consider multiple factors prior to recommending that further treatment with radiotherapy is an important option in many patients (Table 2). Patients will often have many high-risk factors and therefore the benefit from recommending, for example, wide field adjuvant radiotherapy, may justify the potential toxicity and cost. The evidence for many clinical settings is still emerging and further research is needed.

11. SENTINEL NODE BIOPSY

There are only limited data to guide clinicians on the role of sentinel node biopsy (SNB) in HN NMSC. In a recent large systematic review on the topic, a total of 692 patients were identified, however only 85 patients had a nonanogenital cSCC and many of these were extremity lesions [38]. Many studies have also reported on lip SCC although as previously discussed cSCC located around the parotid/upper neck carry the highest risk of developing nodal metastases. Further studies are still needed to better define the role of SNB in HN NMSC.

12. CONCLUSION

Most patients with cSCC will not develop nodal metastases and therefore IC patients with small (<2 cm), thin (<4 mm), adequately excised (>4 mm margins), and previously untreated cSCC are not candidates for further treatment. However, accurately predicting patients at high-risk

and, therefore, justifying the elective treatment of first echelon lymph nodes is difficult. Despite this, patients with more than one high-risk factor (thick/deeply invasive >4 mm, >2 cm in diameter, located near the parotid gland, especially in the recurrent setting) should be considered at risk of developing nodal metastases. In such cases, elective treatment (surgery or radiotherapy) to first echelon nodes may be of benefit and referral to a multidisciplinary head and neck cancer service is encouraged [39]. At a minimum, patients should be followed closely (2-3 months) for at least 3-4 years since late nodal relapse is well documented.

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