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# High-Risk Cutaneous Squamous Cell Carcinoma: A Review for Dermatologists on Definition, Risk Factors, Clinical Staging, and Management

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*Cutaneous squamous cell carcinoma (cSCC) is a common cutaneous malignancy with an increasing incidence that is highly treatable with excellent outcomes in most cases. The goal of this review is to arm the dermatologist with the broad clinical information needed to identify and/or appropriately treat the smaller subset of cSCCs that are high risk and contribute to disease specific morbidity and mortality. Key topics include defining high-risk Squamous cell carcinoma (SCC) risk factors, staging, lymph node assessment, and management strategies. Management of mucosal, locally advanced, and metastatic SCC are beyond the scope of this review.*

## Introduction

Squamous cell carcinoma (SCC) is the second most common cutaneous malignancy, accounting for approximately 20% of skin cancers, and its incidence continues to rise.[1,2] Fortunately, the vast majority of cutaneous SCC (cSCC) cases are associated with an excellent prognosis (>90% 5-year overall survival).[2] However, a small subset of cSCCs progress to locally advanced disease—defined as no longer readily amenable to surgery and/or radiation with curative intent—and have the potential for metastasis, causing significant morbidity and mortality.[1,2] Although cSCC accounts for approximately 20% of skin cancer deaths, given the large number of cases, the absolute number of deaths is comparable to that observed with melanoma.[3]

## Definition of High-Risk SCC

While there is no agreed upon definition, high-risk cSCCs have at least one high-risk feature (often more than one), tend to recur, and/or progress to an advanced stage of disease that includes locally advanced tumours, regional spread to lymph nodes, or metastatic disease.[3] These cases are often inoperable or difficult to treat, requiring systemic therapy.[3] Given the large number of cSCC cases each year, accurate identification of high-risk lesions is of utmost importance. Distinguishing the minority of cSCCs that are high-risk can be clinically challenging; however, timely recognition, appropriate treatment, and referral by dermatologists are essential to prevent high-risk SCC from progressing to locally advanced or metastatic disease.

## High-Risk SCC Risk Factors and Staging Systems

Multiple reported tumour characteristics, patient factors, and histologic features have been associated with high-risk SCC due to their association with poorer outcomes, including increased risks of local recurrence, spread to lymph nodes, distant metastasis, and death. The presence of more than one high-risk feature is thought to portend a worse outcome.

Several international cSCC staging systems incorporate high-risk features in their criteria, with the most widely used being the American Joint Committee on Cancer 8th edition (AJCC8) and the Brigham Women's Hospital (BWH) systems. Both AJCC8 and BWH incorporate high-risk factors into tumour (T) classifications (**Table 1**). However, there is overall less evidence validating the clinical outcomes of AJCC8, whereas the BWH system appears to offer superior prognostication, although it is limited by data derived from a single academic institution.[4,5]

In contrast to staging systems, which provide prognostic information, several published guidelines have been developed on diagnosis and management of cSCC, including those from the American Academy of Dermatology (AAD), the National Comprehensive Cancer Network (NCCN), and the American Society for Radiation Oncology (ASTRO). Among these, the 2022 NCCN guidelines are widely used and stratify cSCC into low-risk, high-risk, and very high-risk categories, requiring the presence of at least one risk factor to qualify for a risk category.[6]

High-risk features include tumour size (diameter >2 cm in AJCC8 and BWH systems, with further subcategorization based on anatomic site (NCCN criteria—see **Table 2**), tumour thickness (>2 mm per NCCN versus >6 mm and/or invasion beyond subcutaneous fat in AJCC8 and BWH), rapidly growing tumours, ill defined borders, and high-risk anatomic locations (e.g., lips/ears). Additional factors include poor differentiation and other rare histologic subtypes (desmoplastic, acantholytic, adenosquamous), perineural invasion (wherein symptomatic perineural invasion [PNI] portends a worse prognosis than incidental/histologic PNI), lymphovasculation invasion, chronic inflammation/wounds, and recurrent tumours (see **Tables 1 and 2**).

Several studies have attempted to quantify the relative risk of metastasis associated with high-risk factors. In a large meta-analysis of 36 retrospective and prospective cohort studies comprising 17,248 patients, Thompson et al., identified the following risk factors as significantly

| AJCC8 and BWH T staging systems | |
|---|---|
| **AJCC 8th Edition** | |
| **T1** | <2 cm in greatest diameter |
| **T2** | ≥2 cm but <4 cm in greatest diameter |
| **T3** | Tumour ≥4 cm in greatest diameter or minor bone invasion or perineural invasion or deep invasion[a] |
| **T4a** | Tumour with gross cortical bone and/or marrow invasion |
| **T4b** | Tumour with skull bone invasion and/or skull base foramen involvement |
| **BWH** | |
| **T1** | 0 high-risk factors[b] |
| **T2a** | 1 high-risk factors |
| **T2b** | 2–3 high-risk factors |
| **T3** | 4 high-risk factors or bone invasion |

**Table 1.** Most widely used cutaneous squamous cell carcinoma staging systems[1]; *adapted from Guzman AK, Schmults CD, Ruiz CS. Squamous Cell Carcinoma: An Update in Staging, Management and Postoperative Surveillance Strategies. Dermatol Clinics. 2023;41(1):1-11. doi:10.1016/j.det.2022.07.004*

[a] Deep invasion defined as invasion beyond the subcutaneous far or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumour), perineural invasion defined as tumour cells in the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.

[b] BWH high-risk factors include tumour diameter 22 cm, poorly differentiated histology, perineural invasion of nerves 20.1 mm in caliber, or tumour invasion beyond subcutaneous fat (excluding bone invasion, which upgrades tumour to BWH stage T3).

associated with metastasis: tumour size >20 mm, thickness >6 mm, poor differentiation, PNI, extension beyond the subcutaneous fat, involvement of high-risk anatomical sites (lip, ear, and temporal region), and immunosuppression (**Table 3** summarizes additional smaller studies).[7,8]

Because most cSCCs with high-risk features do not progress, the ability of staging systems to predict which tumours will develop locoregional spread, metastasis, or disease specific death remains low.[2] The positive predictive value of AJCC8 is only 17% while the BWH staging system performs only slightly better, with a positive predictive value for poor outcomes of 24–38%.[2]

## Lymph Node Assessment

Aggressive cSCC follows a stepwise progression, first to regional lymph nodes before the development of distant metastases. Large cohort studies from Australia suggest the risk of spread to lymph nodes among cSCC patients is approximately 5% over 5 years.[5] Despite its small sample size (459 patients with 680 head and neck cSCCs), the BWH staging system is the only system that has specifically evaluated the risk of lymph node mestastasis, demonstrating an overall risk of positive sentinel lymph node biopsy (SLNB) of 34.7% among patients with T2b/T3 tumours.[5] Additionally, small retrospective studies have demonstrated up to a 92% 5-year survival rate for patients with one small positive node (<3 cm without extracapsular spread), suggesting that early diagnosis could improve patient outcomes.[5] However, while all patients with cSCC should undergo a thorough clinical assessment of draining lymph node basins, there are currently no guidelines specifying which cSCCs should undergo imaging before or after treatment. Similarly, due to insufficient data, there are no established criteria to guide the selection of patients with cSCCs for SLNB.

| NCCN Risk Stratification[a] | | | |
|---|---|---|---|
| Characteristic | NCCN risk group | | |
| | Low | High | Very high |
| **History and physical** | | | |
| **Location and size** | Trunk, extremities <2 cm | Trunk, extremities 2 to <4 cm; head, neck, hands, feet, pretibial, and anogenital (any size) | ≥4 cm (any location) |
| **Borders** | Well-defined | Poorly defined | N/A |
| **Primary vs recurrent** | Primary | Recurrent | NA |
| **Immunosuppression** | Negative | Positive | N/A |
| **Site of prior RT or chronic inflammatory process** | Negative | Positive | N/A |
| **Rapidly growing tumour** | Negative | Positive | N/A |
| **Neurological symptoms** | Negative | Positive | N/A |
| **Pathological findings** | | | |
| **Degree of differentiation** | Well or moderately differentiated | N/A | Poor differentiation |
| **Histologic features: acantholytic (adenoid), adenosquamous (showing mucin production), or metaplastic (carcinosarco- matous) subtypes** | Negative | Positive | Desmoplastic SCC |
| **Depth: thickness or level of invasion** | ≤6 mm and no invasion beyond subcutaneous fat | N/A | >6 mm or invasion beyond subcutaneous fat |
| **Perineural involvement** | Negative | Positive | Tumour cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1 mm |
| **Lymphatic or vascular involvement** | Negative | Negative | Positive |

**Table 2.** In 2022, the National Comprehensive Cancer Network (NCCN) revised its classification of risk factors, expanding from the previous low-risk and high-risk categories to three categories: low-risk, high-risk and higher-risk; however, this updated classification has not been clinically validated[6]; *courtesy of Stevens JS, Murad F, Smile TD, O'Connor DM, Ilori E, Koyfman S, et al. Validation of the 2022 National Comprehensive Cancer Network Risk Stratification for Cutaneous Squamous Cell Carcinoma. JAMA Dermatol. 2023159(7):728-735. doi:10.1001/jamadermatol.2023.1353*

**Abbreviations: NA:** not applicable; **NCCN:** National Comprehensive Cancer Network; **RT:** radiotherapy; **SCC:** squamous cell carcinoma.

[a] Adapted from NCCN 2022 guidelines. Any tumour with 1 or more high- or very high-risk features was categorized as high risk or very high risk, respectively.

| Risk, hazard, or odds ratios for high-risk features of cutaneous SCC with independent risk of metastasis from different studies. | | | | |
|---|---|---|---|---|
| **High-risk features** | **Papers (*n* = number of patients) HR or OR (95% confidence interval), *p* value*** | | | |
| | **Thompson et al.[11] (*n* = 17248), RR** | **Moore et al.[6] (*n* = 193) OR** | **Peat et al.[12] (*n* = 170) HR** | **Mourouzis et al.[13] (*n* = 194) OR** |
| **Tumour size ≥20 mm** | 6.15 (3.56–10.65), *p* < 0.01 | | – | |
| **Depth of invasion** | 10.76† (2.55–45.31), *p* < 0.01 | – | – | |
| | 6.93‡ (4.02–11.94), *p* < 0.01 | | | |
| | 11.21§ (3.59–34.97), *p* < 0.01 | | | |
| **Recurrent lesion** | | | 2.81 (1.28-6.17), *p* < 0.01 | |
| **Poor differentiation** | 4.98 (3.30–7.49), *p* < 0.01 | | – | – |
| **Perineural invasion** | 2.95 (2.31–3.75), *p* < 0.01 | | 4.53 (1.43-14.30), *p* < 0.01‖ | |
| **Lymphovascular invasion** | | 7.54 (2.52-22.6), *p* < 0.0001 | 4.53 (1.43-14.30), *p* < 0.01‖ | |
| **Temple** | 2.82 (1.72–4.63), *p* < 0.01 | | | |
| **Cheek** | 1.30 (0.61–2.77), *p* = 0.49 | | | |
| **Ear/auricular area** | 2.33 (1.67–3.23), *p* < 0.01 | | | – |
| **Lip** | 2.28 (1.54–3.37), *p* < 0.01 | | | |
| **Immunosuppression** | 1.59 (1.07–2.37), *p* = 0.02 | | | |
| **Incomplete excision** | | | | 2.00, (1.00–4.00), *p* = 0.05 |

**Table 3.** Relative risk of metastasis due to high-risk features. Data analyzed retrospectively[8]; *courtesy of Skulsky SL, O'Sullivan B, McArdle O, Leader M, Roche M, Conlon PJ, O'Neill JP. Review of high-risk features of cutaneous squamous cell carcinoma and discrepancies between the American Joint Committee on Cancer and NCCN Clinical Practice Guidelines In Oncology. Head Neck. 2017;39(3):578-594. doi:10.1002/hed.24580*

Study addressing the risk factor is used in Thompson et al.'s meta-analysis, blank cell means risk factor was not examined/reported.

*HR or OR listed, as given by original article
†Breslow thickness >2 mm
‡Breslow thickness >6mm
§For depth beyond subcutaneous fat
‖Combined

**Abbreviations: HR:** hazard ratio, **OR:** odds ratio, **RR:** risk ratio

Despite the limited evidence base, NCCN guidelines suggest considering SLNB in patients with recurrent SCC or SCCs with multiple risk factors, while the European consensus-based interdisciplinary guideline recommends ultrasonography (US) for all patients with high-risk cSCC.[9,10] The optimal imaging modality remains unclear; however, limited retrospective data suggests that US may offer higher sensitivity and specificity for detecting nodal disease compared with computed tomography or magnetic resonance imaging, although performance is highly operator dependent.[5]

In a large systematic review, 1143 patients with high-risk cSCC who underwent SLNB were identified.[7] Among these, 88.1% had cSCC on the head and neck region, and the overall SLNB positivity rate was 12.3% (141/1143).[7] Of note, there was heterogeneity in how the high-risk SCC inclusion criteria were defined between studies, including the use of NCCN, AJCC, and BWH criteria.[7] Despite these differences, the rate of SLNB positivity exceeded 10% across studies, which is higher than the complication rate of approximately 5%, suggesting potential benefit.[7] However, no controlled studies have demonstrated a survival benefit for SLNB in cSCC.

## Adjuvant Radiation Therapy

Radiation therapy is usually not recommended as a primary treatment modality in surgically resectable high-risk cSCC, except in cases where it is used for palliation, based on patient preference, or when surgery would result in significant disfigurement or morbidity. Evidence supporting the use of adjuvant radiation therapy post-resection of high-risk SCC is largely derived from retrospective and small sample size studies.[11] In a multidisciplinary context, adjuvant radiation therapy may be offered for select cases of high-risk SCC, including completely excised high-risk tumours, those with positive margins, tumours exhibiting PNI, and following lymph node dissection in the setting of regional spread.[11] The NCCN guidelines recommend adjuvant radiation following complete surgical excision in cases of PNI (**Table 4**).

## Management of High-Risk SCC

Management of high-risk cSCC often involves a multidisciplinary team, including dermatologists, dermatologic surgeons, plastic surgeons or ear nose throat surgeons, radiation oncologists, and medical oncologists. Surgical resection should achieve complete circumferential and peripheral deep margin assessment, most commonly with the use of Mohs Micrographic Surgery, in which the dermatologist serves as both surgeon and pathologist, examining frozen sections in an en face orientation to achieve tumour extirpation. Depending on identified high-risk features, patients may subsequently undergo imaging of the lymph node basin and potential SLNB. These findings can inform further management decisions, including the use of radiation therapy, lymph node dissection, and, in some cases, immunotherapy as part of multidisciplinary care.

## Discussion

cSCC *in situ* can be managed with a range of options, including electrodessication and curettage, topical agents (e.g., 5-fluorouracil, calcipotriene, imiquimod), cryotherapy, and/or photodynamic therapy.[10] The vast majority of invasive cSCCs are amenable to treatment with wide local excision or Mohs Micrographic Surgery. However, there is a small proportion of cases that warrant consideration of adjuvant treatment, imaging, and multidisciplinary care. As most cSCCs occur on the head and neck region (approximately 80%),[1,2] most will be treated with Mohs Micrographic Surgery to preserve healthy tissue in anatomically sensitive areas while ensuring clear margins prior to reconstruction, adjuvant therapy, or additional diagnostic evaluation if needed.

Gene expression profiles (GEP), while not routinely used in Canada, are clinically available. These tools have been designed to predict the risk of metastasis as low, moderate, or high, and are intended to guide further clinical decision making.[11] The 40-GEP, known as DecisionDx, evaluates 34 prognostic genes and six control genes to estimate the risk of metastasis, with class 1 having the lowest risk, and classes 2a and 2b indicating progressively higher risk.[10] Small studies are

| Treatment | NCCN[7,78] | AAD[79] | ASTRO Task Force[40] |
|---|---|---|---|
| **Radiation therapy** | **Recommends ART to primary site[a]:**<br>• for extensive PNI<br>• with large (nerve caliber ≥0.1 mm) nerve involvement<br>• when there are positive margins postsurgery | **Recommends consideration of ART to primary site:**<br>• for concerning PNI<br>• for high risk for regional or distant metastasis | **Strongly recommends ART to primary site:**<br>• for clinically or radiologically apparent gross PNI<br>• when further surgery cannot correct or close positive margins<br>• when there is recurrence following a margin-negative resection<br>• for T3 and T4 tumors (AJCC8)<br>• for chronically immunosuppressed patients with desmoplastic or infiltrative tumours |

**Table 4.** Recommendations for adjuvant radiation following cutaneous squamous cell carcinoma resection[11]; *courtesy of Newman JG, Hall MA, Kurley SJ, Cook RW, Farberg AS, Geiger JL, et al. Adjuvant Therapy for High-risk Cutaneous Squamous Cell Carcinoma:10-year Review. Head Neck. 2021;43(9):2822-2843. doi:10.1002/hed.26767*

exploring the use of these tools to predict which SCCs would benefit from adjuvant radiation following resection. However, widespread use remains limited by proof of clinical utility and the burden of payer coverage.

Post treatment follow up of cSCC is important for identifying tumour recurrence, regional spread, and screening for new keratinocyte carcinomas.[12] A recent systematic review by Canadian dermatologists, which evaluated 13 different keratinocyte guidelines, found a lack of consensus on follow up frequency and duration.[12] There was also a considerable lack of consensus in how high- versus low-risk cancer was defined.[8] The clinical utility of frequent follow up in immunocompetent patients remains unclear due to limited data, and does not account for healthcare resource constraints, given the low dermatologist-to-population ratio in Canada (1.24 dermatologists per 100,000 people).[12] Nonetheless, in addition to emphasizing the importance of strict sun protection during follow up assessments, dermatologists should also consider prescribing preventive treatments for high-risk SCC patients, including acitretin, niacinamide, and 5-fluorouracil.[2]

## Conclusions

High-risk cSCC is associated with significant morbidity and mortality. Patient outcomes can be improved by early identification of high-risk features, prompt treatment to achieve clear surgical margins, identifying the earliest signs of recurrence, and timely referral for cases that would benefit from adjuvant radiation therapy. Further research is required to better define individual and combined risk factors that are predictive of lymph node metastasis, as well as to identify which patients are most likely to benefit from imaging and SLNB.

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