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Management of High-Risk Cutaneous Squamous Cell Carcinoma

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Cancer Care Alberta

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Background

Cutaneous squamous cell carcinoma (cSCC) is the second most common type of skin cancer, typically arising in areas of chronic sun exposure, such as the head and neck, extremities, trunk, and lower legs. SCC can also develop in areas of chronic inflammation or injury, including chronic wounds (e.g., Marjolin's ulcer in burn scars) and sites of previous actinic keratosis or Bowen's disease (SCC in situ). There may also be a pathogenic role of human papillomavirus (HPV) in the formation of cSCC.

Historically, SCC has been grouped with basal cell carcinoma (BCC) under the umbrella of nonmelanoma skin cancer (NMSC). While SCC and BCC share some risk factors, they can exhibit distinct biological behaviors, with SCC carrying a greater potential for aggressive progression. NMSC is the most prevalent malignancy among Caucasian populations, with incidence rates increasing globally for decades.[1] In Alberta, previous data suggested a plateau in NMSC incidence; however, more recent analysis from 2007 to 2018 indicates a 36% increase, with the most significant rise observed in invasive and in situ SCC (annual percentage change [APC] 3.48, p=0.014 and APC 5.61, p=0.0001, respectively).[1]

A subset of SCC cases is classified as high-risk due to factors such as aggressive histopathology, location, and patient characteristics. High-risk cSCC is associated with a greater likelihood of adverse outcomes, necessitating a more intensive approach to diagnosis, staging, treatment, and follow-up care. As such, this clinical practice guideline provides evidence-based recommendations for clinicians in Alberta on the management of high-risk cSCC.

Guideline Questions

1. What criteria are used to define/identify high-risk cSCCs?
2. Which individuals are susceptible to recurrence, nodal metastasis (NM), and death?
3. What imaging modalities are recommended in the staging of high-risk cSCC?
4. What are the recommended elements for pathology reporting?
5. What role does sentinel lymph node biopsy (SLNB) play in high-risk cSCC?
6. What are the most effective therapeutic approaches for managing high-risk cSCC?
7. What is the recommended follow-up protocol for individuals with high-risk cSCC?

Search Strategy

A literature review was conducted by searching journal articles in the PubMed electronic database from February 11, 2015, to February 11, 2025. The following terms were used in combination: carcinoma, squamous cell [MeSH Terms] AND high-risk [Title/Abstract]. The results were limited to clinical trials, comparative studies, guidelines, meta-analyses, multicenter studies, observational studies, and systematic reviews published in English on human subjects. Articles were further excluded from the review if they focused on patients with SCC arising from mucosal surfaces or if guidelines were older than five years. The references and bibliographies of articles identified through

the search were scanned for additional sources. A separate search for practice guidelines published since January 2020 was also conducted by accessing the websites and/or print publications of relevant national and international organizations. The full literature search strategy and resulting evidence tables are available upon request.

Target Population

The recommendations outlined in this guideline apply to adults over the age of 18 years with high-risk cSCC. SCC arising from mucosal surfaces (i.e., anogenital area and oral cavity) are not addressed in this guideline. Different principles may apply to pediatric patients.

Recommendations

Staging Systems for Treatment and Follow-Up Based on Risk Factors in cSCC

Recommendations

1. The Brigham and Women's Hospital (BWH) staging system is preferred for staging local disease, as it more accurately predicts poor outcomes compared to the American Joint Committee on Cancer (AJCC) system (see Appendix A for more details). *(Level of Evidence: IV[2]: Strength of Recommendation: B)*
2. The AJCC staging system is recommended for staging distant disease and for determining eligibility for immunotherapy. *(Level of Evidence: V: Strength of Recommendation: B)*

Qualifying Statements

a. There is no universally agreed-upon definition for high-risk cSCC, but the most widely used staging systems are BWH and the AJCC 8th Edition (AJCC 8) (Table 1).

Table 1. High-Risk Tumour Definitions in AJCC 8 and BWH Staging Systems

Staging System	High-Risk Tumour Definition
AJCC 8[3]	• T3: Tumour >4 cm in maximum dimension, minor bone erosion, perineural invasion ≥0.1 mm or invading a nerve located deeper than the dermis, invasion >6 mm depth. • T4: Tumour with gross cortical bone/marrow, skull base invasion and/or skull base foramen invasion.
BWH[4,5]	• T2b: Tumour with 2-3 high-risk factors. • T3: Tumour with ≥4 high-risk factors or bone invasion. High-risk factors include tumour diameter ≥2 cm, poorly differentiated histology, perineural invasion (≥0.1 mm), and tumour invasion beyond fat.

b. The National Comprehensive Cancer Network (NCCN) provides an alternative staging system that categorizes cSCC into low-, high-, and very-high groups risk (see Appendix A for more details).[6] However, it is not widely used and requires further validation studies before endorsement.[7]

c. Certain factors not accounted for in the recommended staging systems have been associated with higher recurrence risk and poorer survival and should be considered when assessing risk. These factors may influence treatment decisions and follow-up intensity, even in patients classified as lower risk by staging criteria:
   - Clinical factors: Tumour location (ear, lip, head, neck, or scalp),[8-10] satellitosis or in-transit metastasis (ITM), history of prior SCC, recurrent disease.[11,12]
   - Histological factors: Lymhovascular invasion (LVI),[13] desmoplastic growth pattern,[14] perineural invasion (PNI) involving >3 small diameter nerves, Marjolin ulcers,[15-17] and tumour budding.[18]
   - Patient factors: Immunosuppression (particularly solid-organ transplant recipients),[8,9,14,19-21] chronic lymphocytic leukemia (CLL),[8] and age over 65 years.[8,9]

Key Evidence

- In a cohort study of 459 patients with 680 head and neck cSCCs, the BWH staging system outperformed AJCC 8 in predicting NM and disease-specific death (DSD).[2] BWH showed higher specificity (93%), and positive predictive value (30%) compared to AJCC 8, with superior C-statistics for NM and DSD (p=0.01 and p=0.005, respectively), while AJCC 8 failed to distinguish between T2 and T3 tumours, resulting in a 23% subset with similar poor outcomes.
- The BWH staging system focuses on local and regional staging but does not include a classification for distant metastasis (DM). This makes the AJCC 8 staging system essential for staging distant disease and determining eligibility for immunotherapy in high-risk cSCC.

Radiologic Imaging

Recommendations

1. Radiologic imaging is recommended for the staging and management of individuals suspected of having locally advanced, extensive (e.g., deep involvement such as bone, named nerve, and deep soft tissue), or metastatic disease, including those with BWH T2B or higher and/or AJCC 3 or higher. *(Level of Evidence: IV[22-24] V[6,25]: Strength of Recommendation: B)*
2. Computed tomography (CT) is recommended for evaluating bone involvement and NM in cSCC, while magnetic resonance imaging (MRI) is recommended for assessing PNI and soft tissue involvement. CT or ultrasonography (US) may be used to assess nodal involvement. However, while US is cost-effective and has no radiation or contrast exposure, it has a high false-positive rate and is highly user-dependent. *(Level of Evidence: III[26] V[6,25]: Strength of Recommendation: B)*

Qualifying Statements

a) Due to limited data in the literature, the need for staging procedures in cSCC is not well established. Thus, preferred imaging modalities and the specific patient characteristics that necessitate imaging remain uncertain.[27,28]
b) The choice of imaging modality and the specific area to be targeted should be left to the discretion of the treating team based on their clinical assessment of the suspected extent of disease.[6]

c) When deciding on the appropriate imaging modality, the treating team should also consider factors such as wait times, cost, radiation and contrast exposure, and the burden on the patient.[27]

Key Evidence

- A retrospective cohort study at BWH evaluated 99 high-stage (BWH T2b/T3) cSCC tumours from 93 patients who underwent imaging before or within 30 days of diagnosis.[24] Abnormal findings were detected in 38% of cases. The most common abnormalities were enlarged lymph nodes (26%), lymph node metastasis (24%), and local invasion beyond clinical expectations (18%). These findings altered management in 30% of patients, leading to additional imaging (23%), changes in surgical planning (50%), or initiation of adjuvant radiation (50%) or systemic therapy (20%). Notably, 16% had confirmed metastases, and half of those with enlarged lymph nodes on imaging were biopsy-confirmed for nodal disease.
- A retrospective study conducted at a single center in Ireland over a 3-year period analyzed 682 cSCCs excised from 553 patients, evaluating the use of radiologic imaging in staging and its impact on management decisions.[22] The median patient age was 78 years. Baseline staging imaging was performed in 46 patients (67 tumours), representing 10% of all cSCCs. Imaging was more frequently utilized for high-risk tumours, including BWH T2b (27%), BWH T3 (67%), and AJCC T3 (30%). The most used imaging modalities were CT (73%), US (31%), PET-CT (13%), and MRI (13%), with 19% of patients undergoing multiple imaging techniques. Among those who underwent imaging, 28% had positive findings that altered management, including suspicious lymph nodes (53%), local invasion (26%), distant metastases (16%), and PNI (5%), the latter detected via MRI. Most positive findings occurred in patients with high-risk tumours, specifically BWH T2b (68%) and AJCC T3 (90%).
- A systematic review of 30 studies involving 1,027 patients with cSCC evaluated the performance of various imaging modalities for detecting perineural spread, bony invasion, NM, and DM.[26] The review found that MRI had a sensitivity of 95% for detecting perineural spread, while CT demonstrated a sensitivity of 76% and specificity of 99% for detecting bony invasion. CT also had the highest sensitivity (96%) and specificity (100%) for detecting NM. The review also highlighted that while US has a high negative predictive value (93%), its relatively low sensitivity (69%) and positive predictive value (40%) make it less reliable for confirming the presence of NM compared to other modalities. Imaging led to changes in clinical management in up to 33% of cases.

Pathological Examination

Recommendations

1. The recommended elements for pathology reporting of **excisional specimens** include:
    - Histologic type (including any desmoplastic or sarcomatoid pattern)
    - Histologic differentiation/grade
    - Tumour size (based on clinical measurement)
    - Tumour thickness/depth of invasion

- PNI (if present, report the diameter and number of involved nerves)
- Lymphovascular invasion
- Peripheral and deep margin status
- Tumour invasion into or beyond subcutaneous fat
- Results of immunostaining and other ancillary tests, if performed
- Report on sampling adequacy only if there is concern for incomplete or inadequate representation of the lesion

Qualifying Statement

a) While the College of American Pathologists (CAP) provides standardized cancer protocols for various cancer types, it currently offers a protocol only for cSCC of the head and neck.[29] Since CAP does not provide a protocol for SCCs from other cutaneous sites, input from provincial dermatopathologist experts was used to define the pathology reporting recommendations above, ensuring they accurately reflect the unique aspects of non-head and neck cSCCs.

Sentinel Lymph Node Biopsy (SLNB)

Recommendations

1. SLNB is not routinely recommended in the management of high-risk cSCC but could be considered in patients with Marjolin ulcers and no clinical or radiologic evidence of nodal disease, as the estimated risk of occult NM in this subgroup exceeds the 10% threshold commonly used to justify SLNB. *(Level of Evidence: III[30-32] IV[33]; Strength of Recommendation: C)*
2. Consideration for SLNB could also be informed by the number of high-risk features present, especially for patients with two or more. *(Level of Evidence III[34]; Strength of Recommendation: C)*

Key Evidence

- Existing studies show that SLNB is effective in determining lymph node status, but more robust data are needed to assess its impact on metastasis and tumour-specific survival. Current research is limited by factors such as retrospective design, inconsistent SLNB criteria, variations in surgical techniques, small sample sizes, and short follow-up periods.
- A systematic review and meta-analysis of 705 patients with cSCC of the head and neck from 20 studies demonstrated a high SLN identification rate (98.8%), a low SLNB positive rate (5.6%), and a relatively low regional recurrence rate in patients with negative SLNB (2.9%).[31] Additionally, a systematic review of 23 studies of patients of patients with cSCC (ranging from 5 to 57 patients per study) who underwent SLNB found that only 8 had positive SLNB results.[30] No study could reliably identify predictors of SLN positivity or assess its prognostic utility, as the criteria for recommending SLNB varied significantly. Furthermore, a review of the available evidence on high-risk cSCC suggests that while SLNB may be beneficial for a selected group of patients with a ≥10% risk of harbouring occult NM, the utility of SLNB in this context remains unclear without

high-level evidence.[33] Although SLNB is feasible, there is no consensus on its prognostic value or its impact on patient outcomes in high-risk cSCC.

- The presence of metastases at the time of Marjolin ulcer diagnosis is variably reported across studies. In a systematic review of 31 studies, only 22 reported on the presence or absence of metastases. Based on these data, 12.5% of patients had lymph node metastases and 4.8% had distant metastases at diagnosis.[32]
- A large multicenter cohort study of 16,844 patients with invasive cSCC evaluated the risk of local recurrence (LR), NM, DM, and DSD according to the number of BWH risk factors.[34] The five-year cumulative incidence of NM increased significantly with the number of risk factors, from 3.6% with one risk factor, 11% with two, 20% with three, and 28% with four ($p<0.001$).

Management

Recommendations

Neoadjuvant Therapy

1. *Neoadjuvant cemiplimab[*] is not currently recommended as standard treatment for patients with resectable high-risk cSCC. However, given its demonstrated biological and clinical activity in this population, it may be considered in select patients with borderline resectable or initially unresectable tumours, particularly where surgery is expected to be morbid. Following multidisciplinary review, surgery may be considered if the response to immunotherapy is sufficient to change the status of an initially unresectable cSCC to resectable. (Level of Evidence: II[35,36]; Strength of Recommendation: C)*

Surgical Management

2. Moh's micrographic surgery (MMS) or peripheral and deep *en face* margin assessment (PDEMA) is recommended for patients with high-risk cSCC and surgically resectable tumours, instead of wide local excision (WLE). *(Level of Evidence: II[37] III[38] IV[39-43]; Strength of Recommendation: B)*
3. If standard excision is performed for high-risk SCC, a margin of 6 mm is recommended. In cases of positive margins, re-excision is advised. If margin status is unknown, simpler closures such as linear repair, skin graft, or healing by second intention should be considered to avoid flap reconstruction. *(Level of Evidence: V[6,25]; Strength of Recommendation: B)*

Non-Surgical Management

4. For patients who are not candidates for surgery, radiation therapy (RT) may be considered in consultation with a radiation oncologist. *(Level of Evidence: V[6,25]; Strength of Recommendation; B)*

Adjuvant Radiotherapy

[*] As of July 15, 2025, according to the Alberta Health Services (AHS) Outpatient Cancer Drug Benefit Program, cemiplimab is not provincially funded in the neoadjuvant setting.

5. Adjuvant RT should be considered after surgical excision for patients with positive margins if re-excision is not possible. *(Level of Evidence: V[6,25]; Strength of Recommendation: B)*
6. Adjuvant RT may be considered for patients with high-T-stage tumours (BWH T2b or T3) with negative margins. The decision should be individualized, considering functional status and potential side effects, and the current evidence gaps. *(Level of Evidence: III[44-46] IV[47]; Strength of Recommendation: C)*

Qualifying Statements

a. The NRG-HN014 trial, a randomized phase III study currently under development, will provide critical data on the use of neoadjuvant cemiplimab for patients with resectable stage III/IV cSCC.[48] The trial will compare neoadjuvant cemiplimab followed by response-adapted surgery and possible adjuvant therapy with the standard treatment of surgery followed by adjuvant radiotherapy. The results of this trial could influence future recommendations, particularly for patients who may benefit from a reduction in tumour size or who are at high risk of surgical morbidity.
b. Immunosuppressed patients, including solid organ transplant recipients, those on immunosuppressive therapy, and individuals with hematologic malignancies or HIV, are at higher risk of recurrence and surgical complications, such as increased surgical site infections, the need for complex closures, and deeper tumour invasion. These patients should be closely monitored for recurrence, and postoperative care should be tailored to account for their increased risk of complications.[49]
c. There is no current consensus on the optimal surgical margins for standard excision of high-risk SCC, so adjustments may be necessary based on tumour- or patient-specific factors.

Key Evidence

- **Neoadjuvant cemiplimab**: In a single-arm, phase II multicenter study of 79 patients with resectable stage II–IV (M0) cSCC, neoadjuvant cemiplimab (350 mg every 3 weeks for up to four doses) demonstrated promising early efficacy.[35,36] A pathological complete response (pCR) was observed in 51% of patients (95% confidence interval [CI], 39-62), and a major pathological response (mPR; ≤10% viable tumour) in 13% (95% CI, 6-22). A radiologic objective response was seen in 68% of patients (95% CI, 57-78), although only 6% achieved complete radiologic response, suggesting imaging underestimated the true pathologic response.[35]

  Initial results (median follow-up of 9.7 months) demonstrated strong early activity based on pathologic response rates.[35] Longer-term follow-up (median 18.7 months) showed estimated 12-month event-free survival (EFS) of 89% (95% CI, 79-94), disease-free survival (DFS) of 92% (95% CI, 82-97), and overall survival (OS) of 92% (95% CI, 83-96). No recurrences were observed among patients achieving a pCR, and only 10% of those with an mPR experienced recurrence.[36] However, approximately 14% of patients experienced an event, including

preoperative disease progression in some cases, which occasionally rendered the tumour unresectable.[36]

In current clinical practice, neoadjuvant cemiplimab is primarily used in patients with unresectable or borderline resectable tumours, where it may facilitate surgery or reduce surgical morbidity. However, there remains uncertainty regarding the optimal duration of immunotherapy following surgery, which is typically determined on an individual basis.

While phase II data supports biological activity, limitations include the non-randomized design, limited follow-up, and the lack of long-term outcomes. Treatment-related toxicity is also notable with adverse events of any grade reported in 87% of patients and grade ≥3 events in 18%, despite patients receiving only four doses.[35] Following surgery, investigators could choose among three adjuvant strategies, including adjuvant cemiplimab, adjuvant RT, or observation. Of the 70 patients who had surgery, 93% had post-surgical management data available. Of these, 49% were observed postoperatively, 25% received adjuvant cemiplimab, and 26% received adjuvant RT.[36]

- **Surgical management**: MMS has been shown to offer superior outcomes over WLE for high-risk cSCC. A cohort of 581 high-risk cSCCs treated with MMS reported a 5-year local recurrence-free survival (LRFS) of 96.9% and a regional nodal metastasis-free survival of 93.8%.[39] A similar study of 842 high-risk cSCCs found a LR rate of 2.5% and a metastasis rate of 1.9% for patients treated with MMS.[40] Furthermore, a prospective multicenter study showed 99.3% LRFS and 99.4% disease-specific survival for patients undergoing MMS.[38] A comparison of MMS to WLE in T2a tumours demonstrated that MMS had a significantly lower recurrence rate of 1.2%, compared to 4.0% with WLE, with particular benefit noted for immunocompromised patients.[43] A large cohort study of head and neck cSCCs further reinforced MMS superiority, with MMS showing a 3% recurrence rate versus 8% for WLE.[42] Additionally, a retrospective chart review of 647 high-risk cSCCs treated with MMS found a LR rate of 2.9%, with factors such as poor differentiation and invasion beyond the subcutaneous fat being associated with poorer outcomes.[41] Most recently, a retrospective cohort study using propensity score weighting found that MMS was associated with significantly lower 3-year rates of LR (9.6% vs 19.8%), NM (11.0% vs 17.9%), and DSD (7.1% vs 17.5%) compared to WLE among patients with high-stage cSCC.[37]

- **Adjuvant RT**: Adjuvant RT for high-risk cSCC following clear margin resection has mixed evidence. A 20-year retrospective cohort study found adjuvant RT reduced the 5-year cumulative incidence of LR to 3.6% and locoregional recurrence to 7.5%, compared to 8.7% and 15.3% with observation.[47] High-risk tumours treated with adjuvant RT had a lower locoregional recurrence rate (17.2%) compared to those treated with observation (31%). However, a systematic review and meta-analysis of 33 studies found no significant difference in poor outcomes between surgery alone and surgery with adjuvant RT, with LR rates of 8.8% versus15.2% and regional metastasis

rates of 4.4% versus 11.5%, respectively.[44] Another systematic review comparing reported outcomes of high-risk SCC treated with surgical monotherapy versus surgery plus adjuvant RT noted that adjuvant RT may improve outcomes for high-risk cSCC with PNI, but no controlled trials or sufficient patient-specific data exist to confirm its efficacy.[45] A separate meta-analysis of 20 studies (n=2,605) reported that adjuvant RT was associated with significantly lower recurrence (odds ratio [OR] 0.56), longer DFS (OR 2.17), and longer OS (OR 2.94).[46] Poor prognostic factors included PNI, positive margins, and immunosuppression.

Emerging Evidence with Regulatory and Clinical Limitations

- **Neoadjuvant immunotherapy:** A small phase II study of neoadjuvant pembrolizumab in 27 patients with resectable stage II-IV (M0) cSCC reported a clinical or pathologic complete response in 17 patients (63%; 95% CI, 42-80), including a pathologic complete response in four (15%) and a clinical complete response in 13 (48%). Total de-escalation (i.e., avoidance of planned surgery and RT) and partial de-escalation (i.e., avoidance of adjuvant RT) was achieved in 48% and 15% of patients, respectively.[50] Retrospective data also suggest that response-adapted surgery following neoadjuvant cemiplimab may maintain oncologic safety while reducing morbidity.[51] However, follow-up is limited and randomized data are lacking. As of August 2025, neoadjuvant pembrolizumab is not approved by Health Canada for cSCC.

- **Adjuvant immunotherapy:** In the phase III randomized C-POST trial, 415 patients with resected, high-risk stage II-IV (M0) cSCC who received postoperative RT were randomized to adjuvant cemiplimab (350 mg) or placebo.[52] High-risk features included nodal factors (extracapsular extension with largest node ≥20 mm or ≥3 involved nodes) or non-nodal factors (in-transit metastases, T4 lesion with bone invasion, PNI, or locally recurrent tumour with ≥1 additional risk factor). Cemiplimab significantly improved DFS compared to placebo (HR 0.32; 95% CI, 0.20-0.51; p<0.001), with an estimated 24-month DFS of 87.1% versus 64.1%. It also reduced locoregional recurrence (HR 0.20) and distant recurrence (HR 0.35). Grade ≥3 adverse events occurred in 23.9% of cemiplimab-treated patients versus 14.2% with placebo, and discontinuation due to toxicity occurred in 9.8% and 1.5%, respectively.

  In contrast, the phase III KEYNOTE-630 trial evaluating adjuvant pembrolizumab, another PD-1 inhibitor, in a similar high-risk cSCC population failed to demonstrate a DFS benefit, despite comparable trial design and patient characteristics.[53] No OS benefit has been reported for cemiplimab. The high immunosensitivity of cSCC is reflected in objective response rates of approximately 34% with pembrolizumab in recurrent/metastatic cSCC (KEYNOTE-629) and approximately 45-47% with cemiplimab in advanced disease (EMPOWER-CSCC-1), with many responses being durable.[54,55] These results highlight the effectiveness of PD-1 blockade as salvage therapy in this setting. The elderly, often frail cSCC population may be at higher risk of toxicity, complicating the risk-benefit profile. Because both adjuvant trials required RT, it remains uncertain whether cemiplimab would provide similar benefit without prior RT. As of August 2025,

adjuvant cemiplimab is not approved by Health Canada for cSCC. Experiences in melanoma, where adjuvant immunotherapy enthusiasm has waned in some jurisdictions due to limited long-term benefits, underscore the need for caution. Further studies are needed to clarify adjuvant cemiplimab's role in cSCC, particularly regarding OS and RT necessity.

Surveillance

Recommendations

1. In the absence of evidence supporting current intensive follow-up schedules,[6,25,56] and given the rising incidence of skin cancer and the strain on healthcare resources, surveillance for most high-risk cSCC patients should be de-intensified.[57] The recommendations listed below are based on NCCN guidance as a reference point and to illustrate commonly used follow-up intervals. These intervals may still be relatively intensive and should be applied at the discretion of the treating clinician based on individual patient risk and capacity for self-monitoring. *(Level of Evidence: V[6]; Strength of Recommendation: C)*:
    - Years 1–2: Clinical exams every 3 to 6 months, focusing on patient history, targeted skin exams, and lymph node palpation.
    - Years 3–5: Clinical exams every 6 to 12 months, tailored to individual risk and capacity for self-monitoring.
    - Beyond 5 years: Routine surveillance is generally not recommended, except in select patients (e.g., those who are immunosuppressed), where longer-term follow-up may be appropriate.
2. Provide structured education and personalized discharge materials to support skin and lymph node self-examination. *(Level of Evidence: V[56,58]; Strength of Recommendation: B)*
3. Recommend self-surveillance as a safe and sustainable alternative to routine clinic visits for most patients after the initial follow-up period. *(Level of Evidence: IV[59,60]: Strength of Recommendation: B)*

Qualifying Statements

a) While these recommendations provide a general framework for follow-up of high-risk cSCC patients, follow-up schedules should be individualized based on patient factors (e.g., immunosuppression, comorbidities, ability to self-monitor), tumour characteristics, and the type and extent of treatment received. This personalized approach ensures appropriate surveillance intensity, balancing risk reduction with healthcare resource utilization and patient preferences.
b) Follow-up care does not need to take place in a cancer centre. For most patients, community-based follow-up with a dermatologist is appropriate, provided sufficient expertise and access are available.
c) Evidence from melanoma suggests that reducing follow-up intensity does not adversely affect health outcomes and may reduce healthcare costs and patient anxiety.[61] Similar evaluations are needed for cSCC. Alternative approaches such as structured self-monitoring,[59] personalized

discharge instructions, and health-based mobile applications should be explored to support sustainable, patient-centered follow-up care.[57]

Key Evidence

- Current follow-up schedules for high-risk cSCC are based on expert opinion, informed by recurrence rates and the risk of developing additional skin cancers. The NCCN, European guidelines, and the British Association of Dermatologists (BAD) recommend close, risk-adapted clinical follow-up for patients with high-risk cSCC.[6,25,56] The NCCN advises skin and lymph node exams every 3 to 6 months for the first 2 years, followed by less frequent visits over time, with imaging considered based on clinical findings or recurrence risk.[6] The European guidelines also recommend clinical/physical exams every 3 to 6 months for the first 2 years, followed by annual visits, and include ultrasound of regional lymph nodes or the parotid gland during the initial 2 years.[25] The BAD recommends follow-up every 4 months for the first year and every 6 months for the second year, with lifelong surveillance offered to patients at particularly high risk, such as organ transplant recipients.[56]
- There is no evidence evaluating the effectiveness of follow-up schedules recommended by the NCCN, European guideline, or BAD.

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Appendix A: Cutaneous SCC Staging Systems

American Joint Committee on Cancer (AJCC) 8th Edition TNM Staging of Cutaneous SCC of the Head and Neck[3]

Primary Tumour (T)	
T Category	**T Criteria**
TX	Primary tumour cannot be assessed.
Tis	Carcinoma *in situ*.
T1	Tumour ≤2 cm in greatest dimension.
T2	Tumour >2 cm, but ≤4 cm in greatest dimension.
T3	Tumour >4 cm in maximum dimension or minor bone erosion or perineural invasion or deep invasion*.
T4	Tumour with gross cortical bone/marrow, skull base invasion and/or skull base foramen invasion.
T4a	Tumour with gross cortical bone/marrow invasion.
T4b	Tumour with skull base invasion and/or skull base foramen involvement.
* Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumour); perineural invasion for T3 classification is defined as tumour cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1 mm in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.	
Regional Lymph Nodes (N)	
Clinical N (cN)	
N Category	**N Criteria**
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE (–).
N2	Metastasis in a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE (–); **or** Metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE (–); **or** In bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE (–).
N2a	Metastasis in a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE (–).
N2b	Metastases in multiple ipsilateral nodes, none >6 cm in greatest dimension and ENE (–).
N2c	Metastases in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE (–).
N3	Metastasis in a lymph node >6 cm in greatest dimension and ENE (–); **or** Metastasis in any node(s) and clinically overt ENE [ENE (+)]
N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE (–).
N3b	Metastasis in any node(s) and ENE (+).
A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical, and pathological ENE should be recorded as ENE (–) or ENE (+).	
Regional Lymph Nodes (N)	
Pathological N (pN)	
N Category	**N Criteria**
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE (–).
N2	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE (+); **or** >3 cm but not >6 cm in greatest dimension and ENE (–); **or**

	Metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE (–); or In bilateral or contralateral lymph node(s), none >6 cm in greatest dimension, ENE (–).
N2a	Metastasis in a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE (+); or A single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE (–).
N2b	Metastases in multiple ipsilateral nodes, none >6 cm in greatest dimension and ENE (–).
N2c	Metastases in bilateral or contralateral lymph node(s), none >6 cm in greatest dimension and ENE (–).
N3	Metastasis in a lymph node >6 cm in greatest dimension and ENE (–); **or** In a single ipsilateral node >3 cm in greatest dimension and ENE (+); **or** Multiple ipsilateral, contralateral, or bilateral nodes, any with ENE (+); **or** A single contralateral node of any size and ENE (+).
N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE (–).
N3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE (+); **or** Multiple ipsilateral, contralateral, or bilateral nodes, any with ENE (+); **or** A single contralateral node of any size and ENE (+).
A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical, and pathological ENE should be recorded as ENE (–) or ENE (+).	

Distant metastasis (M)	
M Category	**M Criteria**
M0	No distant metastasis.
M1	Distant metastasis.

Prognostic Stage Groups			
When T is...	**And N is...**	**And M is...**	**Then the stage group is...**
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1	N1	M0	III
T2	N1	M0	III
T3	N1	M0	III
T1	N2	M0	IV
T2	N2	M0	IV
T3	N2	M0	IV
Any T	N3	M0	IV
T4	Any N	M0	IV

Brigham and Women's Hospital (BWH) Tumour (T) Staging System for Cutaneous SCC

Tumour Staging System	Definition
T1	0 high-risk factors*
T2a	1 high-risk factor
T2b	2-3 high-risk factors
T3	≥4 high-risk factors
*High-risk factors include tumour diameter ≥2 cm, poorly differentiated histology, PNI ≥0.1 mm, or tumour invasion beyond fat (excluding bone invasion, which automatically upgrades tumour to T3).	

National Comprehensive Cancer Network (NCCN) Staging System for Cutaneous SCC[6]

Risk Group	Low-Risk	High-Risk	Very-High-Risk
History & Physical			
Location/diameter (cm)	Trunk, extremities ≤2 cm	Trunk, extremities >2 cm to ≤4 cm Head, neck, hands, feet, pretibial, and anogenital area (any size)	>4 cm (any location)
Clinical extent	Well-defined	Poorly-defined	
Primary vs. recurrent	Primary	Recurrent	
Immunosuppression	(-)	(+)	
Site of prior RT or chronic inflammation	(-)	(+)	
Rapidly growing tumour	(-)	(+)	
Neurologic symptoms	(-)	(+)	
Pathology			
Degree of differentiation	Well or moderately differentiated		Poor differentiation
Histologic subtype: acantholytic (adenoid), adenosquamous, metaplastic (carcinosarcomatous), or desmoplastic subtypes in any portion of the tumour.	(-)	(+)	(+)
Depth: thickness or level of invasion	<2 mm thick and no invasion beyond subcutaneous fat	2-6 mm depth and no invasion beyond subcutaneous fat	>6 mm or invasion beyond subcutaneous fat
PNI	(-)	(+)	Tumour cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1 mm
Lymphatic or vascular involvement	(-)	(-)	(+)

Notes:
- Risk category assignment should be based on the highest risk factor present. The high-risk group has elevated risk of local recurrence; the very-high-risk group has elevated risk of local recurrence and metastasis.
- If clinical evaluation of incisional biopsy suggests that microstaging in inadequate, consider narrow margin excisional biopsy.
- Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumour).
- Narrow excision margins because of anatomic and functional constraints are associated with increased recurrence rates with standard histologic processing. Complete margin assessment with Mohs/PDEMA margin is recommended. For tumours <6 mm in size, without other high-risk or very-high-risk features, other treatment modalities may be considered if ≥4 mm clinically tumour-free margins can be obtained without significant anatomic or functional distortions.

Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial Cutaneous Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial Cutaneous Tumour Team who were not involved in the guideline's development, including surgical oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in April 2016 and updated in August 2025.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally, not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of this guideline will be conducted in 2028. However, if critical new evidence is brought forward before that time, the guideline working group members will revise and update the document accordingly.

Abbreviations

AHS, Alberta Health Services; AJCC, American Joint Committee on Cancer; APC, annual percentage change; BCC, basal cell carcinoma; BWH, Brigham Women's Hospital; CAP, College of American Pathologists; CCA, Cancer Care Alberta; CI, confidence interval; CLL, chronic lymphocytic leukemia; cSCC, cutaneous squamous cell carcinoma; CT, computed tomography; DM, distant metastasis; DFS, disease-free survival; DSD, disease-specific death; EFS, event free survival; ENE, extranodal extension; GEP, gene expression profile; HPV, human papillomavirus; ITM, in-transit metastasis; LR, local recurrence; LRFS, local recurrence-free survival; LVI, lymphovascular invasion; MRI, magnetic resonance imaging; MMS, Moh's micrographic surgery; mPR, major pathologic response; NCCN, National Comprehensive Care Network; NM, nodal metastasis; NMSC, nonmelanoma skin cancer; pCR, pathologic complete response; PDEMA, peripheral and deep en face margin assessment; PET, positron emission tomography; PNI, perineural invasion; RT, radiation therapy; OS, overall survival; SCC, squamous cell carcinoma; SLNB, sentinel lymph node biopsy; TNM, tumour, node, metastasis; US, ultrasound; WLE, wide local excision.

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Cutaneous Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

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