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Multidisciplinary management of locally advanced and metastatic cutaneous squamous cell carcinoma

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ABSTRACT

Non-melanoma skin cancers are the most prevalent form of cancer, with cutaneous squamous cell carcinoma (cSCC) being the 2nd most common type. Patients presenting with high-risk lesions associated with locally advanced or metastatic cSCC face high rates of recurrence and mortality. Accurate staging and risk stratification for patients can be challenging because no system is universally accepted, and no Canadian guidelines currently exist.

Patients with advanced cSCC are often deemed ineligible for either or both of curative surgery and radiation therapy (RT) and, until recently, were limited to off-label systemic cisplatin–fluorouracil or cetuximab therapy, which offers modest clinical benefits and potentially severe toxicity. A new systemic therapy, cemiplimab, has been approved for the treatment of locally advanced and metastatic cSCC. In the present review, we provide recommendations for patient classification and staging based on current guidelines, direction for determining patient eligibility for surgery and RT, and an overview of the available systemic treatment options for advanced cSCC and of the benefits of a multidisciplinary approach to patient management.

Key Words Cutaneous squamous cell carcinoma, locally advanced disease, metastatic disease, staging, stratification, multidisciplinary management

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INTRODUCTION

Non-melanoma skin cancers include both basal cell carcinoma and squamous cell carcinoma (SCC)—cancers that are more prevalent than all other cancers combined[1]. In 2014, non-melanoma skin cancer accounted for 28% of all new cancer cases in Canada, 23% of which were cutaneous SCC (cSCC)[2,3]. Most cases of cSCC are associated with a favourable outcome, with low risk of local recurrence (3%), nodal metastasis (4%), and disease-specific death (1.5%)[4]. However, for patients presenting with high-risk features, the risk of local recurrence can be as high as 47.2%, and the rate of regional and distant metastasis can be up to 47.3% depending on the interplay of patient-, disease-, and treatment-related factors[5]. Mortality from cSCC is typically a result of uncontrolled regional disease, and metastatic tumours have been shown to be associated with mortality rates of more than 70%[5,6]. Accurately defining high-risk lesions is vital for prognosis and treatment planning, but current definitions are broad and varied.

With respect to treatment, the primary options for cSCC are excision by standard technique or Mohs micrographic surgery. Typically, radiation therapy (RT) is reserved for adjuvant treatment of high-risk tumours or for patients who are not surgical candidates[7]. Because of disease severity, tumour location, and patient comorbidities, some patients with cSCC are ineligible for curative surgery and curative RT. Historically, that subset of patients has had no effective treatment options and has relied on systemic therapy with cisplatin and fluorouracil (5FU) or with cetuximab, for which limited data support efficacy in cSCC[7]. Recently, Health Canada approved cemiplimab for patients with cSCC who are ineligible for curative surgery and RT[8].

We convened a group of multidisciplinary experts in cSCC, including skin surgeons, an ear-nose-throat physician, dermatologists, a radiation oncologist, a medical oncologist, and a dermatopathologist. In the present review, we offer clinical insights and suggestions from that group for patient staging, risk stratification, treatment selection for curative intent, and the importance of a multidisciplinary approach.

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Patient Classification and Staging

Evaluation of Available Staging and Risk-Stratification Systems

Patient staging and classification are necessary to determine prognosis and optimal treatment strategies, especially when considering advanced cSCC. Although frequently performed by a Mohs surgeon, staging of advanced disease could be performed by dermatologists, plastic surgeons, general surgeons, head-and-neck surgeons, or surgical oncologists, depending on regional access to specialists. A universally accepted staging system for risk stratification in cSCC is not available, and currently, there are no Canadian guideline recommendations. Commonly cited staging systems include those of the American Joint Committee on Cancer (AJCC), Brigham and Women's Hospital (BWH), and the U.S. National Comprehensive Cancer Network (NCCN)[7,9,10]. A dedicated non-melanoma skin cancer task force developed the AJCC staging manual, currently in its 8th edition, to highlight the staging requirements and high-risk features associated with cSCC of the head and neck[9]. The 7th edition marked the first use of an evidence-based medicine approach to cSCC staging, and although the staging system was found to lack distinctiveness, homogeneity, and monotonicity, those concerns are addressed in the new edition[4]. The BWH system was developed as an alternative to the 7th edition of the AJCC staging manual, and it is based on risk factors found to predict more than 1 negative outcome on multivariate analysis[10]. The BWH system might provide superior prognostication for localized cSCC, but it inadequately addresses nodal and metastatic classifications for advanced-stage groups[10,11]. The NCCN system also provides clinical practice guidelines for cSCC and stratifies tumours into high- and low-risk groupings based on clinical and pathology parameters[7,11]. The variation in staging systems has led to broad, non-unified definitions of the features that characterize high-risk lesions. Although all three systems specify certain aggressive risk factors such as a tumour width of 2 cm or greater, perineural invasion, bone invasion or erosion, and invasion beyond subcutaneous fat, each sets out its own distinct definition and risk stratification method[7,9,10].

In our practice, the risk features primarily considered for staging cSCC lesions are width and depth of the tumour (≥2 cm and invasion beyond fat respectively), perineural invasion (within nerves >0.1 mm in diameter), immunosuppression, and recurrence. High-risk locations and poor histologic differentiation are secondary considerations. Some controversy attends the choice of locations to classify as high-risk, but the ear, scalp, and non-hair-bearing lip are generally considered high-risk sites. Poor histologic differentiation has been removed in the 8th edition of the AJCC guidelines, but remains a high-risk factor in the BWH system[4]. Together with Kim *et al.*[11], we recommend using the NCCN guideline recommendations for practical approaches about how to treat localized cSCC, and the BWH and AJCC staging systems in concert to possibly aid in prognostication for patients with localized cSCC.

Considerations for Biopsy

A biopsy should always be performed before treatment, both to provide a tissue diagnosis confirming the clinical diagnosis and to identify the histopathologic parameters essential for risk stratification. The recommended biopsy techniques for cSCC are punch biopsy, deep shave biopsy, or excisional biopsy. The biopsy should be of a good size and depth to provide an evaluation of relevant pathologic features. Repeat biopsy can be considered if the initial biopsy specimen is inadequate for accurate diagnosis[9].

Ideally, we recommend that

- the histologic examination be performed by a dermatopathologist or a pathologist experienced in cutaneous neoplasms[11].
- the biopsy specimen be accompanied by key clinical information, including patient age and sex; anatomic site; any recurrent lesion status; immunosuppression; and history of RT, organ transplantation, chronic leukemia, or use of podophyllum to treat warts (Table I). A clinical photograph of the lesion could also accompany the specimen.

The foregoing information provides the pathologist with clinical context that could greatly assist in interpretation of the histologic findings. If margin status is required, we advise clinicians to ensure that specimens are appropriately oriented before submission.

Although the principal purpose of the histopathology report is to document the tissue diagnosis, a diagnosis of cSCC should be accompanied by additional elements to inform and optimize risk stratification[11]. We therefore strongly recommend that pathology reports include the degree of differentiation; depth of invasion; presence of any perineural invasion (including the diameter of the largest involved nerve), lymphovascular invasion, invasion into or beyond the subcutaneous fat, and invasion of fascia, muscle, or bone; the number of high-risk features (according to BWH[10]); and margin status (Table I). Additional optional elements include the presence of an aggressive histologic subtype or detection of any or all of infiltrative strands, single cells, or small nests. A synoptic report format is an efficient way to provide the foregoing information.

Staging Through Physical Examination and Imaging

In addition to biopsy-confirmed diagnosis, the importance of staging by visual and physical examination for high-risk features, a thorough evaluation of patient history, and palpation of regional lymph nodes in all patients is emphasized (Table I). Given that cSCC usually metastasizes via lymphatic vessels, nodal involvement is a critical prognostic factor, and early detection of nodal disease might increase survival[12]. For patients with palpable lymphadenopathy, clinicians may proceed to ultrasound-guided fine-needle aspiration biopsy[13].

The NCCN guideline recommends radiologic imaging for tumours suspected to represent extensive disease, specifying magnetic resonance imaging with contrast as the best option for tumours with perineural invasion or deep soft-tissue involvement, and computed tomography with contrast for tumours with bone invasion[7]. A study reviewing the role of imaging in the treatment of high-risk cSCC tumours revealed that imaging results altered the treatment plan in 33% of cases, with the most common

TABLE I Recommendations for the diagnosis and staging of advanced cutaneous squamous cell carcinoma

Considerations for biopsy			
Clinical information provided to the pathologist		**Elements included in the pathology report (excision specimen)**	
Strongly recommended	**Recommended**	**Strongly recommended**	**Recommended**

• Age
• Sex
• Anatomic location
• Recurrent lesion
• Immunosuppression
• Patient history
  • Previous treatment with radiation or use of podophyllum to treat warts
  • Recipient of an organ transplant
  • Previous diagnosis with chronic leukemia
	• Width of lesion	• Degree of differentiation
		• Depth of invasion (millimetres)
		• Perineural invasion, including the diameter of the largest involved nerve
		• Lymphovascular invasion
		• Invasion of subcutaneous fat
		• Invasion of fascia, muscle, or bone
		• Number of high-risk features
		• Margin status
			• Presence of aggressive histologic subtype
			• Infiltrative strands, single cells, or small nests

Considerations for physical and imaging-based assessment			

• Stage all patients through a visual and physical examination for high-risk features
• Assess regional lymph node involvement by manual palpitation for all patients
• Perform radiologic imaging on
  • all tumours staged at T3 and above (American Joint Committee on Cancer guidelines) or at T2b and above (Brigham and Women's Hospital guidelines).
  • tumours with high-risk features.
  • tumours located in high-risk sites.
  • patients whose necks cannot be properly palpated (for example, because of obesity or high muscle mass).			

changes being the addition of RT or a change in surgical approach[14]. Additionally, in an analysis adjusted for sex, BWH tumour stage, and tumour location, patients who underwent imaging were 50% less likely to experience local recurrence, nodal metastasis, or disease-related death[14]. Strong consideration should be given to using radiologic imaging for all tumours staged T3 and above (AJCC) or T2b and above (BWH), tumours located at high-risk sites, and tumours in patients whose necks cannot be properly palpated (for example, because of obesity or high muscle mass—Table I).

Role of Sentinel Lymph Node Biopsy

Within the melanoma and breast cancer landscapes, sentinel lymph node biopsy (SLNB) has been shown to be a safe and effective tool for detecting micrometastases, informing prognosis, and guiding treatment[15]. In the absence of radiologic evidence of involved lymph nodes, SLNB can provide a minimally invasive analysis of the nodal basin and is more sensitive than either computed tomography or magnetic resonance imaging for the detection of occult nodal metastases[12,13]. The predictable pattern of metastasis observed in cSCC, in which an estimated 80% of metastases spread first to the regional lymph nodes, suggests that SLNB could be a useful technique for evaluating high-risk tumours. However, the role of SLNB in cSCC is, to date, unclear[15].

The current data suggest a potential role for SLNB in providing early detection of subclinical nodal metastases, although the technique might be limited in patients with advanced cSCC (for example, because of lesion size or anatomic location). Most cSCC lesions (75%–90% of cases) occur in the head and neck[12]. That anatomic location has numerous lymph nodes and complex lymphatic drainage, such as bilateral or contralateral drainage. Those features can present challenges such as the existence of more than 1 sentinel lymph node or difficulties in accurately mapping lymphatics.

Difficulties with lymphatic mapping of head-and-neck lesions can include the ability to visualize the sentinel node through lymphoscintigraphy (because of close proximity to the injection site), the ability to distinguish first-echelon nodes from second-echelon nodes (because of the small anatomic space), and the ability to access small sentinel lymph nodes[12]. For cSCC tumours of the head and neck, the sentinel lymph node is identified within the parotid gland in 70% of cases; however, biopsy carries a small risk of damaging facial nerves[12]. Interestingly, despite the challenges, studies have indicated that the sensitivity of SLNB is highest for lymph nodes located in the head and neck; the highest false negative rates are seen in lymph nodes located in the trunk and extremities[5]. Overall, SLNB is a safe procedure, with complications being rare and typically mild and localized[16].

Research into the benefit of SLNB as a staging or prognostic tool is ongoing; few formal recommendations exist. Currently, Alberta Health Services recommends that SLNB be considered for staging in patients with clinically node-negative cSCC presenting with multiple risk factors, but cautions about its use in patients who have undergone prior wide excision of the primary tumour with rotation flap, extensive surgery, or RT to the head and neck[17]. Schmitt *et al.*[15] suggest using melanoma as a model of care, emphasizing the 10% risk threshold for considering SLNB. Using that threshold, the data suggest that tumours staged as T2 and above (AJCC) or T2b and above (BWH) might warrant a consideration of SLNB. Although discussing the value of SLNB in a cSCC setting is important, the effect on disease management and outcomes in patients with cSCC have yet to be determined[11].

Treatment and Management Considerations for Advanced cSCC

Upon confirmation of diagnosis and appropriate staging, the first step for determining the treatment plan for patients with advanced cSCC is evaluating their eligibility for either or both of curative surgery or RT. Typically, one or more of a Mohs surgeon, an ear-nose-throat surgeon, a plastic surgeon, a dermato-oncologist, a radiation oncologist, a medical oncologist, or a surgical oncologist will assess the patient's disease status and comorbidities to determine candidacy for surgery or RT.

The primary treatment goal for cSCC is complete removal of the tumour, with maintenance of as much function and cosmesis as possible[7]. Tumour removal by surgical excision or Mohs micrographic surgery is the current standard of care for high-risk cSCC[7]. Compared with standard excision, Mohs micrographic surgery has been shown to result in a lower rate of recurrence because it involves the examination of 100% of the margin, and positive margins are re-excised in stages until tumour clearance is achieved[18]. However, Mohs micrographic surgery is resource-intensive and requires clinician expertise[19]. We also note that a dedicated Mohs surgeon might not be accessible in all centres.

Although surgical excision is the first line of treatment, RT provides a tissue-preserving method with the potential to achieve better cosmetic and functional outcomes[19]. For cases in which surgery is not feasible or would result in unacceptable functional morbidity, RT can be used as a definitive treatment[19]. Additionally, we suggest considering RT as a second line of treatment or as adjuvant treatment after surgery if complete surgical excision of the tumour was not achieved, if margins were uncertain, or if perineural invasion within a nerve larger than 0.1 mm in diameter was observed. In addition, RT could also be offered as palliative care[19].

Considerations Regarding Patient Eligibility for Surgery

To our knowledge, no published guidelines have recommended how to determine eligibility for surgery in a patient with advanced cSCC. A surgical approach is often the most efficient and efficacious course of treatment, but the decision becomes more complex in patients with locally advanced disease. In such cases, eligibility for surgery should be based on the morbidity of the procedure and the technical feasibility of removing the tumour. We recommend careful consideration of the following factors: the feasibility of surgical removal with clear margins, the likelihood of achieving cure, the potential for the excision to heal, the capacity of the patient to tolerate adjuvant RT if needed, patient age, the physical and mental state of the patient, and the patient's ability to accept the outcomes associated with the surgery (Table II). It is important to discuss loss of function and cosmetic morbidities with the patient when choosing the treatment plan and to consider the risk–benefit ratio for each individual case.

Considerations Regarding Patient Eligibility for RT

The American Society for Radiation Oncology recently published a guideline for the definitive and postoperative use of RT for basal cell carcinoma and cSCC. The guideline also provides key recommendations for dose fractionation and implementation. The American Society for Radiation Oncology strongly recommended the use of definitive RT in patients who cannot undergo or who decline surgical resection, and conditionally recommended it for patients with basal cell carcinoma or cSCC in an anatomic location in which surgery could compromise function or cosmesis[20]. Similarly, we recommend considering sites ineligible if the morbidity from RT will be significant or if a potential for loss of critical function exists (Table II), such as when the tumour is large or is located on the head, neck, ears, or eyes. To facilitate patient acceptance of RT, it is important to consider patient quality of life and the effect of radiation on existing physiologic structures such as the eyes and auditory canals.

Some patients have comorbidities and contraindications that affect their eligibility for RT. A primary contraindication is previous irradiation in the same or an overlapping location, given the risk of tissue necrosis caused by high cumulative doses of radiation. Consequently, because younger patients (<40 to 50 years of age) presenting with cSCC are likely to develop additional lesions over time, RT is typically preserved for use in later lines of therapy[19]. Caution and careful consideration should precede the use of RT in patients with autoimmune or connective-tissue disorders, disorders that increase the likelihood of developing a second cancer, or disorders that predispose the patient to heightened radiosensitivity[19]. Patients with severe dementia or movement disorders affecting their capacity to remain still and cooperative during the 5–10 minutes required for treatment might also be limited in their ability to receive RT[19].

In a postoperative setting, the American Society for Radiation Oncology guideline strongly recommends the use of RT in incidences of gross perineural spread, high-risk tumours (for example, AJCC T3 or T4), desmoplastic or infiltrative tumours in immunosuppressed patients, cases of close or positive margins that cannot be corrected with further surgery, and the setting of recurrence after prior margin-negative resection[20]. Palliative RT can also offer effective symptom control for focal disease[21].

Systemic Treatment Options

Because of tumour characteristics and potential comorbidities, some patients with advanced cSCC will be ineligible for both curative surgery and curative RT. We consider such patients—as well as those with metastatic, recurrent, and refractory disease—to be candidates for treatment with systemic therapies. Applicable systemic therapies include platinum-based chemotherapy, targeted therapy, and most recently, immunotherapy[8,22]. Here, we review key findings from prospective clinical trials and case series that the group agreed were relevant to Canadian practice.

Platinum-Based Chemotherapy: The platinum-based chemotherapy most often used to treat advanced cSCC is cisplatin–5FU[7,22]. To our knowledge, no prospective clinical trials for cisplatin–5FU therapy have been conducted in a population with advanced cSCC, and only two small case series have been published[23–26]. One case series presented details about 2 patients with locally advanced cSCC who

TABLE II Determining patient eligibility for curative surgery and radiation

Considerations for eligibility	
Surgery	**Radiation**

• Can the tumour be removed with clear margins?
• What is the likelihood of achieving cure?
• Will the excision successfully heal?
• Does the patient have the capacity to tolerate adjuvant radiation, if needed?
• How is the physical and mental state of the patient?
• What are the loss-of-function and cosmetic comorbidities?
• Can the patient accept the outcomes associated with surgery?
	• Has the patient had previous irradiation in the same or an overlapping location?
	• Is the patient young (<40 to 50 years of age)?
	• Does the patient have
	  • an autoimmune disorder?
	  • a connective tissue disorder?
	  • a disorder that increases the likelihood of developing a second cancer?
	  • a disorder that inhibits repair after ultraviolet radiation damage?
	• Can the patient cooperate with treatment requirements (for example, remaining still for 5–10 minutes)?
	• Is there significant morbidity or potential loss of critical function?

achieved complete responses (CRs) with cisplatin–5FU treatment[27]. Another group examined the efficacy of cisplatin–5FU in 7 patients with treatment-naïve advanced cSCC and observed an objective response rate (ORR) of 85.7%[28].

Various randomized phase III trials have explored the response rate for cisplatin–5FU in treating advanced, recurrent, or metastatic head-and-neck SCC (HNSCC). In four different phase III trials, the observed ORR ranged from 29.8% to 32%[23–26]. It is important to note that the genetic profile of HNSCC differs from that of cSCC, and therefore a direct comparison between the two diseases might not be appropriate[29–31].

Our experience indicates that, in addition to its limited efficacy, cisplatin–5FU is often poorly tolerated by patients. Cisplatin is associated with a wide range of toxicities, including ototoxicity, gastrotoxicity, myelosuppression, and allergic reactions; however, the dose-limiting side effect is nephrotoxicity[32]. Although 5FU is unique in that the spectrum of observed toxicities changes depending on the dose and frequency of administration, commonly observed adverse events (with a weekly bolus regimen) are mucositis, myelosuppression, and diarrhea[33]. Cisplatin and 5FU have both demonstrated increased toxicity in older patients, which presents a challenge for the age demographic of patients with advanced cSCC[32,33].

Targeted Therapy: Studies have shown that up to 80% of cSCC tumours and 100% of metastatic cSCC tumours express epidermal growth factor receptors (EGFRs), suggesting targeted EGFR inhibition as a potential therapeutic avenue[34]. In Canada and the United States, cetuximab, an immunoglobulin G1 antibody that prevents ligand-induced activation of EGFR, is indicated for the treatment of locally advanced HNSCC[35,36]. Cetuximab has been used off-label as a systemic treatment option for patients with advanced cSCC[13,37].

Often used in conjunction with RT for unresectable cSCC, cetuximab monotherapy was associated, in a phase II study ($n = 36$), with an ORR of 28%, including 6% CRs. During the course of the study, the best overall disease control rate (DCR) was 69% (Table III)[38]. More than half the patients (61%) experienced serious adverse events (≥grade 3). Most patients experience cutaneous adverse reactions, including acneiform rash, pruritus, and nail changes (including paronychia). Other common adverse events include fatigue, hypomagnesemia, headache, diarrhea, stomatitis, pyrexia, infection, and infusion reactions[36,38,42]. In our practice, cetuximab is not considered standard treatment for advanced cSCC; it is typically used in a palliative setting for patients who cannot tolerate cisplatin–5FU. Furthermore, cetuximab is not universally funded in Canada for use in cSCC, and criteria for reimbursement can vary by province and territory.

Immunotherapy: Anti–PD-1/PD-L1 therapies were initially developed for the treatment of melanoma, with the first U.S. Food and Drug Administration–approved drug entering the market in 2014[43]. Activated T cells express the PD-1 receptor, and binding of PD-L1 or PD-L2 can inhibit T cell proliferation and cytokine production, leading to a reduced antitumour immune response[8,44]. Anti–PD-1/PD-L1 therapies block that interaction and allow for an antitumour response from the immune system. These therapies are now approved for a variety of cancers, including non-small-cell lung carcinoma, HNSCC, Hodgkin lymphoma, gastric cancer, colorectal cancer, urothelial carcinoma, renal cell carcinoma, hepatocellular carcinoma, and Merkel cell carcinoma[43]. Expression of PD-L1 has been observed in 35%–70% of high-risk cSCC tumours and in 58%–100% of cSCC metastases[45,46]. Outside Canada, four case series ($n = 5$, $n = 6$, $n = 1$, $n = 1$) have demonstrated partial responses or CRs in patients with advanced cSCC treated with the anti–PD-1 agents pembrolizumab or nivolumab[39,47–49]. Recently, Health Canada and the U.S. Food and Drug Administration approved the first drug specifically indicated for the treatment of advanced cSCC, the anti–PD-1 systemic immunotherapy cemiplimab[8,40].

The clinical efficacy of cemiplimab in patients with locally advanced or metastatic cSCC has been assessed through phase I and II trials[41,50,51]. Clinical efficacy data from the phase I trial ($n = 26$) showed an ORR of 50% and a DCR of 73%[41]. Initial data from the ongoing phase II trial showed similarly positive results in patients with metastatic and locally advanced disease. In metastatic cases ($n = 59$), the ORR was 49.2%, including 16.9% CRs, and the DCR was 71.2% (Table III)[50]. In locally advanced cases ($n = 78$), the ORR was 43.6%, including 12.8% CRs, and the DCR was 79.5% (Table III)[51]. To date, the safety profile has shown cemiplimab to be well tolerated, with treatment-emergent serious adverse events (≥grade 3) occurring in 24.4%–33.9% of cemiplimab-treated patients with cSCC[8,41]. Several of

TABLE III Overview of prospective clinical trial data for systemic therapies in advanced cutaneous squamous cell carcinoma (cSCC)

Treatment	Study type	Patient and disease characteristics	Pts (*n*)	Primary endpoint	Best ORR (%)	DCR (%)	
						6-Week	Best overall
Cemiplimab[8,39]	Phase I, open-label, multicentre	Median age: 73 years Locally advanced and metastatic cSCC Local disease: 38% Regional metastasis only: 31% Distant metastasis: 31%	26	Safety, AE profile	50 (CR: 0)	Not reported	73
	Safety Grade 3 or greater serious AEs: 23.1% (7.7% related to treatment) Most common AEs: fatigue (26.9%, all grades 1–2); constipation, decreased appetite, nausea, hypophosphatemia, diarrhea (15.4% any grade, all grades 1–2); hypercalcemia (15.4% any grade, 50% grades 1–2); urinary tract infection (15.4% any grade, 75% grades 1–2)						
Cemiplimab[40,41]	Phase II, nonrandomized, global	Median age: 71 years Locally advanced and metastatic cSCC					
		Locally advanced group[41]:	78	Response rate	43.6 (CR: 12.8)	Not reported	79.5
		Safety Grade 3 or greater serious AEs: 24.4% (12.8% related to treatment) Most common AEs: fatigue (42.3% any grade, 97% grades 1–2); diarrhea, pruritus (26.9% any grade, all grades 1–2); nausea (21.8% any grade, all grades 1–2)					
		Metastatic group[40]: (regional only: 24%; distant: 76%)	59	Response rate	49.2 (CR: 16.9)	Not reported	71.2
		Safety Grade 3 or greater AEs: 33.9% (15.3% related to treatment) Most common AEs: diarrhea (28.8% any grade, 94% grades 1–2); fatigue (25.4% any grade, 93% grades 1–2); nausea (23.7% any grade, all grades 1–2)					
Cetuximab[36]	Phase II, open-label, uncontrolled, multicentre	Median age: 79 years Unresectable cSCC Local disease: 47% Regional metastasis: 44% Distant metastasis: 8%	36	DCR at 6 weeks	28 (CR: 6)	69	69
	Safety Grade 3 or greater AEs: 61% (10% related to treatment) Most common AE: acne-like rash (78% any grade, all grades 1–2)						

Pts = patients; ORR = overall response rate; DCR = disease control rate; AE(s) = adverse event(s); CR = complete response.

the most common adverse events are related to immune toxicity (for example, fatigue, diarrhea) and are considered manageable. Additionally, compared with anti-PD-1 therapy in general, no new safety signals were reported in the phase I or phase II trial cohorts[41]. Although no head-to-head comparisons with other therapeutic options in the cSCC landscape have been conducted, cemiplimab is emerging as an efficacious and tolerable systemic option.

Considerations for Immunosuppressed Patients

Disease management in immunosuppressed patients involves special consideration.

Immunocompromised patients such as organ transplant recipients have a risk of developing cSCC that is 65 to 250 times greater than that in the general population, and progression in such patients is typically more aggressive, with greater rates of recurrence and metastasis[52]. Current recommendations state that the course of treatment depends on the type and severity of the tumour, but more frequent surveillance is suggested[52]. Disease management in patients with pre-existing autoimmune diseases can also be complex, especially if treatment involves immune checkpoint inhibitors; treatment planning typically requires a multidisciplinary team[53]. Few data to guide treatment are available, because such patients are often excluded from clinical trials—specifically, the pivotal trials for cemiplimab excluded patients with autoimmune diseases, transplant recipients, and patients with immunosuppressive conditions being treated with more than 10 mg prednisone[41,50,51].

We recommend caution when treating patients with multifocal cSCC who have received an allograft, because the graft could be a contraindication for immune checkpoint inhibition because of an increased risk of graft rejection. However, a case study reported pre-emptive use of oral prednisone prevented allograft rejection in a patient treated with nivolumab[54]. Overall, it is important to balance the benefits of tumour regression against the

risk of graft rejection when treating immunosuppressed patients with advanced cSCC[13]. Canadian data or clinical guidelines recommending precise management strategies for immunosuppressed patients are lacking, illuminating research gaps in the treatment of advanced cSCC. Further studies into effective disease management in this patient population are needed. A clinical trial is currently underway to evaluate the safety and efficacy of cemiplimab in immunocompromised patients, including those with chronic lymphocytic leukemia or a history of HIV (see NCT04242173 at https://ClinicalTrials.gov/).

Importance and Optimization of Multidisciplinary Care

Determining patient eligibility for treatment and managing complex cases involves a multidisciplinary approach. From initial presentation to treatment and monitoring, a variety of health care practitioners might provide helpful insights (Figure 1). Given the wide spectrum of physicians who could be involved, it is important to optimize referral processes to provide the best patient care.

Some specialists—for example, dermatologists or Mohs surgeons—are not readily accessible at all centres. To better optimize the patient referral process, it is important to identify the expertise and specialists located within a region, to decide on the best means of communication within the team, to develop a streamlined referral pathway, to determine obstacles, and to discuss management strategies (Figure 2). We suggest that each region develop a multidisciplinary plan that meets the needs of their centre. General practitioners and geriatricians should also be informed of the prevalence of high-risk tumours and how to provide their patients access to multidisciplinary assessment.

Multidisciplinary tumour boards are an important resource in situations in which a clear treatment path is not defined or the centre lacks access to certain specialties or novel treatment options. Counsel from a tumour board should also be considered if the likelihood of curing a patient's cancer drops significantly, if more than 2 or 3 risk features are present, or if nonsurgical treatments are an option (Figure 3). Although multidisciplinary tumour boards offer a valuable multi-faceted perspective, tumour boards in some regions do not meet frequently. In that event, a regional team can be beneficial for treatment planning between tumour board meetings, with the resulting decisions being discussed at the next meeting so as to obtain additional insight from the broader group.

Depending on the context of the question being asked, multidisciplinary tumour boards can include medical oncologists, surgical oncologists, radiation oncologists, dermatology oncologists, radiologists, and pathologists. It can be useful to include supporting physicians to consider morbidities related to other aspects of a patient's health: for example, geriatricians for elderly patients, and rheumatologists or gastroenterologists for patients with autoimmune diseases. Technology could be leveraged to optimize communication, reducing geographic barriers and facilitating easy sharing of case-specific data.

CONCLUSIONS

Patients with high-risk locally advanced or metastatic cSCC face poor outcomes and few treatment options. Accurate staging of these patients is challenging given the inconsistent definitions of the features that constitute high-risk disease and the techniques to apply. For patients with advanced cSCC deemed ineligible for either or both of curative surgery or RT, treatment options were, until recently, limited to systemic cisplatin–5FU chemotherapy or off-label use of the EGFR inhibitor cetuximab. Unfortunately, the clinical benefits of those therapies in cSCC are modest, and adverse events are frequent and potentially severe. The immune checkpoint inhibitor cemiplimab, which recently obtained Health Canada and U.S. Food and Drug Administration

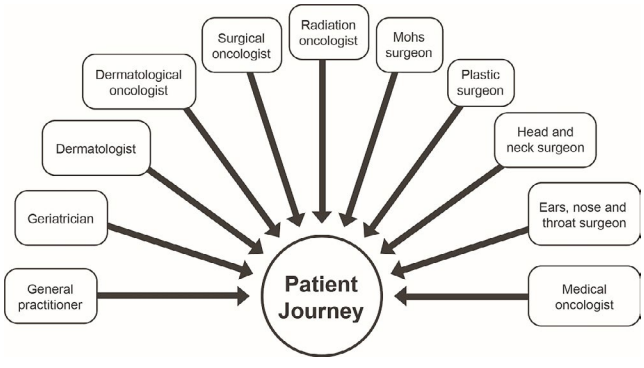

FIGURE 1 Visual representation of the various health care practitioners involved in the journey of a patient with advanced cutaneous squamous cell carcinoma.

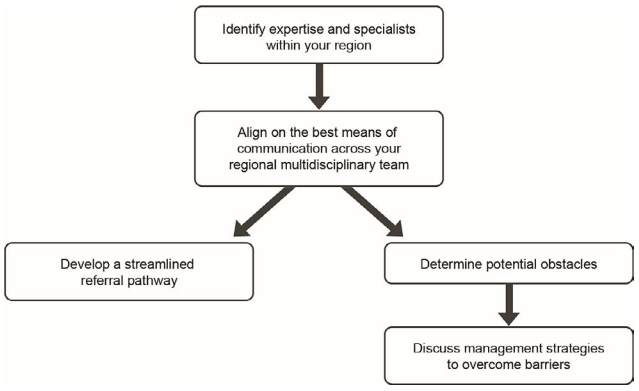

FIGURE 2 Guidance for establishing a regional multidisciplinary team.

Consider consulting a multidisciplinary tumour board if...

- ☐ A clear treatment path is not defined
- ☐ Your centre lacks access to a needed specialist or novel therapeutic option
- ☐ A patient's likelihood for cure has dropped significantly
- ☐ >2 to 3 risk features are present
- ☐ Nonsurgical treatment has become an option

FIGURE 3 Determining the need for a multidisciplinary tumour board.

approval, is the first approved therapy indicated for the treatment of advanced cSCC, and evidence is emerging to suggest that it could be promising, given its tolerability and efficacy. After the recent approval of cemiplimab, future studies should explore the potential uses of this new agent in an adjuvant setting and also the best therapeutic options for patients who relapse after anti–PD-1 immunotherapy. Continued research is also needed to provide better disease management options for immunosuppressed patients.

Regardless of the treatment selected, patient care should take a multidisciplinary approach. Multidisciplinary tumour boards should be considered when the path of treatment is unclear or in complex and high-risk cases. To further facilitate the quality of patient care and to increase accessibility, individual centres should consider the development of regional multidisciplinary teams, and tumour boards can leverage technology for wider reach.

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CONFLICT OF INTEREST DISCLOSURES

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