ABOUT THE AUTHOR

Maxwell B. Sauder, MD, FRCPC

Dr. Sauder is currently an assistant professor in the division of dermatology at the University of Toronto. He is an onco-dermatologist at Princess Margaret Cancer Centre as well as the research director at Toronto Research Centre. He earned his Doctor of Medicine degree at McMaster University, completed a residency in dermatology at The University of Ottawa and completed fellowship training in Cutaneous Oncology at Harvard Medical School.

CUTANEOUS SQUAMOUS CELL CARCINOMA: RISK STRATIFICATION AND STAGING

Introduction

Non-melanoma skin cancer (NMSC) is one of the most common forms of cancer in Canada with an estimated 76,100 cases in 2014, accounting for approximately 28% of all new cancer cases[1]. Cutaneous squamous cell carcinoma (cSCC) is the second most common type of NMSC and has a greater risk of metastases and death compared with the more common NMSC, basal cell carcinoma (BCC). The vast majority of cSCC are primary low risk; however, higher risk primary, locally advanced, regional or distant metastatic cases can result in a significant decrease in survival (**Figure 1**). In 2019, the first systemic therapy for cSCC, cemiplimab, was approved in Canada. The aim of this article is to review the epidemiology, risk stratification and available staging systems for cSCC to help clinicians better identify patients that may benefit from further work-up or treatment.

Epidemiology

Statistics regarding incidence, prevalence, morbidity, and mortality of cSCC is limited. Most Canadian cancer registries do not track cSCC. Additionally, BCC and SCC as well as some other NMSC are often coded together making it difficult to separate individual types of cancers[2].

In 2014, it was estimated that of all the cases of NMSC diagnosed in Canada, approximately 77% were BCC and 23% were SCC[1]. Another study from approximately the same period showed that the ratio of patients treated for BCC and SCC in a cohort of United States Medicare beneficiaries was 1:1[3]. Studies consistently demonstrate that the incidence rate of cSCC is rising. A recent population-based study of incidence and mortality rates of keratinocyte carcinoma in Ontario identified that the incidence rate increased by 30% over a 14-year period from 2003 to 2017 to 369 per

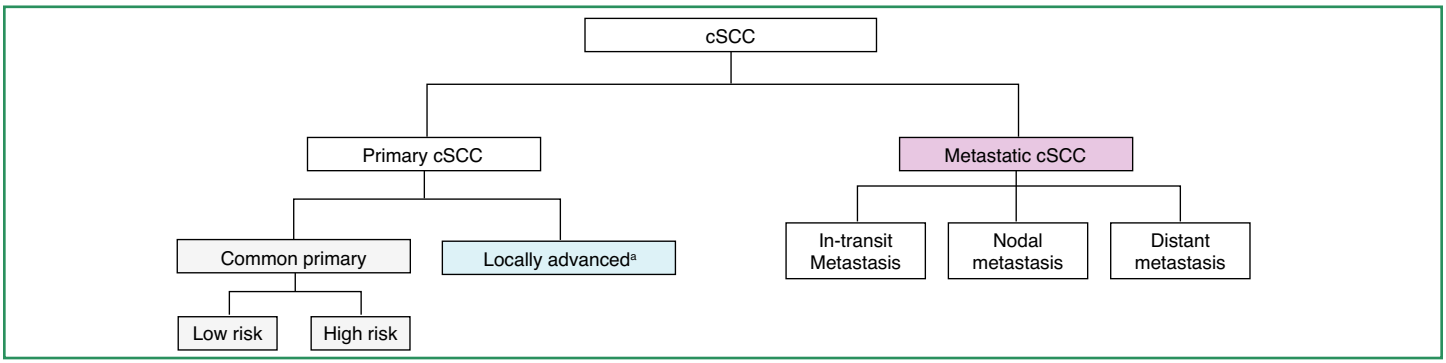

Figure 1: *Classification of cSCC – adapted from Dessinioti C, et al.*

100 000 males and 345 per 100 000 females in 2017 (AAPC [average annual percentage change] 1.9%, 95% confidence interval [CI] 1.7 to 2.1 from 2003 to 2017). Concurrently, the mortality rate from NMSC rose 4.8-fold between 1997 and 2017 (AAPC 8.9%, 95% CI 6.4 to 11.4 in males; 8.0%, 95% CI 5.3–10.8 in females) with the majority of deaths likely from cSCC[4].

Tumour-related high-risk factor	European Guidelines 2020	UK BAD Guidelines		U.S. NCCN 2020
	High-risk	High-risk	Very high-risk	High-risk
Tumour diameter Localization	>20 mm On temple/ear/lip	>20-40 mm On ear/lip	>40 mm	Area L ≥ 20 mm Area M ≥ 10mm Area H
Thickness	>6 mm	>4-6 mm	>6 mm	>6 mm
Invasion	Invasion beyond subcutaenous fat	Invasion into subcutaneous fat	Invasion beyond subcutaenous fat	Invasion beyond subcutaenous fat
Differentiation	Poor grade differentiation	Poor grade differentiation		Poor grade differentiation
Histological Feature	Desmoplasia	Lymphovascular invasion	High-grade histological subtype--adenosquamous, desmoplastic, spindle/ sarcomatoid/metaplastic	Acantholoytic (adenoid), adenosquamous (showing mucin production), desmoplastic, or metaplastic (carcinos arcomatous). Lymphatic or vascular involvement
Perineural invasion (PNI)	Histological/symptomatic/ radiological PNI	PNI--dermal only; nerve diameter < 0.1 mm	PNI present in named nerve; nerve >0.1 mm; or nerve beyond dermis	Histologcal PNI
Bone erosion/invasion	Bone erosion		Any bone invasion	
Tumour on scar/chronic inflmmation/radiotherapy (RT)		Tumour arising within scar or area of chronic inflammation		Site of prior RT or chronic inflammation
In-transit metastasis			In-transit metastasis	
Borders				Poorly defined
Primary vs recurrent				Recurrent
Rapidly growing tumour				Yes
Neurologic symptoms				Yes
Patient-related high-risk factors				
Immunosuppression	Immunosuppression	Iatrogenic immunosuppression or biological therapies, frailty and/or co-morbidities, likely to cause some degree of immune compromise. HIV infection stabilized on HAART.	As for high risk especially: solid organ transplant recipients; haematological malignancies such as CLL or myelofibrosis; other significant immunosuppresion	Immunosuppression
Extrinsic high-risk factors				
Surgical margin status	Postive surgical margins	One or more involved or close (<1 mm) pathology margin in a pT1 tumor. Close pathology margins in a pT2	One or more involved or close pathology margin in a high-risk tumour	

Area L: trunk and extremities (excluding hands, nail units, pretibial, ankles, and feet).
Area M: cheeks, forehead, scalp, neck and pretibial.
Area H: 'mask areas' of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermillion], chin, mandible, preauricular and postauricular skin/sulci, temple and ear), genitalia, hands, and feet.
CLL, chronic lymphocytic leukaemia.
Table 1: *High-risk factors for recurrence and metastasis in the UK BAD, European EADO and US NCCN guidelines; adapted from Dessinioti C et al.*

Most cases of NMSC are associated with a complete response to treatment. cSCC may have a 3% risk of local recurrence and a 4% risk of metastases. A prospective study analysing the risk factors determining prognosis of local recurrence or metastasis of cSCC, observed tumours with a depth of 2.0 mm or less did not metastasize whereas 4% of tumours (12 out of 308) 2.1 mm to 6.0 mm and 16% of tumours (14 out of 90) greater than 6.0 mm metastasized[5]. The mortality risk for metastatic cSCC is high with multiple studies reporting rates greater than 70%[6]. More specifically, the 5-year survival rate for regional metastatic cSCC was 58.3%[7] versus distant metastatic cSCC of 11%[8].

Tumour Characteristic Risk Factors

Predictive characteristics of tumours for local recurrence or metastasis may be valuable for management to improve survival. Multiple variables that are associated with 'higher-risk' have been identified including: tumour diameter, tumour thickness, perineural invasion, location, invasion beyond subcutaneous fat, histological differentiation, and immunosuppression. The National Cancer Comprehensive Network (NCCN) developed clinical guidelines in 2020 that identified high-risk features[9]. Similar guidelines with similar criteria were developed by the British Association of Dermatologists (BAD)[10] and the European Association of Dermato Oncology (EADO)[11] (**Table 1**). Meta-analyses in 2016[12] and 2020[13] identified the relative risk of each of the high-risk factors for local recurrence, metastases, and disease-specific death (**Table 2**). For the Canadian dermatologist, the presence of one or more of these risk factors should prompt consideration of aggressive treatment, further work-up and/or increased frequency of surveillance.

Staging systems

The two main staging systems for cSCC are: American Joint Committee on Cancer (AJCC) and Brigham and Women's Hospital (BWH) tumor staging system (**Table 3**). The AJCC system is used specifically for cSCC of the head and neck and requires information on tumor (T), lymph node involvement (N) and metastasis (M) for full staging. The BWH system only assesses tumor features. A comparison between the two systems demonstrated higher specificity (93%) and positive predictive values (30%) for the BWH staging system in identifying cases at risk for metastasis and death[14]. The AJCC system has a better negative predictive value (99.2%)[15]. The BWH system may provide better prognostication for patients with localized cSCC whereas the AJCC 8th edition may be superior at addressing nodal and metastatic classifications[16].

Conclusion

It has been estimated that cSCC mortality rates are equal to those of renal and oropharyngeal carcinomas and melanomas[17]. The difference between cSCC and

		RR for LR		RR for NM		RR for DSD	
	Risk Factors*	Thompson	Zeng	Thompson	Zeng	Thompson	Zeng
1	Thickness >2 mm	9.64	5.47	10.76	6.11	NR	3.42
2	Thickness > 6 mm	7.13	NR	6.93	NR	NR	NR
3	Invasion beyond subcutaenous fat	7.61	NR	11.21	NR	4.49	NR
4	Perineural invasion	4.30	3.27	2.95		4.06	6.64
5	Tumour diameter > 2 cm	3.22	4.62	6.15	5.01	19.10	ns
6	Primary tumour area						
	Temple	3.20	3.20	2.82	2.77	ns	ns
	Ear	ns	ns	2.33	2.32	4.67	ns
	Lip	ns	ns	2.28	2.15	4.55	ns
7	Poor differentation	2.66	3.54	4.98	6.82	5.65	5.97
8	Immunosuppression (not defined)	ns	ns	1.59	ns	ns**	ns

From the meta-analyses of Thompson et al. 2016 including 36 studies, and Zeng et al. 2020 including 43 studies (the multivariate estimate for each factor was not consistently available in included studies).
NR, not reported.
DSD, disease-specific death; LR, local recurrence; NM, nodal metastasis; ns, not statistically significant; RR, risk ratio.
*Statistically significant ($P < 0.05$).
**Only one included study on immunosuppression and DSD.

Table 2: *Quantification of the risk conferred by the presence of high-risk factors for recurrence, metastasis and disease-specific death; adapted from Dessinioti, C et al.*

Study	Study design, years studied	N, cSCC cases	N, advanced cSCC cases (% of cSCC)	Definition of advanced cSCC	Reported prognostic outcomes in cSCC overall	Reported prognostic outcomes in advanced cSCC
Venables 2019	NCRAS, England, 2013-2015	76.977	Cumulative incidence of mcSCC: 2.1% (median follow-up: 15 m)	Metastatic: nodal or distant metastatic	3-year survival in men: 65% 3-year survival in women: 68%	3-year survival in men: 46% 3-year survivl in women: 29%
Eisemann 2016	12 cancer registries, Germany, 1997-2011	92.108	Regional 1327 (2.2%) Distant metastasis: 194 (0.3%)	Regional: direct extension to adjacent organs/ tissues and/or to regional lymph nodes Distant metastasis	cSCC overall: Absolute 5-year survival: 77.6% Relative 5-year survival: 93.6% Relative 10-year survival: 91.8%	Regional cSCC: Absolute 5-year survival: 48% Relative 5-year survival: 58.3% Relative 10-year survival: 47%
Robsahm 2015	Cancer reistry of Norway, 1963-2011	30.818	641 (2.1%)	Advanced: any infiltration into surrounding structures, regional or distant metastases	Localized in women: 5-year relative survival rates: 0.88 Localized in men: 5-year relative survival rates: 0.82	Advanced in women: 5-year relative survival rates: 0.64 Advanced in men: 5-year relative survival rates: 0.51

N, number; NCRAS, National Cancer Registration and Analysis Service
Table 3: *Studies reporting the population-based incidence and mortality of advanced cSCC; adapted from Dessinioti, C et al.*

these other malignancies is that other malignancies have consistent staging systems and care pathways already established and identified. Unfortunately, there is no universally accepted or consistently applied system for cSCC. The 2018 American Academy of Dermatology cSCC guidelines recommended the BWH system for prognostication and the NCCN stratification for practical clinical guidance[16]. In Canada, there are now immunotherapies such as cemiplimab and pembrolizumab that have been approved for locally advanced or metastatic cSCC. Further work is required to develop a Canadian approach to cSCC. In the interim, using any of the risk factors or staging systems for cSCC discussed in this article will assist in the identification of tumours that are at risk for deleterious outcomes and patients that may benefit from further lymph node evaluation or therapies[14].

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