Chapter 2
Tumor Staging Systems and Prognostic Stratification

Anokhi Jambusaria-Pahlajani

Introduction

Squamous cell carcinoma (SCC) is the 2nd most common cancer diagnosed worldwide with an estimated 186,000–420,000 cases diagnosed per year [1]. While the overall prognosis is excellent, a small subset of tumors recur, metastasize, and cause death. A reported 3.6–4 % of patients develop nodal metastasis and 1.5–2 % die from CSCC according to academic medical center cohort studies [2, 3]. Accurate identification of a high-risk subgroup at risk for these poor outcomes is important for both patients and clinicians. Providing appropriate counseling to low-risk patients can provide them with peace of mind and avoid unnecessary aggressive treatment. Conversely, if a patient's tumor is high-risk, clinicians can be alerted to follow this patient more closely and/or consider adjuvant staging or treatment. This chapter will review the available data on high-risk CSCC, summarize the current staging and prognostic stratification systems, and discuss areas of research that may improve future prognostic stratification systems.

Risk Factors Associated with Poor SCC Outcomes

Risk factors associated with recurrence and metastasis from CSCC in case series studies include size > 2 cm, depth beyond Clark's Level IV or V (reticular dermis or subcutaneous fat), poorly differentiated histology, location on the vermillion lip or ear, perineural invasion (PNI), growth within a chronic scar, recurrent tumors, and

A. Jambusaria-Pahlajani, MD, MSCE (✉)
Department of Dermatology, Mayo Medical School, Mayo Clinic Florida,
4500 San Pablo Road, Jacksonville, FL 32224, USA
e-mail: Jambusaria.anokhi@mayo.edu

C.D. Schmults (ed.), *High-Risk Cutaneous Squamous Cell Carcinoma*,
DOI 10.1007/978-3-662-47081-7_2

patient immunosuppression. There have been several cohort studies that have attempted to identify which of these risk factors are independently associated with poor outcomes and these are summarized in Table 2.1 [2, 4–10, 12]. The number of tumors evaluated in these studies ranged from 149 to 8997. The majority of these studies examined common variables previously associated with poor outcomes including tissue depth, PNI, diameter, location, and histologic differentiation. Five out of nine papers examined the role of immunosuppression [2, 3, 8–10]. Risk factors for regional (nodal) metastasis was reported in six out of nine studies and was the most common outcome studied. In the remaining three studies, recurrence free survival or metastasis free survival was reported. Local recurrence was an endpoint in four of the studies. Risk factors found to be significant predictors of poor outcomes in these studies are explored further below.

Perineural Invasion

The perineurium is a thin membrane that covers nerve fascicles. CSCC tumor cells can invade the space between the nerves and perineurium and track along the nerves in this plane into the central nervous system. Tumors with PNI may exhibit "skip" areas along the nerve track and therefore histologic margins may be imprecise and not be possible in all cases, even with complete circumferential and deep histopathologic margin evaluation [13]. This may explain the higher rate of recurrence and metastasis, even when negative surgical margins are obtained.

Less than 5 % of CSCC tumors exhibit PNI [11, 14]. As the majority of PNI cases occur on the head and neck, the most common nerves involved are the V2 (mandibular) and V3 (maxillary) branches of the trigeminal nerve or branches of the facial nerve [13, 15, 16]. PNI is more common in tumors with other high risk factors, such as recurrent tumors, large tumors, or poorly differentiated tumors [17]. PNI can be divided into incidental PNI, where PNI is noted on histopathology in an asymptomatic patient, or clinical PNI, where the patient has signs or symptoms of PNI.

Tumors with PNI demonstrate a more aggressive biological behavior and have a higher risk of local recurrence, nodal metastasis, and disease specific death according to the studies in Table 2.1. Multivariable analysis in these studies demonstrated that PNI was a significant predictor for at least one outcome of interest in seven out of eight (88 %) studies [2–4, 6, 7, 9, 10]. Of note, in one study, desmoplasia was reported as a significant predictor which was always associated with PNI [2]. Presence of PNI and the associated imprecision of histologic margins is one of the main reasons that clinicians recommend adjuvant radiotherapy or radiologic imaging. However, various levels of PNI appear to have different prognostic implications. For example, clinical PNI (symptomatic PNI with features such as formication, dysesthesias, numbness, etc), PNI of named nerves, or extensive PNI of multiple smaller unnamed nerves has been associated with poor outcomes [18, 19]. More recently, nerve diameter has been identified as a reliable prognostic indicator.

Table 2.1 Published studies reporting adjusted risks of recurrence of cutaneous squamous cell carcinoma

Author, Year	Type of study	Number of tumors	Variables examined	High-risk factors for local recurrence on multivariable analysis	High-risk factors for nodal metastasis on multivariable analysis	High-risk factors for disease specific death on multivariable analysis	High-risk factors for overall survival on multivariable analysis	High-risk factors for recurrence free survival on multivariable analysis
Clayman et al. [4] (2005)	Retrospective Cohort Study of all SCC, single institution	277	Recurrent tumors, tissue depth beyond subcutaneous tissue, PNI, diameter	NR	NR	NR	NR	*Diameter ≥4 cm*- HR 4.5; 95 % CI 1.9–11.1[a] *Perineural invasion*- HR 2.8; 95 % CI 1.2–6.6[a]
Mullen et al. [5] (2006)	Prospective Cohort Study of all SCC, single institution	149	Presence of nodal disease at presentation, tumor diameter >2 cm, presence of scar carcinoma, histologic differentiation	NR	NR	NR	NR	*Regional nodal disease at presentation*- HR 7.6; 95 % CI 3.1–18.6
Brantsch et al. (2008)	Prospective Cohort Study of all SCC, single institution	615	Gender, tumor thickness, diameter, histologic differentiation, desmoplastic growth, location on the ear or vermilion lip, immunosuppression	*Tumor thickness >6 mm*- HR 6.0; 95 % CI 2.7–13.4 *Desmoplasia*- HR 16.11; 95 % CI 6.6–39.5[b]	*Tumor thickness >6 mm*- HR 4.8; 95 % CI 2.2–10.4 *Diameter ≥2 cm*- HR 2.2; 95 % CI 1.2–4.2 *Location on the ear*- HR 3.6; 95 % CI 1.5–8.7 *Immunosuppression*- HR 4.3; 95 % CI 1.6–11.5	NR	NR	NR

(continued)

Table 2.1 (continued)

Author, Year	Type of study	Number of tumors	Variables examined	High-risk factors for local recurrence on multivariable analysis	High-risk factors for nodal metastasis on multivariable analysis	High-risk factors for disease specific death on multivariable analysis	High-risk factors for overall survival on multivariable analysis	High-risk factors for recurrence free survival on multivariable analysis
Kyrgidis et al. [6] (2010)	Prospective Cohort Study of Head and Neck CSCC, single institution	315	AJCC stage (6th Ed), location (excluded lip), PNI, tissue depth, inflammation around tumor, treatment, age of pt at diagnosis, gender, histologic differentiation	NR	*Depth beyond subcutaneous fat*- OR 16.6; 95 % CI 4.7–59	NR	*Histologic differentiation*- good-moderate vs, good (HR 3.9; 95 % CI 1.8–8.3); moderate differentiation vs. good (HR 1.9; 95 % CI 1.2–3.4)	*Increasing T stage*- T2 vs. T1 not significant; T3 vs T1 (HR 11.3, 95 % CI 2.0–62.8); T4 vs T1 (HR 9.7; 95 % CI 2.8–34.2)
					Inflammation- OR 4.0; 95 % CI 1.5–10.6			*N stage*- HR 2.3; 95 % CI 1.2–4.5
							Perineural invasion- HR 2.0; 95 % CI 1.1–3.8	*Inflammation*- HR 2.3; 95 % CI 1.3–4.5
							Inflammation- HR 2.6; 95 % CI 1.5–4.4	*Perineural invasion*- HR 3.3; 95 % CI 1.5–7.4

Brougham et al. [7] (2012)	Prospective Cohort Study of all SCC, central New Zealand	8997	Patient age, gender, diameter (analyzed as continuous variable), histologic differentiation, location, PNI, lymphovascular invasion	NR	NR	NR	NR	*PNI*- HR 5.3; 95 % CI 2.5–11.21[c]
								Location- cheek (HR 3.2; 95 % CI 1.2–8.8), auricular area (HR 3.3; 95 % CI 1.2–9.3), lip (HR 4.8; 95 % CI 1.5–16)[c]
								Poorly differentiated histology- HR 4.3; 95 % CI 2.3–7.9[c]
								Diameter- HR 1.4; 95 % CI 1.3–1.6[c]
Roozeboom et al. [8] (2012)	Retrospective Cohort study of all SCC	224	Location, immunosuppression, tumor diameter (analyzed as a continous variable), tumor thickness (mm), invasion of deeper structures (beyond subcutaneous fat), histologic differentiation, PNI	*Tumor diameter in mm*- HR 1.1; 95 % CI 1.0–1.1	*Location on ear*- HR 21.3; 95 % CI 2.5–182.2[d]	NR	NR	NR
				Tumor thickness in mm- HR 1.3; 95 % CI 1.1–1.5	*Tumor diameter in mm*- HR 1.1; 95 % CI 1.0–1.1[d]			
					Tumor thickness in mm- HR 1.2; 95 % CI 1.1–1.4[d]			
					Invasion of deeper structures- HR 20.8; 95 % CI 4.6–93.7[d]			
					Poorly differentiated histology- HR 15.7; 95 % CI 3.5–70.3[d]			

(continued)

Table 2.1 (continued)

Author, Year	Type of study	Number of tumors	Variables examined	High-risk factors for local recurrence on multivariable analysis	High-risk factors for nodal metastasis on multivariable analysis	High-risk factors for disease specific death on multivariable analysis	High-risk factors for overall survival on multivariable analysis	High-risk factors for recurrence free survival on multivariable analysis
Peat et al. [9] (2012)	Retrospective Case–control Study	170 (92 metastatic, 78 non-metastatic)	Immunosuppression, ulceration, tissue depth, diameter, histologic differentiation, PNI, lymphovascular invasion, incomplete excision	NR	*Poorly differentiated histology:* HR 5.63[d]	NR	NR	NR
					PNI/lymphovascular invasion: HR 4.53[d]			
					Diameter ≥2 cm: HR 3.1[d]			
					Tumor recurrence: HR 2.81[d]			
					Clark level V: HR 2.33[d]			
Jambusaria-Pahlajani et al. [10] (2013)	Retrospective Cohort Study of a subset of high risk SCC, single institution	256	Diameter, location on ear or vermilion lip, tissue depth, immunosuppression, histologic differentiation, PNI, infiltrative histology, age of pt at diagnosis, gender	*Poorly differentiated histology*- SHR 2.5; 95 % CI 0.8–7.5	*Depth beyond subcutaneous fat*- SHR 7.2; 95 % CI 3.1–17.1	*Poorly differentiated histology*- SHR 4.1; 95 % CI 1.1–14.9	*Poorly differentiated histology*- SHR 1.9; 95 % CI 1.1–3.3	NR
				Diameter ≥2 cm- SHR 4.2; 95 % CI 1.4–13.3	*Poorly differentiated histology*- SHR 3.3; 95 % CI 1.4–7.8	*Diameter ≥2 cm*- SHR 3.7; 95 % CI 0.9–15.1	*Diameter ≥2 cm*- SHR 2.6; 95 % CI 1.5–4.3	
				Immunosuppression- SHR 3.5; 95 % CI 1.2–10.7	*Perineural invasion*- SHR 2.2; 95 % CI 0.9–5.1	*PNI*- SHR 3.4; 95 % CI 0.9–13.3		
						Depth beyond subcutaneous fat- SHR 4.1; 95 % CI 1.3–13.4		

Schmults et al. [11] (2013)	Retrospective Cohort Study of all SCC, single institution	1818	Diameter, location on ear or lip, diameter, tissue depth, immunosuppression status, histologic differentiation, PNI, infiltrative histology, age of pt at diagnosis, gender	*Diameter ≥2 cm*- SHR 5.8; 95 % CI 3.1–11.2	*Diameter ≥2 cm*- SHR 9.9; 95 % CI 3.5–27.7	*Diameter ≥2 cm*- SHR 17.2; 95 % CI 5.2–57.4	No significant variables found	NR
				Poorly differentiated histology- SHR 4.1; 95 % CI 2.3–7.4	*Poorly differentiated histology*- SHR 7.3; 95 % CI 2.9–18.3	*Poorly differentiated histology*- SHR 8.6; 95 % CI 3.0–24.2		
				Depth beyond subcutaneous fat- SHR 7.0; 95 % CI 3.3–14.8	*Depth beyond fat*- SHR 7.4; 95 % CI 2.2–25.1	*Depth beyond subcutaneous fat*- SHR 10.7; 95 % CI 3.3–34.8		
				PNI- SHR 3.8; 95 % CI 1.8–8.0		*PNI*- SHR 4.7; 95 % CI 1.5–15.0		
				Ear/temple location- SHR 3.3; 95 % CI 1.5–7.3		*Ear/temple location*- SHR 5.4; 95 % CI 1.3–23.2		

NR not reported
[a]Disease specific survival
[b]Always associated with PNI in this dataset
[c]Metastasis free survival
[d]Outcome reported in manuscript as metastasis

PNI of small caliber nerves (<0.1 mm diameter) have a very low rate of local recurrence, nodal metastasis, and disease specific death, particularly if no other high risk factors are present (moderate or poor differentiation, diameter ≥2 cm, or deep invasion beyond the subcutaneous fat). Conversely, if there is PNI of large caliber nerves ≥ 0.1 mm diameter, there is an elevated risk of poor outcomes and this risk increases further if other risk factors are present [20, 21].

Desmoplastic or Sclerosing Growth Pattern

Desmoplasia is defined as the induction of activated fibroblasts and subsequent production of a densely collagenous stroma in the tissue surrounding the tumor. Typically, the periphery of desmoplastic SCC consists of fine branches of atypical tumor cells and a prominent trabecular/infiltrative growth pattern. Unfortunately, the role of desmoplasia has not been well studied, as it is not reported routinely on pathology reports at many institutions. In a study of 44 CSCCs where at least 1/3 of the tumor mass met criteria for desmoplasia, the rate of local recurrence, nodal metastasis and both local recurrence and nodal metastasis was 27.3 % (n = 12), 22.7 % (n = 10), and 15.9 % (n = 7) respectively. This was in stark contrast to rates of local recurrence and/or nodal metastasis in the comparison group with no evidence of desmoplasia (1.1–3.8 %). Only one study has evaluated the role of desmoplasia in tumor recurrence when adjusting for other known risk factors and found that tumors with desmoplasia were 16 times more likely to develop a local recurrence (95 % CI 6.6–39.5). In this study, desmoplastic growth was always associated with PNI, suggesting these two variables may be colinear making it difficult to know the contribution of each to poor outcomes [2]. In a similar study of 73 desmoplastic CSCCs, where at least 50 % of the tumor met criteria for desmoplasia, PNI was present in 53 (73 %) cases. During a median follow-up of 36 months, 100 % of tumors treated with cryotherapy or electrodessication and curettage (n = 7) locally recurred, 80 % of tumors treated with wide local excision (n = 15) locally recurred, and 9 % of tumors treated with Mohs micrographic surgery (n = 34) locally recurred. The rate of local recurrence after Mohs micrographic surgery dropped to 3 % when postoperative adjuvant radiotherapy was added after clear surgical margins were obtained. No patients developed regional nodal metastasis [22].

Tumor Diameter

Tumor clinical diameter most often is measured at the initial office visit based on the pre-biopsy clinical examination. As a general rule, tumors with a larger diameter have a greater risk of recurrence. The relationship is likely linear and continuous. However, investigators have often used defined but somewhat artificial prognostic cut-points to facilitate care recommendations. Tumor diameter was a significant

predictor of recurrence in seven out of eight studies in Table 2.1 [3–5, 7–10]. Five papers reported diameter dichotomously [2–4, 9, 10], while the remaining two studies examined tumor diameter as a continuous variable [7, 8]. When diameter was examined as a dichotomous variable, the majority of studies found an increase in rates of recurrence in tumors ≥ 2 cm [2, 3, 9, 10]. Therefore, clinical tumor diameter ≥2 cm is the keystone risk factor in prior AJCC and UICC tumor staging systems. In Clayman, et al. a 4 cm diameter cutoff was significant, with tumors ≥4 cm in diameter being 4.5 times more likely to recur than those <4 cm [4]. Jambusaria-Pahlajani et al. found that when other size cutoffs were tested, 2 cm remained the optimal cut-point to differentiate low vs. high risk tumors. Roozeboom et al. and Brougham et al. evaluated tumor diameter as a continuous variable and found that there was a significantly higher risk for recurrence and metastasis in larger tumors (Table 2.1) [7, 8].

Location

For over 30 years, the "mask areas" of the face, which include the periorbital area, nose, periauricular area, lateral face and temples have been considered high-risk locations [23]. More recent studies using multivariate modeling indicate location may have a lesser impact than previously thought [3, 6–8, 10]. Locations associated with worse outcomes include the ear [3, 7, 8], cheek [7], lip [7], and temple [3]. However, it is important to note that four of nine studies did not find location to be an independent risk factor (Table 2.1).

Current prognostic stratification systems include location on the lip or ear as a high-risk site (Table 2.2). The inclusion of the lip is a result of several reports demonstrating an above-average risk of poor outcomes in this subgroup [24–27]. In the largest study of 1252 lip tumors, of which 96 % were squamous cell carcinomas, there were 118 (9.4 %) local recurrences, 95 (7.6 %) cervical metastasis, and 75 (7.2 %) disease specific deaths [24]. However, this study may have had an over-representation of tumors with other risk factors which led to poor outcomes overall. For example, tumors that were >3 cm diameter, had nodal metastasis at the time of presentation, or were poorly/undifferentiated had lower survival rates. In a similar retrospective study of 38 lower lip SCCs without metastasis and 16 SCCs that metastasized to the lymph nodes, those that developed metastasis were more likely to be >2 cm diameter, poorly differentiated or undifferentiated, and >6 mm in thickness. In five studies from Table 2.1 that included lip as a potential predictive variable [2, 3, 7, 8, 10], only one found location on the lip as an independent risk factor (for recurrence free survival).

The precise anatomic area(s) of the lip that portend a higher risk of recurrence warrants further discussion, as this has been an area of confusion in the literature and staging systems. The lip is divided into three distinct zones (Fig. 2.1). (1) The *mucosal lip* (also referred to as the wet lip) extends from the junction of the wet and dry mucosa of the lip posteriorly into the oral cavity. (2) The *vermilion lip*

Table 2.2 Definition of risk factors

	AJCC 7th Edition	UICC 7th Edition	NCCN 2014
Diameter	>2 cm diameter	>2 cm diameter	≥2 cm on the trunk and extremities (excluding the hands/feet/pretibia), ≥ 1 cm on the cheeks, forehead, scalp, neck and pretibia, or ≥0.6 cm on the mask areas of the face (central face, eyelids, eyebrows, periorbital, nose, lips (cutaneous and vermilion), chin, mandible, ears, temple, pre-auricular and postauricular skin/sulci), genitalia, hands and feet
Depth	>2 mm thickness	>4 mm thickness	≥2 mm thickness
	Clark Level ≥ IV	Clark Level ≥ IV	Clark level ≥ IV
Invasion of nerves/vessels	Perineural invasion	Perineural invasion	Perineural invasion
		Lymphovascular invasion	Vascular invasion
Anatomic location	Ear	Ear	As above in NCCN size criteria
	Cutaneous lip	Vermilion lip	
Histology	Poorly differentiated	Poorly differentiated	Poorly differentiated
	Undifferentiated	Undifferentiated	Adenoid (acantholytic), adenosquamous, or desmoplastic subtype
Historical/clinical factors	Not applicable[a]	Not applicable[a]	History of XRT
			Development of tumor in chronic inflammatory process
			Patient immunosuppression
			Recurrent tumors
			Clinically ill-defined borders
			Neurologic symptoms

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com; and permission from Sobin, LH, Gospodarowicz MK, Wittekind, C. TNM Classification of Malignant Tumours, 7th ed. New York: Wiley; 2009; and with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Basal Cell and Squamous Cell Skin Cancers V.2.2014. © National Comprehensive Cancer Network, Inc 2014. All rights reserved. Accessed [2/6/14]. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

[a]AJCC and UICC do not include clinical factors as risk factors (with the exception of clinical tumor diameter)

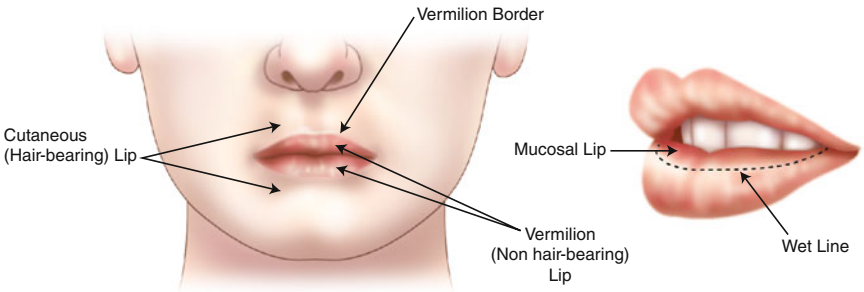

Fig. 2.1 The lip is divided into three distinct zones: mucosal lip, vermilion lip, and cutaneous lip. The wet line divides the mucosal and vermilion lip while the vermilion border divides the vermilion lip and cutaneous lip

(also referred to as non-hair bearing lip) begins at the exterior edge of the intraoral labial mucosa and extends outwards, terminating at the extraoral labial-cutaneous junction (also known as the vermilion border). (3) The *cutaneous lip* (also referred to as hair bearing lip) begins at the vermillion border and extends outwards onto hair bearing skin and approximates the area of skin overlying the orbicularis oris muscle. The high-risk zones of the lip are not consistent between published studies. In the five studies examining the role of lip location on CSCC outcomes, two defined it as tumor arising on the vermilion lip, whereas the remaining three did not specify the lip boundaries.

In AJCC staging, different zones of the lip are staged using different staging systems. According to the AJCC, tumors arising on the mucosal lip should be staged using the Lip and Oral Cavity Staging System, rather than the CSCC staging system. However, the boundaries of the mucosal lip defined in the AJCC manual differ from the standard definition of mucosal lip stated above. In the 7th Edition AJCC Lip and Oral Cavity Staging Manual, the mucosal lip "begins at the junction of the vermilion border with the skin and includes only the vermilion surface or that portion of the lip that comes into contact with the opposing lip". This definition is problematic since the vermillion lip does not come into contact with the opposing lip. The portion of the lip that comes into contact with the opposing lip describes the wet-dry line which is the junction between the vermillion and mucosal lip. Based on the biological behavior of SCC arising on different zones of the lip, it makes more sense to include SCC on the vermilion lip with the CSCC staging system as tumors arising on the vermilion lip are sun induced tumors, similar to SCC elsewhere on the skin. In contrast, SCC arising on the mucosal lip is a non-sun induced SCC that is often virally induced and therefore more akin to SCC arising elsewhere in the oral mucosa.

Tumors arising on the cutaneous lip are clearly staged using the SCC Staging System and this location is considered a high-risk feature for T staging. However, it is likely that most of the increased risk of poor outcomes associated with lip location

is due to vermillion lip involvement. There is no zone of adipose tissue between skin and muscle on the vermillion lip so tumors arising on the vermillion lip more quickly have access to the increased lymphovascular space of muscle and thus higher potential for metastasis.

The UICC defines location on the vermilion lip as a high-risk location [28] (Table 2.2), while the National Comprehensive Cancer Network® (NCCN®) includes both the vermilion and cutaneous lip as a high-risk location as long as the tumor is ≥0.6 cm[1] (Table 2.2).

Thickness/Depth

The vertical growth of a tumor can be measured either by tissue level (Clark's level) or millimeter depth (Breslow's depth). When Breslow's depth is used, the tumor should be measured from the stratum granulosum down to the deepest portion of the tumor. However, since the stratum granulosum is lost in SCC, it must be measured from the adjacent normal skin and this is not always provided on biopsy. It is important that the exophytic component of the tumor not be included in the final measurement. Another difficulty in using Breslow depth is that most CSCCs are diagnosed with a shave biopsy and therefore are often transected or only partially sampled. In these cases, millimeter depth is either not possible to assess or may be inaccurate. Millimeter depth is not routinely reported by most dermatopathologists [29] and may not be feasible in clinical practice given the high number of CSCC diagnoses rendered by pathologists. Tissue level depth is easier to evaluate and pathologists tend to report when tumors penetrate beyond the dermis. However, it is unknown whether tissue level (Clark's level) or millimeter depth (Breslow's depth) is of greater prognostic significance.

In studies examining independent risk factors for poor outcomes (Table 2.1), tumor depth (either mm or tissue level) is an independent significant predictor of any recurrence in six out of seven studies [2, 3, 6, 8–10]. Four studies measured depth by Clark's level; three of these studies found invasion beyond the subcutaneous fat to be an important predictor of poor outcomes [3, 6, 10] whereas one study found invasion of the subcutaneous fat as well as deeper structures to be a prognostic factor. Despite this evidence that invasion into the subcutaneous fat or deeper structures (Clark's level V or greater) is a high-risk factor, the AJCC and UICC continue to identify more superficial invasion (Clark's level IV/papillary dermis or greater) as a high-risk feature.

[1] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Basal Cell and Squamous Cell Skin Cancers V.2.2014. © National Comprehensive Cancer Network, Inc 2014. All rights reserved. Accessed [July 7, 2014]. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

Two of six studies examined the prognostic significance of millimeter depth. One study measured millimeter depth for each CSCC and found a 0 % risk of metastasis in tumors <2 mm [2]. The metastatic risk increased with increasing depth from 4.0 to 4.5 % for tumors between 2.1–6.0 mm, and 15–16 % for tumors ≥6.0 mm [2, 30]. On multivariable analysis, thickness ≥6 mm remained significant with a HR of 5.98 (95 % CI 2.06–17.37) for local recurrence and 5.88 (95 % CI 2.36–14.69) for nodal metastasis. Roozeboom et al. found that increased millimeter depth carries a significantly higher hazard of local recurrence and metastasis with a 30 % increased risk of local recurrence and 10 % increased risk of nodal metastasis for each 1 mm increase in tumor depth [8]. In an analysis of 81 patients with metastatic CSCC with a reported tumor millimeter depth, 65 % of these cases had a tumor depth >4 mm [31]. Therefore, the available data point towards a prognostic threshold somewhere between 2 and 6 mm. Additional prognostic studies of CSCC will help to clarify the prognostic contributions of tissue level vs. millimeter depth and establish the most useful prognostic cut-points. The methods for measuring millimeter depth have not been clearly reported in prior studies. A standardized methodology needs to be developed for SCC since the granular layer used in melanoma is often lost in SCC and large exophytic components such as those seen in keratoacanthoma may not have prognostic significance and should likely be discounted. Measuring from the basal cell layer immediately adjacent to the tumor to the tumor base may be the most practical way of measuring millimeter depth in SCC.

Histologic Differentiation

SCC is categorized based on the degree of differentiation into well-differentiated, moderately differentiated, poorly differentiated/undifferentiated subtypes. Histopathologically, well-differentiated tumors have abundant squamous epithelium demonstrating keratinization. Intercellular bridges between epithelial cells are readily apparent. Tumor cells are not pleomorphic and if mitotic figures are present, they are typically at the base of the tumor only. Moderately differentiated tumors possess greater structural disorganization when compared to well-differentiated SCC. The squamous derivation of cells is less obvious with keratinization being limited to presence of keratin 'pearls', horn cysts, or scattered individually keratinized cells. At the cellular level, there is significant cellular pleomorphism and atypical mitotic figures are common. Poorly differentiated or undifferentiated tumors are often difficult to characterize as being epithelial in origin and may thus require additional immunohistochemical stains to establish the diagnosis. Keratinization is not a prominent feature. Typically, significant pleomorphism and numerous mitotic figures are present. Desmoplasia (a stroma with increased numbers of activated fibroblasts) is also often seen in association with poor differentiation. If features of more than one category of differentiation are present within the tumor, tumors should be characterized based on the least differentiated area, even if it constitutes a minority of the tumor. Classification of the

differentiation of tumors may be somewhat subjective (e.g. number of mitoses upstages tumors from well to moderately differentiated and from moderately to poorly differentiated but standard mitotic count thresholds for upgrading do not exist). Therefore differentiation classifications can vary amongst pathologists [32].

Several studies have identified an increased risk of local recurrence, nodal metastasis, and disease specific death in tumors with poorly differentiated or undifferentiated histology (Table 2.1). Poorly differentiated histology was identified as an independent predictor of recurrence in six of eight studies [3, 6–10]. The largest of these studies found that patients with poorly differentiated tumors had a significantly elevated risk of nodal metastasis (HR 4.3; 95 % CI 2.3–7.9) [7]. The impact of moderately differentiated histology on prognosis has yet to be fully elucidated. In one study, moderately differentiated tumors had a lower survival than well differentiated tumors (HR 1.9; 95 % CI 1.2–3.4), but the risk was lower than for poorly differentiated tumors [6].

Immunosuppression

This topic is covered more fully in Chap. 10.

Patients with conditions that result in defective CD4 T cell immunity, such as that seen in solid organ transplantation, HIV, and chronic lymphocytic leukemia (CLL), have a higher morbidity and mortality from CSCC than nonimmunosuppressed patients. The majority of the data regarding the relationship of immunosuppression and CSCC development are in the solid organ transplant population. Transplant patients are at higher risk of developing aggressive cutaneous malignancies (defined as tumors with extensive local infiltration, regional metastasis at diagnosis, poor differentiation, and locoregional/systemic relapse following treatment). The risk of developing an aggressive cutaneous malignancy is approximately 4.4–10 % during the post-transplant period [33, 34]. CLL patients have an elevated risk of developing high-risk SCC's as well. In a case control study of 28 CLL patients with SCC, the CLL group was more likely to develop metastasis or die from their SCC than the non-CLL group (11 % in the CLL group and 0 % in the control group) [35]. In fact, patients with advanced CLL (Rai stage III/IV) have as high a risk of dying from CSCC as they do from CLL (12 %), regardless of whether the CLL is in remission. Thus CSCC is a major cause of morbidity and mortality in CLL patients [36]. HIV patients also have defective T cell immunity and may therefore be at higher risk of recurrence from SCC. In a cohort study of 1202 patients, of which 34 were HIV positive, CSCC arising in the HIV positive patients were 9.6 times more likely to recur ($p<0.01$) than CSCC occurring in healthy patients over a 5 year period [37].

In the majority of studies examining overall prognostic factors for CSCC (Table 2.1), the number of tumors arising in immunosuppressed patients is low [2, 3, 10], which limits study of the relative contribution of immunosuppression towards risk

of poor outcomes compared to other well-known prognostic factors. Two cohort studies have identified immunosuppression as an independent risk factor for recurrence. Jambusaria-Pahlajani et al. found immunosuppression increased the risk of local recurrence (SHR 2.5; 95 % CI 1.2–10.7) [10] and Brantsch et al. found immunosuppression was associated with a 4.3-fold higher risk of nodal metastasis (95 % CI 1.6–11.5) [2].

Published Consensus Statements on High-Risk Criteria

The American Joint Committee on Cancer (AJCC) [38], Union for International Cancer Control (UICC) [28], and NCCN® (see footenote 1) have all published consensus statements on the criteria for high-risk CSCC. All three groups have developed these criteria based on consensus opinion and review of available data summarized above. While the AJCC and UICC have developed staging systems based on these high-risk criteria, the NCCN recommends differential treatment options for low-risk vs. high-risk tumors. The definitions of high-risk for each of the three groups are detailed in Table 2.2 and include tumor diameter, depth, invasion of nerves/vessels, tumor location, histopathologic differentiation and other historical or clinical factors.

Important discrepancies in the definition of high-risk between the groups are:

1. While the AJCC and NCCN have a diameter cutoff of 2 cm for high-risk regardless of location, the NCCN uses smaller diameter cutoffs for tumors on the head and neck, hands, feet, and genitalia. In the NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®), tumors that are ≥0.6 cm on the "mask areas" of the face (central face, eyelids, eyebrows, periorbital area, nose, vermillion lip, cutaneous lip, chin, mandible, ear, pre-auricular and post-auricular skin), genitalia, hands, and feet are considered high-risk. Tumors on the cheeks, forehead, scalp, neck and pretibia that are ≥1 cm and tumors ≥2 cm elsewhere on the trunk and extremities are defined as high-risk.
2. The AJCC and NCCN identify tumors >2 mm thick as high risk while the UICC categorizes tumors >4 mm thick as high risk.
3. There is no mention of lymphovascular invasion as a high-risk feature in AJCC, but it is noted in UICC and NCCN.
4. Location on the vermilion lip is considered high-risk in AJCC and UICC, whereas NCCN defines location on either the cutaneous or vermillion lip as high risk (as long as the tumor is ≥0.6 cm).
5. Certain histologic SCC subtypes (e.g. adenoid, adenosquamous, desmoplastic) are considered high-risk in NCCN, but not AJCC or UICC criteria.

Despite the discrepancies, these variables likely identify tumors with a high risk of poor outcomes. NCCN Guidelines® state that any SCC having one of its high-risk criteria can be excised with either Mohs surgery (or another form of complete circumferential peripheral and deep margin assessment with frozen or permanent sections)

or wide local excision with a surgical margin greater than 6 mm and linear or delayed repair (no flap or graft closures until clear margins are histologically verified). If margins are positive after wide local excision, Mohs surgery or resection with complete circumferential peripheral and deep margin assessment is recommended. As most high-risk CSCC occurs on the head and neck, there are relatively few high risk SCCs where excision can be done with wide margins and closed in a linear fashion; thus Mohs surgery or another form of complete circumferential peripheral and deep margin assessment is routinely employed. See Chap. 6 for a full discussion of the surgical management of high-risk SCC.

Tumor Staging Systems

Cancer staging is important for both patients and clinicians. Staging aids the clinician in the planning of cancer treatment and can help to standardize treatment across patients. For patients, it provides some indication of prognosis and for those diagnosed with early stage cancer, it provides them with the peace of mind that their cancer is unlikely to recur. Finally, unified cancer staging allows for clear communication amongst health care providers and promotes advances in treatment of cancer by providing rationales for inclusion criteria in clinical trials and providing structure for treatment recommendations and evaluation of their impact.

A clinically useful staging system possesses several important qualities. First, it must be distinctive in that it groups tumor characteristics such that survival differs between tumor stages. Second, it must be monotonous in that survival decreases with increasing stage, ideally with equal differences in survival between consecutive stages. Finally, it must be homogenous with similar survival rates within an individual stage [39]. From a practical standpoint, staging systems should be easy to interpret and incorporate into daily practice. In tumors where the risk of poor outcomes is low overall as with CSCC, staging systems should be able to concentrate those who are at highest risk of developing poor outcomes into the highest stage group [40].

History of Cancer Staging Systems

The concept of developing unified cancer staging began in the early 1930s, when cancer researchers recognized the need to standardize classification of cancer in order to share knowledge and expertise globally. To achieve this, the International Union for Cancer Control (UICC) was formed. In the 1940s that the Tumor-Lymph Node-Distant Metastasis (TNM) Classification System which is still used today was developed by Pierre Denoix [41]. Dr. Denoix astutely observed that patients with localized cancer tended to have better outcomes than those with cancer that had already spread beyond the primary site. He developed a system that took into account

not only the extent of the tumor in the primary site (T Stage) but also extent of tumor in distant organs (regional lymph nodes and distant organs, N and M Stage, respectively). This TNM classification was adopted by the UICC in the 1950s and served as the basis for cancer staging across all body sites. In 1958, the Committee on Clinical Stage Classification published the first cancer staging book for breast and laryngeal cancer. One year later, the American Joint Committee on Cancer (AJCC) was developed to complement the work of the UICC and published its own cancer staging manual. Since the 1980s, the AJCC and UICC have been coordinated and publish revisions of their cancer staging manuals simultaneously. Revisions of staging systems occur every 6–8 years, allowing ample time for advances in cancer care to be incorporated into the newer versions [28, 38].

Refinements to the UICC and AJCC staging systems are typically based on expert consensus evaluation of high-quality data from large population-based registries. For example, addition of mitotic rate to the melanoma staging system was due to analysis of the AJCC Melanoma Staging Database, which included outcome data for greater than 60,000 melanoma patients across the world. Unfortunately, there are no active population-based registries for CSCC, and therefore limited outcome data, which has hindered development of accurate prognostic stratification systems for CSCC.

Rules of the TNM Classification System and Staging

As the TNM classification system is the foundation of any tumor staging system, the AJCC and UICC have provided clinicians with general guidelines on how to classify tumors:

1. Pathologic documentation of a malignancy must be confirmed before TNM categories are assigned to an individual tumor.
2. The TNM system is primarily a dual system where classification is done based on clinical data and then once again when pathological data is obtained. In general, clinical TNM helps to choose the appropriate treatment whereas pathologic TNM is important for prognosis and decision to perform adjuvant treatments. Clinical staging occurs prior to treatment of primary tumor or within 4 months of diagnosis (whichever is shorter), as long as the cancer has not clearly progressed. It may take into account factors acquired prior to treatment, such as physical examination, results of imaging studies, histopathologic findings, and surgical exploratory procedures. A lowercase “c” prior to the T, N, and/or M designates a clinical stage. Pathologic staging occurs post-surgically or within 4 months after the date of diagnosis (whichever is longer), as long as the cancer has not clearly progressed. It is based on the factors taken into clinical staging as well as evidence acquired during treatment of the primary tumor and subsequent histopathologic review. A lowercase “p” prior to the T, N, and/or M identifies a pathologic confirmation was made. A designation of “X” after the T and/or N indicates

that the stage could not be adequately assessed. MX is not considered a valid category as if there is no evidence of metastasis, cM0 should be assigned.

3. In cases where there is documented progression of cancer prior to the initiation of therapy or surgery, TNM classification should be based on information obtained prior to disease progression.
4. If there is doubt regarding the T, N, or M category to which a tumor should be assigned, the lower category should be chosen. For example, if a CT scan shows a small lymph node in the draining basin of a high-risk SCC that is not amenable to biopsy, the tumor should be staged as N0 despite the concern for metastatic disease.
5. For patients that develop two or more synchronous primary tumors in a single organ (e.g. three synchronous CSCCs in a transplant recipient), the tumor with the highest T stage should be classified and a designation of multiplicity (m) or number of multiple tumors should be reported in parentheses (e.g. T2(m) or T2(3)). If metachronous primary tumors occur in a single organ (patient develops two independent cancers at different time points), each tumor should be staged separately.
6. If there is direct extension of the primary tumor into the lymph node, it is defined as a lymph node metastasis. Metastasis in a lymph node other than the draining nodal basin is considered a distant metastasis. Table 2.3 lists regional lymph node basins by primary tumor site. In cases where the N classification is based on the size of metastasis, the critical discrimination points are based on the measurements of the metastatic foci within lymph nodes, not measurements of the lymph nodes themselves (unless specified otherwise in disease-specific rules).

Table 2.3 Draining lymph node basin by primary tumor location [42]

Location	Draining nodal basin
Head, neck	Ipsilateral preauricular, submandibular, cervical, and supraclavicular lymph nodes
Thorax	Ipsilateral axillary lymph nodes
Upper limb	Ipsilateral epitrochlear and axillary lymph nodes
Abdomen, loins, buttocks	Ipsilateral inguinal lymph nodes
Lower limb	Ipsilateral popliteal and inguinal lymph nodes
Anal margin and perianal skin	Ipsilateral inguinal lymph nodes
Boundary zones[a]	
Right/left	Midline
Head,neck/thorax	Clavicular-acromion-upper shoulder blade edge
Thorax/upper limbs	Shoulder-axilla-shoulder
Thorax/abdomen,loins,buttocks	Front: middle abdomen between navel and costal arch
	Back: lower border of thoracic vertebrae (mid-transverse axis)
Abdomen,loins,buttock/lower limb	Groin-trochanter-gluteal sulcus

[a]4 cm wide bands along these anatomic zones are considered boundary zones and may drain to either side lymph nodes

Reprinted with permission from Wittekind Ch, Compton CC, Brierley J, and Sobin LH. *TNM Supplement: A Commentary on Uniform Use*. 4th Ed, Wiley-Blackwell 2012

The final cTNM classification and tumor stage should be established just prior to initiating treatment or before making the decision to not treat. Once the final pTNM and stage has been assigned, it must remain unchanged. Once cTNM or pTNM classifications have been made, they are grouped into stages (Stages 0–IV) based on permutations and combinations of T, N, and M categories that place patients in clearly defined risk groups. Traditionally, Stage 0 is reserved for non-invasive cancer and Stage IV is reserved for cancer that has spread to distant sites. Stages I, II, and III are intermediate categories, with increased tumor burden and decreased survival with increasing stage.

In addition to the clinical and pathologic TNM classifications, three additional sub-classifications may be described for each site:

1. ycTNM or ypTNM- Post-therapy classification to assess extent of cancer after neoadjuvant or primary systemic and/or radiation therapy. These patients should also have a clinical TNM classification documented prior to starting treatment.
2. rTNM- Retreatment or recurrence classification. This is utilized when the tumor has recurred after a disease free interval or progressed.
3. aTNM- Autopsy classification. This is typically done when the first classification is performed during autopsy.

There are optional patient and tumor parameters that may be documented in addition to the TNM classification. Tumor histopathologic grade or presence of perineural/lymphovascular invasion are features that may be recorded. As the current system tries to group tumors into prognostic categories independent of treatment and it is well known that residual tumor after treatment often impacts further management and prognosis, the Residual Classification can also be recorded to document the margin status after surgery. These classification systems are described in Table 2.4. Finally, a designation of "i" can be included after the TNM stage to designate the tumor arose in an immunosuppressed individual (e.g. T2N0M0i). Based on the 2010 AJCC recommendation, only centers that are studying CSCC are encouraged to document immunosuppression status. Currently, the TNM classification system does not provide designations for other clinical risk factors, such as history of XRT or tumor formation in a chronic ulcer.

Current Staging Systems

The AJCC and UICC have both published staging systems for CSCC. Up until very recently, these two systems grouped cutaneous squamous cell carcinoma (CSCC) with other nonmelanoma skin cancers, including basal cell carcinoma (BCC). Due to the varied biological behavior between these tumors, the recent 7th edition of the AJCC created a staging system for CSCC separate from BCC [38]. The UICC staging system continues to group CSCC with BCC [28].

Table 2.4 AJCC and UICC optional descriptors [28, 38]

Grading classification		Lymphatic classification		Perineural classification		Venous invasion		Residual tumor classification	
Gx	Grade or differentiation cannot be assessed	LX	Lymphatic invasion cannot be assessed	PnX	Perineural invasion cannot be assessed	VX	Venous invasion cannot be assessed	R0	No residual tumor
G1	Well differentiated	L0	No lymphatic invasion	Pn0	No perineural invasion	V0	No venous invasion	R1	Microscopic residual tumor (Tumor identified microscopically at margin)
G2	Moderately differentiated	L1	Lymphatic invasion	Pn1	Perineural invasion	V1	Microscopic venous invasion	R2	Macroscopic residual tumor (Tumor identified grossly at margin)
G3	Poorly differentiated[a]					V2	Macroscopic venous invasion	RX	Presence of residual tumor cannot be assessed
G4	Undifferentiated[a]								

[a]In some circumstances, G3 and G4 can be combined

7th Edition AJCC Staging System

The development of a new CSCC staging system was part of a multidisciplinary effort which included dermatologists, otolaryngology head and neck surgeons (ENT surgeons), surgical oncologists, dermatopathologists, medical oncologists, plastic surgeons and oral and maxillofacial surgeons. This task force reviewed the available outcome data on CSCC. Given most studies analyzing early stage CSCC are retrospective in nature or do not conduct multivariable analysis, the Stage I and II revision was primarily based on consensus opinion of the AJCC task force. CSCC on any part of the body can be staged using this system, with the exception of eyelid SCC which is staged with the Carcinoma of the Eyelid staging system. Because the majority of CSCC tumors occur on the head and neck, the 7th edition AJCC staging system for SCC was developed to parallel the AJCC Head and Neck Cancer staging system.

For accurate staging, the AJCC recommends the following factors be collected on a routine basis: Tumor thickness (in mm), Clark's level, presence vs. absence of perineural invasion, primary site location on the ear or cutaneous lip, histologic grade based on the recommended grading system, and size of largest lymph node metastasis.

T Classification

The current Tumor (T) classification system (Tables 2.5 and 2.6) incorporates several clinical and pathologic risk factors including diameter >2 cm, >2 mm thickness, Clark level ≥IV (reticular dermis), perineural invasion, location on the ear or hair-bearing lip, or poorly differentiated or undifferentiated histology.

Clinical diameter size >2 cm was identified as the sentinel high-risk feature to differentiate T1 vs. T2 tumors for two main reasons. First, it has been shown in multiple studies to be independently associated with tumor recurrence. Second, this breakpoint allowed for congruence between cutaneous and head and neck SCC staging systems. In the 6th edition AJCC staging, size ≥5 cm was a significant breakpoint. The task force argued that prognostically important cutoffs other than 2 cm were difficult to establish based on available data, and therefore the 5 cm threshold was removed.

Other risk factors of importance include depth (>2 mm or Clark level ≥ IV), location on the cutaneous lip or ear, poorly differentiated or undifferentiated histology, and perineural invasion. As there is evidence that tumors ≤2 cm have the potential to metastasize, particularly when one or more of the other risk factors are present, those factors were incorporated into T classification. The task force felt that there was insufficient evidence to accurately categorize each remaining factor into stage specific locations. Therefore, these risk factors were treated with equal weight and grouped as "high-risk" with presence of ≥2 features upstaging to T2 classification.

Table 2.5 AJCC 7th edition TNM staging system definitions

T classification		N classification		M classification	
Tx	Primary tumor cannot be assessed	Nx	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumor	N0	No regional lymph node metastasis	M1	Distant metastasis
Tis	Carcinoma in-situ	N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension		
T1	Tumor 2 cm or less in greatest dimension with less than two high-risk features[a]	N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension		
T2	Tumor greater than 2 cm in greatest dimension or tumor of any size with to or more high-risk features[a]	N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension		
T3	Tumor with invasion of maxilla, mandible, orbit, or temporal bone	N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
T4	Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base	N3	Metastasis in a lymph node, more than 6 cm in greatest dimension		

[a]High-risk features: depth >2 mm thickness, Clark level >=IV, perineural invasion, primary site ear, primary site cutaneous lip, poorly differentiated or undifferentiated histology

Table 2.6 AJCC 7th edition TNM staging

Stage	**T**	**N**	**M**
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	Any T	N3	M0
	T4	Any N	M0
	Any T	Any N	M1

N Classification

The lymph node classification system was adopted to mirror the staging system for head and neck mucosal SCC (e.g. larynx, oral cavity). While adopting an established staging system has advantages such as familiarity, it was not developed based on primary outcome data from CSCC. In this system, N0 indicates there is no evidence of regional metastatic disease. If regional lymph node disease is present, the N classification divided into three main groups (N1, N2, and N3) based on the size of the metastatic focus and number of lymph nodes involved. N2 is further divided into three groups (N2a, N2b, and N2c) based on the laterality (ipsilateral vs. contralateral) of the lymph node and size of the metastatic focus (<3 cm, ≥3 cm but less than 6 cm, or ≥6 cm) (Tables 2.5 and 2.6).

Lymph node involvement in a non-regional draining basin is classified as distant metastasis. Table 2.3 lists the regional lymph node basins based on anatomic site of primary tumor. Lymph node drainage from head and neck CSCC can be ambiguous due to disparate drainage between patients as well as potential for contralateral drainage if the tumor is near the midline. Therefore classification of positive lymph node involvement as regional or metastatic can be subjective, particularly if the tumor is midline.

M Classification

The current Metastases (M) classification system is dichotomous, where M0 designates no metastatic disease and M1 designates presence of distant metastasis. A classification of M0 is inferred unless M1 status is known.

Stratification of TNM Classifications into Stages

The Task Force then combined the various permutations of the TNM classification into specific stages. (See Tables 2.5 and 2.6) In the 7th edition AJCC staging system, the task force did not discuss the rationale for these stage groupings. Stages 0–II are relatively straightforward with Stage 0 reserved for intraepidermal squamous cell carcinoma, Stage I indicative of a T1N0M0 tumor, and Stage II used for a T2N0M0 tumor. There are several TNM classifications that categorize Stage III or Stage IV tumors. Stage III tumors include T3 tumors with no evidence of nodal or distant metastasis or T1–T3 tumors with metastatic focus in a single ipsilateral lymph node <3 cm in diameter. Stage IV tumors are for the remainder of the TNM classifications.

7th Edition UICC Staging System

The UICC organizes CSCC staging based on tumor diameter and depth of invasion. All nonmelanoma skin cancers other than Merkel cell carcinoma are staged by this system (Tables 2.7 and 2.8).

Table 2.7 UICC 7th edition TNM staging system definitions

T classification		N classification		M classification	
TX	Primary tumor cannot be assessed	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumor	N0	No regional lymph node metastasis	M1	Distant Metastasis
Tis	Carcinoma in situ	N1	Metastasis in a single lymph node, 3 cm or less in greatest dimension		
T1	Tumor 2 cm or less in greatest dimension	N2	Metastasis in a single lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple lymph nodes, none more than 6 cm in greatest dimension		
T2	Tumor more than 2 cm in greatest dimension	N3	Metastasis in a lymph node, more than 6 cm in greatest dimension		
T3	Tumor with invasion of deep structures (e.g. cartilage, muscle, bone, jaws, and orbit)				
T4	Tumor with direct or perineural invasion of skull base or axial skeleton				

Table 2.8 UICC 7th edition TNM staging

Stage	**T**	**N**	**M**
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV	T1	N2 or N3	M0
	T2	N2 or N3	M0
	T3	N2 or N4	M0
	T4	Any N	M0
	Any T	Any N	M1

Reprinted from LH Sobin, MK Gospodarowicz, C Wittekind. Union for International Cancer Control: TNM Classification of Malignant Tumors, 7th Ed (2009), with permission from Wiley-Blackwell

T Classification

The UICC Tumor (T) classification is based primarily on the diameter of the primary tumor, tissue level depth of invasion, whether there is perineural invasion into the skull base or invasion of the skeleton. Other high-risk features defined by the UICC in Table 2.2 are not incorporated into current staging.

N Classification

The UICC Nodal (N) classification system is a 3 tiered system based on the number of lymph nodes involved (single vs. multiple) and size of the metastatic focus (<3 cm, ≥3 cm but less than 6 cm, or ≥6 cm). The laterality of lymph nodes is not taken into account in the UICC N classification system.

M Classification

The UICC Metastasis (M) classification is the same as the AJCC where M0 indicates no evidence of metastatic disease and M1 is used when there is presence of metastatic disease.

Stratification of TNM Classifications into Stages

Based on the above UICC TNM classification criteria, tumors are assigned to a specific stage. Stage 0 is limited to SCC in situ. Stage I tumors are invasive CSCC that are ≤2 cm in diameter. Stage II is assigned to invasive tumors that are >2 cm in diameter. Stage III is reserved for T3N0M0 tumors (tumors that are infiltrating into deeper structures such as the muscle, bone, cartilage, jaws, and orbit) or tumors of any T classification with nodal metastasis to a single lymph node ≤ 3 cm in greatest dimension. Stage IV is assigned for tumors that have more advanced nodal disease or distant metastasis, regardless of T classification.

Factors Excluded from Current AJCC and UICC Staging Systems

There are several factors that are currently not incorporated into current AJCC and/or UICC staging, although there is evidence of the importance of these factors regarding prognosis. These factors include recurrent tumors and immunosuppressed status of the patient. In addition, there is evidence PNI of large caliber nerves is prognostically more significant than PNI of small caliber nerves [20, 21]. Histopathologic grading is an area that has yet to be explored further. The metastatic

risk of moderately differentiated tumors is not well known, although there is some evidence demonstrating it may be prognostically significant [6]. For poorly differentiated tumors, it is likely that a tumor with a small focus of poor differentiation may behave more aggressively than a tumor that is completely poorly differentiated, but there is little evidence to support this hypothesis. Whether tissue level depth (Clark Level) or millimeter depth (Breslow's depth) better predicts recurrence also has yet to be studied. Other than lip and ear, there are other high-risk locations, such as the temple or the scalp. These factors that are not currently incorporated into the staging systems may be important, but play a less significant role towards risk of poor outcomes. Unfortunately, studies conducted thus far have been underpowered to detect these small differences and therefore these factors have been excluded from current staging.

Important Differences between 7th Edition AJCC and UICC Staging Systems

There are several important differences to note between the two current staging systems:

1. The AJCC staging system is applicable to only CSCC whereas the UICC staging system continues to group CSCC with other nonmelanoma skin cancers (excluding Merkel cell carcinoma).
2. The AJCC staging system takes into account high risk factors other than diameter and depth such as histopathologic grade, perineural and/or lymphovascular invasion, and location on the cutaneous lip or ear. UICC continues to stratify tumor classification based on diameter and depth alone. Tumors that are <2 cm and do not invade deep structures but have two or more other high risk factors would be upstaged to T2 in AJCC but remain T1 in UICC (and therefore would be Stage 2 in the AJCC system but only Stage 1 in the UICC system).
3. It is easier for a tumor to be upgraded to T3 in the UICC system as a tumor is UICC T3 if it invades muscle or cartilage whereas AJCC T3 requires invasion of bone.
4. There is lack of congruence regarding tumor depth between the staging systems. The AJCC identifies a high-risk tumor if it is >2 mm deep or Clark's level IV or greater (reticular dermis or deeper structures). The UICC identifies >4 mm depth as a high-risk feature, but this breakpoint is not incorporated into the system. Instead, the T system depth is broadly defined as tumor invasion into deeper structures, such as muscle, bone or fascia.
5. The AJCC Nodal classification is based on the number of involved lymph nodes, greatest dimension of a tumor focus within a node, and location of the involved nodes in relation to the primary tumor (ipsilateral or contralateral). While the diameter of the lymph node metastatic foci and number of lymph nodes with metastases are included in UICC, the lateralization of involved nodes is not incorporated in UICC N classification.

Validation of Current Staging Systems

Since the AJCC and UICC were developed largely on expert opinion of limited data, a few studies have attempted to validate these systems with cohort data. The majority of studies have been performed on the 7th Edition AJCC staging system, as this separated out CSCC from other NMSC's.

Validation of Tumor Classification

There are four published studies that have validated the AJCC tumor (T) classification system. One of these studies was limited to CSCC occurring in immunosuppressed individuals [43]. It included data on 41 organ transplant recipients who developed 225 CSCCs during the study period. During followup, there were 19 local recurrences. The authors found that T2 tumors had nearly 10 times increased risk of local recurrence than T1 tumors (HR 9.9; 95 % CI 3.0–32.7) when they also adjusted for duration of immunosuppression, treatment modality, and patient gender.

The remaining three studies [10, 12, 44] were retrospective cohort studies of CSCC. In each of these studies, tumors were classified according to the AJCC T classification system. The risk of local recurrence, nodal metastasis, and disease specific death by T classification is detailed in Table 2.9. Two studies examined the risk of local recurrence by T classification. Of the 2074 tumors amongst two studies, there were a total of 63 local recurrences. The rate of local recurrences for T1, T2, T3 and T4 tumors were 0.8 % (95 % CI 0.4–1.4 %), 8.4 % (95 % CI 6–11 %), 60 % (95 % CI 23–88 %), and 60 % (95 % CI 23–88 %) respectively. Three studies examined the risk of nodal metastasis by T classification. These studies included 2689 primary CSCC's and there were a total of 83 nodal metastases. The rate of nodal metastasis for T1, T2, T3 and T4 tumors were 0.2 % (95 % CI 0.1–0.7 %), 6.9 % (95 % CI 5.5–8.6 %), 22 % (95 % CI 9–45 %), and 36.4 % (95 % CI 15–65 %) respectively. Two studies examined the risk of disease specific death by T classification. Of the 2074 included tumors, there were 31 disease specific deaths. The rate of disease specific death for T1, T2, T3 and T4 tumors were 0 % (95 % CI 0–0.2 %), 4.3 % (95 % CI 3–7 %), 60 % (95 % CI 23–88 %), and 80 % (95 % CI 38–96 %) respectively.

Based on this data, the AJCC fulfilled a basic requirement of distinctiveness, with rates of recurrence increase with increasing T stage. However, when looking at the data closely, it did not appear monotonous or homogenous. T3 and T4 tumors accounted for only a small minority of the cohort in the three datasets (29/2689 or approximately 1 % of the cohort). The majority of the local recurrences (45/63; 71 %), nodal metastases (71/83; 85.6 %), and disease specific deaths (23/31; 74.2 %) subsequently occurred in T2 classification. With relatively few tumors meeting T3/T4 criteria as well as the vast majority of poor outcomes being clustered in AJCC T2, the authors of all three studies concluded that the current AJCC staging system offered little prognostic discrimination.

Table 2.9 Published validation studies of 7th edition AJCC CSCC tumor (T) classification

Validation for local recurrence							
Study	# Tumors	Total number of local recurrences	AJCC T1 local recurrences	AJCC T2 local recurrences	AJCC T3 local recurrences	AJCC T4 local recurrences	Percentage of local recurrences in T1 or T2
Jambusaria-Pahlajani et al. [10]	256	16	3/112 (2.7 %)	11/91 (12.1 %)	1/2 (50 %)	1/2 (50 %)	87.50 %
Karia et al. [12]	1818	47	9/1361 (0.6 %)	34/447 (7.6 %)	2/3 (66 %)	2/3 (66 %)	91.50 %
Total	2074	63	12/1473 (0.8 %)	45/538 (8.4 %)	3/5 (60 %)	3/5 (60 %)	91 %
Validation for lymph node metastasis							
Study	# Tumors	Total number of LN metastasis	AJCC T1 LN metastasis	AJCC T2 LN metastasis	AJCC T3 LN metastasis	AJCC T4 LN metastasis	Percentage of nodal metastases in T1 or T2
Breunninger et al. [44]	615	26	0/107 (0%)	24/490 (4.9 %)	1/13 (7.7 %)	1/6 (16.7 %)	92 %
Jambusaria-Pahlajani et al. [10]	256	24	2/112 (1.7 %)	20/91 (22 %)	1/2 (50 %)	1/2 (50 %)	91.70 %
Karia et al. [12]	1818	33	2/1361 (0.2 %)	27/447 (6 %)	2/3 (66 %)	2/3 (66 %)	87.90 %
Total	2689	83	4/1580 (0.2 %)	71/1028 (6.9 %)	4/18 (33.3 %)	4/11 (36.4 %)	90.40 %
Validation for disease specific death							
Study	# Tumors	Total number of disease specific deaths	AJCC T1 disease specific deaths	AJCC T2 disease specific deaths	AJCC T3 disease specific deaths	AJCC T4 disease specific deaths	Percentage of disease specific deaths in T1 or T2
Jambusaria-Pahlajani et al. [10]	256	12	0/112 (0 %)	11/91 (12.1 %)	0/2 (0 %)	1/2 (50 %)	91.20 %
Karia et al.[12]	1818	19	0/1361 (0 %)	12/447 (2.7 %)	3/3 (100 %)	3/3 (100 %)	63.20 %
Total	2074	31	0/1473 (0 %)	23/538 (4.3 %)	3/5 (60 %)	4/5 (80 %)	74.20 %

The discriminative properties of the UICC 7th Edition CSCC staging system have been evaluated in only one study of 1818 CSCC tumors [12]. As with AJCC stage, the rates of LR, NM and DSD increased with increasing T classification. However, the majority of poor outcomes occurred in early UICC T stages, with 80.1 % LR, 66 % NM, and 44 % DSD occurring in UICC T1 and T2 tumors. Conversely, only 19 % LR, 33 % NM, and 56 % DSD occurred in UICC T3 and UICC T4 stages. In addition, when 10 year cumulative incidence rates for LR, NM, and DSD were tabulated for each UICC T stage, there was significant overlap between the 95 % confidence intervals, indicating each stage was not distinct from the next. Thus, the authors concluded the UICC system offered limited prognostic discrimination as well.

Validation of Nodal Classification

Only one study has validated the AJCC nodal (N) classification system based on 603 patients with nodal metastasis from CSCC located on the head and neck [45]. In this dataset, <10 % of tumors fell in the N2 category with 12/603 (2 %) tumors classified as N2c (requirement of contralateral lymph nodes involved). The Kaplan Meier curves demonstrated that several of the survival curves overlapped between two N categories. On multivariable analysis, the adjusted hazards ratios for recurrence for N2a, N2b, N2c, an N3 compared to N1 was 1.1, 1.5, 1.4, and 2.1, respectively, and had widely overlapping confidence intervals. These analyses indicate these categories were neither distinctive nor monotonous. The authors suggested the AJCC Nodal system was suboptimal and questioned the clinical utility of incorporating the laterality of lymph nodes (N2c category), given the paucity of tumors that fell into this category.

Alternative Staging Systems

As discussed earlier, the 7th Edition AJCC staging system for CSCC was developed to parallel the staging system for mucosal SCC from the head and neck. The major advantage of using an established system is its familiarity in clinical practice and relative ease of use. However, the clinical presentation and biological behavior of CSCC is not the same as mucosal SCC and therefore it may be flawed to base a CSCC staging system on that of mucosal SCC. The above validation studies have demonstrated that this approach is suboptimal. Several groups have published reports that have proposed alternative stratification systems that may offer improved prognostic discrimination over current AJCC and UICC T and N staging (Table 2.10).

Table 2.10 Alternative staging systems

Tumor	
BWH system, Jambusaria-Pahlajani et al. system[a]	
T1	0 High-risk factors
T2a	1 High-risk factor
T2b	2-3 High-risk factors
T3	All 4 high-risk factors or bone invasion
Peat, et al System[b]	
Low-Risk	1 Relative risk factor
Intermediate Risk	2 or 3 Relative risk factors
High-risk	At least 1 absolute risk factor or all 3 relative high risk factors
Nodal	
N1S3 system	
N1	Single lymph node metastasis <3 cm
N2	Multiple lymph node metastasis ≤3 cm or a single lymph node metastasis >3 cm
N3	Multiple lymph node metastasis with at least one metastatic focus being >3 cm

[a]HR factors include size >2 cm, depth beyond subcutaneous fat, poorly differentiated histology, and perineural invasion. PNI of any nerve diameter is a risk factor in Jambusaria-Pahlajani, Schmults et al. Only PNI of nerves ≥0.1 mm is a risk factor in the BWH System

[b]Relative risk factors include size >=2 cm, moderately differentiated histology, Clark's Level V or greater. Absolute risk factors include poorly differentiated histology or PNI/Lymphovascular invasion

Reprinted with permission from references #: [9, 10, 12, 46]

Alternative Tumor (T) Classification Systems

In 2012, Peat et al. [9] performed a case control study of 92 metastatic and 78 non-metastatic head and neck CSCCs. Based on multivariable analysis, they categorized risk factors independently associated with metastasis into two groups based on the magnitude of their hazard ratios. Absolute risk factors had the greatest predictive value for metastasis, and included tumors with poorly differentiated histology and neural, lymphatic or vascular invasion. Relative risk factors had a lower predictive value for metastasis and included tumors with a diameter ≥2 cm, moderate differentiation, and Clark's level V (depth into subcutaneous fat). The authors recommended a stratification system based on the number of absolute and relative risk factors (Table 2.10) with three categories (low, intermediate, and high risk). In their dataset, 78 % of metastatic tumors were high risk, 18 % were intermediate risk, and 4 % were low-risk. Conversely, 72 % of nonmetastatic tumors were low risk, 20 % were intermediate risk, and 8 % were high-risk.

Jambusaria-Pahlajani et al. [10] performed a retrospective cohort study of 257 CSCCs having at least one histologic or clinical risk factor. Based on multivariable analysis for LR, NM, and DSD, an alternative staging system was developed based on four risk factors of interest: PNI (regardless of the diameter of the nerve involved),

Table 2.11 10-Year cumulative incidence of outcomes by T stage in alternative T classification systems

		Local recurrence		Nodal metastasis		Disease specific death		All cause death	
	No. of tumors	10 year CIN (%)	95 % CI	10 year CIN (%)	95 % CI	10 year CIN (%)	95 % CI	10 year CIN (%)	95 % CI
Jambusaria-Pahlajani et al. [10]									
T1	134	2	1–6	0.8	0.1–4	No events		27	20–35
T2a	67	9	4–18	4	2–12	No events		30	20–41
T2b	49	18	10–31	37	25–51	20	11–34	53	39–66
T3	6	50	19–81	50	19–81	33 %	10–70	50	19–81
BWH system [12]									
T1	1393	0.6	0–1	0.1	0–0.4	No events		32	30–35
T2a	332	5	3–8	3	1–5	1	0–3	32	28–37
T2b	86	21	13–27	21	13–27	10	6–19	51	41–58
T3	6	67	30–90	67	30–90	1000	61–100	100	60–100

CIN cumulative incidence, *CI* confidence interval
Reprinted with permissions from: [10, 12]

poorly differentiated histology, size >2 cm, and depth beyond the subcutaneous fat. One point was given for the presence of each of these risk factors, and four tumor stage categories were developed based on statistical analysis. The final tumor (T) staging system is outlined in Table 2.10. Cumulative Incidence Function curves for LR, NM, and DSD demonstrated an interval increased incidence of LR, NM, and DSD with increased alternative T classification, suggesting a Tumor classification system which gives equal weight to risk factors including tumor diameter may be of greater utility. In addition, the clustering of poor outcomes previously seen in AJCC T2 was now largely shifted to a T2b category with T2a having a relatively low risk of poor outcomes.

A similar study was conducted at Brigham and Women's Hospital in 1818 CSCC tumors histologically diagnosed over a 10-year period at a single institution [12]. The alternative T staging system above was validated with the modification that PNI was only considered a risk factor if the diameter of the nerve involved was ≥ 0.1 mm. This system, termed the Brigham and Women's Hospital (BWH) tumor staging system demonstrated greater homogeneity, monotonicity, and distinctiveness over the AJCC and UICC T classifications. The cumulative incidence function curves demonstrated an increased risk of LR, NM, and DSD with increasing BWH T stage. In addition, the 10-year cumulative incidence rates of LR, NM, and DSD increased with increasing BWH T stage, with minimal overlap in 95 % confidence intervals, indicating that these were statistically different categories.

The incidence and 95 % confidence intervals of LR, NM or DSD for T1 vs. T2a vs. T2b vs. T3 for both the Jambusaria-Pahlajani et al. and BWH systems is tabulated in Table 2.11. In the BWH system, there was a sequentially higher risk of recurrence or death with each alternative T stage and very little overlap in the 95 % confidence interval, suggesting these are indeed distinct categories.

While the Peat system and the BWH system both appear to offer improved prognostic discrimination over current staging, the BWH system aligns well with the AJCC and UICC systems, which both use a 4-tiered T classification system. More importantly, the BWH system was developed by analyzing risk factors for all endpoints of interest (LR, NM, and DSD) whereas the Peat system was developed based on risk factors for metastasis only. Thus, the BWH system may be more easily used to refine the current staging systems already in use.

Alternative Nodal (N) Classification Systems

The discrepancy between mucosal head and neck SCC nodal staging and CSCC nodal staging has prompted several groups to develop alternative nodal classification systems. Initially, the alternative systems were developed for cutaneous SSC arising on the head and neck and were based on separating regional parotid involvement from cervical lymph node involvement, as separating parotid and cervical involvement was thought to improve prognostic discrimination [47]. However, this system did not perform well when validated in external datasets [48, 49]. When compared to prior staging systems, it was rather complex and difficult to incorporate into daily practice and therefore fell out of favor.

Recently, an alternative nodal system called the "N1S3" staging system [46] (Table 2.10) has been proposed. This system takes into account the number of lymph nodes involved (single vs. multiple) and the size of metastatic foci within the nodes (≤3 cm vs. >3 cm). In a validation study of 603 patients with nodal metastasis, the Kaplan Meier curves using the N1S3 system had a statistically significant difference in survivor functions between the groups with decreased survival with increasing N1S3 stage. On multivariable analysis, adjusted hazards ratios showed a HR of 1.4 (95 % CI 1.2–1.5) for N1S3 Stage II vs. N1S3 Stage I and HR of 2.6 (95 % CI 2.06–2.18) for N1S3 Stage III vs. N1S3 Stage II [45]. Based on this analysis, the N1S3 Nodal Staging system for CSCC appears to offer improved prognostic discrimination over the AJCC Nodal Staging system. Another advantage of this 3-tiered system is that it is much easier to incorporate into daily clinical practice than the current AJCC 5-tiered system.

Conclusion

While there are approximately 186,000–420,000 new cases of CSCC each year, a subset of tumors are considered high-risk based on certain histopathologic or clinical characteristics. Generally accepted high-risk factors include tumor diameter>2 cm, deep tumors, poorly differentiated histology, perineural invasion, location on certain anatomic sites, and immunosuppression. The relative contributions of each of these factors towards prognosis have only recently begun to

be quantified. The AJCC and UICC staging systems for CSCC were developed based on consensus opinion and review of very limited available data. When recently validated using new datasets, the current systems offered limited prognostic utility. Alternative staging systems, which appear to offer improved prognostic discrimination, have been developed and validated and are currently undergoing further validation and refinement. Improved staging in CSCC will aid clinicians and patients, offering accurate prognostic estimates which will promote further study to determine optimal treatment strategies.

References

1. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. J Am Acad Dermatol. 2013;68(6):957–66.
2. Brantsch KD, Meisner C, Schonfisch B, Trilling B, Wehner-Caroli J, Rocken M, Breuninger H. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol. 2008;9(8):713–20.
3. Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma: a 10-year, single-institution cohort study. JAMA Dermatol. 2013;149(5):541–7.
4. Clayman GL, Lee JJ, Holsinger FC, Zhou X, Duvic M, El-Naggar AK, Prieto VG, Altamirano E, Tucker SL, Strom SS, Kripke ML, Lippman SM. Mortality risk from squamous cell skin cancer. J Clin Oncol. 2005;23(4):759–65.
5. Mullen JT, Feng L, Xing Y, Mansfield PF, Gershenwald JE, Lee JE, Ross MI, Cormier JN. Invasive squamous cell carcinoma of the skin: defining a high-risk group. Ann Surg Oncol. 2006;13(7):902–9.
6. Kyrgidis A, Tzellos TG, Kechagias N, Patrikidou A, Xirou P, Kitikidou K, Bourlidou E, Vahtsevanos K, Antoniades K. Cutaneous squamous cell carcinoma (SCC) of the head and neck: risk factors of overall and recurrence-free survival. Eur J Cancer. 2010;46(9): 1563–72.
7. Brougham ND, Dennett ER, Cameron R, Tan ST. The incidence of metastasis from cutaneous squamous cell carcinoma and the impact of its risk factors. J Surg Oncol. 2012;106(7):811–5.
8. Roozeboom MH, Lohman BG, Westers-Attema A, Nelemans PJ, Botterweck AA, van Marion AM, Kelleners-Smeets NW. Clinical and histological prognostic factors for local recurrence and metastasis of cutaneous squamous cell carcinoma: analysis of a defined population. Acta Derm Venereol. 2013; 93(4): 417–21.
9. Peat B, Insull P, Ayers R. Risk stratification for metastasis from cutaneous squamous cell carcinoma of the head and neck. ANZ J Surg. 2012;82(4):230–3.
10. Jambusaria-Pahlajani A, Kanetsky PA, Karia PS, Hwang WT, Gelfand JM, Whalen FM, Elenitsas R, Xu X, Schmults CD. Evaluation of AJCC tumor staging for cutaneous squamous cell carcinoma and a proposed alternative tumor staging system. JAMA Dermatol. 2013;149(4):402–10.
11. Ballantyne AJ, McCarten AB, Ibanez ML. The extension of cancer of the head and neck through peripheral nerves. Am J Surg. 1963;106:651–67.
12. Karia PS, Jambusaria-Pahlajani A, Harrington DP, Murphy G, Qureshi AA, Schmults CD. Evaluation of AJCC, UICC, and Brigham and Women's Hospital tumor staging for cutaneous squamous cell carcinoma. J Clin Oncol. 2014; 32(4): 327–34.
13. Matorin PA, Wagner Jr RF. Mohs micrographic surgery: technical difficulties posed by perineural invasion. Int J Dermatol. 1992;31(2):83–6.

14. Mohs FE, Lathrop TG. Modes of spread of cancer of skin. AMA Arch Derm Syphilol. 1952;66(4):427–39.
15. Goepfert H, Dichtel WJ, Medina JE, Lindberg RD, Luna MD. Perineural invasion in squamous cell skin carcinoma of the head and neck. Am J Surg. 1984;148(4):542–7.
16. Dodd GD, Dolan PA, Ballantyne AJ, Ibanez ML, Chau P. The dissemination of tumors of the head and neck via the cranial nerves. Radiol Clin North Am. 1970;8(3):445–61.
17. Leibovitch I, Huilgol SC, Selva D, Hill D, Richards S, Paver R. Cutaneous squamous cell carcinoma treated with Mohs micrographic surgery in Australia II. Perineural invasion. J Am Acad Dermatol. 2005;53(2):261–6.
18. McNab AA, Francis IC, Benger R, Crompton JL. Perineural spread of cutaneous squamous cell carcinoma via the orbit. Clinical features and outcome in 21 cases. Ophthalmology. 1997;104(9):1457–62.
19. Mendenhall WM, Ferlito A, Takes RP, Bradford CR, Corry J, Fagan JJ, Rinaldo A, Strojan P, Rodrigo JP. Cutaneous head and neck basal and squamous cell carcinomas with perineural invasion. Oral Oncol. 2012;48(10):918–22.
20. Ross AS, Whalen FM, Elenitsas R, Xu X, Troxel AB, Schmults CD. Diameter of involved nerves predicts outcomes in cutaneous squamous cell carcinoma with perineural invasion: an investigator-blinded retrospective cohort study. Dermatol Surg. 2009;35(12):1859–66.
21. Carter JB, Johnson MM, Chua TL, Karia PS, Schmults CD. Outcomes of primary cutaneous squamous cell carcinoma with perineural invasion: an 11-year cohort study. JAMA Dermatol. 2013;149(1):35–41.
22. Salmon PJ, Hussain W, Geisse JK, Grekin RC, Mortimer NJ. Sclerosing squamous cell carcinoma of the skin, an underemphasized locally aggressive variant: a 20-year experience. Dermatol Surg. 2011;37(5):664–70.
23. Swanson NA, Grekin RC, Baker SR. Mohs surgery: techniques, indications, and applications in head and neck surgery. Head Neck Surg. 1983;6(2):683–92.
24. Zitsch 3rd RP, Park CW, Renner GJ, Rea JL. Outcome analysis for lip carcinoma. Otolaryngol Head Neck Surg. 1995;113(5):589–96.
25. Babington S, Veness MJ, Cakir B, Gebski VJ, Morgan GJ. Squamous cell carcinoma of the lip: is there a role for adjuvant radiotherapy in improving local control following incomplete or inadequate excision? ANZ J Surg. 2003;73(8):621–5.
26. Vukadinovic M, Jezdic Z, Petrovic M, Medenica LM, Lens M. Surgical management of squamous cell carcinoma of the lip: analysis of a 10-year experience in 223 patients. Journal Oral Maxillofac Surg. 2007;65(4):675–9.
27. Daniele E, Rodolico V, Leonardi V, Tralongo V. Prognosis in lower lip squamous cell carcinoma: assessment of tumor factors. Pathol Res Pract. 1998;194(5):319–24.
28. Sobin L, Gospodarowicz M, Wittekind C, editors. Union for International Cancer Control. Chichester: UICC and Wiley; 2010
29. Khanna M, Fortier-Riberdy G, Dinehart SM, Smoller B. Histopathologic evaluation of cutaneous squamous cell carcinoma: results of a survey among dermatopathologists. J Am Acad Dermatol. 2003;48(5):721–6.
30. Breuninger H, Schaumburg-Lever G, Holzschuh J, Horny HP. Desmoplastic squamous cell carcinoma of skin and vermilion surface: a highly malignant subtype of skin cancer. Cancer. 1997;79(5):915–9.
31. Veness MJ, Palme CE, Morgan GJ. High-risk cutaneous squamous cell carcinoma of the head and neck: results from 266 treated patients with metastatic lymph node disease. Cancer. 2006;106(11):2389–96.
32. Calonje E, Brenn T, Azar AL, McKee PH. McKee's pathology of the skin. 4th edn. Tumors of the surface epithelium, vol 2. Elsevier; 2012; Philadelphia, PA
33. Euvrard S, Kanitakis J, Pouteil-Noble C, Disant F, Dureau G, Finaz de Villaine J, Claudy A, Thivolet J. Aggressive squamous cell carcinomas in organ transplant recipients. Transplant Proc. 1995;27(2):1767–8.
34. Veness MJ, Quinn DI, Ong CS, Keogh AM, Macdonald PS, Cooper SG, Morgan GW. Aggressive cutaneous malignancies following cardiothoracic transplantation: the Australian experience. Cancer. 1999;85(8):1758–64.

35. Mehrany K, Weenig RH, Lee KK, Pittelkow MR, Otley CC. Increased metastasis and mortality from cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia. J Am Acad Dermatol. 2005;53(6):1067–71.
36. Velez NF, Karia PS, Vartanov AR, Davids MS, Brown JR, Schmults CD. Association of advanced leukemic stage and skin cancer tumor stage with poor skin cancer outcomes in patients with chronic lymphocytic leukemia. JAMA Dermatol. 2014;150(3):280–7.
37. Hausauer AK, Maurer T, Leslie KS, Parvataneni R, Stuart SE, Chren MM. Recurrence after treatment of cutaneous basal cell and squamous cell carcinomas in patients infected with human immunodeficiency virus. JAMA Dermatol. 2013;149(2):239–41.
38. Edge SB. American Joint Committee on Cancer (AJCC): cancer staging manual. 7th ed. New York: Springer; 2010.
39. Ishwaran H, Blackstone EH, Apperson-Hansen C, Rice TW. A novel approach to cancer staging: application to esophageal cancer. Biostatistics. 2009;10(4):603–20.
40. Miller SJ. Staging cutaneous squamous cell carcinoma. JAMA Dermatol. 2013;149(4): 472–4.
41. Denoix P. Enquete permanent dans les centres anticanceraux. Bulletin Institut national d'hygiene. 1946;1:12–7.
42. Wittekind C, Compton CC, Brierley J, Sobin LH. TNM supplement: a commentary on uniform use. 4th ed. Oxford: Wiley-Blackwell; 2012.
43. Metchnikoff C, Mully T, Singer JP, Golden JA, Arron ST. The 7th edition AJCC staging system for cutaneous squamous cell carcinoma accurately predicts risk of recurrence for heart and lung transplant recipients. J Am Acad Dermatol. 2012;67(5):829–35.
44. Breuninger H, Brantsch K, Eigentler T, Hafner HM. Comparison and evaluation of the current staging of cutaneous carcinomas. J Dtsch Dermatol Ges. 2012;10(8):579–86.
45. Clark JR, Rumcheva P, Veness MJ. Analysis and comparison of the 7th edition American Joint Committee on Cancer (AJCC) nodal staging system for metastatic cutaneous squamous cell carcinoma of the head and neck. Ann Surg Oncol. 2012;19(13):4252–8.
46. Forest VI, Clark JJ, Veness MJ, Milross C. N1S3: a revised staging system for head and neck cutaneous squamous cell carcinoma with lymph node metastases results of 2 Australian Cancer Centers. Cancer. 2010;116(5):1298–304.
47. O'Brien CJ, McNeil EB, McMahon JD, Pathak I, Lauer CS, Jackson MA. Significance of clinical stage, extent of surgery, and pathologic findings in metastatic cutaneous squamous carcinoma of the parotid gland. Head Neck. 2002;24(5):417–22.
48. Andruchow JL, Veness MJ, Morgan GJ, Gao K, Clifford A, Shannon KF, Poulsen M, Kenny L, Palme CE, Gullane P, Morris C, Mendenhall WM, Patel KN, Shah JP, O'Brien CJ. Implications for clinical staging of metastatic cutaneous squamous carcinoma of the head and neck based on a multicenter study of treatment outcomes. Cancer. 2006;106(5):1078–83.
49. Palme CE, O'Brien CJ, Veness MJ, McNeil EB, Bron LP, Morgan GJ. Extent of parotid disease influences outcome in patients with metastatic cutaneous squamous cell carcinoma. Arch Otolaryngol Head Neck Surg. 2003;129(7):750–3.