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A new American Joint Committee on Cancer staging system for cutaneous squamous cell carcinoma: Creation and rationale for inclusion of tumor (T) characteristics

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Abstract

Background—The incidence of cutaneous squamous cell carcinoma (cSCC) is increasing. Although most patients achieve complete remission with surgical treatment, those with advanced

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disease have a poor prognosis. The American Joint Committee on Cancer (AJCC) is responsible for the staging criteria for all cancers. For the past 20 years, the AJCC cancer staging manual has grouped all nonmelanoma skin cancers, including cSCC, together for the purposes of staging. However, based on new evidence, the AJCC has determined that cSCC should have a separate staging system in the 7th edition AJCC staging manual.

Objective—We sought to present the rationale for and characteristics of the new AJCC staging system specific to cSCC tumor characteristics (T).

Methods—The Nonmelanoma Skin Cancer Task Force of AJCC reviewed relevant data and reached expert consensus in creating the 7th edition AJCC staging system for cSCC. Emphasis was placed on prospectively accumulated data and multivariate analyses. Concordance with head and neck cancer staging system was also achieved.

Results—A new AJCC cSCC T classification is presented. The T classification is determined by tumor diameter, invasion into cranial bone, and high-risk features, including anatomic location, tumor thickness and level, differentiation, and perineural invasion.

Limitations—The data available for analysis are still suboptimal, with limited prospective outcomes trials and few multivariate analyses.

Conclusions—The new AJCC staging system for cSCC incorporates tumor-specific (T) staging features and will encourage coordinated, consistent collection of data that will be the basis of improved prognostic systems in the future.

Keywords

American Joint Committee on Cancer staging system; anatomic site; cutaneous squamous cell carcinoma; depth of tumor; high-risk tumor features; histopathologic grade or differentiation; perineural invasion; prognosis; skin cancer; staging criteria; tumor diameter

The incidence of nonmelanoma skin cancers (NMSCs) varies globally, but is thought to be increasing overall since the 1960s, at a rate of 3% to 8% per year[1] and is the most frequent cancer worldwide,[2] with more than 1 million new cases diagnosed each year in the United States alone.[3] The term “nonmelanoma skin cancer” includes approximately 82 types of tumors with wide variability in prognosis, ranging from those that generally portend a poor prognosis, such as Merkel cell carcinoma (MCC) to the more frequent and typically less aggressive basal cell carcinoma and cutaneous squamous cell carcinoma (cSCC). Although the vast majority of cSCC tumors present with early-stage disease, a minority progress to regional or distant metastasis[4] accounting for a reported ~20% of all skin cancer—related deaths.[5] For more than 20 years, the American Joint Committee on Cancer (AJCC) has staged cancers according to prognosis and during this time it has included cSCC within a NMSC chapter that encompassed the entire array of NMSC tumors. There are several important shortcomings in its presented classification of NMSCs that limit its clinical applicability when staging cSCC. These deficiencies have been the subject of several reviews.[6-8]

After the AJCC has approved the cancer staging criteria, hospital registries are required to implement the staging system and collect prospective clinical and pathologic data elements

on each form of cancer. Because the vast majority of NMSC tumors are early stage, registries are presented with a logistical challenge with regard to NMSC: the collection of statistically meaningful data on the relatively small subset of NMSC tumors that metastasize. Because the task of proper data collection has been prohibitive to date for NMSC, very few prognostic factors are currently well understood regarding cSCC tumor characteristics (T), lymph node status (N), and metastasis (M), which are the ultimate guidelines for staging cancers.

For the first time, the AJCC has formed a NMSC staging committee with the charge to create a staging system for cSCC that is separate from all other NMSC tumors. The objective was to devise a system that more accurately and specifically reflects the natural history and stage-specific prognostic outcome of cSCC. In addition, we sought a system that would allow collection of prospective data for future evidence-based revision. Because the majority of cSCC tumors occur on the head and neck, the AJCC requested that the NMSC task force also make the cSCC staging system congruent with the staging criteria used for head and neck cancers. The new cSCC staging system is included in the 7th edition of the AJCC cancer-staging manual[9] that was implemented by tumor registries in January 2010. Here we describe the AJCC cSCC staging system and rationale for the T (tumor characteristics) staging.

METHODS

In 2006, the AJCC executive committee established the NMSC staging committee under the direction of Dr Arthur Sober. The committee was charged with responsibility of establishing new staging systems for MCC and cSCC separate from the existing NMSC staging system because of their metastatic potential. The MCC staging system is described and the NMSC chapter will be discontinued from the AJCC classification. There were two main objectives for the new cSCC staging system that is included in the 7th edition of the AJCC cancer manual.[9] First, the system had to be more evidence-based than the previous NMSC system featured in the 6th edition.[10] Because the majority of cSCC tumors occur on the head and neck, the AJCC executive committee requested the second goal of making the cSCC system congruent with the head and neck staging system.

Available published studies on prognostic factors for cSCC were reviewed and analyzed over a period of 3 years from 2005 through 2008. Members of the NMSC committee held a series of meetings to analyze data and decide on staging criteria for cSCC reflective of the best data available. An important focus of the discussions was delineating tumor characteristics (T) as the vast majority of cSCC present in an early stage. When large prospective data sets or multivariate analysis was lacking, univariate data with consensus opinion of the cSCC staging subcommittee were accepted. For nodal (N) criteria, prospective data from randomized trials, case-controlled studies, or multivariate analyses were prioritized over case series and retrospective reviews.

RESULTS

The 6th edition[10] (Table I) relied on the TNM staging system, classifying patients into primary tumor (T), regional lymph nodes (N), and distant metastasis (M). Although histopathologic grade (G) was recognized as significant and included in the characterization, this feature was not included in final stage grouping because the importance of grade was not established for all types of NMSC. In the 7th edition,[9] the overall TNM staging concept is maintained but the G designation is eliminated with histopathologic grade of cSCC being characterized under tumor characteristics (T). The 6th edition staging system[10] excluded eyelid, a common anatomic site for cSCC development, and the nonglabrous lip, vulva, and penis. Because cSCC frequently develops on the ear and nonglabrous lip,[5,11] the 7th edition AJCC cSCC staging system[9] includes the ear and nonglabrous lip. cSCC of the eyelid will be staged by the ophthalmic task force in a separate chapter as per the decision of the AJCC cancer staging manual editorial board. Because vulvar and penile squamous cell carcinoma (SCC) are already staged in the AJCC manual and their pathogenesis and prognosis is correlated with human papillomavirus rather than ultraviolet light, the cSCC staging will continue to exclude these sites.

According to reports from tertiary centers, approximately 5% of cSCCs metastasize, usually to regional lymph nodes.[4,5,12,13] The rate of metastasis increases depending on clinical and pathologic features of the tumor (T stage) to more than 10% to 20% in high-risk tumors.[4,5,14] Reported high-risk factors for metastasis from cSCC include: size of the primary tumor greater than 2 cm, Breslow tumor thickness greater than 2 mm, Clark level IV or greater, perineural invasion (PNI), poor differentiation, anatomic sites that are high risk for recurrence or metastasis, an immunocompromised state of the patient, and locally recurrent tumors.[5,15-19] However, many of these T high-risk factors were not included in the 6th edition AJCC staging system,[10] preventing accurate stratification for patients at higher risk of developing metastatic cSCCs and the system was not broadly used in studies of cSCC. Although there are numerous reported clinicopathologic high-risk tumor characteristics affecting tumor prognosis, multivariate analyses comparing all variables are generally lacking. This poses a challenge for stratification of prognostic clinicopathologic T variables for the 7th edition of the staging system.[9] Based on best available evidence and/or consensus opinion, the AJCC NMSC task force formulated the following staging system for cSCC with particular emphasis on T staging and prognostic value of high-risk tumor features.

Tumor diameter

Tumor size refers to the maximum clinical diameter of the cSCC lesion. In the 6th edition AJCC staging system,[10] 2- and 5-cm tumor size thresholds were used to define the primary tumor (T) and were the sole criterion for T1, T2, and T3. Multiple studies corroborate a correlation among tumor size, more biologically aggressive disease, local recurrence, and metastasis in univariate analysis.[5,15,20-24] Tumor size remains a significant variable on multivariate analysis in some studies.[24,25] Several published studies point toward 2 cm as a threshold beyond which tumors are more likely to metastasize to lymph nodes.[5,15,20,22,23,26-28] A 3.8-fold risk of recurrence and metastasis for tumors greater than 2

cm was noted by Mullen et al[23] when reviewing MD Anderson Cancer Center (Houston, TX) database of 149 cSCC on the trunk and extremities. In a large review of all published literature on the prognosis of SCC occurring on the skin and lip since 1940, Rowe et al[5] found that among tumors that exceeded 2 cm in diameter, the local recurrence rate was double (15% vs 7%) and metastatic rates were triple (30% vs 9%).

In a German study, 78% of metastasizing tumors were larger than 2 cm.[29] However, the metastatic potential of tumors smaller than 2 cm cannot be ignored, as they too can metastasize.[19,21] In a prospective study of 266 patients with head and neck cSCC metastatic to lymph nodes, the majority of patients had tumors less than 2 cm in size, leading the investigators to conclude that size alone is a poor predictor of outcome.[16] A review of 915 cSCC in Netherlands' national registry over a 10-year period (comparing nonmetastatic and metastatic lesions matched for gender, location, and other clinicopathologic variables) suggested that the risk of metastasis significantly increased with tumors greater than 1.5 cm.[24]

After considering all of the data, the AJCC cSCC task force decided to continue 2 cm as one of the key delineating features between T1 and T2 cSCC staging in the 7th edition AJCC manual[9] (Table II). This threshold was decided based on the existing published data that greater than 2 cm clinical diameter is associated with a poor prognosis. In addition, this breakpoint allowed congruence between cSCC and head and neck staging. Prognostically relevant breakpoints beyond 2 cm are difficult to establish. A limited number of studies suggest 3 cm and 4 cm as significant thresholds,[25] whereas others show no difference in metastatic rates for tumors between 2 and 5 cm and those greater than 5 cm.[20] Therefore, there is little evidence to support the 5-cm breakpoint featured in the previous NMSC staging system. Thus, a 5-cm breakpoint has been removed from the 7th edition AJCC T staging for cSCC.[9]

Depth of tumor

Recent studies show that both tumor thickness and the depth of invasion are important variables for the prognosis of cSCC.[5,6,20,21,30] Two prospective studies showed that increasing tumor thickness and anatomic depth of invasion correlated with an increased risk of metastases.[14,20] In a study of 673 SCCs of the skin and lower lip, no metastases were associated with primary tumors less than 2 mm in depth (tumor thickness) (n = 325), but a metastatic rate of 15% was noted with tumors greater than 6 mm in depth (n = 60).[20] This study also reported increasing metastatic rates as tumor invasion progressed from dermis to subcutaneous adipose tissue (4.1%), to muscle (12.5%), or bone (12.5%).[20] Similar conclusions regarding the significance of tumor thickness and depth of invasion were reached in studies by other groups.[5,21,31-33] Based on the above data and in analogy to Breslow tumor thickness and Clark level of invasion as used in melanoma, the revised 7th edition AJCC cSCC staging system[9] incorporates both greater than 2 mm Breslow depth and Clark level IV or higher as high-risk features in the T classification (Table II).

In the 6th edition T staging system,[10] the T4 designation was used for tumors that "invaded extradermal structures." The most common and important instances of deep anatomic extension for cSCC involve extension to bone of the head and neck and perineural extension

to bony structures versus the skull base. Based on these considerations, in the 7th edition cSCC staging system,[9] T3 designation denotes direct invasion of cSCC into cranial bone structures. The T4 designation is reserved for direct invasion or PNI of the skull base independent of tumor thickness or depth (Table II) consistent with data from several head and neck studies suggesting that cSCC extending to skull base is associated to poor prognosis similar to advanced lymph node disease.[34-39] The task force reached consensus that, similarly, extension of cSCC to axial (cranial bones are not included in this classification of axial as they are given a separate T designation) or appendicular skeleton should also be a T4 parameter.

High-risk tumor features

In conceptualizing how to integrate the multiple other clinicopathologic tumor characteristics into the overall staging system, the task force believed that the independent prognostic validity of the multiple other features was insufficient to accurately place them into stage-specific locations. Instead, the task force approved a group of high-risk features that are combined with diameter to classify tumors as T1 or T2 (Table II).

In addition, because of data suggesting that immunosuppression correlates with worse prognosis as described in several studies,[40-43] strong consideration was given toward including immunosuppression. However, because strict TNM criteria preclude inclusion of clinical risk factors in the staging system, the AJCC executive committee decided that this factor could be collected by registries as an additional factor rather than in the final staging system. For centers collecting such data and performing studies, this could be designated with an “I” after the staging to reflect the immunosuppressed status.

Anatomic site

Specific anatomic locations on the nonglabrous lip and ear appear to have an increased local recurrence and metastatic potential and thus have been categorized as high risk in the 7th edition system[5,21,44-50] (Table II).

Perineural invasion

Goepfert et al,[44] in their review of 520 patients with 967 cSCC of the face, found an increased incidence of cervical lymphadenopathy and distant metastasis, along with significantly reduced survival in patients with tumors that showed PNI. Leibovitch et al[45] reported a large prospective multicenter study in Australia that included all patients with cSCC who were treated with Mohs micrographic surgery between 1993 and 2002. The report demonstrated that 70/1177 (5.95%) of cancers exhibited PNI and was more common in males (77.1%) and recurrent cSCC (4.7% in primary cSCC vs 6.9% in recurrent cSCC). The cSCC with PNI were associated with location on the face, lower degrees of differentiation (54.3% were moderately differentiated and 28.6% were poorly differentiated), larger preoperative tumor sizes (58.5% of tumors ≥ 2 cm in PNI vs 31.7% in no PNI), postoperative defect sizes (28.6% <3 cm in PNI vs 67.9% in no PNI), subclinical extension, and higher recurrence rate (8% for patients with PNI vs 3.7% for patients without PNI). For recurrent cSCC, PNI was associated with previous surgical excisions or

cryotherapy but not curettage and cautery or radiotherapy.[45] Several univariate studies, all retrospective, have also confirmed that PNI has a negative prognostic factor in cSCCs.[46-49]

Histopathologic grade or differentiation

Early studies recognized that the histologic grade or degree of differentiation of a cSCC affects prognosis: the more differentiated, the less aggressive the clinical course.[50] In 1978, Mohs,[51] in his review of microscopically controlled surgery, reported significant differences in cure rates for well-differentiated tumors (99.4%) compared with poorly differentiated tumors (42.1%). A multivariate analysis has also confirmed that histopathologic grade correlates with recurrence.[52] The 6th edition staging system used a separate G classification system to denote histopathologic grade; however, grade did not contribute toward overall stage grouping (Table I). For the 7th edition AJCC cSCC staging,[9] histopathologic grade includes poorly differentiated tumors as one of several high-risk features.

Classification of N and M staging criteria

The classification of regional lymph nodes (N) in the 6th staging system[10] is based simply on the absence (N0) or presence (N1) of lymph node metastasis (Table I), and does not account for the size, number, or location of regional lymph node metastases, all of which are important independent prognostic factors based on recent data. The N classification has been revised substantially (Table III) and the genesis of this classification is described elsewhere (N. J. Liégeois, MD-PhD, unpublished data, December 2010).

The M classification has not changed from the 6th edition.[10] It accounts for the presence and absence of distant metastasis (Table IV). The new staging system encompassing the TNM system for the cSCC chapter for the 7th edition AJCC manual is summarized in Tables V and VI.

Classification of cSCC of the eyelid

Staging systems for cSCC of the eyelid were developed by both the ophthalmic task force and cSCC task force. The AJCC cancer staging manual editorial board concluded that eyelid cSCC will be staged in the chapter on ophthalmic carcinoma of the eyelid. The cSCC task force will continue to collect data for assessing the prognosis of cSCC of the eyelid using the staging criteria set forth in the cSCC chapter for potential use in future editions.

DISCUSSION

cSCC poses a significant health concern because of its metastatic potential. cSCC is thought to claim approximately 2500 lives per year in the United States, almost a third the number of Americans who die from melanoma each year.[3] Although prognosis and survival-based outcomes have been studied for over 25 years for melanoma, comparatively little is known in terms of the prognostic variables affecting cSCC survival. The incidence of aggressive or advanced cSCC may be increasing for several reasons. First, the older population is generally expanding as a result of demographic trends. cSCC tumors increase strikingly with age.[53] Indeed, the incidence is 30 times higher for those older than 70 years compared with those between ages 50 and 55 years.[53] The highest reported cSCC incidence is in patients

older than 85 years with a rate of 436.4/100,000, almost 3 times the rate for patients between the ages of 70 to 75 years.[53] Further expansion of the elderly population is thus likely to yield higher rates of cSCC. Second, because of improved medical treatments, organ transplant recipients (OTR) currently have longer posttransplantation survival, often living decades posttransplantation. OTR are particularly vulnerable to high rates of cSCC and their tumors tend to feature more aggressive histologic types. Although the general population has a 5:1 ratio of basal cell carcinoma/cSCC, OTR have reported ratios ranging from 1:1.8 to 1:15.[54,55] There is a 65-fold increase in risk of developing cSCC in OTR compared with the general population.[56] OTR are not only susceptible to frequent cSCC but also poor outcome in advanced disease.[42] Because the aged and/or immunosuppressed populations are rising, there is cause for concern that the incidence of poor prognosis or advanced cSCC disease will concomitantly increase over the next several decades. Therefore, cSCC is an important disease for which prognostic data must be accurately recorded and analyzed.

Compared with the 6th edition AJCC NMSC staging, the 7th edition AJCC staging manual will feature MCC as its own independent chapter and the new NMSC chapter will be based on cSCC staging. The remainder of NMSC tumors (eg, appendageal tumors and basal cell carcinoma) will also be included within the same NMSC chapter because those tumors can be advanced and are described to undergo metastasis, albeit rarely. As the first published staging system devoted specifically to cSCC prognosis, this represents an important step for better understanding and studying the prognosis of this potentially metastatic tumor. By covering more than 80 types of skin tumors that are often vastly different in biologic behavior, the existing AJCC 6th edition staging system for NMSC failed to delineate prognostic variables that help predict outcome in NMSC in general or potentially metastatic tumors in particular, such as MCC or cSCC. In addition, because many cSCC tumors occur on the head and neck, the 7th edition cSCC staging system[9] is congruent with head and neck cancer staging system. Furthermore, the new T system for the 7th edition cSCC AJCC staging system[9] now captures additional features believed to correlate with high-risk cSCC to more meaningfully stratify patients based on prospective systematic data. Certainly there is still a need for multivariate data analysis, particularly to determine the relative contributions of the various described T factors influencing cSCC prognosis.

Challenges still remain for researchers and health care providers who seek to better understand cSCC prognosis. Although a significant number of deaths from cSCC are thought to occur annually, the high incidence of early-stage disease and low rate of metastasis creates a formidable task for registries aspiring to collect data on cSCC tumors. The stage grouping of cSCC as described in the 7th edition of the AJCC cancer staging manual[9] is an important step toward identifying the etiological factors involved in the prognosis of cSCC. The knowledge of such factors will enable the implementation of evidence-based studies to further improve prognosis and treatment algorithms for cSCC. For centers currently collecting prospective data on cSCC, this new 7th edition AJCC cSCC (NMSC) staging system[9] will facilitate improved data collection and multicenter collaborations for research studies involving cSCC prognosis.

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Abbreviations used

AJCC	American Joint Committee on Cancer
cSCC	cutaneous squamous cell carcinoma
MCC	Merkel cell carcinoma
NMSC	nonmelanoma skin cancer
OTR	organ transplant recipients
PNI	perineural invasion
SCC	squamous cell carcinoma

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CAPSULE SUMMARY

- A new staging system for nonmelanoma skin cancers was recently adopted by the American Joint Committee on Cancer.
- Unlike prior staging systems for these cancers, the new system was based on data-derived, evidence-based medicine.
- High-risk features are now explicitly included in T staging, such as greater than 2-mm thickness, Clark level greater than IV, perineural invasion, anatomic site, and degree of histologic differentiation.
- This system provides the basis for future clinical trials and prognostic studies across multiple centers.

Table I

Nonmelanoma skin cancer (including cutaneous squamous cell carcinoma) staging system in 6th edition of American Joint Committee on Cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm, but not >5 cm, in greatest dimension
T3	Tumor >5 cm in greatest dimension
T4	Tumor invades deep extradermal structures
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage grouping

Stage	T	N	M
0	In situ	N0	M0
I	T1	N0	M0
II	T2	N0	M0
	T3	N0	M0
III	T4	N0	M0
	Any T	N1	M0
IV	Any T	Any N	M1

Histopathologic grade (G)	
Gx	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Sixth edition TNM system did not include histopathologic grade (G) in final stage criteria.

Table II

Definition of cutaneous squamous cell carcinoma tumor (T) staging system in 7th edition of American Joint Committee on Cancer

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 2 cm in greatest dimension with <2 high-risk features*
T2	Tumor >2 cm in greatest dimension with or without one additional high-risk feature,* or any size with ≥ 2 high-risk features*
T3	Tumor with invasion of maxilla, mandible, orbit, or temporal bone
T4	Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base

* High-risk features include depth (>2-mm thickness; Clark level ≥IV); perineural invasion; location (primary site ear; primary site nonglabrous lip); and differentiation (poorly differentiated or undifferentiated).

Table III

Definition of cutaneous squamous cell carcinoma nodal (N) staging for 7th edition of American Joint Committee on Cancer manual

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in single ipsilateral lymph node, ≤ 3 cm in greatest dimension
N2	Metastasis in single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N2a	Metastasis in single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N3	Metastasis in lymph node, > 6 cm in greatest dimension

Sixth American Joint Committee on Cancer edition classified regional lymph nodes into absence (N0) or presence (N1) of lymph node metastasis; 7th edition incorporates other prognostic factors, including size, number, and location of regional lymph node metastases.

Table IV

Seventh edition American Joint Committee on Cancer definition of cutaneous squamous cell carcinoma distant metastasis (M) staging

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Present distant metastasis

Compared with 6th edition of American Joint Committee on Cancer, there were no changes in M classification. Presence and absence of distant metastasis defines M stage grouping.

Table V

Final 7th edition American Joint Committee on Cancer stage grouping for cutaneous squamous cell carcinoma

Stage	T	N	M
0	In situ	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0 or N1	M0
	T1 or T2	N1	M0
IV	T1, 2, or 3	N2	M0
	Any T	N3	M0
	T4	Any N	M0
	Any T	Any N	M1

TNM staging is incorporated within. Further modifications for 8th edition American Joint Committee on Cancer cutaneous squamous cell carcinoma staging system will be determined by studies that rely on evidence-based medicine.

Table VI

Major T classification changes: 6th edition compared with 7th edition American Joint Committee on cancer staging for cutaneous squamous cell carcinoma

Factor	6th Edition	7th Edition	Comments
Size threshold	T1 ≤ 2 cm 2 cm < T2 < 5cm T3 ≥ 5 cm	Only 2 cm as size cutoff	Little evidence to support 5 cm as important threshold
Histopathologic grade	Not included (separate G system that was not taken into account for staging)	Poor differentiation one of the factors of high-risk features; G eliminated	Studies show degree of differentiation is major prognostic factor for cSCC
Thickness, level of invasion	Only T4 accounts for extradermal invasion (not homogeneous group of tumors)	Clark level IV and >2-mm thickness as high-risk features applicable throughout T1-T4	Both level and thickness of invasion are significant prognostic factors
Location	Not included Eyelid, nonglabrous lip excluded	Primary site ear or nonglabrous lip as high-risk features; nonglabrous lip included	Certain anatomic sites correlated with increased recurrence and metastatic potential
Perineural invasion	Not included vs no specific consideration (as T4 extradermal invasion)	One of the factors of high-risk features	Correlated with increased rate of local recurrence and metastasis
Cranial, facial bone involvement	Not included	Maxilla, mandible, orbit, temporal bone invasion as T3	Correlates with head and neck cancer staging
Invasion of skull base	Not included	T4 determinant	Studies indicate this correlates with poor prognosis disease
Invasion of axial or appendicular skeleton	Not included	T4 determinant	Correlates with poor prognosis per consensus opinion
Eyelid	Not included	Staging of eyelid will be included in chapter on ophthalmic carcinoma of eyelid, although prognostic and risk factor data will continue to be collected by cSCC task force for future AJCC editions	cSCC of eyelid is common and data from SCC task force staging system could potentially be used to define high-risk features of this clinical presentation in future editions of AJCC cancer staging manual

AJCC, American Joint Committee on Cancer; *cSCC,* cutaneous squamous cell carcinoma; *SCC,* squamous cell carcinoma.