Chapter 04

Updates in Cutaneous Squamous Cell Carcinoma

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Abstract

As the second most common skin cancer, cutaneous squamous cell carcinoma (cSCC) is one of the major public health problems in the United States, with 700,000 estimated cases per year [1]. Although cSCC is mostly associated with favorable prognosis, a subset of high risk cSCC exhibits more aggressive clinical behavior, increased risk of local recurrence, metastasis, and death [2-4]. Early identification of this high risk subset with an appropriate staging system is important to ensure adequate treatment. Due to the heterogeneous outcomes that can occur within each Tumor (T) stage, staging systems have been poorly implemented in practice for cSCC, and clinical guidelines have been mainly based on high risk factors rather than on the T stage itself [5-7]. Therefore, multiple research groups have attempted to define alternative staging systems for cSCC during recent years [8,9].

In 2010, the 7th edition of American Joint Committee on Cancer (AJCC-7) published a revised staging system for cSCC. Although AJCC-7 included some high risk factors that would upgrade the T-stage in small tumors [10], the major criticism of the AJCC-7 was based on the evaluation of patients with T2-stage cSCC, as risk and prognosis was widely heterogeneous in these patients. In addition, the clustering of poor outcomes in low T stages (T1 and T2) implicated poor homogeneity (outcomes are similar within categories) and monotonicity (outcomes worsen with increasing categories), and limited the prognostic value of T3 and T4 tumors because bone invasion is rarely seen [9]. While the 8th edition of AJCC (AJCC-8) has emerged to overcome these limitations, this new edition does not include all of the risk factors [11] and it is only dedicated to the head and neck cSCCs [12]. An alternative staging protocol, the Brigham and Women's Hospital (BWH) staging protocol, was also designed to include some risk factors of both staging systems, although not all [13].

In this review, we will provide an overview of the high risk factors of cSCC along with an update in regard to prognostic factors, staging of cSCC and potential treatment options.

Proposed High Risk Factors

Tumor Location

Multiple studies have identified tumor location as an important prognostic factor for metastasis. In a review of 71 studies, it was reported that tumors located on the ear or lip exhibit an increased risk of metastasis compared to other sun-exposed areas [14]. Additional high risk sites based on European guidelines would include the nose, eyelids, and scalp [15]. Tumors arising in certain non-sun-exposed sites, such as anogenital areas, are also associated with a high risk of recurrence [16].

Tumor Diameter

Tumor diameter > 2 cm is an independent risk factor and demonstrated over 2 folds increased risk for tumor recurrence and metastasis based on numerous studies [14,17]. Risk of metastasis and death increased over 4.5 folds when tumor diameter was > 4 cm [18].

Tumor Depth

Tumor thickness and anatomic depth of invasion are other important prognostic factors for cSCC. In a multivariate analysis of risk factors in a prospective cohort of cSCC patients, the metastatic rate increased from 4% to 15% when tumor depth increased from 2 mm to 6 mm [17]. According to the AJCC-8 data, tumor thickness > 6 mm is significantly associated with poor prognosis in cSCC [19].

Tumor Subtype

Several tumor subtypes are associated with higher risk for metastasis including invasive Bowen's disease, desmoplastic SCC, acantholytic SCC, adenosquamous carcinoma, basaloid SCC and SCC arising in the context of predisposing factors (i.e. burn scars, immunosup-

pression, radiation) [4,17,20,21]. Spindle cell (sarcomatoid cSCC) is a variant that predominantly occurs on the head and neck with relatively good prognosis in the absence of deep invasion or other high risk factors. However, genital lesions have been described to have bad prognosis although this may be related to size and depth of invasion [4]. The diagnosis of this variant often requires immunohistochemistry support (Figure 1).

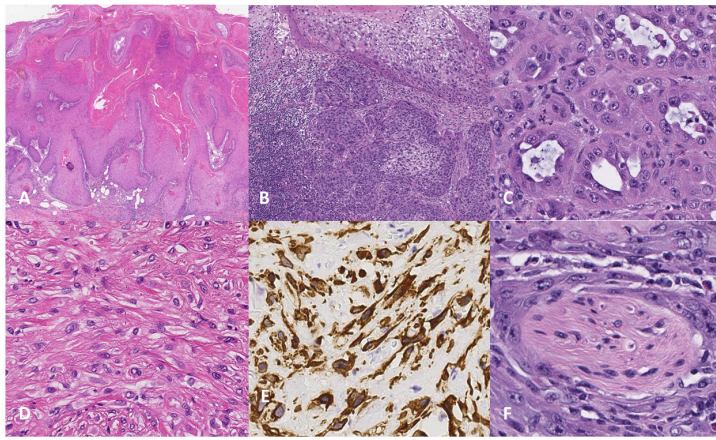

Figure 1: Examples of cutaneous squamous cell carcinoma (cSCC). A. Keratinizing SCC, 20x. B. Bowenoid SCC, 40x. C. Acantholytic SCC with pseudoglandular feature, 200x. D. Sarcomatoid SCC, 200x. E. Sarcomatoid SCC, CK5 immunohistochemistry positive. 200x. F. Perineural invasion, 200x.

Perineural Invasion

Perineural invasion (PNI) is a risk factor for local recurrence and is associated with larger tumor diameter, location on the head and neck, and presence of palpable lymph nodes [22,23]. Involved nerves with a caliber ≥ 0.1 mm are also associated with an increased risk of metastasis, although this may be in part due to other risk factors associated with large-caliber nerve invasion [24]. In the study by Canueto

et al., PNI of nerves ≥ 0.1 mm was the most important risk factor in predicting poor outcome [19] and this is included in the most current staging systems.

Lymphovascular Invasion

Lymphovascular invasion (LVI) is an independent predictor of lymph node metastasis [18,25] and is associated with tumor recurrence, although it is not included in the AJCC and BWH staging systems.

Histologic Differentiation

Tumor histologic grade or differentiation also affects prognosis with an increase in local recurrence and metastatic rate in poorly differentiated tumors (14). Furthermore, due to the heterogeneous nature of cSCCs, metastasis can still occur from predominantly well-differentiated cSCCs that contain poorly differentiated areas, especially in the presence of additional risk factors (26). While the poor degree of differentiation was considered a risk factor in the BWH and in the AJCC-7 staging systems, it was not considered in the AJCC-8, despite several works highlighting its prognostic relevance [19].

Immunosuppression

Patients with solid organ transplantation followed by immunosuppression carry a significantly increased risk of developing cSCC (26), particularly in the setting of persistent HPV infection [27]. These patients tend to develop cSCCs at a younger age, and their lesions are often more numerous and aggressive. Acantholytic and spindle/sarcomatoid variants of cSCC appear to be particularly frequent in transplant patients [2].

Recurrent Tumors

Recurrent tumors more often exhibit high risk features such as LVI, PNI, deep invasion and nodal metastasis. In a study of 100 patients examining neck lymph node metastases from primary cSCC,

regional spread was identified in 14% of patients with recurrent tumors [2].

Staging Systems

T Stage

The T stage categories are based on the presence of risk factors that have been shown to be independent prognostic factors for adverse outcomes (local recurrence, metastasis, and death) in multivariate analyses and are combined to sort tumors in terms of prognosis. Although the AJCC-7 staging system incorporated some high risk factors, it was found to have limitations. Recently, the AJCC-8 staging protocol emerged as an upgraded classification system (Table 1). Similar to the AJCC-7, a clinical size of > 2 cm distinguishes T1 from T2 lesions. T3 of AJCC-7 requires bone invasion which is rarely seen in cSCC. Tumors with a diameter ≥ 4 cm are now classified as T3 in AJCC-8. AJCC-8 also incorporates depth of invasion, which is defined as either > 6mm in depth or invasion past the subcutaneous tissue, as one of the high risk features requiring T3 classification. Large caliber PNI (≥ 0.1mm) or PNI within or beyond the subcutaneous tissue elevates tumor classification to T3, while small caliber PNI is no longer reflected in staging as a high risk feature [28]. Minor bone erosion is another high risk feature that classifies the tumor as T3. Although AJCC-8 continues to include aggressive histologic features (poorly differentiated tumors) as one of the several high risk features and expands that definition to include the desmoplastic and sarcomatoid growth patterns, none of these features have been used as determinants for T staging. Likewise, anatomic location no longer affects the T classification. Although immunosuppression may be recorded as "I" in the final stage report, it still does not affect the T classification. cSCC that arises in burns, scars, or chronic inflammation demonstrates a high rate of metastasis of up to 40%. Finally, local recurrence does not upstage tumors despite evidence demonstrating a higher rate of lymph node metastasis and decreased survival.

Table 1: Definition of cSCC Tumor (T) Staging in AJCC-7, AJCC-8 and BWH staging systems.

	AJCC-7		AJCC-8		BWH
T1	Tumor diameter ≤ 2 cm	**T1**	Tumor diameter < 2 cm	**T1**	0 high risk factors[c]
	with < 2 high risk factors				
T2	Tumor diameter > 2 cm or tumor	**T2**	Tumor diameter ≥ 2 cm and < 4 cm	**T2a**	1 high risk factor
	of any size with ≥2 high risk factors[a]			**T2b**	2-3 high risk factors
T3	Tumor with invasion of maxilla,	**T3**	Tumor diameter ≥ 4 cm, or with	**T3**	≥4 high risk factors
	mandibula, orbit, or temporal bone		one of the high risk features[b]		or bone invasion
T4	Tumor with invasion of skeleton (axial	**T4a**	Tumor with gross cortical bone/marrow invasion	**T4**	Not applicable
	or appendicular) or perieural invasion	**T4b**	Tumor with skull base invasion and/or		
	of skull base		skull base foramen involvement		

[a]High risk factors: Tumor thickness > 2 mm, Clark level IV/V, poor or undifferentiated, perineural invasion (PNI), location at ear or lip

[b]High risk features: PNI (of a nerve lying beneath the dermis, or ≥ 0.1mm in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression), deep invasion (involvement beyond the subcutaneous fat or > 6 mm), and minor bone erosion

[c]High risk factors: Tumor diameter ≥ 2 cm, poorly differentiated, PNI ≥ 0.1 mm, or tumor invasion beyond fat

AJCC-7, seventh edition of the American Joint Committee on Cancer

AJCC-8, eighth edition of the American Joint Committee on Cancer

BWH, Brigham Women's Hospital

cSCC, cutaneous squamous cell carcinoma

Data reveals that all three of the new risk factors incorporated into the AJCC-8 (i.e. the PNI with nerve caliber of > 0.1 mm, tumor thickness > 6mm and the invasion of the tumor beyond the subcutaneous fat) are significantly associated with poor prognosis in cSCC. While the poor degree of differentiation was considered a risk factor in the BWH and the AJCC-7 staging systems, it was not considered in the AJCC-8 staging system. In a recent cohort study, it has been shown that the AJCC-8 is better than the AJCC-7 in terms of prognosis stratification. In this cohort study the majority of cSCC tumors that were associated with poor prognosis were staged as T2 based on the AJCC-7; however, when the AJCC-8 was used on the same cohort, poor prognosis was seen in tumors in the T3 stage. Additionally, classification with the AJCC-8 showed that T1 tumors displayed the best outcome and T2 tumors had an intermediate prognosis. Thus,

with the AJCC-8 system, the higher the T stage, the poorer the outcome. Another significant improvement in AJCC-8 is the designation of T4 to all tumors with bone invasion. Therefore, the AJCC-8 was considered to show increased homogeneity and monotonicity compared to the AJCC-7 [18,28,29]. However, one of the major limitations of AJCC-8 is that this staging protocol only applies to the head and neck (H&N) cSCCs. The BWH's cSCC staging protocol uses four independent prognostic factors (tumor diameter ≥ 2 cm, poor differentiation, PNI ≥ 0.1 mm in caliber, and invasion beyond subcutaneous fat). The BWH's stratification was found to be superior to AJCC-7 by improving prognostic discrimination (outcomes differ between categories) and monotonicity [18] and may have some advantages over AJCC-8 as well, since it applies to tumors beyond the H&N area. However, according to this study, the BWH system did not show significant advantages in staging cSCCs of the H&N over the AJCC-8 [18]. Additional large and multi-institutional studies are necessary to validate the benefits of these staging systems.

N Stage

In order to increase congruency with other head and neck cancer staging protocols, the AJCC-7 considered the size, distribution and number of lymph node metastases [30,31], and adopted the head and neck mucosal SCC (mSCC) nodal staging system for cSCC [10]. Although this lymph node staging system has been well established in mSCC, multi-institutional studies have demonstrated no clinical prognostic value and limited utility for cSCC [30,32,33]. The AJCC-8 increased the complexity further by including extranodal extension (ENE), an adverse prognostic factor (Table 2) [12,34]. Presence of ENE results in upstaging of AJCC-7 N1 disease to N2a and of N2–3 disease to the new N3b category in AJCC-8. Recent studies revealed poor prognostic utility of AJCC-8 N staging system compared with AJCC-7 in cSCC, and found that while inclusion of ENE in AJCC-8 increased the proportion of patients in N3b category, it performed poorly in terms of stratifying survival by N category, especially in

cSCC [35,36]. The data indicate that cSCC merits an independent nodal staging system from that for mSCC.

Table 2: Definition of cSCC Nodal (N) Staging in AJCC-8.

Clinical N (cN)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE-
N2a	Metastasis in single ipsilateral lymph node, > 3cm but not > 6cm in greatest dimension and ENE-
N2b	Metastasis in multiple ipsilateral lymph nodes, none > 6cm in greatest dimension and ENE-
N2c	Metastasis in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension and ENE-
N3a	Metastasis in a lymph node > 6cm in greatest dimension and ENE-
N3b	Metastasis in any node(s) and clinically overt ENE (ENE+)
Pathologic N (pN)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE-
N2a	Metastasis in single ipsilateral or contralateral lymph node, ≤ 3 cm in greatest dimension and ENE+; or in a single ipsilateral lymph node, > 3cm but not > 6cm in greatest dimension and ENE-
N2b	Metastasis in multiple ipsilateral lymph nodes, none > 6cm in greatest dimension and ENE-
N2c	Metastasis in bilateral or contralateral lymph nodes, none > 6cm in greatest dimension and ENE-
N3a	Metastasis in a lymph node > 6cm in greatest dimension and ENE-
N3b	Metastasis in a single ipsilateral node > 3 cm in greatest dimension and ENE+; or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE+

AJCC-8,eighth edition of the American Joint Committee on Cancer; cSCC, cutaneous squamous cell carcinoma; ENE, extranodal extension.

M Stage and TNM Classification

Distant metastasis is staged as M1 in AJCC-8, unchanged from the AJCC-7. The TNM classification permits stratification of patients with cSCC based on prognosis. T1, T2, and T3 lesions, without any lymph node metastasis or distant metastases, are assigned stage I, stage II, and stage III status, respectively. Stage III also includes T1 to T3 with N1 disease. Stage IV is reserved for N2 or N3 nodal disease burden, T4 tumors, and distant metastasis (M1) [28].

Treatment

Primary localized cSCC is usually treated with topical agents, surgical wide local excision, Mohs surgery, cryotherapy, electrotherapy, and radiotherapy. Excellent cure rates have been documented with curettage and cautery for small (< 1 cm), well-differentiated, primary, and slow-growing tumors located on sun-exposed sites [14]. Similarly, excellent short-term cure rates have been reported for cryosurgery [37]. Surgical excision remains the treatment of choice for most cSCC, especially for those with high risk factors [38,39]. Mohs surgery is considered in high risk tumors when margin control is challenging or a critical anatomical site is involved. Radiotherapy is considered when surgical excision is difficult to perform or is likely to cause unacceptable functional results [40].

Despite these treatment measures, 3-4% of patients with cSCC will develop local recurrence, metastasis, or both with poor clinical outcome and a 5-year survival rate of 30% in the case of metastatic cSCC [14,41]. While combination therapy with cisplatin, 5-flouro-uracil, doxorubicin or bleomycin, and in selected cases radiotherapy, have demonstrated some response, there is still limited efficacy of standard-of-care chemotherapy and radiotherapy for patients with locally aggressive or systemic diseases. Novel studies are therefore underway to evaluate the genomic background of cSCC with the hope of establishing targeted therapies. In a recent study by Al-Rohil et al, comprehensive genomic profiling was performed and revealed that

88% of the 122 patients with recurrent, refractory, and metastatic cSCC, harbored at least one clinically relevant genomic alteration capable of potentially guiding therapeutic decisions. The most frequent alterations include NOTCH1, followed by patched 1 (PTCH1), BRCA2, HRAS, ataxia telangiectasia mutated (ATM), erb-B2 receptor tyrosine kinase 4 (ERBB4), neurofibromatosis type 1 (NF1), erb-B2 receptor tyrosine kinase 2 (ERBB2), phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA), cyclin D1 (CCND1), epidermal growth factor receptor (EGFR), F-box and WD repeat domain containing 7, and E3 ubiquitin protein ligase (FBXW7) [42].

Conclusion

The current incidence of cSCC is expected to rise 2-4% per year mainly due to an aging population and chronic ultraviolet B exposure (4). With the growing incidence of cSCC, clinicians should be prepared to encounter a higher volume of high risk primary cSCC. While most patients with cutaneous squamous cell carcinoma have an excellent prognosis after surgical clearance, there is a subset of cSCC that carries increased risk of local recurrence, lymph node metastasis, and death.

Recent data show high cure rates for H&N cSCC with lymph node metastasis when detected and treated early. Thus, accurate identification of patients with cSCC who are at risk for metastasis is beneficial and emphasis should therefore be placed on identifying high risk lesions early on and recognizing important pathologic parameters including tumor diameter of >2 cm, invasion of the subcutaneous tissue and beyond, depth of invasion > 6mm, PNI (especially of large-caliber nerves of ≥ 0.1mm), and poorly differentiated histology.

The limitation in prognostic utility of the AJCC-7 staging system was that T3 and T4 classifications were reserved for rare tumors with bone invasion, causing most of the poor outcomes to occur in patients with T2 tumors. The changes made in the recently published

AJCC-8 will hopefully make the 4 tumor stages more distinct, increasing both homogeneity and monotonicity. This will improve our ability to identify the high risk cSCCs and consolidate them in the higher stages. However, it should be emphasized that AJCC-8 is not able to adequately stratify all patients with cSCC because it is specific to the H&N area. In addition to this limitation, some high risk factors, such as the degree of differentiation, are not considered in the AJCC-8. The BWH's alternative staging system shows overlap with the AJCC-8 both in high stage and low stage tumor assignment and allows the classification of cSCC beyond the H&N area. Further work is needed to validate AJCC-8 with population-level data and to compare AJCC-8's performance against alternative tumor classifications. Identification of potential targeted therapeutic options for metastatic cSCC would require further evaluation of the genomic background of advanced cSCC.

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