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Comparing the eighth and the seventh editions of the American Joint Committee on Cancer staging system and the Brigham and Women's Hospital alternative staging system for cutaneous squamous cell carcinoma: Implications for clinical practice

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Background: The new eighth edition of the American Joint Committee on Cancer staging system (AJCC-8) incorporates changes regarding cutaneous squamous cell carcinoma (CSCC).

Objectives: We aimed to compare the AJCC-8 staging system with the previous seventh edition of the AJCC staging system (AJCC-7) and the Brigham and Women's Hospital (BWH) alternative staging system to identify their usefulness and the utility of their risk factors in defining prognostic groups in CSCC.

Methods: A series of 186 CSCCs of the head and neck were retrospectively collected. All 3 staging systems were compared from the standpoint of their ability to predict poor prognosis. Binary logistic regression models were built to determine which risk factors were most relevant.

Results: Poor prognosis was mainly associated with stage T2 of the AJCC-7, with stages T2b/T3 of the BWH system, and with stage T3 of the AJCC-8. The AJCC-8 and the BWH staging systems displayed overlap with each another in predicting poor prognosis, and both were superior to the AJCC-7. The new risk factors incorporated into the AJCC-8 and the poor degree of differentiation were independently associated with poor outcome.

Limitations: Retrospective study and few cases with bone invasion.

Conclusions: The AJCC-8 is more distinctive, monotonous, and homogeneous than the AJCC-7 and shows some overlap with the BWH system in stratification of tumors. (J Am Acad Dermatol 2019;80:106-13.)

Key words: AJCC; American Joint Committee on Cancer; Brigham and Women's Hospital; cutaneous squamous cell carcinoma; poor degree of differentiation; prognosis; skin cancer staging.

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Forty years after publication of the first edition of the American Joint Committee on Cancer (AJCC) staging system,[1] the eighth and latest edition of the staging system (AJCC-8) was published in 2017 with relevant changes regarding skin cancer, including cutaneous squamous cell carcinoma (CSCC).[2,3] CSCC is the second most frequent cancer in humans, with 700,000 estimated cases per year in the United States, and it can be both locally invasive and metastatic.[4] Staging systems have been poorly implemented in practice for CSCC, and clinical guidelines have been based mainly on high-risk factors rather than on the T stage itself.[5-7] This practice has been due mainly to the heterogeneous outcomes that can occur within each T stage and to the fact that the majority of tumors are staged as T1 when the seventh edition of the AJCC staging system (AJCC-7) is used. In addition, several research groups have attempted to define alternative staging systems for CSCC during recent years.[8,9]

CAPSULE SUMMARY

- The eighth edition of the American Joint Committee on Cancer staging system incorporates changes regarding cutaneous squamous cell carcinoma.
- Poor prognosis was mainly associated with stage T2 of the seventh edition of the American Joint Committee on Cancer staging system but was diverted to stage T3 of the eighth edition. The eighth edition is more distinctive, monotonous, and homogeneous than the former seventh edition and shows some overlap with the Brigham and Women's Hospital alternative staging system.
- The subgroup of tumors staged as T3 in the eighth edition of the American Joint Committee on Cancer staging system, which also showed a poor degree of differentiation, is a subgroup with greater risk.

In 2002, the AJCC stated that stratification of patients by using a cancer staging system should make it possible to sort patients into distinctive (meaning that outcomes should be different among staging categories), monotonous (meaning that outcomes should worsen as the stage increases), and homogeneous (indicating that outcomes should be similar within a staging category) groups.[10] Until 2010, very few changes had been included in the stratification of the T category of CSCC[11] despite the publication of relevant works in the 1990s[12-15] and 2000s.[16-21] The AJCC-7, which was published in 2010, included some high-risk factors that upgraded the T stage, even in small tumors.[11] Specifically, perineural invasion, poor degree of differentiation, tumor thickness greater than 2 mm, Clark levels IV to V, and location of the primary tumor (ear or lower lip), along with the tumor's horizontal size, were the relevant risk factors used for defining T stages.[11] The major criticism of the AJCC-7 was based on evaluation of the stage T2, as patients with stage T2 disease exhibited a wide range of heterogeneity in terms of risk and prognosis.[9] For example, a small 3-mm-thick CSCC in the ear with no other risk factors would be staged as T2 with use of the AJCC-7. A 7-mm-thick tumor with a diameter of 2.5 cm, poor degree of differentiation, and muscle and perineural invasion (even with the involvement of nerves greater than 0.1 mm) with a location within a high-risk area would also be staged as T2 with use of the AJCC-7 if the bone was not affected. In addition, the clustering of poor outcomes in low T stages (T1 and T2), with more than 80% of poor outcome events, implicated poor homogeneity and monotonicity and limited the prognostic usefulness of stages T3 and T4.[9]

Thus, the AJCC-8 emerged with the aim of overcoming these limitations. This new edition considers other relevant prognostic factors of CSCC to stratify the T stage, such as the influence of a tumor thickness greater than 6 mm,[16] perineural invasion (when the nerve diameter is at least 0.1 mm),[9,22] and invasion of the CSCC beyond the subcutaneous fat.[9] However, this new edition excludes some well-known risk factors[23] and stages only tumors of the head and neck (H&N), because most CSCC cases occur in the H&N area. For this reason, the AJCC-8 was developed for these tumors by the Head and Neck Expert Panel and thus was not dedicated to staging tumors located outside of the H&N area.[2] Alternatively, the Brigham and Women's Hospital (BWH) staging protocol includes some risk factors of both staging systems, but not all.[9,22]

The aim of this study was to compare the T stages in a series of patients with CSCC by using both AJCC staging systems (AJCC-7 and AJCC-8) and the BWH alternative staging system, because the BWH classification system has been reported to be superior to AJCC-7[9] and is able to stage tumors beyond the H&N area. Moreover, we have attempted to explore the significance of risk factors to predict poor outcomes in CSCC through binary logistic regression.

Abbreviations used:

AJCC:	American Joint Committee on Cancer
AJCC-8:	eighth edition of the American Joint Committee on Cancer staging system
AJCC-7:	seventh edition of the American Joint Committee on Cancer staging system
BWH:	Brigham and Women's Hospital
CSCC:	cutaneous squamous cell carcinoma
SLNB:	sentinel lymph node biopsy
ME:	major events

PATIENTS AND METHODS

Patients and variables

We evaluated a retrospectively collected cohort of 186 CSCCs located in the H&N. The study included 103 male and 83 female patients with a median age of 85.5 years (range, 47-105) and a median follow-up of 79 months (range, 18.5-190.2). The data used were derived from a database of 2391 CSCCs registered from January 2008 to December 2016 at the University Hospital of Salamanca, Spain. Tumors other than those from the H&N (n = 430), recurrent tumors (n = 20), and tumors of the H&N with missing clinical data (n = 549) were excluded from the study. Of the remaining 1392 tumors, all that had evolved poor outcome were selected (n = 52) and 1 out of every 10 CSCCs with a good prognosis was randomly chosen (n = 134) to complete the cohort of 186 CSCCs. The local institutional ethics review board approved the study.

The following data were considered: (1) patient history (age and sex; previous history of actinic keratosis, nonmelanoma skin cancer [NMSC], and CSCC; and immunosuppression), (2) tumor traits (location of the primary tumor [lower lip, ear, or other locations in the H&N]; tumor size and tumor thickness, as measured using the OV100 software [Olympus, Center Valley, PA]; degree of differentiation [classified as good to moderate or poor]; perineural invasion [PNI] [both the presence and infiltration of nerves ≥0.1 mm in diameter]; and Clark level IV-V), (3) staging system (all tumors were classified according to the AJCC-7, AJCC-8, and the BWH alternative staging system), and (4) disease-specific poor outcome events (DSPOs) (local recurrence, metastasis [to the parotid gland or to lymph nodes], and disease-specific death). Specifically, instances of metastasis and disease-specific death were considered major events (MEs) of poor outcome.

Statistical analysis

The McNemar test was used on paired categoric data to analyze changes in T stages among classification systems. The binary logistic regression was applied to identify those variables used in the staging systems that were associated with DSPOs and MEs. The Wald backward approach was used by discarding the nonsignificant variables at each step via use of the IBM SPSS software (version 24, IBM Corporation, Armonk, NY). For all procedures, P values less than .05 were considered significant.

RESULTS

T-stage classification using the AJCC-7, AJCC-8, and BWH staging systems

The characteristics of our cohort are described in Table I. First, the tumors were classified according to both the AJCC-7 and the AJCC-8. Some tumors were staged the same with use of both systems, but for other tumors the T stage was either upgraded or downgraded with use of the AJCC-8. Specifically, 71 of the 186 tumors (38.2%) remained in the same T stage with use of both systems, 95 tumors (51.1%) were up-staged with use of the AJCC-8, and 20 tumors (38.7%) were down-staged with use of the AJCC-8 (Table II). Next, we stratified our cohort by using the BWH alternative staging system. When the BWH staging system was compared with the AJCC-8, 77 tumors (41.39%) remained in the same stage, 92 tumors (49.47%) were down-staged, and 17 tumors were up-staged (9.14%) with use of the BWH system (Table III).

When we compared each T stage of the AJCC-8 with its counterpart in the other 2 staging systems by using the McNemar test, we observed significant differences for T2 and T3 ($P < .0001$) of the AJCC-7 and all 3 T stages of the BWH staging system ($P < .05$) (Supplemental Table I; available at http://www.jaad.org).

Distinctiveness, homogeneity, and monotonicity among staging systems

The highest proportion of tumors that evolved into poor prognosis appeared in T3 with use of the AJCC-8 (84.6% of DSPOs and 86.96% of MEs). Also, as the T stage increased, the proportion of tumors with poor outcome also increased. In contrast, when the AJCC-7 was used, the highest proportion of tumors that evolved poor prognosis belonged to the stage T2 (76.9% of DSPOs and 91.3% of MEs). Thus, with the AJCC-8, the higher the T stage, the poorer the outcome; however, this was not the case when the AJCC-7 was used to evaluate these tumors. With the BWH classification system, the majority of tumors in our cohort that evolved poor prognosis were staged as T2b (42.30% of DSPOs and 39.13% of MEs). Homogeneity was assessed by comparing poor outcome between low T stages (T1 and T2 in

Table I. Descriptive data on the cohort of 186 patients with CSCCs of the head and neck

Variable	Frequency	%
Patient history		
Median age, y (range)	85.5 (47-105)	
Sex	103 M:83 F	
History of AK	113	61.4
History of NMSC	81	43.5
History of CSCC	71	38.2
Immunosuppression*	30	16.13
Tumor traits		
Median horizontal size, mm (range)	15 (4-73)	
Median thickness, mm (range)	5.5 (1-28)	
Degree of differentiation		
Good to moderate	139	74.7
Poor	47	25.3
Perineural invasion	43	26.1
Perineural invasion of nerves >0.1 mm	31	17.7
Invasion beyond the subcutaneous fat	36	19.4
Clark level IV or beyond	148	79.5
Muscle invasion	36	19.4
Bone invasion	3	1.6
Tumor location		
Lower lip	20	10.8
Ear	23	12.4
Other location	140	76.8
Growth pattern		
No infiltrative	99	53.5
Infiltrative	87	46.8
Desmoplasia	37	19.9
Poor prognosis		
Disease-specific poor outcome	52	28
Local recurrence	37	19.9
Major events†	23	12.4
Metastasis to the parotid gland	6	3.2
Nodal metastasis	23	12.4
Disease-specific death	6	3.2

Percentages refer to the total number of patients (N = 186). The median follow-up period was 79 months (range, 18.5-190.2).
AK, Actinic keratosis; *CSCC*, cutaneous squamous cell carcinoma; F, female; *M*, male; *NMSC*, nonmelanoma skin cancer.
*Chronic lymphocytic leukemia, HIV, poorly controlled diabetes, and long-term use of immunosuppressants.
†Major events are metastasis and death due to CSCC.

both AJCC staging systems and T1 and T2a in the BWH staging system), and monotonicity was assessed by comparing poor prognosis between high T stages (T3 in both AJCC staging systems and T2b and T3 in the BWH system), as previously described[9] (Table IV). Venn diagrams show the distribution of T stages among classification systems, as well as the homogeneity and the monotonicity (Supplemental Fig 1; available at http://www.jaad.org).

Poor prognosis depending on T-stage changes among classification systems

Taking into account the changes in T stage with use of the AJCC-8 versus with use of the AJCC-7 and the associated poor outcomes, it was observed that events developed during follow-up in tumors in which the T stage increased from T1 to T3 (5 of 14 [35.7 %]) and in almost half of those in which the T stage increased from T2 to T3 (38 of 80 [47.5 %]). More importantly, DPSOs did not develop in any of the tumors in which the T stage decreased with use of the AJCC-8. Thus, the increase in T stage with use of the AJCC-8 system was associated with a higher risk of poor outcome, and its decrease was associated with good prognosis. When tumors were compared by using the BWH and AJCC-8 systems, it was observed that in a significant proportion of the tumors that were down-staged with the BWH staging system (39 of 93), DSPOs developed during follow-up, whereas only 1 of the 17 tumors that was up-staged behaved aggressively (Table V).

Risk factors independently associated with poor outcome

In a final step to determine which variables were the most important in the stratification of tumors according to their risk of evolving poor outcomes, several binary logistic regression models were built. All risk factors included in all of the 3 staging systems analyzed were used as starting variables, and DSPOs and MEs were considered response variables. The significant risk factors of each staging system after a backward stepwise selection are shown in Table VI.

Finally, all risk variables included in the AJCC-7, AJCC-8, and BWH staging systems were combined. It was observed that PNI of 0.1 mm or more and a tumor thickness greater than 6 mm were significantly associated with DSPOs and the invasion of the tumor beyond the subcutaneous fat and the poor degree of differentiation were both independently associated with MEs (Table VI). Furthermore, of the tumors staged as T3 with the AJCC-8, 38 exhibited a poor degree of differentiation. Of those tumors, 12 tumors developed MEs during follow-up and 20 developed DSPOs.

DISCUSSION

In 2010, the AJCC-7 incorporated some high-risk factors and built a completely new T stage,[11] but it was found to exhibit limitations.[8,9] Recently, the AJCC-8 emerged as an upgraded classification system.[2] Here, it has been shown that the AJCC-8 is better than the AJCC-7 in terms of prognosis stratification.

Table II. Changes in T-stage assignment of the CSCC tumors of our cohort of 186 patients after evaluation of the tumors with use of the AJCC-7 versus the AJCC-8

Systems compared	No changes in T stage	n (%)	Up-staging/down-staging		n (%)
AJCC-7 (N = 186) vs	T1-T1	58 (31.2% [*])	Up-staged	T1-T2	1 (0.5%)
AJCC-8 (N = 186)	T2-T2	10 (5.4%)		T1-T3	14 (7.5%)
	T3-T3	3 (1.6%)		T2-T3	80 (43.0%)
	Total tumors with no change = 71 (38.2%)		Down-staged	T2-T1	20 (10.8%)

AJCC-7, American Joint Committee on Cancer staging system, seventh edition; *AJCC-8*, American Joint Committee on Cancer staging system, eighth edition; *CSCC*, cutaneous squamous cell carcinoma.
*Percentages refer to the initial number of patients (N = 186).

Table III. Changes in T-stage assignment of the CSCC tumors of our cohort of 186 patients after evaluation of the tumors with use of the AJCC-8 versus the BWH staging system

Systems compared	No changes in T stage	n (%)	Up-staging/down-staging		n (%)
AJCC-8 (N = 186) vs			Down-staged	T3-T1	11 (5.9%)
BWH (N = 186)	T1-T1	64 (34.4%*)		T3-T2a	37 (19.9%)
	T2-T2a	8 (4.3%)		T3-T2b	44 (25.3%)
	T3-T3	5 (2.7%)	Up-staged	T1-T2a	14 (7.5%)
	Total tumors with no change = 77 (41.4%)			T2-T2b	3 (1.6%)

AJCC-8, American Joint Committee on Cancer staging system, eighth edition; *BWH*, Brigham and Women's Hospital; *CSCC*, cutaneous squamous cell carcinoma.
*Percentages refer to the initial number of patients (N = 186).

The vast majority of CSCC tumors associated with DSPO in the AJCC-7 were staged as T2 in our cohort, which included tumors with a heterogeneous prognosis (which is a weak point that others have already highlighted).[9] Conversely, when the AJCC-8 was used on this same cohort, poor prognosis was diverted toward 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, the AJCC-8 is more homogeneous and monotonous than its predecessor, the AJCC-7. Furthermore, the proportion of poor outcomes in each T stage was more distinctive with the AJCC-8 than with the AJCC-7.

The BWH stratification has proved to be superior to the AJCC-7[9] and may have some advantages over the AJCC-8 as well, being a good choice for staging tumors beyond the H&N area. However, according to our data, this system did not appear to have great advantages over the AJCC-8 in staging CSCCs of the H&N. Whereas the BWH system shows clear differences with respect to the AJCC-7,[9] many overlaps are observed with the AJCC-8 in terms of homogeneity and monotonicity. More series, including series with T4 tumors, are needed to further evaluate these similarities and differences.

The T-stage categories are based on the presence of some high-risk factors that are combined to sort tumors in terms of prognosis. Our data showed that all 3 of the new risk factors incorporated into the AJCC-8, namely, PNI of 0.1 mm or more, thickness greater than 6 mm, and invasion of the tumor beyond the subcutaneous fat, are significantly associated with poor prognosis in CSCCs. Moreover, the poor degree of differentiation, which is considered a risk factor in the BWH staging system[9] and in the AJCC-7,[11] is a relevant risk factor according to our data but was not considered in the AJCC-8,[2] even though several works have highlighted its prognostic relevance.[20,23-27] In our cohort, MEs developed in almost 1 in 3 tumors staged T3 (according to the AJCC-8) and having a poor degree of differentiation. Hence, this apparent subset could be more aggressively managed, and adjuvant radiotherapy and sentinel lymph node biopsy (SLNB) could be considered in some cases. SLNB, although well established in the management of melanoma,[28] is not routinely recommended in CSCC. The risk of SLNB positivity in intermediate-thickness melanoma is around 20%,[28] and the risk of nodal metastasis in the AJCC-8 T3 subgroup with poor degree of differentiation in our series is greater than 30%,

Table IV. Distinctiveness, homogeneity, and monotonicity among the different staging systems

	Disease-specific poor outcome			Major events		
Classification system	**Stage**	**Yes**	**No**	**Stage**	**Yes**	**No**
Distinctiveness among the staging systems						
AJCC-7	T1 (n = 73)	11/73 (15.06%)	62/73	T1 (n = 73)	3/73 (4.11%)	70/73
	T2 (n = 110)	40/110 (36.36%)	70/110	T2 (n = 110)	20/110 (18.18%)	90/110
	T3 (n = 3)	1/3 (33.33%)	2/3	T3 (n = 3)	0/3 (0%)	3/3
AJCC-8	T1 (n = 78)	6/78 (7.69%)	72/78	T1 (n = 78)	2/78 (2.56%)	76/78
	T2 (n = 11)	2/11 (18.18%)	9/11	T2 (n = 11)	1/11 (9.09%)	10/11
	T3 (n = 97)	44/97 (45.36%)	53/97	T3 (n = 97)	20/97 (20.62%)	77/97
BWH	T1 (n = 75)	8/75 (10.66%)	67/75	T1 (n = 75)	3/75 (4%)	72/75
	T2a (n = 59)	17/59 (28.81%)	42/59	T2a (n = 59)	6/59 (10.17%)	53/59
	T2b (n = 47)	22/47 (46.8%)	25/47	T2b (n = 47)	9/47 (19.14%)	38/47
	T3 (n = 5)	5/5 (100%)	0/5	T3 (n = 5)	5/5 (100%)	0/5
Homogeneity among the staging systems*						
AJCC-7	T1 and T2	51 of 52 (98.07%)		T1 and T2	23 of 23 (100%)	
AJCC-8	T1 and T2	8 of 52 (15.38%)		T1 and T2	3 of 23 (13.04%)	
BWH	T1 and T2a	25 of 52 (48.07%)		T1 and T2a	9 of 23 (39.13%)	
Monotonicity among the staging systems*						
AJCC-7	T3	1 of 52 (1.93%)		T3	0 of 23 (0%)	
AJCC-8	T3	44 of 52 (84.61%)		T3	20 of 23 (86.96%)	
BWH	T2b and T3	27 of 52 (51.93%)		T2b and T3	14 of 23 (60.86%)	

AJCC-7, American Joint Committee on Cancer staging system, seventh edition; *AJCC-8*, American Joint Committee on Cancer staging system, eighth edition; *BWH*, Brigham and Women's Hospital.
*For disease-specific poor outcome, n = 52; for major events, n = 23.

Table V. Poor prognosis depending on changes in T stage when assessment is done using the AJCC-7 versus the AJCC-8 and the AJCC-8 versus the BWH systems

Systems being compared			**DSPOs**	**MEs**	**MPAR**	**LYMPHM**	**LR**	**DSD**
AJCC-8 vs AJCC-7								
Up-staged	T1-T2	1	0/52 (0)	0/23 (0)	0/6 (0)	0/23 (0)	0/37 (0)	0/6 (0)
(n = 95)	T1-T3	14	5/52 (9.6%)	1/23 (4.3%)	1/6 (16.6%)	1/23 (4.35%)	4/37 (10.8%)	0/6 (0)
	T2-T3	80	38/52 (73.1%)	20/23 (86.7%)	4/6 (66.6%)	20/23 (86.7%)	26/37 (70.3%)	6/6 (100%)
Down-staged (n = 20)	T2-T1	20	0/52 (0)	0/23 (0)	0/6 (0)	0/23 (0)	0/37 (0)	0/6 (0)
AJCC-8 vs BWH								
Up-staged	T1-T2a	14	1/52 (1.92%)	0/23 (0)	0/6 (0)	0/23 (0)	1/37 (2.7%)	0/6 (0)
(n = 17)	T2-T2b	3	0/52 (0)	0/23 (0)	0/6 (0)	0/23 (0)	0/37 (0)	0/6 (0)
Down-staged	T3-T2a	37	14/52 (26.92%)	5/23 (21.2%)	1/6 (16.6%)	5/23 (21.7%)	9/37 (24.32.9%)	1/6 (16.67%)
(n = 95)	T3-T2b	44	22/52 (42.3%)	9/23 (39.13%)	2/6 (33.3%)	10/23 (43.48%)	17/37 (45.94%)	3/6 (50%)
	T3-T1	11	3/52 (5.76%)	1/23 (4.3%)	1/6 (16.6%)	1/23 (4.3%)	2/37 (5.4%)	0/6 (0)

AJCC-7, American Joint Committee on Cancer staging system, seventh edition; *AJCC-8*, American Joint Committee on Cancer staging system, eighth edition; *BWH*, Brigham and Women's Hospital; *DPSO*, disease-specific poor outcome; *DSD*, disease-specific death; *LR*, local recurrence; *LYMPHM*, lymphatic metastasis; *ME*, major event; *MPAR*, metastasis to the parotid gland.

which means that some of these tumors may benefit from SLNB; however, clinical trials are needed to address this issue. The problem with the degree of differentiation may lie with the subjectivity that could exist upon tumor evaluation.[2,29] According to the AJCC Expert Panel, specific associations of the degree of differentiation with prognosis of CSCC independently of other risk factors are not

Table VI. Variables used in the stratification of AJCC T stages that are significantly associated with prognosis in CSCC after building of binary logistic regression models

Staging system	Response variables	Selected predictive variables	OR	95% CI	*P* value
AJCC-7*	Disease-specific poor outcome	Location to the ear or lower lip	2.75	1.02-7.42	**.045**
		PNI	6.72	3.15-14.31	**.0001**
	Major events	Degree of differentiation	3.31	1.23-8.91	**.018**
		PNI	2.93	1.08-7.93	**.034**
AJCC-8†	Disease-specific poor outcome	PNI >0.1 mm	7.99	3.42-18.64	**.0001**
		Thickness >6 mm	2.6	1.27-5.30	**.009**
	Major events	PNI >0.1 mm	5.47	2.12-14.10	**.0001**
		Thickness >6 mm	2.32	0.91-5.87	.077
BWH‡	Disease-specific poor outcome	PNI >0.1 mm	5.53	2.16-14.13	**.0001**
		Beyond subcutaneous fat	2.212	0.87-5.62	.095
	Major events	Degree of differentiation	4.18	1.63-10.75	**.003**
		Beyond subcutaneous fat	4.45	1.69-11.68	**.002**
AJCC-7 + AJCC-8 + BWH§ (&)	Disease-specific poor outcome	PNI >0.1 mm	7.99	3.42-18.65	**.0001**
		Thickness >6 mm	2.59	1.27-5.30	**.009**
	Major events	Degree of differentiation	4.19	1.63-10.75	**.003**
		Beyond subcutaneous fat	4.45	1.69-11.68	**.002**

Boldface indicates statistical significance.

AJCC, American Joint Committee on Cancer; *AJCC-7*, American Joint Committee on Cancer staging system, seventh edition; *AJCC-8*, American Joint Committee on Cancer staging system, eighth edition; *BWH*, Brigham and Women's Hospital; *CI*, confidence interval; *CSCC*, cutaneous squamous cell carcinoma; *OR*, odds ratio; *PNI*, perineural invasion.

*Starting variables entered in the logistic regression for AJCC-7 were tumor size (<2 cm vs >2 cm), tumor thickness (<2 mm vs >2 mm), PNI (no vs yes), location of the primary tumor (other locations vs ear and lower lip), degree of differentiation (good and moderate vs poor), Clark level (I-II vs IV-V), bone invasion (no vs yes).

†Starting variables entered in the logistic regression for AJCC-8 were tumor size (<2 cm vs >2 cm), tumor size (<4 cm vs >4 cm), tumor thickness (<6 mm vs > 6 mm), invasion beyond the subcutaneous fat (no vs yes), PNI of nerves >0.1 mm (no vs yes), bone invasion (no vs yes).

‡Starting variables entered in the logistic regression for the BWH staging system were tumor size (<2 cm vs >2 cm), degree of differentiation (good and moderate vs poor), tumor thickness (<2 mm vs >2 mm), PNI of nerves >0.1 mm (no vs yes), bone invasion (no vs yes).

§Variables entered in the logistic regression of all 3 staging systems were included.

definitive,[2] and thus, degree of differentiation was not included in the AJCC-8. However, this is an issue that should be assessed in future studies.

Another weak point of the AJCC-8 may be that the newly incorporated prognostic factors are given similar importance even though not all are equally as important. Also, it has been shown that the presence of 2 or more risk factors is more highly predictive of poor outcomes than is presence of only1 factor.[9,22] Considering the odds ratio in the logistic regression models in our study, PNI of 0.1 mm or more seems to be the most important risk factor in predicting poor outcome, whereas the relevance of a thickness greater than 6 mm seems to be less relevant. Hence, establishing a hierarchy of risk factors would be useful in the management of CSCC.

The retrospective design of our study implies that the patients and their records were not conceived of before this particular study. However, the archived slides did provide the possibility of a detailed re-examination of all histopathologic tumor traits. Another limitation of this study could be the absence of T4 tumors in our series, but given their rarity, the present study may still prove useful to physicians in the stratification and management of most CSCCs.

According to our data, the AJCC-8 is more distinctive, monotonous, and homogeneous than the AJCC-7, and it is better at predicting poor outcomes in CSCC. However, the AJCC-8 is not able to adequately stratify all patients with CSCC because it is specific to the H&N area.[2,29] In addition to this limitation, some high-risk factors, such as the degree of differentiation, are not considered in the AJCC-8 but may be useful in identifying subgroups of tumors with a greater risk of poor outcomes. The BWH alternative staging system shows overlap with the AJCC-8 both in high-stage and low-stage tumor assignment and allows classification of CSCCs beyond the H&N area. This system also considers the cumulative risk of risk factors when they are combined, which may also improve the accuracy of the AJCC-8. Finally, according to our data, the new AJCC-8 seems to be considerably better than its

predecessor, the AJCC-7. But future studies are required to better refine T3 tumors in AJCC-8 and to build a staging system for CSCC that can be used to classify tumors located outside the H&N area.

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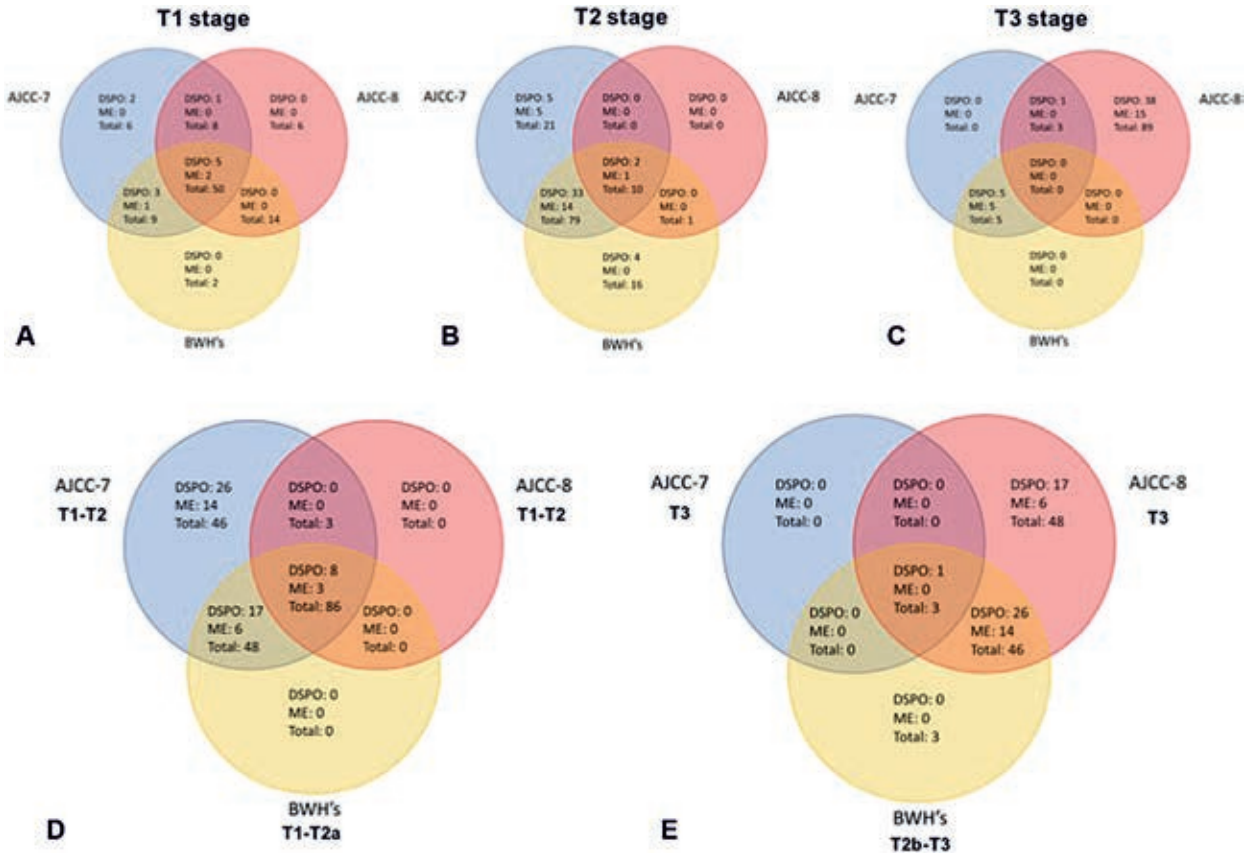

Supplemental Fig 1. Venn diagrams representing the distribution of T stages among the different classification systems. Each circle represents 1 staging system; sectors correspond with the overlap of 2 or 3 staging systems. Numeric data in each sector: disease-specific poor outcome (DSPO) in the corresponding sector, major events (MEs) in the corresponding sector, and total number of patients in the corresponding sector (total). **A**, **B**, and **C**, How tumors are classified in the different staging systems. In these schemes, subcategories T2a and T2b were grouped within stage T2 for the Brigham and Women's Hospital (BWH) alternative staging system. The greatest overlap among all 3 systems occurs for T1 tumors (50 tumors are staged as T1 among all 3 systems [see the central sector]) (**A**); there is a medium overlap for T2 tumors (**B**); and the smallest overlap among all 3 systems occurs for T3 tumors (none of the 186 tumors are staged as T3 in all 3 systems at the same time) (**C**). **D**, Classification of low-stage tumors among all 3 staging systems (ie, homogeneity). There is no equivalence between the seventh edition of the American Joint Committee on Cancer (AJCC-7) staging system and the other 2 systems (ie, eighth edition of the American Joint Committee on Cancer [AJCC-8] and BWH alternative staging system). A total of 86 tumors were classified within low T stages with use of all 3 classification systems (*central sector*), and it is in these tumors in which 8 DSPOs and 3 MEs occurred. All but 1 tumor that evolved DPSOs (n = 51) were classified as T1 or T2 with the AJCC-7, which means that the AJCC-7 is the worst staging system in terms of homogeneity. The majority of tumors classified as T1 or T2 with the AJCC-8 are classified as T1 or T2a with the BWH alternative staging system. Thus, both the AJCC-8 and the BWH systems display great overlap (64.2 % for the BWH system and 96.6 % for the AJCC-8 system). **E**, Classification of high-stage tumors among all 3 staging systems (ie, monotonicity). The scheme shows no equivalence between the AJCC-7 staging system and the other 2 classification systems (ie, AJCC-8 and BWH). The majority of tumors classified as T3 with the AJCC-8 system are classified within the high T stages in the BWH system (T2b and T3); hence, these systems have an overlap of 94% and 51%, respectively. However, use of the AJCC-8 resulted in 48 high-stage cases that were not classified the same way with use of the BWH system, according to which 17 DSPOs and 6 MEs occurred. According to our data, the AJCC-8 seems to be the best staging systems in terms of monotonicity.

Supplemental Table I. Pairwise comparison of each T stage between the AJCC-7 and AJCC-8 staging systems and between the AJCC-8 and BWH staging categories (McNemar test)

Version of T1		T1 (AJCC-8)		*P* value	Version of T2		T2 (AJCC-8)		*P* value	Version of T3		T3 (AJCC-8)		*P* value
T1 (AJCC-7)		Yes	No	.5 (NS)	T2 (AJCC-7)		Yes	No	**.0001**	T3 (AJCC-7)		Yes	No	**.0001**
	Yes	58	15			Yes	10	100			Yes	3	0	
	No	20	93			No	1	75			No	94	89	
T1 (BWH)		Yes	No	**.0001**	T2 (BWH)*		Yes	No	**.003**	T3 (BWH)		Yes	No	**.030**
	Yes	64	11			Yes	11	95			Yes	5	0	
	No	14	97			No	0	80			No	92	89	

AJCC-7, American Joint Committee on Cancer, seventh edition; *AJCC-8*, American Joint Committee on Cancer, eighth edition; *BWH*, Brigham and Women's Hospital; *NS*, not significant.
*The stage T2 in the BWH's staging system includes the subcategories T2a and T2b; as these 2 subcategories exhibit differences in prognosis, the grouping of both of them in only 1 T2 group in this table for methodologic purposes might be somewhat imprecise. Boldface indicates statistical significance.

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