Evaluation of AJCC Tumor Staging for Cutaneous Squamous Cell Carcinoma and a Proposed Alternative Tumor Staging System

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Importance: This study proposes an alternative tumor staging system for cutaneous squamous cell carcinoma (CSCC) that more precisely defines the small subset of tumors with a high risk of metastasis and death.

Objective: To identify risk factors for poor outcomes in CSCC and evaluate the 2010 American Joint Committee on Cancer (AJCC) tumor (T) staging system’s ability to stratify occurrence of these outcomes.

Design: Retrospective cohort study.

Setting: A single academic hospital.

Participants: Study participants were identified via a pathology and dermatopathology database search for patients diagnosed as having high-risk CSCC.

Results: Two hundred fifty-six primary high-risk CSCCs were included. Outcomes for AJCC tumor stages T2 to T4 were statistically indistinguishable because only 4 cases (<2% of the cohort) were AJCC stages T3 or T4, which require bone invasion. Subsequently, the bulk of poor outcomes (83% of nodal metastases, 92% of deaths from CSCC) occurred in AJCC stage T2 cases. An alternative tumor staging system was developed with the aim of better stratifying this stage T2 group. Four risk factors were found to be statistically independent prognostic factors for at least 2 outcomes of interest in multivariate modeling. These factors (poor differentiation, perineural invasion, tumor diameter ≥2 cm, invasion beyond subcutaneous fat) were incorporated in the alternative staging with 0 factors indicating T1, 1 factor indicating T2a; 2 to 3 factors, T2b; and 4 factors or bone invasion, T3. Stages T2a and T2b significantly differed in incidences of all 4 end points. Stage T2b tumors comprised only 19% of the cohort but accounted for 72% of nodal metastases and 83% of deaths from CSCC.

Conclusions and Relevance: The proposed alternative tumor staging system offers improved prognostic discrimination via stratification of stage T2 tumors. Validation in other cohorts is needed. Meanwhile, stage T2b tumors are responsible for most poor outcomes and may be a focus of high-risk CSCC study.

uniformity in how patients with HRCSCC are treated. Once distant organ metastasis or unresectable locoregional recurrence develops, treatment options are limited. Accurate prediction of poor outcomes could improve patient care by allowing physicians to target staging and adjuvant therapy.

The American Joint Committee on Cancer (AJCC) published revised staging systems for CSCC in 2010. The new tumor (T) staging system incorporated risk factors of tumor thickness greater than 2 mm, Clark level of IV or higher, location on ear or non–hair-bearing (vermillion) lip, and poorly differentiated histologic findings for the first time, as well as tumor diameter of 2 cm or greater, which had been part of prior T staging. Little outcome data are available validating the AJCC CSCC staging system. However, recent publications have pointed out difficulties with AJCC T staging, and an alternative N staging system has been proposed based on outcome data for patients with nodal metastasis.

In the present study, the AJCC T staging system was evaluated via patient outcome data with regard to nodal metastasis, local recurrence, disease-specific death, and all-cause death. Study data were used to identify independent prognostic risk factors for these end points, and a proposed alternative T staging system was developed based on these prognostic factors, which seems to offer improved prognostic discrimination.

### METHODS

A retrospective cohort study was conducted of patients diagnosed as having primary CSCC with 1 or more risk factors (defined in this section) from January 1, 1998, through June 30, 2005. Patients without risk factors were excluded since the risk of recurrence and metastasis in this group is low (Joseph et al; Brantsch et al). Recurrent tumors were also excluded.

Eligible tumors were identified through a keyword search of the pathology and dermatopathology databases for 6 risk strata: perineural or lymphovascular invasion, poorly differentiated histologic characteristics, depth beyond subcutaneous fat, diameter of at least 2 cm, location on the ear, or location on the vermilion lip. For risk strata that contained more than 100 cases (ear and lip locations), a randomly selected subgroup of 100 cases was included to ensure even representation of different risk factors in model building. Cases of squamous cell carcinoma in situ, keratoacanthoma, and basosquamous carcinoma were excluded.

Primary exposure variables were abstracted from pathology reports and included perineural or lymphovascular invasion, histologic differentiation, tumor depth, tumor diameter, and location. Other variables of interest and outcome data were collected through medical record review (age at diagnosis; sex; history of prior CSCC at the same site; treatment; margin status; and local, regional, and distant recurrence) and patient interview (prior history of skin cancer, UV light exposure, radiation exposure, arsenic exposure, and immunosuppression) by 2 of us (A.J.-P. and F.M.W.). Outcomes of interest were local recurrence, nodal metastasis, disease-specific death, and all-cause death. Local recurrence was defined as a biopsy-proven CSCC within the excision scar. Lymph node metastasis was defined as a biopsy-proven CSCC in the draining lymph node basin. Disease-specific death was defined as death occurring from metastatic or locally advanced CSCC. Time to each outcome of interest was determined by calculating the time elapsed between diagnosis of the primary tumor and time of outcome occurrence. Those who did not develop outcomes of interest were censored (follow-up period ceased) on the date of death or on the date of medical record review if alive.

Descriptive statistics and frequency tabulation were used to descriptively evaluate variables. The competing risk analysis by Fine and Gray was used to determine univariate and multivariate associations of risk factors with development of outcomes of interest. Competing risk models were chosen over Cox models for all outcomes of interest (except all-cause death) because the latter assume that there are no other competing events that preclude the occurrence of events of interest. Cox models are not ideally suited to this elderly study population with CSCC because death from non-CSCC causes occurs commonly, and the risk of patients dying from these other causes before they have an opportunity to develop disease recurrence, metastasis, or death from CSCC is quite high. Competing risk models take the risk of these non-CSCC occurrences into account. For the all-cause death end point, competing risks for other causes of death do not apply since all-cause death incorporates all causes of death, so Cox modeling was used for this outcome. For competing risk models, a subhazard ratio (SHR) is reported and represents a cause-specific hazard ratio (HR) that is interpreted similarly to a Cox model standard HR. The proportionate hazards assumption (which applies to both competing risk and Cox models) was checked via Schoenfeld residual plots.

Multivariate models were built for each outcome of interest through forward stepwise variable addition followed by backward elimination. In this form of model building, modeling begins with the variable with the largest effect estimate on univariate modeling. Other variables are added based on the next variable with the largest effect estimate and are retained in the model if (1) the P value of the Wald test comparing the smaller model to the larger model was significant at P < .05 or (2) the P value of the Wald test was borderline (P > .05 - .10), but addition of the variable changed the SHR or HR by at least 10%, and the variable is considered clinically relevant to the outcome in question. Sensitivity analyses were performed in which 1 tumor per patient was randomly selected for analysis in those patients with multiple tumors.

Tumors were classified according to 2010 AJCC T stage. A tumor was classified as AJCC stage T1 if the diameter was 2 cm or smaller and had 1 of the following high-risk factors: poorly differentiated histologic characteristics, location on the vermilion lip or ear, perineural invasion, or depth to Clark level IV or greater or more than 2 mm. A tumor was classified as AJCC stage T2 if it was more than 2 cm in diameter or had at least 2 of the high-risk features listed herein. A tumor was classified as AJCC stage T3 if it invaded maxilla, mandible, orbit, or temporal bones, and as AJCC stage T4 if it invaded other bones or invaded the skull base.

A proposed alternative T staging system was developed based on the presence or absence of risk factors found to be strong independent prognostic predictors on multivariate analysis (SHR ≥ 2.0 for at least 2 end points of interest in the fully adjusted multivariate models). Cumulative incidence function (CIF) curves were generated to illustrate T-stage survival probabilities for competing risk end points (local recurrence, nodal metastasis, and disease-specific death), while Kaplan-Meier survival curves were used for the Cox end point of all-cause death. Pair-wise comparison tests (Gray test for CIFs and log-rank test for Kaplan-Meier curves) were performed to determine whether the T-stage curves significantly differed from one another.

All statistical analyses were performed using STATA software (version 12.0; STATA Corp) and R software (R Development Core Team) using a 2-sided, 5% type I error rate. The study was approved by the University of Pennsylvania institutional review board.
RESULTS

COHORT CHARACTERISTICS

The pathology database search resulted in 523 CSCC tumors that met inclusion criteria. A total of 267 cases were not included owing to deceased patient without a surrogate to consent for review of noninstitutional records (n = 107), inability to contact patient owing to outdated or incorrect contact information (n = 55), medical records that were no longer available (n = 81), and patient declining to participate (n = 24). This left 256 tumors in 237 patients in the final study group. No difference was found between included and excluded cases in the proportion of tumors with risk factors of interest including perineural invasion (PNI), poor differentiation, depth beyond dermis, depth beyond subcutaneous fat, location, and diameter (data not shown).

Demographics, tumor characteristics, and clinical information are described in Table 1. Most patients (97%) had a single tumor. For the 14 patients (6%) with 2 to 3 tumors, each tumor was considered independent from the others in data analysis. The median age at diagnosis was 80 years (interquartile range [IQR], 73-86 years), and most patients were male (n = 183; 77%). Thirty-five patients (15%) were immunosuppressed (15 organ transplant patients, 7 patients with CLL, 12 patients undergoing nontransplant steroid therapy, and 1 patient with human immunodeficiency virus/AIDS).

Sixty-two tumors (24%) had PNI. Two of these had vascular invasion as well. Fifty-one tumors (20%) were poorly differentiated. Thirty-eight tumors (15%) penetrated beyond the subcutaneous fat. Forty-six tumors (18%) were 2 cm or greater in diameter. One hundred forty-eight tumors (58%) were located on the lip or ear; of these, 104 tumors (41% of the case cohort) had no other risk factors.

TREATMENT

Approximately half of the tumors (133 [52%]) were treated with wide local excision (WLE). Mohs surgery (MMS) was performed for 70 tumors (27%) and electrodesication and curettage was used for 39 tumors (15%). Less common treatments included biopsy alone (5 patients [2%]), MMS followed by WLE (3 patients [1%]), and primary radiation therapy (XRT) (2 patients [1%]). Twenty-seven tumors (11%) were treated with postoperative XRT. The most common indication for postoperative XRT was PNI (24 patients [89%]).

OUTCOMES

The median follow-up time was 44 months (IQR, 27-67 months). During the follow-up period, there were 21 local recurrences, 25 nodal metastases, 12 disease-specific deaths, and 85 all-cause deaths, corresponding to 8%, 10%, 5%, and 33% of tumors, respectively. Most disease-specific deaths were due to complications from extensive locoregional disease rather than distant organ metastasis (of which there were only 4 cases).
EVALUATION OF OUTCOMES BY AJCC (T) STAGE

The distribution of cases by AJCC T stage is listed in Table 1. One hundred twelve tumors (54% of cohort) were AJCC stage T1 and 91 (44%) were AJCC stage T2. Only 4 tumors were AJCC stage T3 or stage T4 owing to the rarity of bone invasion that is required for AJCC stage T3/T4 staging. Cumulative incidence or survival curves and life tables for each end point by AJCC T stage are presented in Figure 1. Forty-nine tumors could not be classified by AJCC T stage because tumor diameter data were unavailable. However, there were few events of interest in this group, with 5 cases of local recurrence, 0 disease-specific deaths, and 19 all-cause deaths. In the AJCC stage T1 group, there were 3 cases of local recurrence, 2 cases of nodal metastasis, 0 disease-specific deaths, and 25 all-cause deaths. Most events occurred in the AJCC stage T2 group, including 11 of 16 cases of local recurrence (69%), 20 of 24 cases of nodal metastasis (83%), 11 of 12 disease-specific deaths (92%), and 39 of 66 all-cause deaths (59%). The remaining events occurred in the 4 cases with stage T3 and stage T4 (T3/T4) with 2 cases of local recurrence, 2 cases of nodal metastasis, a single disease-specific death, and 2 all-cause deaths.

Pair-wise comparison testing of differences between incidence and survival curves for AJCC stage T1 vs stage T2 showed incidence of poor outcomes to be significantly higher in stage T2 than in stage T1. (Gray test = 7.9

Figure 1. American Joint Committee on Cancer (AJCC) tumor (T) staging results. Cumulative incidence function curves for local recurrence (A), lymph node metastasis (B), disease-specific death (C), Kaplan-Meier survival curve for all-cause death (D), and life tables by AJCC T stage.
RESULTS OF UNIVARIATE MODELING OF OUTCOMES OF INTEREST

Many of the risk factors under study were shown to be significantly associated with adverse outcomes. Tumor location modified the association between tumor depth and outcomes; tumors greater than 2 cm in diameter located on the lip or ear had a higher risk of nodal metastasis and disease-specific death than tumors this size located elsewhere on the body. Perineural invasion of nerves greater than 0.1 mm in caliber was significantly associated with nodal metastasis and disease-specific death, whereas neither of these events occurred in cases in which nerve diameter was less than 0.1 mm. Immunosuppression was a significant predictor of disease-specific death.

RESULTS OF MULTIVARIATE MODELING OF OUTCOMES OF INTEREST

Results of multivariate models are summarized in Table 2. Poorly differentiated histologic characteristics, tumors 2 cm or greater in diameter, PNI, and deep tumor invasion (invading beyond subcutaneous fat) were significantly associated with more than 1 outcome of interest. Poor differentiation, diameter of 2 cm or greater, and PNI remained in final models for local recurrence, disease-specific death, and nodal metastasis/disease-specific death, respectively (although 95% confidence intervals included 1), because the models including these variables showed borderline statistical significance on the Wald test, addition of these variables changed the SHR by 10% or more, and the variables are considered clinically relevant in CSCC outcomes (see “Methods” section).

DEVELOPMENT OF AN ALTERNATIVE TUMOR STAGING SYSTEM

Because most outcomes of interest (87%) occurred in AJCC stage T2, an alternative tumor staging system was developed with the aim of prognostically stratifying this group. The system is based on the risk factors that were strongly predictive (SHR ≥2.0) of at least 2 end points of interest. These risk factors include a tumor diameter of 2 cm or greater, poorly differentiated histologic characteristics, PNI, and tumor invasion beyond the subcutaneous fat (excluding bone invasion, which automatically upstages tumors to alternative stage T3).

### Table 2. Fully Adjusted Multivariate Models for Each Outcome of Interest

<table>
<thead>
<tr>
<th>Tumor Characteristic</th>
<th>Local Recurrence (SHR [95% CI])</th>
<th>Nodal Metastasis (SHR [95% CI])</th>
<th>Disease-Specific Death (SHR [95% CI])</th>
<th>All-Cause Death (HR [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly differentiated</td>
<td>2.5 (0.8-7.5)</td>
<td>3.3 (1.4-7.8)</td>
<td>4.1 (1.1-14.9)</td>
<td>1.9 (1.1-3.3)</td>
</tr>
<tr>
<td>Diameter ≥2 cm</td>
<td>4.2 (1.4-13.3)</td>
<td>NS</td>
<td>3.7 (0.9-15.1)</td>
<td>2.6 (1.5-4.3)</td>
</tr>
<tr>
<td>PNI</td>
<td>NS</td>
<td>NS</td>
<td>3.4 (0.9-13.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Depth beyond subcutaneous fat</td>
<td>NS</td>
<td>7.2 (3.1-17.1)</td>
<td>4.1 (1.3-13.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>3.5 (1.2-10.7)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Table 3. Alternative T Staging System**

<table>
<thead>
<tr>
<th>Alternative T Staging System</th>
<th>Definition</th>
<th>Patients in Study Cohort, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>In situ SCC</td>
<td>Not included</td>
</tr>
<tr>
<td>T1</td>
<td>0 Risk factors</td>
<td>134 (52)</td>
</tr>
<tr>
<td>T2a</td>
<td>1 Risk factor</td>
<td>67 (26)</td>
</tr>
<tr>
<td>T2b</td>
<td>2-3 Risk factors</td>
<td>49 (19)</td>
</tr>
<tr>
<td>T3</td>
<td>4 Risk factors or bone invasion</td>
<td>6 (2)</td>
</tr>
</tbody>
</table>

*A risk factors include tumor diameter 2 cm or greater, poorly differentiated histologic characteristics, perineural invasion, and tumor invasion beyond the subcutaneous fat (excluding bone invasion, which automatically upgrades tumor to alternative stage T3).*
currence, 3 cases of nodal metastasis, 0 disease-specific deaths, and 20 all-cause deaths. These events correspond to 5-year cumulative incidences of 6% (95% CI, 2%-14%), 4% (95% CI, 2%-12%), 0, and 24% (95% CI, 15%-35%), respectively. In the stage T2b group (49 cases [19% of cohort]) there were many more poor outcomes with 9 cases of local recurrence, 18 cases of nodal metastasis, 10 disease-specific deaths, and 26 all-cause deaths, corresponding to 5-year cumulative incidences of 18% (95% CI, 10%-31%), 37% (95% CI, 25%-51%), 20% (95% CI, 11%-34%), and 47% (95% CI, 34%-61%). Very few cases (6 [2% of cohort]) met stage T3 criteria, but prognosis was poor in these rare cases, with half (n = 3) developing local recurrence, nodal metastasis, and all-cause death, and one-third (n = 2) experiencing disease-specific death. Thus, most CSCC-related outcomes in this cohort (9 of 21 cases of local recurrence [43%], 18 of 25 cases of nodal metastasis [72%], and 10 of 12 of disease-specific deaths [83%]) arose from stage T2b tumors. Table 4 shows the proportion of poor outcomes occurring within each AJCC and alternative T stage. Pair-wise comparison testing of differences between incidence or survival curves confirmed that incidence of poor outcomes was significantly higher in stage T2b tumors compared with stage T2a tumors, except for local recurrence. Gray test results were 18.8 (P < .01) for nodal metastasis and 14.8 (P < .01) for disease-specific death. The log-rank test result was 7.7 (P < .01) for all-cause death. Cumulative incidence or survival curves and life tables for each end point by alternative T stage are presented in Figure 2. Table 5 compares 5-year cumulative incidences of the 4 outcomes of interest between stages T2a and T2b, again showing them to be statistically distinct with much higher incidences of poor outcomes occurring in stage T2b.

### Table 4. Proportion of Outcomes Occurring Within Each American Joint Committee on Cancer (AJCC) Stage and Alternative T Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Local Recurrence</th>
<th>Nodal Metastasis</th>
<th>Disease-Specific Death</th>
<th>SCC-Related Events</th>
<th>All-Cause Death</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AJCC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>3/16 (19)</td>
<td>2/24 (8)</td>
<td>0/12</td>
<td>5/52 (10)</td>
<td>25/66 (38)</td>
</tr>
<tr>
<td>T2</td>
<td>11/16 (69)</td>
<td>20/24 (84)</td>
<td>11/12 (92)</td>
<td>42/52 (80)</td>
<td>39/66 (59)</td>
</tr>
<tr>
<td>T3/T4</td>
<td>2/16 (12)</td>
<td>2/24 (8)</td>
<td>1/12 (8)</td>
<td>5/52 (10)</td>
<td>2/66 (3)</td>
</tr>
<tr>
<td><strong>Alternative T staging system</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>3/21 (14)</td>
<td>1/25 (4)</td>
<td>0/12</td>
<td>4/58 (7)</td>
<td>36/85 (41)</td>
</tr>
<tr>
<td>T2a</td>
<td>6/21 (29)</td>
<td>3/25 (12)</td>
<td>0/12</td>
<td>9/58 (16)</td>
<td>20/85 (24)</td>
</tr>
<tr>
<td>T2b</td>
<td>9/21 (43)</td>
<td>18/25 (72)</td>
<td>10/12 (83)</td>
<td>37/58 (64)</td>
<td>26/85 (31)</td>
</tr>
<tr>
<td>T3</td>
<td>3/21 (14)</td>
<td>3/25 (12)</td>
<td>2/12 (17)</td>
<td>8/58 (13)</td>
<td>3/85 (4)</td>
</tr>
</tbody>
</table>

The 2010 AJCC system was developed via expert review of available data regarding CSCC prognosis. It represents a significant improvement from prior staging since CSCC (together with other cutaneous carcinomas) were separated from Merkel cell carcinoma and factors other than diameter and depth were included as staging parameters. The data from the present study of CSCC outcomes were applied to 2010 AJCC tumor (T) staging. It was found that only 2% of the cohort (4 cases) met AJCC stage T3 or T4 criteria owing to the rarity of bone invasion that is required for these stages. These 4 patients with stage T3/T4 tumors had a poor prognosis. However, most poor CSCC outcomes were clustered in AJCC stage T2 with 69% of local recurrences, 83% of nodal metastases, and 92% of deaths from CSCC occurring in this AJCC stage T2 group. Stages T3 and T4 apply to so few patients that they have little impact on overall CSCC prognostics. Together they accounted for only 8% of nodal metastases and deaths from CSCC. The clustering of poor outcomes in a relatively low tumor stage (AJCC T2) essentially divides CSCC into a very low risk stage T1 group, and a heterogeneous stage T2 group that combines a large fraction of patients who do well with those who do poorly. We thus sought to develop a tumor staging system that would better stratify this heterogeneous stage T2 group into a low-risk group in which poor outcomes are rare and a high risk group containing most poor CSCC outcomes.

The alternative staging system herein was built on the 4 risk factors found to predict more than 1 outcome of interest on multivariate modeling. These include:

1. Poorly differentiated histologic characteristics
2. Diameter of 2 cm or greater
3. Perineural invasion (of any caliber)
4. Invasion beyond subcutaneous fat (excluding bone invasion, which automatically upgrades a tumor to alternative stage T3).

The prognostic importance of these factors is consistent with prior work. The best prognostic stratification occurred with the staging system shown in Table 3. This alternative T staging system differs from 2010 AJCC T staging in the following regards:

1. Stage T1 comprises tumors that have no risk factors. There are 3 scenarios in which current AJCC stage T1 tumors are upstaged to stage T2a in the alternative T staging:
   - Presence of perineural invasion OR
   - Poor or undifferentiated OR
   - Depth beyond subcutaneous fat (except for bone invasion which automatically upstages to alternative stage T3).
2. Alternative stage T2 tumors (those with 1-3 risk factors) are categorized into 2 substages based on number of risk factors (stage T2a, 1 risk factor; stage T2b, 2-3 risk factors).

3. Alternative stage T3 is broader than AJCC stage T3 and includes all cases of bone invasion (AJCC stages T3/T4) as well as tumors without bone invasion but with all 4 risk factors.

4. There is no stage T4 in the alternative staging. Alternative stage T3 tumors are rare and prognostically similar (with risks of nodal metastases and death from CSCC of 30% to 50%), so no stage T4 was required.

Table 5. Comparison of Stage T2a and Stage T2b 5-Year Cumulative Incidences of Outcomes of Interest

<table>
<thead>
<tr>
<th>Alternative T Stage</th>
<th>Local Recurrence</th>
<th>Nodal Metastasis</th>
<th>Disease-Specific Death</th>
<th>All-Cause Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>6 (2-14)</td>
<td>4 (2-12)</td>
<td>0 (No events)</td>
<td>24 (15-35)</td>
</tr>
<tr>
<td>T2b</td>
<td>18 (10-31)</td>
<td>37 (25-51)</td>
<td>20 (11-34)</td>
<td>47 (34-61)</td>
</tr>
<tr>
<td>χ² P value</td>
<td>.03 &lt;.01</td>
<td></td>
<td>&lt;.01</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Figure 2. Alternative T staging results. Cumulative incidence function curves for local recurrence (A), lymph node metastasis (B), disease-specific death (C) Kaplan-Meier survival curve for all-cause death (D), and life tables by alternative T stage.
5. Definition of risk factors differ from AJCC in the following ways:

- Location on the ear and vermilion lip are not considered risk factors as they were not independently associated with poor outcomes on multivariate analysis in this study.
- Breslow (millimeter) tumor depth was not used as a risk factor in this analysis since it was not routinely reported on pathology reports (since most SCCs are transected on shave biopsy and Breslow depth is not measured).
- Invasion beyond subcutaneous fat was the best prognostic cutpoint in this data set defining elevated risk of poor outcomes. However, current AJCC staging considers shallower invasion (invasion of reticular dermis or beyond Clark level ≥4) as a risk factor.

Alternative stage T1, like AJCC stage T1, is a low-risk group with few poor outcomes. It comprised about half (52%) of the cohort. Alternative stage T3, like AJCC T3/4, is comprised of rare, advanced tumors with a poor prognosis. The goal of the alternative staging system was to subdivide the large heterogeneous group of tumors within AJCC T2 into 2 prognostically distinct groups. These groups were designated stage T2a and stage T2b to reflect that they comprise AJCC T2 tumors (as well as a few AJCC stage T1 tumors). Alternative stage T2a (which comprised 26% of the study cohort) has rare poor outcomes, with 5-year cumulative incidences of local recurrence, nodal metastasis, death from CSCC, and all-cause death of 6%, 4%, 0%, and 24%, respectively, accounting for 16% of CSCC-related events (local recurrence, nodal metastasis, and death from CSCC). Alternative stage T2b (19% of the cohort) had significantly higher incidences of all end points of interest (18%, 37%, 20%, and 47%, respectively) and included 64% of SCC-related events (43% of local recurrences, 72% of nodal metastases, and 83% of deaths from CSCC). Since stage T2b tumors are relatively uncommon but account for the bulk of poor CSCC outcomes, this group (in addition to the very rare stage T3 cases) may be the focus of future studies of high-risk CSCC treatment.

There are several limitations of this study. There may be unknown factors that have an impact on the risk of poor outcomes, including molecular-genetic factors. These may be addressed in future outcome studies as more becomes known about the molecular basis of CSCC tumor progression. To our knowledge, this is the first study of CSCC outcomes with sufficient events for multivariate modeling of multiple risk factors and outcomes. Four important risk factors predicting poor outcomes were identified. However, the study may have been underpowered to fully evaluate the impact of less robust prognostic factors, such as immunosuppression or nerve caliber in PNI cases.20,22 Future large-scale population-based studies may be able to include such additional risk factors in prognostic modeling and tumor staging systems and may narrow confidence ranges of prognostic estimates. Many patients in the potential study cohort could not be included owing to an inability to contact them or unavailable medical records. However, a sensitivity analysis showed that there was no difference in risk factor profile between those included and excluded so this was unlikely to have an impact on study results. The study cohort is from a single academic hospital. Such hospitals may see more severe tumors, thus inflating risk estimates of poor outcomes. However, the point estimates of risk by tumor substage were calculated by including tumors with clearly defined risk factors. Similar case subsets can be easily compared at other centers and in future population-based studies of CSCC.

Patients who did not fall within 1 of 6 predetermined risk strata were excluded from this study since such patients have a low risk of poor outcomes.3,23 This could potentially limit generalizability of results. However, of the 104 cases with ear or lip location as the sole risk factor (41% of cohort), there were only 3 cases of local recurrence, 0 cases of nodal metastasis, and 0 disease-specific deaths. Since these figures are similar to those for CSCC as a whole, this subgroup served as a low-risk prognostic comparison group within the analysis, enhancing generalizability of the resulting tumor staging system to CSCC in general. Furthermore, tumors with no risk factors (as defined in the alternative staging system as T1) comprised 52% of the cohort (n = 134) but had few poor outcomes (3 cases of local recurrence, 1 case of ND, and no deaths from CSCC). Such patients with no known risk factors were adequately represented in the study cohort and will likely have little statistical impact on future prognostic models owing to few poor outcomes in this group.

Since primary CSCC presenting with nodal or distant metastases is very rare, this study was confined to N0 and M0 tumors. Validation of the AJCC nodal (N) and metastasis (M) staging systems for CSCC will likely require very large population-based cohort studies. Meanwhile, 1 article has shown that improvements in AJCC nodal (N) staging may be possible.16

Current consensus guidelines are conflicted regarding treatment of CSCC. Subsequently, there is wide variability in treatment, particularly of high-risk cases.7 Until reliable and clinically useful prognostic models and tumor staging systems exist, treatment decisions will continue to be made with a degree of uncertainty regarding a patient's risk of poor outcomes. The alternative tumor staging system herein may be useful in designing inclusion criteria for those contemplating clinical trials of patients with CSCC but requires further validation prior to widespread clinical use. Optimal treatment of CSCC, particularly high-risk disease, awaits accurate prognostic estimates, validated tumor staging systems, and clinical trials regarding nodal staging and adjuvant therapy. Meanwhile, these data indicate that alternative stage T2b tumors (together with rare stage T3 presentations) include most of the cases of CSCC that will result in poor outcomes. Thus, these tumors may be the focus of future study aimed at high-risk CSCC.

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