Survival of Patients with Cutaneous Squamous Cell Carcinoma: Results of a Prospective Cohort Study

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Cutaneous squamous cell carcinoma (cSCC) is an increasing health burden in white populations. We prospectively assessed risk factors for tumor-specific and overall survival in 1,434 patients who underwent surgery for cSCC between January 24, 2005, and May 29, 2015. A total of 2,149 invasive cSCCs were analyzed. Univariate and multivariate survival analyses included tumor thickness, horizontal size, body site, histological differentiation, desmoplastic growth, history of multiple cSCCs, and immunosuppression. The primary endpoint was time to tumor-specific death. During a median follow-up period of 36.5 months (range = 0–137 months), 515 patients died; 40 because of cSCC (2.8%). Of those, 12 died because of visceral metastases and 28 because of tumor growth by local infiltration. On multivariate analyses, prognostic factors for tumor-specific survival were increased vertical tumor thickness (hazard ratio = 6.73; 95% confidence interval = 3.47–13.08; $P < 0.0001$), desmoplastic growth (hazard ratio = 4.14; 95% confidence interval = 2.68–9.83; $P < 0.0001$), and immunosuppression (hazard ratio = 2.07; 95% confidence interval = 1.04–4.12; $P = 0.039$). Defining a point list out of those factors and grouping them into four cohorts resulted in comprehensively separating survival curves ($P < 0.001$). Using a cut-off for tumor thickness of 6 mm or greater, the presence of desmoplastic growth and immunosuppression identifies patients at high risk for tumor-specific death.

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INTRODUCTION

Nonmelanoma skin cancer (NMSC) is the most frequent malignant neoplasm in white populations, with dramatically increasing incidence rates over the last decades (Eisemann et al., 2014; Karia et al., 2013; Leiter et al., 2014). Reliable data covering incidence and mortality rates of NMSC are difficult to obtain because most cancer registries do not register NMSC patients. Therefore, the real disease burden of NMSC is likely highly underestimated.

Approximately two thirds of NMSC patients suffer from basal cell carcinoma, and one third suffer from cutaneous squamous cell carcinoma (cSCC) or other rare nonmelanoma skin cancers (Burton et al., 2016; Carsin et al., 2011; Rudolph et al., 2015). Although basal cell carcinomas rarely metastasize, 4% of patients suffering from cSCC experience metastases or local recurrence even after complete excision (Brantsch et al., 2008; Schmults et al., 2013). The current tumor node metastases (TNM) classification for skin tumors defines the T stage through horizontal lesion size and infiltration of deep cutaneous structures. Potential risk factors for upstaging by one category have been introduced (Edge et al., 2010). However, the current American Joint Cancer Committee/Union Internationale Contre le Cancer classification still lacks any prognostic evidence. Although reliable data exist for progression-free and local recurrence-free survival in cSCC patients, data for tumor-specific and overall survival are scarce (Brantsch et al., 2008; Karia et al., 2014). We therefore prospectively studied predictors affecting overall and tumor-specific survival of patients suffering from cSCC.

RESULTS

A total of 1,434 patients diagnosed with 2,149 invasive cSCCs and treated between January 24, 2005, and May 29, 2015, were included in this prospective cohort study. In patients in whom multiple cSCCs were simultaneously present, the cSCC with the highest risk profile for progression as defined in Brantsch et al. (2008) was included in the analyses. Patient characteristics are displayed in Table 1. Of the 1,434 patients, 962 were men (67.1%). The mean age at diagnosis was 78 years (standard deviation = ±3; median = 79, range = 28–101). Male sex correlated with tumors localized at the ear (Spearman rho; $R = 0.18$, $P < 0.001$). Immunosuppression correlated with the presence of desmoplasia (Spearman rho; $R = 0.17$, $P < 0.001$) and the appearance of multiple cSCCs (Spearman rho; $R = 0.22$, $P < 0.001$). Further associations between the candidate predictors are illustrated in Supplementary Figure S1 online.

A total of 515 patients died during the follow-up period, 40 because of cSCC (2.8%). Of those, 12 died because of

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Abbreviations: CI, confidence interval; cSCC, cutaneous squamous cell carcinoma; HR, hazard ratio; NMSC, nonmelanoma skin cancer; PNI, perineural invasion; TNM, tumor node metastases

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Table 1. Patient demographic and baseline characteristics

Variable	n	%
Sex		
Male	962	67.1
Female	472	32.9
Tumor thickness		
≤2.0 mm (small)	344	24.0
2.1–5.9 mm (intermediate)	772	53.8
≥6.0 mm (thick)	318	22.2
Tumor horizontal size		
≤20 mm (small)	875	62.3
21–49 mm (intermediate)	447	31.8
≥50 mm (large)	83	5.9
Missing	29	0.2
Tumor differentiation		
Good	982	69.4
Moderate	251	17.7
Poor	182	12.9
Missing	19	1.3
Desmoplastic growth		
No	1,293	90.4
Yes	137	9.6
Missing	4	0.3
Tumor site		
Ear	206	14.4
Lip (lower vermilion surface)	92	6.4
Other	1,136	79.2
Face, other	940	65.6
Body, other	196	13.7
>1 simultaneous cSCC		
Absent	1,156	80.6
Present	278	19.4
Immunosuppression		
No	1,263	88.1
Yes	171	11.9
Solid organ transplant recipients	46	3.2
Chemotherapy	29	2.0
CLL	58	4.0
Other hematologic malignancies	37	2.6
HIV	1	0.1

Abbreviations: CLL, Chronic lymphatic leukemia; cSCC, cutaneous squamous cell carcinoma.

visceral metastases and 28 because of tumor growth by local infiltration in the head region or regional infiltration into neck lymph nodes. Of those patients, 23 suffered from desmoplastic cSCC (82%). Compared with the common type of cSCC, desmoplastic cSCC had an almost 8-fold higher local recurrence rate (3.1% vs. 23.5%, respectively), even though local excision with three-dimensional histology was performed with the same accuracy. The median overall survival for the entire cohort was 51.8 months (95% confidence interval (CI) = 48.1–54.6 months) (Figure 1a) with 1-, 2-, 3-, 5-, and 10-year overall survival rates of 92.3%, 79.0%, 65.7%, 41.0%, and 13.2%, respectively. The 1-, 2-, 3-, 5-, and 10-year disease-specific survival rates were 99.6%, 97.9%, 95.3%, 93.6%, and 93.6%, respectively (Figure 1b). The median follow-up period was 36.5 months (95% CI = 32.2–38.4 months). Univariate survival analyses showed tumor thickness, horizontal tumor size, tumor differentiation, desmoplastic growth, and immunosuppression as significant predictors for cSCC-specific survival. Tumor thickness, horizontal tumor size, desmoplastic growth, and presence of one versus more than one cSCC were significant predictors of overall survival (Table 2). Supplementary Figure S2 online illustrates Kaplan-Meier estimates of 10-year overall and 10-year cSCC-specific survival using tumor thickness, tumor horizontal size, tumor differentiation, desmoplastic growth, tumor site, number of cSCCs, and immunosuppression as predictors.

We calculated different multivariate models to predict cSCC-specific survival. The full model included all seven variables and showed tumor thickness (hazard ratio [HR] = 7.29; 95% CI = 3.52–15.10), desmoplastic growth (HR = 5.14; 95% CI = 2.67–10.15), and immunosuppression (HR = 2.04; 95% CI = 1.01–4.13) as significant risk factors. The predictive accuracy was 0.828 for this model. The best predictive model with an accuracy of 0.835 was selected using forward and backward selection of variables per the Akaike information criterion and included tumor thickness, desmoplastic growth, and immunosuppression as relevant variables (Table 2). A calibration plot for the best Cox model is illustrated in Supplementary Figure S3 online using 250 bootstrapped resamples. Based on these data, we separated the patient cohort into groups based on number of predictive variables (0, 1, 2, or all relevant best predictive variables). Figure 2 illustrates Kaplan-Meier estimates of tumor-specific survival for these cohorts according to a point list of 0–4 points ($P < 0.001$). These results could be transferred into a T classification with T1 = 0–1 point, T2 = 2 points, T3 = 3 points, and T4 = 4 points.

Using the current TNM cSCC classification consisting of the horizontal tumor size and tumor differentiation, we found a predictive accuracy of only 0.573. Adding high-risk features as recommended by the 2010 TNM classification system (Edge et al., 2010) (T1 = tumor is 2 cm across or smaller and has no or only one high-risk feature, T2 = tumor is larger than 2 cm or is any size with two or more high-risk features [tumor thickness > 2 mm, tumor started on an ear or on part of the lip, tumor cells are poorly differentiated or undifferentiated]) increased the predictive accuracy to 0.705.

Using a classification proposed by the Brigham and Women's Hospital (Boston, MA) (Karia et al., 2014) that considers tumor diameter of 20 mm or greater, poorly differentiated histology, perineural invasion [PNI] of 0.1 mm or greater, or tumor invasion beyond fat (excluding bone invasion, which automatically upgrades the tumor to Brigham and Women's Hospital stage T3) as high risk factors, we calculated a concordance of 0.818 in a cohort of 851 patients.

Finally, we calculated a competing risk model for death due to cSCC and other causes. Figure 3 illustrates this competing risk analysis as a stacked cumulative incidence function using Aalen-Johansen estimates.

DISCUSSION

Our model showed a predictive accuracy of tumor staging that is superior to the current TNM classification of NMSCs