



# 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 non-melanoma 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 =  $\pm 3$ ; 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.

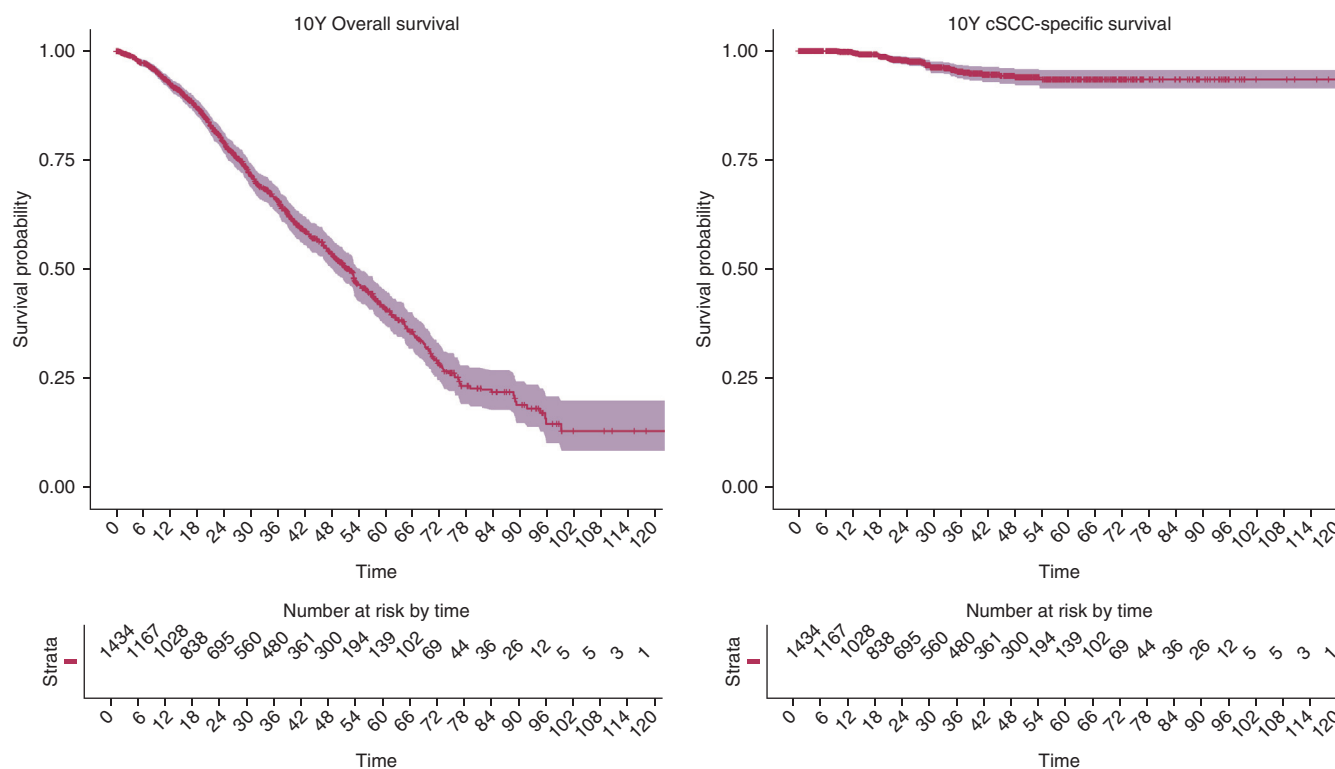
Using the current TNM cSCC classification consisting of the horizontal tumor size and tumor differentiation, we found a predictive accuracy of only 0.573. Adding high-risk features as recommended by the 2010 TNM classification system (Edge et al., 2010) (T1 = tumor is 2 cm across or smaller and has no 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



**Figure 1. Prognosis of cSCC.** (a) Overall survival. (b) cSCC-specific survival. cSCC, cutaneous squamous cell carcinoma; Y, year.

(Edge et al., 2010). Our findings suggest that TNM staging for cSCC should include tumor thickness, immunosuppression, and the presence or absence of desmoplasia, instead of Broders grading (Edge et al., 2010). As already proposed for disease-free survival by Brantsch et al. (2008) and Breuninger et al. (2012), a TNM classification of cSCC would stage tumors with a thickness of 2.0 mm or less as T1 tumors, tumors between 2.1 and 5.9 mm as T2 tumors, and tumors with a thickness of 6.0 mm or more as T3 tumors. The presence of either desmoplastic growth and/or immunosuppression should result in an upstaging by one category each.

In the analysis of tumor-specific survival, categorization of the three main risk variables into a point list results in a rank of 0–4 risk points. There was a sufficient dissemination of 0/1 vs. 2 vs. 3 vs. 4 risk points. This scale could easily be transferred into a prognostic classification of T1–T4 similar to the TNM scale.

In 2014, Karia et al. (2014) proposed a new cSCC classification involving tumor diameter, differentiation, PNI, and tumor invasion beyond fat as high-risk factors, leading to a consecutive T classification. We validated this T classification for tumor-specific survival in a subgroup of our patients with an excellent concordance of 0.818 and a goodness of fit comparable to our prognostic models. Therefore, such new cSCC classifications should be considered for adoption in clinical settings.

Generally considered a low-grade malignant tumor, cSCC led to death in about 3% of our patients. This is similar to a rate of 2.1% published by Schmults et al. (2013) and reflects the current care situation of a specialized center dealing with advanced skin cancers (Karia et al., 2013; Schmults et al., 2013). Surprisingly, 28 of 40 patients died because of

tumor growth per continuitatem and only 12 because of visceral metastases. Most of these cSCCs (82%) were of the desmoplastic type. These tumors recurred despite histologic monitoring of all tumors with hematoxylin and eosin stained three-dimensional histology. In some cases, multiple reoperations were required until complete resection with no microscopic residuals (R0) was achieved. It seems that fine tumor strands sometimes consisting of only one cell layer cannot be detected by routine histologic monitoring of surgical margins. This point is highlighted by the fact that in this study the local recurrence rate of desmoplastic cSCCs is nearly 8-fold higher than nondesmoplastic cSCCs. We speculate that an epithelial-to-mesenchymal transition may contribute to this infiltrative behavior (Biddle et al., 2011; Hu et al., 2012). Only the desmoplastic type showed additional PNI in some cases.

The median overall survival in our cohort was 51.8 months. The 3-year overall survival and disease-specific survival rates were 65.7% and 95.3%, respectively. Clayman et al. (2005) reported an overall survival of 70% in a high-risk patient cohort but a disease-specific survival of only 85%. One explanation for the unfavorable overall survival outcome in our cohort may be a likely higher rate of comorbidities associated with the 10-year increased median age in our study (78 years) compared with the median age of 68 years reported by Clayman et al.

Based on previously described candidate variables, univariate analyses showed that tumor thickness, horizontal size, desmoplastic growth, and the presence of multiple cSCCs were associated with significant differences in overall survival (Brantsch et al., 2008; Breuninger et al., 1990; Breuninger et al., 1997; Quaedvlieg et al., 2006). Tumor

**Table 2. Univariate and multivariate Cox regression models for cSCC-specific survival**

Variable	Patients with Events/Number of Patients	Univariate Model		Multivariate Models						
		HR (95% CI)	P	Full model <sup>1</sup>		Best model <sup>2</sup>		Limited TNM model <sup>3</sup>		
				HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	
Tumor thickness										
Small or intermediate	14/1,116	1	—	—	—	—	—	—	—	
vs. Thick	26/318	8.64 (4.51–16.57)	<0.001	7.29 (3.52–15.10)	<0.001	6.73 (3.47–13.08)	<0.001	—	—	
Tumor horizontal size										
Small or intermediate	23/1,322	1	—	—	—	—	—	—	—	
vs. Large	13/83	9.54 (4.83–18.85)	<0.001	1.23 (0.62–2.43)	0.553	—	—	2.16 (1.16–4.02)	0.015	
Tumor differentiation										
Good or moderate	25/1,234	1	—	—	—	—	—	—	—	
vs. Poor	14/181	4.15 (2.16–7.99)	<0.001	1.08 (0.44–2.65)	0.868	—	—	1.0 (0.44–2.25)	0.992	
Desmoplastic growth										
Absent	22/1,292	1	—	—	—	—	—	—	—	
vs. Present	17/138	7.77 (4.12–14.68)	<0.001	5.14 (2.67–10.15)	<0.001	5.14 (2.68–9.83)	<0.001	—	—	
Tumor site										
Other	32/1,136	1	—	—	—	—	—	—	—	
vs. Ear	6/206	1.01 (0.42–2.40)	0.991	1.01 (0.20–5.08)	0.988	—	—	—	—	
vs. Lip	2/92	0.59 (0.14–2.48)	0.473	0.99 (0.23–4.19)	0.984	—	—	—	—	
>1 cSCC										
No	28/1,156	—	—	—	—	—	—	—	—	
vs. Yes	2/92	1.55 (0.79–3.05)	0.205	1.07 (0.53–2.14)	0.858	—	—	—	—	
Immunosuppression										
No	28/1,263	1	—	—	—	—	—	—	—	
vs. Yes	12/171	3.32 (1.69–6.53)	<0.001	2.04 (1.01–4.13)	0.047	2.07 (1.04–4.12)	0.039	—	—	
C-Index	—	—	—	0.828	—	0.835	—	0.573	—	

Abbreviations: CI, confidence interval; HR, hazard ratio; TNM, tumor node metastases.

<sup>1</sup>Global Schoenfeld test: *P* = 0.871.

<sup>2</sup>Global Schoenfeld test: *P* = 0.723.

<sup>3</sup>Global Schoenfeld test: *P* = 0.641.

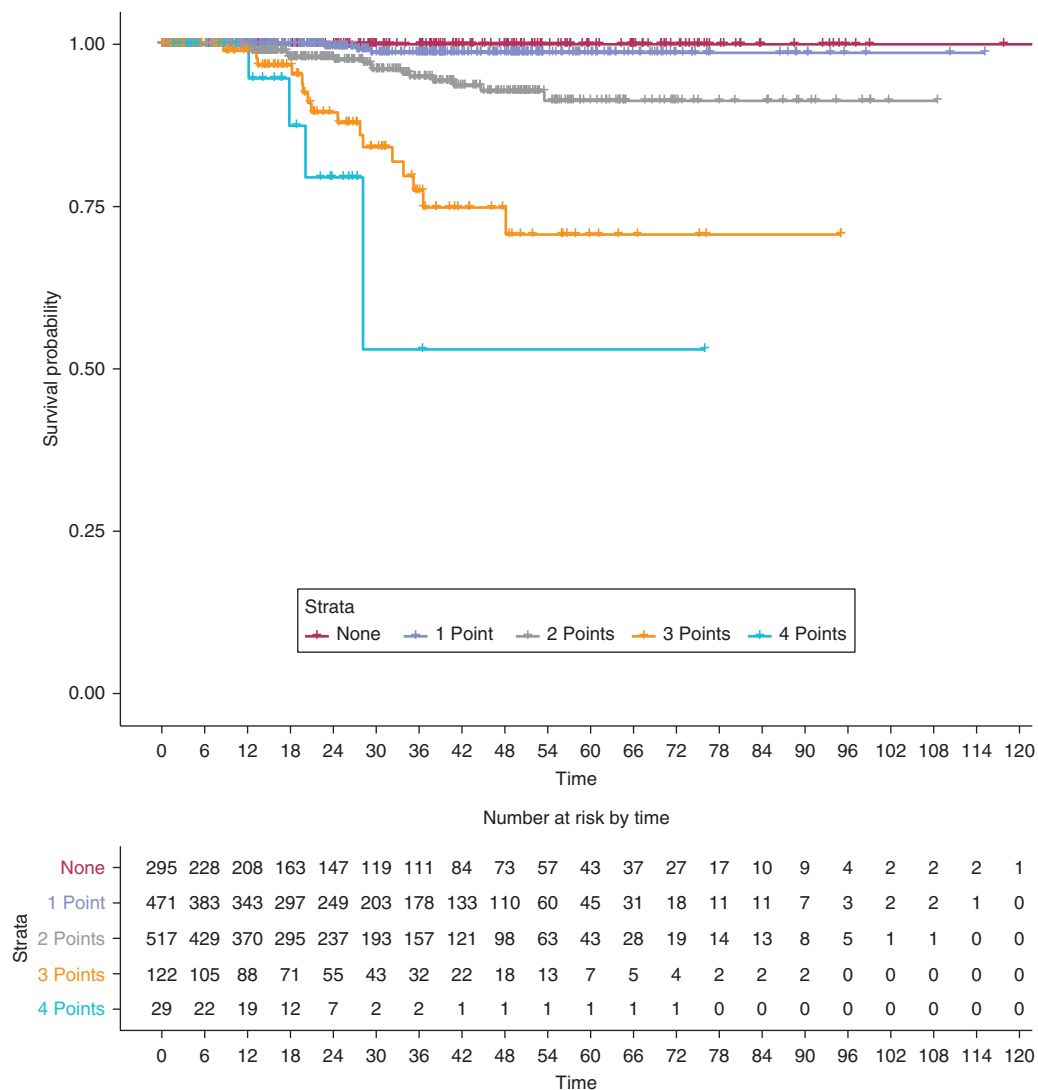
differentiation, but not multiple simultaneous cSCCs, showed significant differences in the Kaplan-Meier estimates of tumor-specific survival. These findings partially concur with those of the [Schmultz et al. \(2013\)](#) study, in which disease-specific survival was associated with tumor horizontal size of 2 cm or larger, poor tumor differentiation, tumor depth to deep anatomic structures, PNI, and location perianally or genitally ([Schmultz et al., 2013](#)).

Tumor thickness and desmoplastic growth were the two major factors associated with worse prognosis in our multivariate models, followed by immunosuppression. The importance of absolute tumor thickness (in mm) was previously described in studies evaluating risk of recurrence ([Brantsch et al., 2008](#); [Veness et al., 2006](#)). Data for immunosuppression in our patient cohort was limited to the causes provided in [Table 1](#). Unfortunately, immunosuppressive drug regimens were not recorded in our clinical tumor registry. The number of patients with immunosuppression may therefore be underestimated. Especially in solid organ transplant recipients, the application of cyclosporine may drive tumor progression by favoring T cell polarization toward IL-22-producing T22 cells ([Abikhair et al., 2016](#)). Future studies should more accurately classify immunosuppression drug regimens to determine their contributions to survival outcomes.

A recently published systemic review and meta-analysis of 36 studies of low to moderate evidence quality

comprised 17,248 patients with 23,421 cSCCs ([Thompson et al., 2016](#)). In contrast to our analyses including Kaplan-Meier estimates and Cox proportional hazard models, [Thompson et al. \(2016\)](#) focused on description of risk ratios for several factors. They confirmed the prognostic relevance of the maximal tumor diameter exceeding 20 mm and tumor thickness described as invasion beyond subcutaneous fat. In contrast to our findings, the Thompson study also found an increased risk for poor differentiation, location on the ear or lip, and PNI. cSCCs of the ear and lip, believed to be high-risk locations because of high UV exposure ([Thompson et al., 2016](#)), did not influence tumor-specific survival in either univariate or multivariate analyses in our studies. The main difference between the Thompson study and ours was in the multivariate analysis.

Most patients in our study did not die from cSCC but from other causes due to advanced age. Only four patients died because of cSCC within the first year of the observation period, and the others died within the following 4 years. Our Kaplan-Meier estimates and competing risk models suggest that no patients died from cSCC 5 years after the initial diagnosis, confirming our approach to follow up high-risk patients every 3 or 4 months by clinical investigation and every 4 or 5 years by ultrasonography of regional lymph nodes ([Brantsch et al., 2008](#)). Visual patient inspection should nevertheless be performed regularly, and patients



**Figure 2. Survival plots.** Kaplan-Meier estimates of categorized risk profile per point list. Tumor thickness  $\leq 2.00$  mm = 0 points; tumor thickness 2.01–4.00 mm = 1 point; tumor thickness  $\geq 4$  mm = 2 points; desmoplasia present = 1 additional point; immunosuppression present = 1 additional point.

should be expressly instructed on self-examination to detect subsequent cSCCs early.

## CONCLUSION

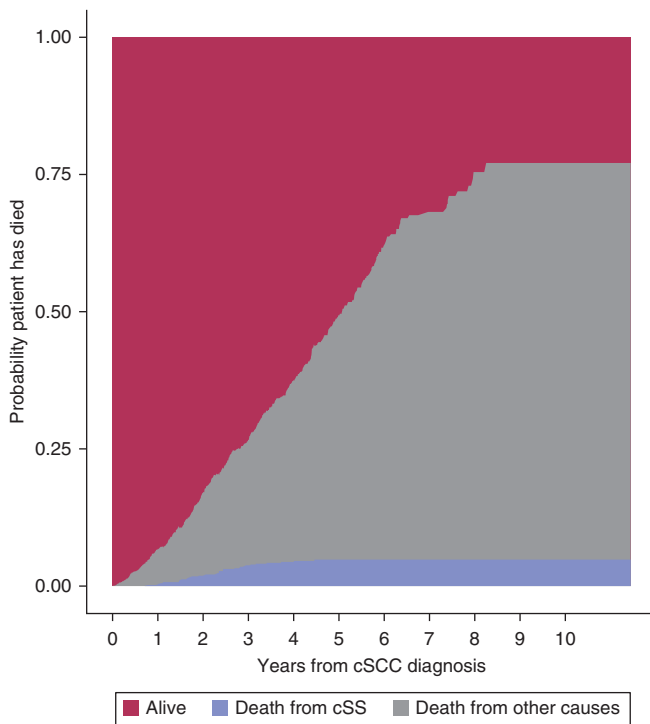
Using a cutoff for tumor thickness of 6 mm, desmoplastic growth, and immunosuppressive status, all easily clinically assessable, our model could identify patients at risk for low tumor-specific survival. We therefore recommend adding these factors into the next revision of the American Joint Cancer Committee/Union Internationale Contre le Cancer TNM classification for skin tumors.

## MATERIALS AND METHODS

### Patients

Patients with cSCC treated at the Department of Dermatology, University of Tübingen, Germany were included in the analysis. All tumors were excised, followed by a complete histological evaluation of the excisional margins by routine paraffin procedure with hematoxylin and eosin staining (three-dimensional histology) (Eberle et al., 2014; Moehrle et al., 2007). In the case of tumor positive

margins, reoperations were done until a complete resection with no microscopic residuals (i.e., R0) was proved by histology. Patient data were recorded by the hospital-based comprehensive cancer center and included data from the primary tumor and the further course of disease. Survival data were gathered from the State Statistics Office of Baden-Württemberg and aligned to those of the comprehensive cancer center once yearly. Baseline patient demographic and clinical characteristics, as well as pathological data, were summarized using descriptive statistics and frequency tabulation. The primary endpoint was tumor-specific survival, defined as time from date of diagnosis of the primary tumor to date of death caused by cSCC, or to date of last observation, or to date of death for reasons other than cSCC. To identify predictors of fatal outcomes, seven previously described candidate variables were selected based on previous studies and smaller case series: (i) tumor thickness ( $\leq 2$  mm, 2.1–6.0 mm, and  $>6$  mm) as histologically measured from the highest cellular elevation to the deepest infiltration under low magnification or, in very thick tumors, by bare eye measurement; (ii) clinical horizontal size ( $\leq 0$  mm, 21–50 mm, and  $>50$  mm) defined according to the 6th edition of the American Joint Cancer Committee



**Figure 3. Stacked cumulative incidence.** Stacked cumulative incidence functions of death from cSCC and other causes. cSCC, cutaneous squamous cell carcinoma.

classification manual (Greene et al., 2002); (iii) grade of differentiation (good, medium, or poor); (iv) presence of desmoplastic growth where at least one third of the representative tumor specimen met the criteria, defined by Breuninger et al. (1997) as “fine branches of tumor cells at the periphery and a surrounding stromal reaction” (p. 916) (findings of perivascular or PNI were always associated with desmoplasia, but desmoplasia not always with PNI); (v) site of primary tumor; (vi) number of cSCCs; and (vii) presence of immunosuppression (Brantsch et al., 2008). Immunosuppression occurred as a result of organ transplantation, cytostatic therapy, HIV, chronic lymphatic leukemia, or as a consequence of another hematologic malignancy. The tumor thickness cutoffs of 2 mm and 6 mm were based on our previous work defining margins for risk of developing metastases (Brantsch et al., 2008). The 20-mm and 50-mm cutoffs for horizontal tumor size were based on the TNM staging system (Breuninger et al., 2012). The ears and lower vermillion surface of the lip were considered as special locations because of the high exposure of those areas to UVR (Kimlin et al., 1998). Our evaluation was approved by the Independent Ethics Committee of the University Hospital Tübingen (reference number: 568/2016BO1) and was carried out according to the STROBE (i.e., STrengthening the Reporting of OBServational studies in Epidemiology) guidelines for observational studies. All patients were informed about the purpose of the study and agreed to allow their data to be registered by signing a standardized form.

### Statistics

Univariate HRs were calculated with 95% CIs using the Cox proportional-hazards model. Probabilities of overall and tumor-specific survival were calculated using the Kaplan-Meier estimator, and the Wald test from the corresponding Cox models was used to compare time-to-event distributions (Therneau and Grambsch,

2001). Calibration was performed using a bootstrap approach. Competing risk models were established using Aalen-Johansen estimates to differentiate between tumor-related and other causes of death (Moore, 2016). The simultaneous prognostic effect of various factors was determined in a multivariate analysis using the Cox proportional-hazards regression model (forward and backward selection of variables according to the Akaike information criterion). Missing values were imputed using multivariate imputation by chained equations strategies (van Buuren and Groothuis-Oudshoorn, 2011). In the planning phase of the study we had no information concerning the expected number of events, so no sample size calculation was presupposed. Statistical analyses were performed using R software (version 3.3.0, R Foundation for Statistical Computing, Vienna, Austria; packages used were survival, mice, and rms). *P*-values less than 0.05 were considered statistically significant.

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### CONFLICT OF INTEREST

The authors state no conflict of interest.

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### AUTHOR CONTRIBUTIONS

TKE performed study design, data analyses, data interpretation, literature search, figure preparation, and writing. UL performed data collection, data interpretation, and writing. H-MH performed data collection, data interpretation, and writing. CG performed study design, data interpretation, and writing. MR performed study design, data interpretation, and writing. HB performed study design, data collection, data analyses, data interpretation, and writing.

### SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at [www.jidonline.org](http://www.jidonline.org), and at <http://dx.doi.org/10.1016/j.jid.2017.06.025>.

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