



Contemporary update of overall prognosis and nomogram to predict individualized survival for Chinese patients with eyelid sebaceous carcinoma

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ABSTRACT

Background: The prognosis of Chinese patients with eyelid sebaceous carcinoma (SC) has not been updated for >3 decades. The prognostic predictors are multifactorial, and there is no validated prognostic model for eyelid SC.

Methods: This study included 238 consecutive patients with eyelid SC. All eligible patients were followed up for metastasis and mortality. The predictors of tumor-related survival were explored by Cox analyses. A prognostic nomogram was developed and validated using bootstrap resampling. The predictive accuracy and discriminative ability were compared between the nomogram and the Tumor, Node, Metastasis (TNM) staging system.

Findings: After a median follow-up period of 55.5 months, 27 (11.3%) patients died of metastatic SC, with a median survival time of 48.0 months. The 5-year and 10-year tumor-related survival rates were 88.1% and 77.9%, respectively. Orbital involvement (HR: 3.11, $p = .022$), the greatest tumor basal diameter (HR: 1.06, $p = .003$), the presence of pagetoid spread (HR: 2.90, $p = .017$), and having lymph node metastasis at initial diagnosis (HR: 13.66, $p < .001$) were independent risk factors for tumor-related death. A nomogram integrating these 4 factors was developed with a C-index of 0.887, which is significantly better than that of the TNM staging system ($p = .002$). The risk groups stratified by nomogram scores ($p < .001$ (low vs intermediate risk); $p = .001$ (intermediate vs high risk)) displayed better discrimination ability than TNM staging (T1 vs T2: $p = .358$; T2 vs T3: $p = .171$; T3 vs T4: $p < .001$) in patients at an early stage.

Interpretation: The prognosis of Chinese patients with eyelid SC has improved over the last 3 decades, and it is comparable to that of patients from other countries. This nomogram provides more accurate individualized estimates of survival for eyelid SC patients and may guide clinicians in their therapeutic decisions.

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1. Introduction

Sebaceous carcinoma (SC) is not a rare eyelid tumor in Chinese populations [1,2], accounting for approximately 32.7–41.6% of all eyelid malignancies in Chinese patients [1,2]. This tumor often masquerades as a

benign or less malignant lesion, resulting in diagnostic delays, inappropriate management, high morbidity and mortality [3,4].

Based on a retrospective case series, the 5-year tumor-related mortality varies from 2 to 30% [3–6]. To our knowledge, only 2 studies have explored the prognosis of SC in Chinese patients. In 1979, Ni C et al. observed an overall tumor-related death rate of 41% in his case series of 100 patients [7]. Later, in 1982, the same group reported a 29% tumor-related mortality rate at 4 years in a cohort study of 82 patients [1]. However, the sample sizes of these studies were small, and it is not clear whether they were from the same patient population in these 2 articles. In addition, the knowledge in this field has not been updated for >3 decades.

Known risk factors for the prognosis of eyelid SC include a prolonged diagnostic delay [8,9], greater tumor size [4,6,7,9–12], canthal tumor location [6,13], involvement of both upper and lower eyelids [9,14],

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Research in context

Evidence before this study

The prognosis of Chinese patients with eyelid sebaceous carcinoma (SC) has not been updated for >3 decades. The predictors for the prognoses are multifactorial, there is no validated prognostic model for eyelid SC.

Added value of this study

The 5- and 10-year tumor-related survival rate for Chinese patients of eyelid SC was 88.1% and 77.9%, respectively. A novel nomogram for individualized estimates of tumor-related survival were developed, which consists of 4 independent risk factors, lymph node metastasis at initial diagnosis, orbital involvement, greatest tumor basal diameter, and the presence of pagetoid spread. And it was demonstrated of better discrimination ability than TNM staging for patients of early stage.

Implications of all the available evidence

The prognosis of Chinese patients of eyelid SC has been improved for the last 3 decades. This nomogram provides more accurate individualized estimates of survival for eyelid SC patients, and may guide clinicians in their therapeutic decisions.

pagetoid spread [9,14,15], multicentric origin [9,14], poor differentiation [9,10], vascular, lymphatic, and orbital invasion [8,9], a nonlobular pattern [14], and an advanced T category [4,8,11,14,15], as defined by the American Joint Committee on Cancer (AJCC) [16]. The predictors for the prognoses of eyelid SC are multifactorial, therefore, the identification of core risk factors to construct an individualized prediction model is warranted for risk stratification.

Currently, the most widely used staging system for eyelid SC is Tumor, Node, Metastasis (TNM) staging. T classification is primarily based on tumor size and location. However, to make a precise prediction for the prognosis of an individual patient, other factors, such as a remarkable medical history and initial treatments, pathological indices, such as pagetoid growth, perineural invasion, and histology differentiation should also be taken into consideration.

Recently, clinical risk scoring systems have been developed for several other carcinomas, e.g., prostate cancer [17], oropharyngeal cancer [18] and breast cancer [19]. However, there is no validated prognostic model for patients with eyelid SC. Because survival probability can be highly variable, clinical decision-making needs to be discussed on an individual basis in terms of the risk benefit for each patient. In this context, the development of clinical tools that specifically estimate the patient's probability of tumor-related death is important for guiding doctors' decisions.

The purpose of this retrospective cohort study was first, to provide a contemporary update on the prognosis of eyelid SC in Chinese patients and second, to develop and validate a nomogram risk scoring system for the individualized prediction of tumor-related survival in Chinese patients with eyelid SC.

2. Methods

2.1. Patients

After the approval by the Shanghai Jiao tong University research ethics committee, a search of "eyelid SC" was performed at the pathologic database of Ninth People's Hospital between January 1991 to

December 2016, and 323 patients were identified. All these patients underwent either wide local excision or Mohs microscopic surgery and received one-stage reconstruction in our hospital. We contacted all these patients or their relatives and explained the purpose of the study, and they participated in this study voluntarily without any additional compensation. Every patient or their relatives were interviewed about the conditions after discharge from our hospital. The vital status was also confirmed via mandatory Chinese resident registry, and the cause of death was checked by reviewing the data recorded in Chinese Center for Disease Control. Of the 323 patients, 53 patients were not reached, and 22 declined to participate in this study for other reasons, such as geographic or time limitations. Of the 248 subjects who agreed to participate in the follow-up visit, 10 patients were excluded for incomplete data collection, leaving a final sample comprising 238 eyes of 238 patients.

2.2. Data collection

The institutional review board waived the requirement for informed consent from the patient. This study adhered to the tenets of the Declaration of Helsinki. The medical records and pathologic data of each patient were reviewed. Data collected included patient demographics, clinical and pathological characteristics, treatments and final outcomes at the follow-up. The demographics consisted of age and gender. The clinical characteristics comprised of history of second primary tumor, diagnostic delay (the duration from the onset of symptoms until the diagnosis of eyelid SC), initial referral diagnoses and treatments, anatomic locations, greatest tumor basal diameter, the presence of intraepithelial neoplasia (pagetoid growth pattern), perineural invasion and muscle infiltration, the degree of histology differentiation, and surgical approaches. The degree of differentiation was subdivided as described elsewhere [20]; well-differentiated tumors presented as lobules with sebaceous differentiation. Moderate differentiation primarily consisted of anaplastic cells and a few areas of highly differentiated sebaceous cells. Poor differentiation was defined as the tumors rich with pleomorphic nuclei, prominent nucleoli, and amphophilic-positive cytoplasm. The patients were also stratified by their clinicopathologic presentations according to the 8th edition of AJCC staging system for eyelid SC [16]. If the patient had received treatment elsewhere, his/her prior clinical details and pathological sections before referral were retrieved for review. For outcome measures, the months from the initial diagnosis to metastasis and death were documented. The time from the first metastasis to death was also calculated. The time of metastasis was the date on which dissemination was confirmed by biopsy, imaging or clinical examination. In addition, the locations of metastases were recorded.

2.3. Statistical analysis

The data were analyzed using survival and RMS packages in R 3.4.1 (Vienna, Austria; <http://www.R-project.org/>). Frequency (percentage), mean \pm standard deviation and median (interquartile range) were reported for the description of categorical variables and continuous variables with normal and skewed distribution, respectively. Means, medians and proportions were compared using the Student's *t*-test, the nonparametric Mann-Whitney *U* test and the chi-square test (or Fisher's exact test, if appropriate), respectively.

First, to identify the possible correlates of tumor-related survival, demographic and clinical indicators at the initial presentation of the patients with different outcomes were compared using univariate Cox proportional hazards regressions. The significant factors ($p < .05$) were entered into the multivariate Cox regression models as independent variables after considering collinearity among variables with a correlation matrix and testing of proportional hazards assumption. Tumor-related death was modeled as a major outcome (dependent factor). Patients who were alive at the end of follow-up were censored at the time of last follow-up, and those that died of other causes were

censored at the date of death. The regression coefficients and hazard ratios (HRs) with 95% confidence intervals were recorded. Survival and metastasis rates were determined according to the Kaplan-Meier method and were compared using the log-rank test.

Sensitivity analyses to examine the robustness of the final multivariable model were performed with full-model, stepwise, backward, and forward procedures. To improve the discrimination ability of our final model, other pragmatic parameters, such as, age, gender and initial treatment with Mohs surgery as initial treatment were alternatively added to the model. The concordance index (C-index) [21] and Akaike information criterion (AIC) of the models were compared. A model with a larger C-index and smaller AIC was considered to have greater explanatory effect.

Finally, a nomogram was developed based on the multivariate Cox proportional hazards regressions for 5-year and 10-year tumor-related survival. The discrimination ability of this model was evaluated by C-index. Calibration curves of the nomogram for 5-year and 10-year tumor-related survival were examined to assess the agreement between the predicted and the observed outcomes. Comparisons between the nomogram model and the TNM staging system were analyzed by Net Reclassification Improvement (NRI) using the *rcorrccens* function in the *Hmisc* package in R. All tests were two sided, and a *p* value <.05 was considered statistically significant.

3. Results

3.1. Descriptive statistics

A total of 238 eyes of 238 patients were evaluated in this study, and the study included 106 (44.5%) male patients and 132 (55.5%) female patients. The median age at diagnosis was 62.5 years (mean: 62.8 ± 13.3 years), with a range of 27 years to 94 years. The demographic and baseline clinical characteristics are summarized in Table 1. Of note, 13 (5.5%) patients had second primary tumor, 3 (1.3%) of them were afflicted with a third primary tumor, and the clinical details of these patients are presented in Table 2. Surgical treatment before referral to our hospital was noted for 105 (44.1%) patients. It is noteworthy that the delay elsewhere from the onset of symptoms until definitive diagnosis of SC ranged from 0.3 to 240 months, with a median of 18 months (mean: 28.3 ± 34.7 months). Blepharitis (31, 13.0%) was the second most common referral diagnosis other than SC. At the time of diagnosis, 12 (5.0%) patients exhibited regional lymph node metastasis, and none of them had distant metastases. Various clinical appearances of Chinese patients with eyelid SC are displayed in Fig. 1. Typical pathological presentations are showed in supplementary Fig. 1.

3.2. Overall prognoses

After a median follow-up period of 55.5 months (mean: 65.3 ± 50.8 months; range: 6.0–342.0 months), 45 (18.9%) patients developed metastasis during follow-up. The initial metastasis locations included the parotid lymph node (29, 12.2%), cervical lymph nodes (6, 2.5%), submandibular lymph node (5, 2.1%), skull base (2, 0.8%), mediastinal lymph node (1, 0.4%), brain (1, 0.4%) and lung (1, 0.4%). Twenty-seven (11.3%) patients presented metastases involving multiple sites. The median duration between the initial diagnosis and first metastasis was 17.0 months (mean: 21.2 ± 23.4 months; range: 0–100.0 months). By Kaplan-Meier survival estimates, the 5-year and 10-year metastasis rates were 20.4% and 25.0%, respectively. The predictors of metastasis were explored by Cox analysis, and results were summarized in Supplementary Table 1.

During this follow-up, 50 (21.0%) patients died, with a median survival time of 58.0 months (mean: 58.3 ± 29.0 months; range: 15.0–132.0 months). Among these patients, 27 (54.0%) of them died of metastatic SC, with a median survival time of 48.0 months (mean: 51.0 ± 25.1 months; range: 15.0–107.0 months). By Kaplan-Meier

Table 1
Demographics and baseline clinical characteristics.

| Variables | Median (IQR)/n(%) |
|---|-------------------|
| Gender | |
| Male | 106(44.5) |
| Female | 132(55.5) |
| Age | 62.5(53.8–73.0) |
| Having second primary tumor | 13(5.5) |
| With lymph node metastasis at initial diagnosis | 12(5.0) |
| Diagnostic delay (months) | 18.0(6.0–36.0) |
| Surgery times before diagnosis | 1(1–2) |
| Initial Clinical Diagnosis | |
| Sebaceous carcinoma | 155(65.1) |
| Squamous cell carcinoma | 22(9.2) |
| Basal cell carcinoma | 15(6.3) |
| Chalazion | 10(4.2) |
| Blepharitis | 31(13.0) |
| Dermoid | 4(1.7) |
| Nevus | 1(0.4) |
| Tumor location | |
| Upper eyelid | 144(60.5) |
| Lower eyelid | 86(36.1) |
| Both Upper and lower eyelid | 14(5.9) |
| Caruncle | 21(8.8) |
| Bulbar conjunctiva | 12(5.0) |
| With orbital involvement | 19(8.0) |
| Greatest tumor basal diameter (mm) | 10.0(7.0–17.3) |
| The presence of pagetoid spread | 43(18.1) |
| The presence of perineural invasion | 21(8.8) |
| The presence of muscle infiltration | 44(18.5) |
| Ki 67 (%) | 39.5(20.0–50.0) |
| Histology differentiation | |
| Well or moderately differentiated | 179(75.2) |
| Poorly differentiated | 59(24.8) |
| With positive surgical margin | 37(15.5) |
| Initial treatment with Mohs surgery | 113(47.5) |
| T stage | |
| T1 | 112(47.1) |
| T2 | 65(27.3) |
| T3 | 29(12.2) |
| T4 | 32(13.4) |

T: Tumor category according to 8th edition of American Joint Committee on Cancer (AJCC) staging system; IQR: interquartile range.

survival estimates, the 5-year and 10-year tumor-related survival rates were 88.1% and 77.9%, respectively. The median survival time from initial metastasis to death was 20.0 months (mean: 28.1 ± 18.1 months; range: 9.0–76.0 months). We further did subgroup analysis comparing the patients recruited during the year of 1991–2004 vs 2005–2016, the results indicated that the patients recruited during 2005–2016 exhibited better survival than those admitted to our hospital during 1991–2004 (log-rank *p* = .037).

3.3. Uni- and multivariable analyses for tumor-related survival

To explore the independent risk factors for eyelid SC-related mortality, univariable and multivariable Cox proportional hazards regression analyses were performed, and the results are summarized in Table 3. In the univariate analysis, having lymph node metastasis at initial diagnosis (*p* < .001), diagnostic delay (*p* = .040), tumors with caruncular involvement (*p* = .029), orbital involvement (*p* < .001), the greatest tumor basal diameter (*p* < .001), the presence of pagetoid spread (*p* < .001), perineural invasion (*p* = .001), muscle infiltration (*p* = .027), Ki-67 (*p* = .002), and poor differentiation (*p* < .001) were potential risk factors for SC-related death. The collinearity among baseline clinical indicators was tested with a correlation matrix; when a correlation was identified, only the most clinically relevant parameter was entered into the multivariable model. With collinearity tests, 4 parameters, namely, the presence of perineural invasion, the presence of muscle infiltration, Ki67 and histological differentiation, were excluded from the multivariable Cox analysis (Supplementary Table 2). The final multivariable model (C-index = 0.887, AIC = 209.7), which retained the

Table 2
Clinical characteristics for 13 patients with second primary tumor.

| Patient no. | Gender | Age (years) | Second primary tumor | Follow-up duration (months) | Metastasis of SC (yes/no) | Death (yes/no) | Direct cause |
|-------------|--------|-------------|-------------------------------------|-----------------------------|---------------------------|----------------|---|
| 1 | Female | 77 | Gastric carcinoma and breast cancer | 19 | No | Yes | Infection caused by abdominal abscess |
| 2 | Female | 73 | Bladder carcinoma | 88 | Yes | Yes | Metastasis of SC |
| 3 | Female | 70 | Colon cancer | 29 | Yes | Yes | Metastasis of SC |
| 4 | Female | 85 | Gingival carcinoma | 76 | Yes | Yes | Cachexia caused by gingival carcinoma |
| 5 | Male | 71 | Laryngocarcinoma | 31 | No | No | NA |
| 6 | Female | 80 | Colon cancer and breast cancer | 55 | No | No | NA |
| 7 | Female | 80 | Colon cancer | 60 | No | Yes | Metastasis of colon cancer |
| 8 | Female | 49 | Breast cancer and tongue cancer | 60 | No | Yes | Metastasis of breast cancer |
| 9 | Male | 73 | Esophageal cancer | 101 | No | No | NA |
| 10 | Female | 41 | Gastric carcinoma | 120 | No | No | NA |
| 11 | Male | 80 | Prostate cancer | 73 | No | No | NA |
| 12 | Female | 73 | Pancreatic adenocarcinoma | 44 | No | Yes | Metastasis of pancreatic adenocarcinoma |
| 13 | Female | 57 | Breast cancer | 63 | No | No | NA |

SC: sebaceous carcinoma; NA: not available.

statistically and clinically relevant factors, indicated that orbital involvement (HR: 3.11, $p = .022$), the greatest tumor basal diameter (HR: 1.06, $p = .003$), the presence of pagetoid spread (HR: 2.90, $p = .017$), and having lymph node metastasis at initial diagnosis

(HR: 13.66, $p < .001$) were independent predictors of tumor-related survival. In the sensitivity analysis, the association between tumor-related survival and these 4 factors remained unchanged, and no other significant variable could be entered into this model

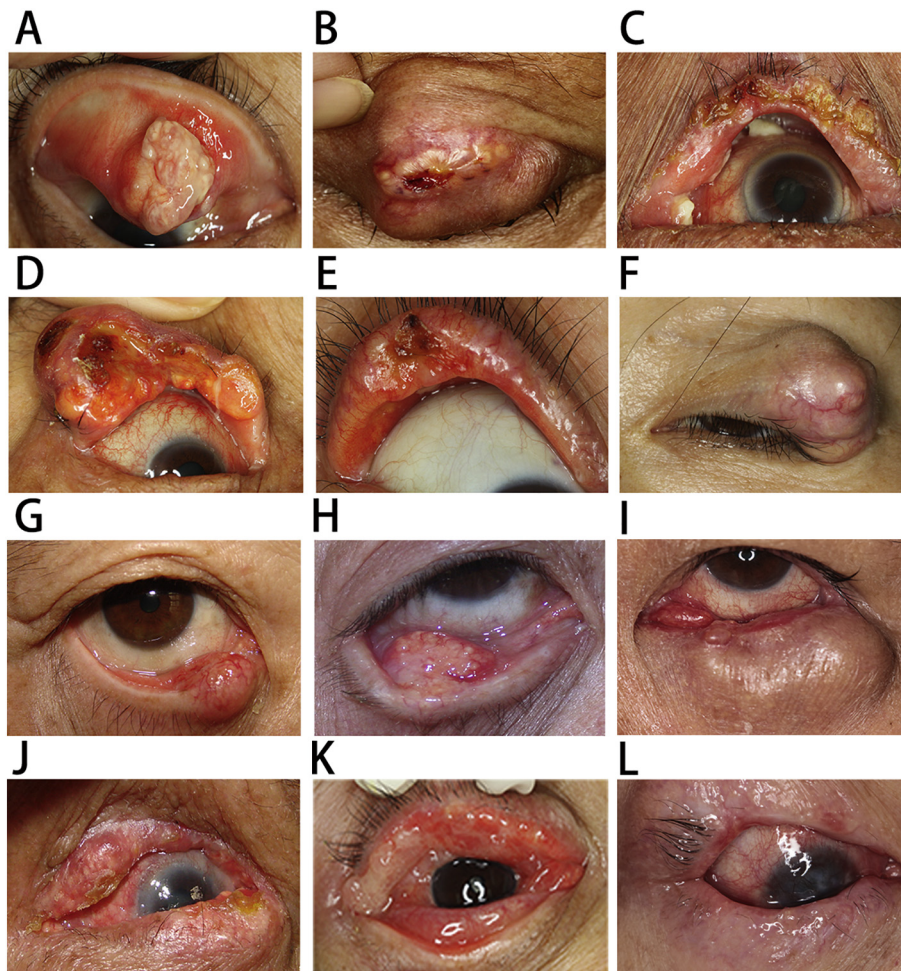


Fig. 1. Clinical appearances in Chinese patients with eyelid sebaceous carcinoma (SC). (A) Solitary eyelid nodule arising from the meibomian glands of the upper eyelid. (B) Large ulcerated nodule. (C) Diffuse thickening of the upper eyelid with extensive loss of cilia. (D) Large nodule with large sunken ulceration of the upper tarsus. (E) Diffuse thickening of the upper eyelid with ulceration. (F) Large nodule causing ptosis. (G) Sebaceous carcinoma arising near the caruncle. (H) Nodular mass of the lower eyelid. (I) Large nodule of the lower eyelid with orbital involvement. (J) Multicentric nodules involving both eyelids and bulbar conjunctiva. (K) Recurrent fleshy mass in the medial upper palpebral conjunctiva presenting with pseudoinflammatory signs. (L) Extensive diffuse sebaceous carcinoma involving both eyelids, bulbar conjunctiva, and cornea pagetoid growth pattern.

Table 3
Uni- and multivariable Cox proportional hazards regression analyses for the predictors of tumor-related death.

| | Univariable | | Multivariable (full-model) | |
|--|--------------------|---------|----------------------------|---------|
| | HR (95% CI) | p | HR (95% CI) | p |
| Gender (female vs male) | 0.64 (0.30–1.37) | 0.247 | | |
| Age (year) | 1.00 (0.97–1.03) | 0.976 | | |
| Second primary tumor (yes vs no) | 1.97 (0.59–6.56) | 0.27 | | |
| Lymph node metastasis at initial diagnosis (yes vs no) | 19.01 (6.94–52.09) | <0.001* | 13.66 (3.70–50.40) | <0.001* |
| Diagnostic delay (months) | 1.01 (1.00–1.01) | 0.040* | 1.00 (0.99–1.01) | 0.665 |
| Surgery times before diagnosis | 1.23 (0.86–1.75) | 0.257 | | |
| With caruncular involvement (yes vs no) | 2.75 (1.11–6.85) | 0.029* | 1.68 (0.61–4.66) | 0.32 |
| With orbital involvement (yes vs no) | 10.04 (4.58–22.05) | <0.001* | 3.11 (1.18–8.21) | 0.022* |
| Greatest tumor basal diameter (mm) | 1.08 (1.06–1.12) | <0.001* | 1.06 (1.02–1.10) | 0.003* |
| The presence of pagetoid spread (yes vs no) | 4.55 (2.13–9.71) | <0.001* | 2.90 (1.21–6.94) | 0.017* |
| The presence of perineural invasion (yes vs no) | 4.57 (1.93–10.83) | 0.001* | | |
| The presence of muscle infiltration (yes vs no) | 2.41 (1.10–5.27) | 0.027* | | |
| Ki 67 (%) | 1.03 (1.01–1.05) | 0.002* | | |
| Histology differentiation (well or moderately differentiated vs poorly differentiated) | 5.82 (2.66–12.73) | <0.001* | | |
| Initial treatment with Mohs surgery (yes vs no) | 0.92 (0.43–1.96) | 0.819 | | |
| With positive surgical margins (yes vs no) | 1.88 (0.79–4.45) | 0.153 | | |

HR, Hazard Ratio; SE, standard error; CI, confidence interval.

* Statistically significant.

(Supplementary Table 3). Furthermore, to improve the discrimination ability of our model, pragmatic parameters, such as, age, gender and initial treatment with Mohs surgery, were alternatively entered into the model. However, the addition of these clinical indicators did not seem to improve the explanatory effect compared with this base model (Supplementary Table 4).

3.4. Prognostic nomogram for tumor-related survival

A prognostic nomogram integrating all independent predictors for tumor-related survival was built (Fig. 2A). The C-index, which quantifies the level of concordance between the predicted and observed survival probability, was 0.887 for this model. The bias-corrected C-index generated by bootstrap validations was 0.872, indicating the excellent discrimination ability of this model. The predicted 5-year (Fig. 2B) and 10-year (Fig. 2C) survival probability increased as the prognostic score elevated. The calibration plots displayed fair agreement between the predictions and actual observations for 5-year (Fig. 3A) and 10-year (Fig. 3B) tumor-related survival.

This prognostic score generated by the nomogram assumed a skewed distribution (Supplementary Fig. 2). Patients were classified into 3 risk groups (low, intermediate and high) by the Cox method. Tumor-related survival was significantly different across risk groups (Fig. 4A; log-rank $p < .001$ (overall); $p < .001$ (low vs intermediate risk); $p = .001$ (intermediate vs high risk)).

3.5. Comparison of the nomogram with the TNM staging system

The discrimination accuracy of the nomogram was compared with the conventional TNM staging system. The C-index of TNM staging was 0.868, which was slightly but significantly smaller than that of nomogram ($p = .002$). The details of the comparisons are summarized in Table 4. Furthermore, Kaplan-Meier curves were generated according to the T category of the TNM staging systems. Although it exhibited good prognostic stratification ($p < .001$ for the combined cohort), the overlap of the survival curves was notable. The discriminative ability of the T designation was unsatisfactory in stratifying patients with early stage eyelid SC (Fig. 4B; log-rank $p = .358$ (T1 vs T2); $p = .171$ (T2 vs T3); $p < .001$ (T3 vs T4)).

4. Discussion

This study represents a large report of eyelid SC, and it provides a detailed update on the prognosis for Chinese patients. By Kaplan-

Meier survival estimates, the 5-year and 10-year tumor-related survival rates were 88.1% and 77.9%, respectively. This survival probability is lower than Muqit MM et al. reported in United Kingdom (5-year: 96.9%) [10] and Song et al. reported in United States of America (7-year: 93.3%) [22], but it is higher than several other authors reported in United States of America (5-year: 79% [4], 70% [5], 78% [9], 76% [23]) and Kaliki S et al. reported in India (5-year: 81%, 10-year: 65%) [8]. The survival rate for eyelid SC has improved for Chinese patients over the past 3 decades, as our results compared favorably with the findings reported by Ni C et al. (4-year: 71%) [1]. In our study, the 5-year and 10-year metastasis rates were 20.4% and 25.0%, respectively, which are better than those in India (5-year: 26%, 10-year: 40%) [8] but worse than the results in England (5-year: 3.1%) [10]. The above findings demonstrated that, when compared with patients from other parts of the world, Chinese patients with eyelid SC presented with comparable chances of tumor-related survival and metastasis. Potential explanations for these discrepancies may lie in the different sample sizes, varied follow-up periods, management variances, racial differences, and multiple surgeons with diverse experiences.

This study has created a novel nomogram prediction that integrate 4 independent risk factors of tumor-related survival: orbital involvement, the greatest tumor basal diameter, the presence of pagetoid spread, and having lymph node metastasis at initial diagnosis. Tumor size and location are the main determinants of T category in the TNM staging system and have been rigorously evaluated in numerous studies for their relationship with clinical outcomes [4,6–14]. Likewise, it is not surprising that patients with lymph node metastasis at initial diagnosis had a lower chance of survival. Among the 12 (5%) patients with regional lymph node metastasis at initial diagnosis, 6 of them died of eyelid SC, and the median survival time after initial diagnosis was only 28.0 months.

Our study corroborates published reports that pagetoid spread is associated with poorer survival [15,24]. Patients with pagetoid spread often have diffuse tarsus and conjunctival epithelium infiltration, which tends to present inflammatory signs that confound the clinician and pathologist. In this condition, SC is usually misdiagnosed as chronic blepharoconjunctivitis initially, often leading to a diagnostic delay [25]. Consequently, heightened awareness and early recognition of SC are critical, and clinicians should possess adequate suspicion for SC, especially when encountering elderly patients with relapsed blepharoconjunctivitis. In our cohort, the mean diagnostic delay for patients with pagetoid invasion was as long as 35.6 months, whereas for patients without this sign, the delay was 26.6 months. Among the 43

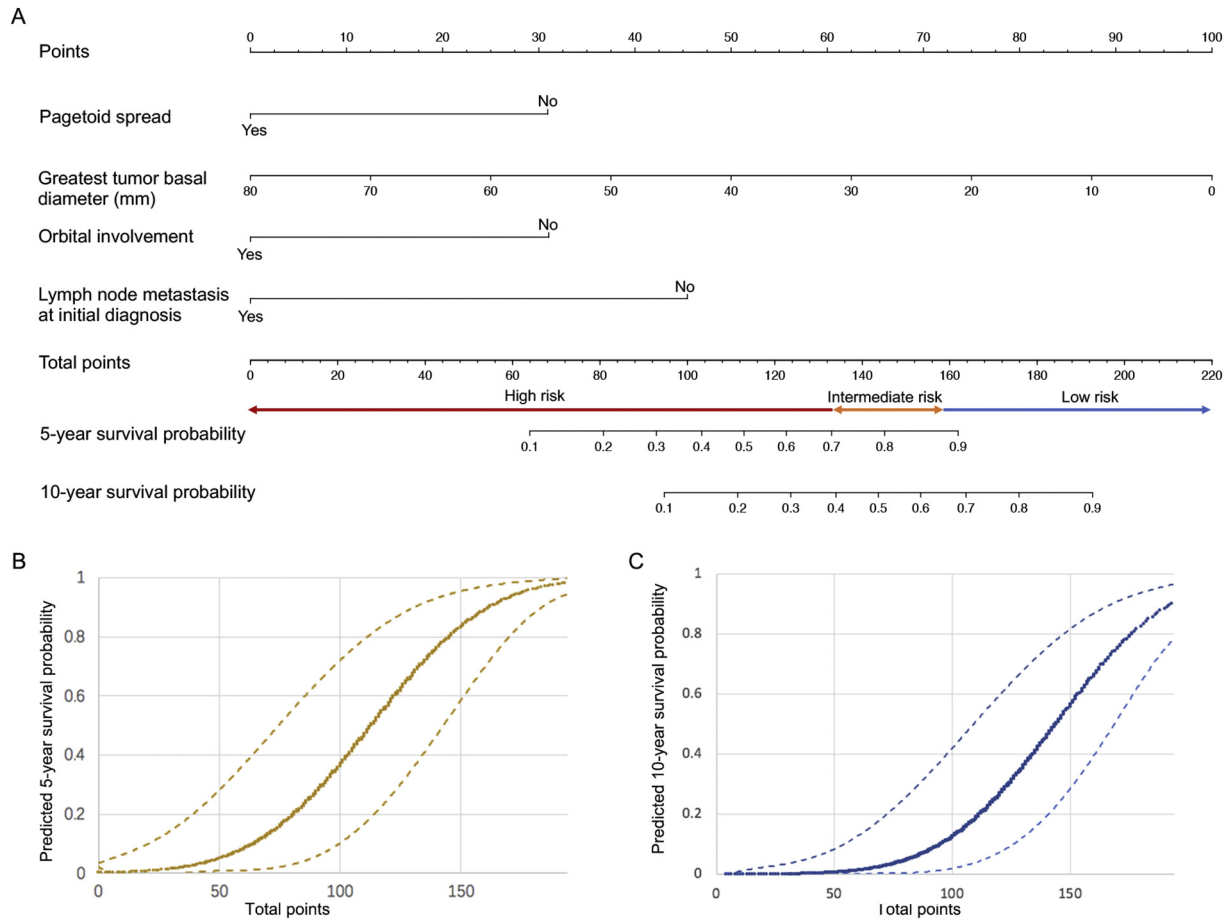


Fig. 2. Nomogram for tumor-related survival. (A) Nomogram for predicting the probability of tumor-related survival at 5 and 10 years. To use it, locate pagetoid spread (yes/no) and draw a vertical line up to the “Points” axis to obtain the score of pagetoid spread. Repeat for the other 3 variables: orbital involvement (yes/no), lymph node metastasis at initial diagnosis (yes/no) and greatest tumor basal diameter (mm). Then, the scores were summed and locate the total number on the line labeled “Total Points”. Draw a vertical line downwards from the total point dot to determine the tumor-related survival prediction at the intersection with the 5-year and 10-year survival probability axes. Predicted 5-year (B) and 10-year (C) tumor-related survival probability according to nomogram score. Dashed lines stand for 95% confidence intervals.

(18.1%) patients with pagetoid growth patterns, 12 (5.04%) of them experienced orbital involvement, and 13 (5.46%) patients died of metastatic SC. Therefore, the extension of pagetoid spread is a frequent indication for exenteration conventionally, but currently, this management is under debate [26]. Conservative surgery guided by map biopsies and augmented with adjuvant therapies, such as cryotherapy [27] and

the application of Mitomycin C, might be more appropriate to eradicate local disease with pagetoid spread [26].

Of note, 13 (5.5%) patients in this cohort had a second primary tumor, and the most common cancers included breast cancer (4, 1.7%), colon cancer (3, 1.3%), and gastric carcinoma (2, 0.8%). Among these patients, 7 (2.9%) died, and 5 (2.1%) died of the second

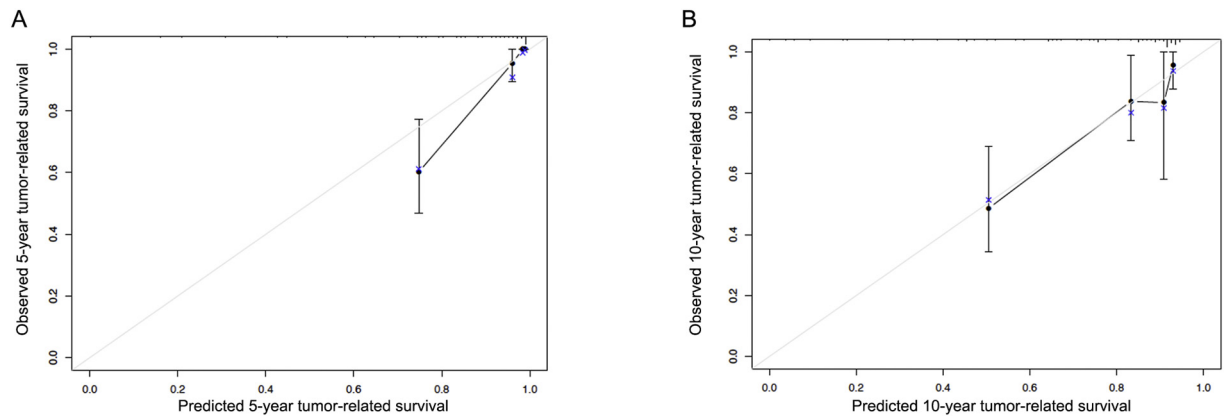


Fig. 3. Calibration plots at 5 (A) and 10 years (B) for tumor-related survival probability. Nomogram-predicted survival probability is plotted on the x-axis, with observed survival probability on the y-axis. 95% confidence intervals of the estimates are indicated with vertical lines. The gray line through the origin point represents the perfect calibration models in which the predicted probabilities are identical to the actual probabilities. Black dot: predicted probabilities based on the nomogram; blue cross: bootstrap corrected estimates. B = 200 repetitions for bootstrap.

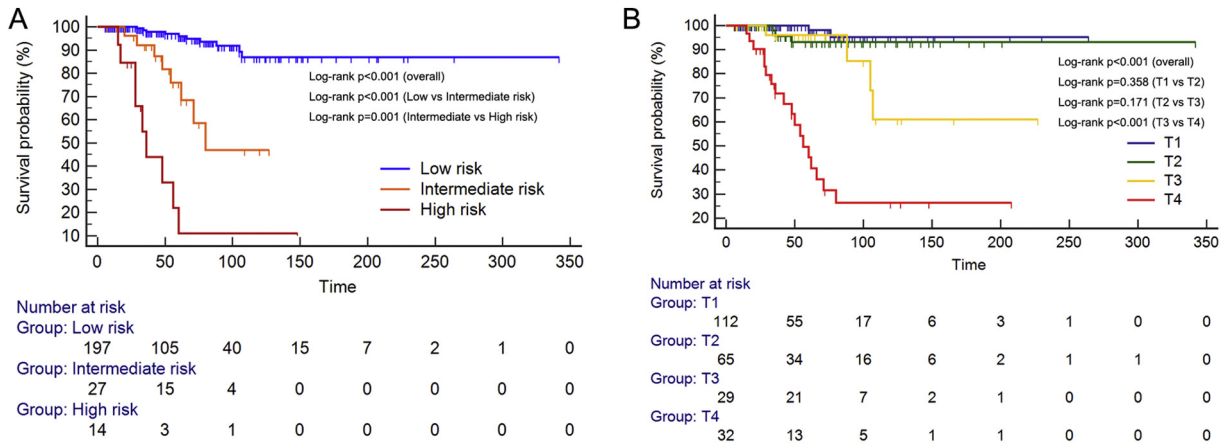


Fig. 4. (A) Kaplan-Meier curves of tumor-related survival for low, moderate, and high risk groups stratified by nomogram score. (B) Kaplan-Meier curves of tumor-related survival according to the tumor (T) category of the Tumor, Node, Metastasis (TNM) staging system according to the 8th edition of the American Joint Committee on Cancer (AJCC). Log-rank p value <.05 was considered statistically significant.

primary tumor. Although this factor could not be entered into the final model, it was an independent predictor for all-cause mortality (Supplementary Table 5); consequently, lifelong vigilance is required to detect any second primary malignancies for patients with eyelid SC.

Cancer staging is important for evaluating the prognosis and directing therapeutic management and is of great significance for both the patients and clinicians in decision-making. The nomogram is a graphic calculating tool that uses statistical models to increase the predictive accuracy of individuals. Nomograms have been proven to provide more precise predictions than the traditional staging systems for many other carcinomas [28,29], and they have been proposed as alternatives or even as a new standard to guide the treatment for cancer patients. In this study, we established a novel, easy-to-use, and effective nomogram to evaluate the survival probability for eyelid SC on an individual basis. Furthermore, the performance characteristics of the nomogram and the TNM staging system were compared. Our tool achieved higher discriminative accuracy, for patients at an early stage of disease. The TNM staging system is mainly based on tumor location and size, and it was only developed and validated in Caucasian patients. To improve our collective understanding of prognostic factors related to eyelid SC, we pooled detailed clinicopathological data associated with mortality over the past 25 years in our medical center, which attracts >200,000 patients with ocular diseases annually.

This study should be regarded as an initial exploration in terms of the application of a nomogram in ocular tumors. However, caution should be exercised when interpreting the findings due to a number of limitations. First, compared to the sample sizes in studies of “large tumors”, our patient population was small, and all the patients were recruited from a single tertiary hospital. They entered this study voluntarily. The drop-outs tended to be older and have more serious conditions. This could also cause selection bias. The small sample size and limited number of outcome events might produce large confidence intervals for the estimates in the calibration plot. Second, although a bootstrap method was used for internal validation, we did not have an

independent cohort outside Shanghai Ninth People's Hospital to validate this nomogram externally. Without external validation, whether this nomogram can be generalized to the entire SC patient population remains unclear. Nevertheless, the detailed clinical and pathological data prevent us from validating our model in an external cohort in the community setting. We will continue to seek such datasets for future validation studies from other medical centers. In addition, as the prognostic predictors of SC are multifactorial, other factors, such as adjuvant therapies, DNA mismatch and microsatellite instability tests for patients with a second primary tumor and patient-reported outcomes, were not included in this study. Nevertheless, we tried to circumvent these limitations as follows: First, our cohort constitutes the largest report of eyelid SC to date and the use of objective statistical methods and adjustment of various interactions enabled us to eliminate bias and improve the validity of this model.

The prognosis of Chinese patients with eyelid SC has improved over the last 3 decades and is comparable to that of patients from other countries. A novel predictive nomogram was developed and validated to provide accurate individualized estimates of survival for eyelid SC patients, and it demonstrated a better discrimination ability than the traditional staging system. To our knowledge, this is the first and only evaluation of the application of a nomogram in ocular disease. Therefore, a large series, especially an external validation, is warranted to fully validate our findings.

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Declaration of interests

No conflict of interest to declare.

Author contributions

C.D.Z., R.B.J., X.Q.F. and H.Y.H designed study. R.B.J. and X.Q.F. provided the data of patients. C.D.Z. and Y.Y.S did literature search. P.W.C. and X.Y.H. designed the figs. C.D.Z. and Y.Y.S did data collection drafted the manuscript; F.W. and W.W.X. assisted in data collection and revision. C.D.Z., X.Y.H., Y.S. and H.Y.H did data analysis and interpretation. C.D.Z and Y.Y.S contributed equally to this paper. R.B.J., X.Q.F. and

Table 4
The comparison of predictive discrimination ability of the nomogram and TNM staging system

| | C-index | Goodness of fit | | Comparison of models | | | |
|----------|---------|-----------------|----------------|----------------------|------|-------|--------|
| | | LR | R ² | Dxy | SD | Z | p |
| Nomogram | 0.887 | 52.50 | 0.25 | - | - | - | - |
| TNM | 0.868 | 64.15 | 0.24 | -0.19 | 0.16 | -3.13 | 0.002* |

TNM: Tumor, Node, Metastasis staging system according to 8th edition of American Joint Committee on Cancer

H.Y.H are the co-corresponding authors. All authors approved this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ebiom.2018.09.011>.

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