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Retrospective Cohort Study

Development and validation of novel nomograms to predict survival of patients with tongue squamous cell carcinoma

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Abstract

BACKGROUND

There is no unified standard to predict postoperative survival in patients with tongue squamous cell carcinoma (TSCC), hence the urgency to develop a model to accurately predict the prognosis of these patients.

AIM

This study aimed to develop and validate nomograms for predicting overall survival (OS) and cancer-specific survival (CSS) of patients with TSCC.

METHODS

A cohort of 3,454 patients with TSCC from the Surveillance, Epidemiology, and End Results (SEER) database was used to develop nomograms; another independent cohort of 203 patients with TSCC from the Department of Oral and Maxillofacial Surgery, First Affiliated Hospital of Zhejiang University School of Medicine, was used for external validation. Univariate and multivariate analyses were performed to identify useful variables for the development of nomograms. The calibration curve, area under the receiver operating characteristic curve (AUC) analysis, concordance index (C-

index), net reclassification index (NRI), and decision curve analysis (DCA) were used to assess the calibration, discrimination ability, and clinical utility of the nomograms.

RESULTS

Eight variables were selected and used to develop nomograms for patients with TSCC. The C-index (0.741 and 0.757 for OS and CSS in the training cohort and 0.800 and 0.830 in the validation cohort, respectively) and AUC indicated that the discrimination abilities of these nomograms were acceptable. The calibration curves of OS and CSS indicated that the predicted and actual values were consistent in both the training and validation cohorts. The NRI values (training cohort: 0.493 and 0.482 for 3- and 5-year OS and 0.424 and 0.402 for 3- and 5-year CSS; validation cohort: 0.635 and 0.750 for 3- and 5-year OS and 0.354 and 0.608 for 3- and 5-year CSS, respectively) and DCA results indicated that the nomograms were significantly better than the tumor-node-metastasis (TNM) staging system in predicting the prognosis of patients with TSCC.

CONCLUSION

Our nomograms can accurately predict patient prognoses and assist clinicians in improving decision-making concerning patients with TSCC in clinical practice.

INTRODUCTION

Tongue squamous cell carcinoma (TSCC) is the most common malignancy of the oral cavity and pharynx and has a high risk of local invasion and lymph node metastasis[1–3]. Surgical resection is the first-line treatment, followed by adjuvant radiotherapy, chemotherapy, or chemoradiation therapy. Despite substantial improvements in diagnostic techniques and multimodal treatment in recent years, the survival rate of TSCC remains low[4,5].

Treatment strategies for TSCC and its prognosis are based principally on the tumor-node-metastasis (TNM) cancer staging system established by the American Joint

Committee on Cancer (AJCC)[6]. However, the prognoses can vary among patients with the same TNM stage who are receiving similar treatments[7–9]. Such variation suggests that the TNM staging system does not adequately predict prognosis because it does not consider patient characteristics (e.g., age and marital status) or treatment (e.g., type of surgery)[10,11]. Therefore, a new model that incorporates these variables is required to supplement the TNM staging system and accurately predict patient prognoses.

A nomogram is a graphical model that estimates the probability of a clinical event for an individual patient based on specific biological and clinical factors[12]. Nomograms are more accurate than the TNM staging system in predicting prognoses; they have been widely used to evaluate gastric[13–15], hepatocellular[16–19], and head and neck[20–23] carcinomas. However, there are few studies regarding the prediction of the prognosis of TSCC. Although Mair et al.[24] predicted the prognosis of TSCC, the clinical utility of the prediction model (i.e., whether they facilitate decision-making and thus improve patient outcomes[12]) was not evaluated; thus, the model would be difficult to apply in clinical practice. Currently, individually predicting the prognosis of patients with TSCC remains insufficient.

Therefore, this study aimed to develop nomograms for predicting overall survival (OS) and cancer-specific survival (CSS) in patients with TSCC to externally validate the established nomograms (discrimination, calibration, and clinical utility) and to assist clinicians in improving therapeutic decision-making.

MATERIALS AND METHODS

Patient selection

Patients diagnosed with TSCC between 2010 and 2015 were selected from the Surveillance, Epidemiology, and End Results (SEER) database using SEERStat 8.3.9.2. The inclusion and exclusion criteria are shown in Figure 1. Overall, 3,454 cases were selected as the training cohort for the development of new nomograms. When performing the internal validation, it was assigned by the bootstrapping method.

Another independent cohort that was diagnosed between January 2010 and December 2020 was obtained from the Department of Oral and Maxillofacial Surgery, First Affiliated Hospital of Zhejiang University School of Medicine. The National Comprehensive Cancer Network diagnosis and treatment guidelines for TSCC were followed. Using the same inclusion and exclusion criteria, 203 cases were selected as a the validation cohort to externally validate the established nomograms (Figure 1).

We retrospectively retrieved data regarding age, sex, marital status, ethnicity, tumor site, T stage, N stage, TNM stage, pathology grade, neck dissection status, and radiation treatment status. The tumor grading system of the 7th edition of the AJCC Cancer Staging Manual was used. The subclassifications of each variable are shown in Table 1. The study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine.

Statistical analysis and nomogram development

First, descriptive statistics were generated for the demographic and tumor clinicopathological characteristics. Then, univariate and multivariate Cox proportional hazards models were constructed. Coefficients, hazard ratios, and 95% confidence intervals (CIs) were obtained for prognostic factors in the training cohort. Finally, nomograms that integrated significant independent risk factors were constructed based on the predicted 3- and 5-year OS and CSS in the training cohort. OS was defined as the time from surgery until death from any cause or the last follow-up. CSS was defined as the time from surgery until death from TSCC or the last follow-up.

Validation and evaluation of nomograms

Internal and external validation analyses were performed to assess the predictive accuracies of the nomograms for the training and validation cohorts. Discriminative ability was evaluated based on the concordance index (C-index) and area under the receiver operating characteristic curve (AUC). The C-index and AUC values are often used interchangeably and range from 0.5 to 1 (no discrimination ability and perfect

discrimination, respectively)[12]. Meanwhile, a C-index or AUC value of >0.7 indicates satisfactory discrimination. The concordance between predicted and actual survival was assessed using calibration curves. The reference line is a 45° diagonal line that ideally includes both predicted and actual survival rates.

The clinical benefits and utility of the nomograms were compared with those of the TNM staging system using the net reclassification index (NRI) and decision curve analysis (DCA). The NRI is used to assess the predictive accuracies and utility of nomograms[25,26]. The DCA is used to estimate the clinical and net benefits of nomograms based on threshold probabilities[27,28]. A horizontal reference line indicates that no intervention was performed (i.e., there was no clinical benefit), while an oblique line indicates that all patients underwent the intervention (i.e., the clinical benefit was maximized).

R statistical software (ver. 4.0.5; R Development Core Team, Vienna, Austria) was used to perform all analyses. *P*-values <0.05 were considered statistically significant.

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RESULTS

Clinicopathological characteristics

The clinicopathological characteristics of the SEER cohort and our cohort are described in Table 1. Most of the patients (training cohort, *n* = 1,049 [30.4%]; validation cohort, *n* = 65 [32.0%]) were aged 50–59 years, and approximately 60% patients were men. Overall, the proportion of married patients was significantly greater than that of unmarried patients; the proportion of married patients was greater in the validation cohort (*n* = 179 [88.2%]) than in the training cohort (*n* = 2,098 [60.7%]). Approximately 90% of patients in the training cohort were White, whereas all patients in the validation cohort were Asian. In both cohorts, the proportion of TSCCs located on the anterior 2/3 of the tongue was greater than that located on the base of the tongue (training cohort, 74.6% vs. 25.4%; validation cohort, 82.3% vs. 17.7%, respectively). In both cohorts, most TSCCs were stage T1 and T2 (training cohort, *n* = 2,815 [81.5%]; validation cohort, *n* = 186 [91.6%]). Meanwhile, more than half of all TSCCs were stage N0 (training cohort, *n*

= 1,920 [55.6%]; validation cohort, *n* = 133 [65.5%]), while a few TSCCs were stage N3 (training cohort, *n* = 48 [1.4%]; validation cohort, *n* = 1 [0.5%]). The proportion of TSCCs was evenly distributed across subclassifications of TNM stages. Approximately half of the TSCCs in the training cohort was moderately differentiated, whereas 69.5% of TSCCs in the validation cohort was well-differentiated. Most of the patients in both cohorts underwent neck dissection (training cohort, *n* = 2,491 [72.1%]; validation cohort, *n* = 194 [95.6%]). The proportion of patients who did and did not undergo radiation after surgery was 49.2% and 49.2% in the training cohort, and 52.7% and 36.0% in the validation cohort, respectively.

Nomogram development

Eleven candidate variables associated with OS and CSS were evaluated by univariate and multivariate Cox analyses of the SEER cohort. Univariate analysis showed that age, marital status, ethnicity, tumor site, T stage, N stage, TNM stage, pathology grade, neck dissection status, and radiation treatment status were significantly associated with OS and CSS in ($P < 0.05$ for all; Tables 2 and 3). Multivariate analysis showed that age, marital status, tumor site, T stage, N stage, pathology grade, neck dissection status, and radiation treatment status were independently associated with OS and CSS ($P < 0.05$ for all; Tables 2 and 3).

Based on the results of the multivariate analysis, eight prognostic variables (age, marital status, tumor site, T stage, N stage, pathology grade, neck dissection status, and radiation treatment status) were used to develop the nomograms. Figure 2 shows the OS and CSS predictions from the nomograms. N and T stages had the greatest effects on OS followed by tumor site and age. N stage had the greatest effect on CSS followed by T stage and tumor site. Generally, OS and CSS were better in younger patients with lower T and N stages. The predicted 3- and 5-year OS and CSS for individual patients are shown at the bottom of the nomograms based on the sum of scores across variables.

Nomogram validation and evaluation

The results of the internal and external validation analyses are shown in Figure 3. In the training cohort, the internal calibration curves indicated excellent consistency between the predicted and actual 3- and 5-year OS and CSS (Figs. 3A, B, E, and F), which was also observed in the validation cohort (Figs. 3C, D, G, and H). The C-index values were 0.741 (95%CI: 0.725, 0.756) and 0.757 (95%CI: 0.739, 0.775) for OS and CSS in the internal validation analysis; these respective values were 0.800 (95%CI: 0.747, 0.853) and 0.830 (95%CI: 0.779, 0.881) in the external validation analysis, respectively (Table 4). Overall, the nomograms exhibited satisfactory discrimination and calibration.

Comparison of clinical utility between the nomograms and the TNM staging system

The C-index values of the TNM staging system for OS and CSS were also estimated in both the internal and external validation analyses (Table 4). The C-index values of the nomograms were higher than those of the TNM staging system (Table 4). In terms of predictive accuracy, the AUC values for the nomograms were higher than those of the TNM staging system (3-year OS, 74.2 vs. 66.0; 5-year OS, 73.9 vs. 65.9; 3-year CSS, 75.4 vs. 68.3; 5-year CSS, 75.7 vs. 69.4) in the training cohort (Figs. 4A, B, E, and F) as well as in the validation cohort (3-year OS, 83.3 vs. 75.3; 5-year OS, 87.1 vs. 71.3; 3-year CSS, 86.4 vs. 80.4; 5-year CSS, 87.9 vs. 75.0) (Figs. 4C, D, G, and H).

As shown in Table 4, the NRI values for the 3- and 5-year OS and CSS in the training cohort were 0.493 (95%CI: 0.418, 0.589) and 0.482 (95%CI: 0.413, 0.613), and 0.424 (95%CI: 0.354, 0.523) and 0.402 (95%CI: 0.345, 0.536), respectively, which were confirmed in the validation cohort (Table 4). Notably, the nomograms performed significantly better than the TNM staging system in both the training and validation cohorts.

The DCA was used to compare clinical benefits between the nomograms and the TNM staging system. As shown in Figure 5, the nomograms exhibited greater net benefits than the TNM staging system at all threshold probabilities in the training cohort (i.e., they were better able to predict both 3- and 5-year OS and CSS). For the 3-year OS and CSS in the validation cohort, the net benefits of the TNM staging system were generally

equivalent to the nomograms, whereas the nomograms showed greater net benefits than the TNM staging system at almost all threshold probabilities for the 5-year OS and CSS.

DISCUSSION

We developed new nomograms to predict the 3- and 5-year OS and CSS in patients with TSCC, evaluated their discrimination and calibration abilities, and compared their clinical utilities with those of the TNM staging system. Our results showed that our nomograms accurately predicted both the OS and CSS of patients with TSCC. Additionally, the C-index and AUC values along with the calibration curves showed that the nomograms had satisfactory discrimination and calibration. Moreover, compared with the TNM staging system, the predictive accuracies of OS and CSS were higher for the nomograms, as revealed by the NRI values and DCA curves. Thus, the aforementioned results indicate that our nomograms exhibited satisfactory discrimination, calibration, and clinical utility.

In this study, age, marital status, tumor site, T stage, N stage, pathology grade, neck dissection status, and radiation treatment status were selected to develop nomograms to predict the 3- and 5-year OS and CSS of patients with TSCC. As an example, Figure 2 compares two patients with similar staging results but different treatments. The first patient was 60 years old, married, and with T2 and N1 stage cancer on the anterior 2/3 of the tongue that exhibited moderate differentiation; that patient underwent neck dissection and received postoperative chemotherapy. The second patient was 70 years old, unmarried, and with T2 and N1 stage cancer on the anterior 2/3 of the tongue that exhibited high differentiation; that patient underwent neck dissection but did not receive radiation treatment. According to the conventional TNM staging system, both patients had the same TNM stage and therefore should have similar OS. However, our nomograms predicted that the respective 3- and 5-year OS were 64% and 55% for the first patient, whereas they were 43% and 33% for the second patient. The inclusion of additional information regarding clinicopathological characteristics and

demographics provides our nomograms with a more accurate prognosis prediction ability; we expect these nomograms to serve as a powerful supplement to the TNM staging system for predicting prognoses.

The N stage had the greatest prognostic power followed by T stage, tumor site, and age (Figure 2). Advanced T and N stages were associated with poor OS and CSS, consistent with findings in previous studies[4,9]. These results indicate that the prognosis of patients with TSCC is greatly affected by the T and N stages; the more advanced the T and/or N stage, the worse the OS and CSS. Meanwhile, the inclusion of age and radiation treatment status in our nomograms may be considered controversial. Previous studies revealed that age was independently associated with both OS and CSS; younger patients had better survival, whereas older patients had a significantly greater mortality risk[29–31]. Moreover, compared with younger patients, older patients with advanced tumor stages (III, IV) had a nearly two-fold greater mortality risk. Similar to radiation treatment, surgery alone is generally associated with a high risk of relapse, particularly in patients with advanced TSCC; adjuvant therapies are thus necessary[32]. Radiation treatment has been shown to improve locoregional control and survival in patients with TSCC after surgery, particularly in advanced cases[33–36]. Here we found that the ability of radiation treatment status for predicting OS and CSS was not inferior to that of pathology grade (Figure 2). Additionally, as shown in Tables 2 and 3, age and radiation treatment status were independent predictors of OS and CSS in patients with TSCC. Taken together, our results indicate that age and radiation treatment status have prognostic significance. It has been demonstrated that marital status is an independent prognostic factor in patients with TSCC[9]. Married patients had better OS and CSS than unmarried patients[37], which is consistent with our findings in this study. We found the independent and significant role of marital status as a prognostic factor of patients with TSCC. In addition to the above variables, our study identified tumor site, pathology grade, and neck dissection status as independent prognostic factors of patients with TSCC. The OS and CSS of patients with TSCC are affected by these factors, which are shown in Tables 2 and 3 and Figure 2.

Our nomograms accurately and effectively predicted the prognosis of patients with TSCC and exhibited high clinical potential. The satisfactory discrimination and calibration abilities of these nomograms were confirmed by the calibration and receiver operating characteristic curves as well as the C-index and AUC values. The C-index values in external validation were higher than that in the training cohort, which is consistent with that constructed by Lu and Zhang for predicting tongue cancer and low-grade endometrial stromal sarcoma, respectively[7,38]. These results may indicate the extensionality and applicability of the constructed model. Moreover, we also compared the clinical utilities of the established nomograms with that of the TNM staging system, with the NRI values indicating that our nomograms had significantly better predictive accuracy. Similarly, DCA revealed that the nomograms had more clinical benefits and were better able to predict survival compared with the TNM staging system.

To reduce potential bias, we used multi-institution and multi-population data from the SEER database to develop our nomograms and to validate their discrimination and calibration abilities as well as their clinical utilities in both internal and external cohorts. Additionally, we adhered to the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis statement[39]. In summary, our nomograms were used to accurately determine the clinical prognosis of patients with TSCC.

Due to its retrospective nature, this study has some limitations. First, the depth of invasion (DOI) has been recognized as an independent predictor of survival[8,40]. Among the tumor parameters that were significant for prognosis, such as the tumor width, area, volume, and depth, the DOI was considered the most important[41]. Additionally, extranodal extension (ENE) has been widely recognized as a significant poor prognostic factor for patients with HNSCC[42,43]. Hence, the DOI and ENE were incorporated into the T and N classification, respectively, in the AJCC 8th edition of the cancer staging manual[44]. However, they were not available in the SEER database, thus not being included in our constructed model. Further improvements by incorporating

these factors into the constructed nomogram should be undertaken in the future. Second, the current model only incorporates clinicopathological parameters to predict patient outcomes, which is nonsufficient for screening patients appropriate for adjuvant therapies, especially preoperative/postoperative adjuvant immunotherapy. More molecular markers should be incorporated into the constructed model to improve its clinical application value, such as PD-1[45–47], CD47[48], CXCL11[49], and CXCR3[50], which have been reported to engage in tumor immunity and included in some efficient predictive models. Third, this retrospective study had an unavoidable risk of selection bias. Thus, prospective validation studies are needed before these nomograms can be used in clinical practice.

CONCLUSION

We used two databases to develop and validate new nomograms for predicting the 3- and 5-year OS and CSS in patients with TSCC. Compared with the TNM staging system, these nomograms exhibit greater accuracy, effectiveness, and clinical utility for predicting the prognosis of patients with TSCC. Thus, they are a strong complement to the TNM staging system in the prediction of patient prognosis.

ARTICLE HIGHLIGHTS

Research background

There is no unified standard to predict postoperative survival in patients with TSCC, hence the urgency to develop a model to accurately predict the prognosis of these patients.

Research motivation

Development of new models for predicting survival in patients with TSCC is important for facilitating patient-clinician communications and assisting clinicians in improving decision-making.

Research objectives

This study aimed to develop nomograms for predicting overall survival and cancer-specific survival in patients with TSCC based on demographic and histopathological variables, and to externally validate the established nomograms.

Research methods

Two databases of patients with TSCC were used to develop nomograms and to perform external validation, respectively.

Research results

Eight variables were selected and used to develop nomograms for patients with TSCC. The C-index and AUC indicated that the discrimination abilities of these nomograms were acceptable. The calibration curves indicated that predicted and actual values were consistent. The NRI values and DCA results indicated that the nomograms were significantly better than the TNM staging system in predicting the prognosis of patients with TSCC.

Research conclusions

The nomograms we developed exhibit great accuracy, effectiveness, and clinical utility for predicting the prognosis of patients with TSCC.

Research perspectives

In addition to the demographic and histopathological characteristics, some molecular markers that have an impact on survival, such as PD-1, CD47, CXCL11, may be incorporated to predict the prognosis of patients with TSCC in future.

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