Observational Study

Medicine®

OPEN

Nomograms to predict survival of stage IV tongue squamous cell carcinoma after surgery

Wei Sun, MD[a], Minghua Cheng, MD[a], Shaohui Zhuang, MD[a], Huimin Chen, MD[b], Shaohui Yang, MD[a], Zeting Qiu, MD[a,*]

Abstract

To develop clinical nomograms for prediction of overall survival (OS) and cancer-specific survival (CSS) in patients with stage IV tongue squamous cell carcinoma (TSCC) after surgery based on the Surveillance, Epidemiology, and End Results (SEER) program database.

We collected data of resected stage IV TSCC patients from the SEER database, and divided them into the training set and validation set by 7:3 randomly. Kaplan–Meier analysis and Cox regression analysis were adopted to distinguish independent risk factors for OS and CSS. Clinical nomograms were constructed to predict the 3-year and 5-year probabilities of OS and CSS for individual patients. Calibration curves and Harrell C-indices were used for internal and external validation.

A total of 1550 patients with resected stage IV TSCC were identified. No statistical differences were detected between the training and validation sets. Age, race, marital status, tumor site, AJCC T/N/M status, and radiotherapy were recognized as independent prognostic factors associated with OS as well as CSS. Then nomograms were developed based on these variables. The calibration curves displayed a good agreement between the predicted and actual values of 3-year and 5-year probabilities for OS and CSS. The C-indices predicting OS were corrected as 0.705 in the training set, and 0.664 in the validation set. As for CSS, corrected C-indices were 0.708 in the training set and 0.663 in the validation set.

The established nomograms in this study exhibited good accuracy and effectiveness to predict 3-year and 5-year probabilities of OS and CSS in resected stage IV TSCC patients. They are useful tools to evaluate survival outcomes and helped choose appropriate treatment strategies.

Abbreviations: AJCC = American Joint Committee on Cancer, CI = confidence interval, C-index = concordance index, CSS = cancer-specific survival, HNSCC = head and neck squamous cell carcinoma, HR = hazard ratio, ICD-O-3, International Classification of Diseases for Oncology, Third Edition, OS = overall survival, SEER = Surveillance, Epidemiology, and End Results, TNM = tumor node metastasis, TSCC = tongue squamous cell carcinoma.

Keywords: cancer-specific survival, nomogram, overall survival, resected, SEER database, tongue squamous cell carcinoma

1. Introduction

Cancer of lip and oral cavity caused about 300,373 new patients and killed about 145,353 people all over the world in 2012.[1] Tongue squamous cell carcinoma (TSCC) is a type of squamous cell carcinoma derived from the tongue. According to the tumor node metastasis (TNM) staging system of American Joint Committee on Cancer (AJCC), TSCC can be classified into AJCC stage I-IV.[2] Both treatment strategies and prognosis prediction for patients with TSCC are based on the AJCC TNM staging system. When it comes to stage IV advanced TSCC, surgery is generally preferred as the initial step, and postoperative radiation therapy or chemoradiotherapy should be considered to control disease progress.[3,4] According to a retrospective study of 262 patients with base of tongue cancer, the 5-year disease-specific survival rates were 27% for stage IV.[5] However, the AJCC TNM staging system does not take other risk factors into account, including age, gender, race, histological grade, surgical therapy, radiation therapy, and so on, which seriously affects the prediction of individual patient prognosis in some cancers.[6–8] Therefore, it is necessary to develop a new model to make the accurate prognostic prediction of stage IV TSCC, especially for resected patients.

Currently, nomograms have been widely developed to estimate individual prognosis of death and recurrence in many cancer types.[9–12] By creating a visualized graph of the predictive model, nomogram has been considered to be a strong tool for prediction. And it was proved to be more effective than the traditional staging system.[13–15] However, nomograms to individually predict survival of stage IV TSCC patients after surgery have been rarely studied yet.

In this study, in order to evaluate the overall survival (OS) and cancer-specific survival (CSS) outcomes in patients with stage IV TSCC after surgery, we developed effective nomogram models

Editor: Antonio Palazón-Bru.

The authors report no conflicts of interest.

Supplemental Digital Content is available for this article.

[a] Department of Anesthesiology, The First Affiliated Hospital of Shantou University Medical College, [b] Department of Stomatology, The First Affiliated Hospital of Shantou University Medical College, Shantou, Guangdong, People's Republic of China.

[*] Correspondence: Zeting Qiu, Shantou University Medical College Shantou, Guangdong, People's Republic of China (e-mail: doctorqiuzt@gmail.com).

Medicine (2019) 98:26(e16206)

Received: 22 October 2018 / Received in final form: 6 May 2019 / Accepted: 3 June 2019

http://dx.doi.org/10.1097/MD.0000000000016206

and validated it based on a large population-based database of Surveillance, Epidemiology, and End Results (SEER) program.

2. Methods

2.1. Data sources

The SEER program covers approximately 30% of the population in the United States.[16,17] Author QZT received research data by SEER*Stat software after authorization (Reference number: 12738-Nov2016). The demographic, clinicopathological, and follow-up data of all the tongue cancer patients were extracted from the SEER database. The SEER database was publicly available and all the research data were de-identified. Moreover, the study complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. So, the approval was waived by the local ethics committee and the institutional review board, and no informed consents were needed.

2.2. Inclusion and exclusion criteria

We identified patients with tongue cancer (International Classification of Diseases for Oncology, Third Edition [ICD-O-3], anatomic code C01.9, C02.0, C02.1, C02.2, C02.3, C02.4, C02.8, C02.9) for our study. Patients were included when meeting the following criteria:

1. diagnosed between 2004 and 2011;
2. limited to squamous cell carcinoma (ICD-O-3, histologic code: 8050, 8051, 8052, 8070, 8071, 8072, 8073, 8074, 8075, 8076, 8081, 8082, 8083 and 8084);
3. aged between 18 and 80 years old at diagnosis;
4. diagnosed with AJCC TNM stage IV;
5. receiving definite surgical treatment.

Patients were excluded according to the following criteria:

1. unknown race or marital status information;
2. unknown histologic grade, TNM stage information;
3. unknown causes of death or unknown survival month;
4. surviving less than or equal to 1 month;
5. incomplete treatment information;
6. multiple primary tumors;
7. Autopsy or death certificate only cases.

2.3. Variable selection

Data of gender, age group, marital status, race, tumor site, histological grade, AJCC T status, AJCC N status, AJCC M status, radiotherapy, chemotherapy, causes of death, and survival months were collected from the SEER database. Age group was classified as 1st quartile (68–80 years old), 2nd quartile (61–67), 3rd quartile (53–60), 4th quartile (18–52). Marital status was classified as married and unmarried (including divorced, separated, single, widowed patients). Race was classified as white, black, and others. Tumor site was classified as base of tongue and other sites. Histologic grade was classified as grade I/II and III/IV. AJCC tumor (T) status was classified as T1, T2, T3, and T4. AJCC node (N) status was classified as N0, N1, N2 and N3. AJCC metastasis (M) status was classified as M0 and M1.

2.4. Construction of the nomogram

We randomly divided all the included patients into the training set and validation set according to the ratio of 7:3. For OS analysis, any cause of death was defined as events, and survivors were defined as censored events. For CSS analysis, deaths caused by tongue cancer were considered as events, and deaths by other causes or survivors were considered as censored events. We compared OS and CSS among different variables to get statistically significant characteristics associated with OS and CSS using the Kaplan–Meier analysis. After adjusting those significant variables in the multivariate Cox regression analysis, independent prognostic factors were discovered. Then an effective nomogram model for resected stage IV TSCC was constructed based on the training set.

2.5. Validation of the nomogram

The accuracy of the nomogram model was estimated by internal and external validation using the SEER training and validation sets. Bootstrap with 500 resamples and 5-fold cross-validation was performed. Calibration curves, plotting the predictive estimate of nomogram model against the actual observation, were created to evaluate the nomogram performance visually. The perfect predictions should fall on a 45-degree straight line passing through the origin, called the standard curve. The Harrell's concordance indices (C-index) were measured to quantify the predicting ability of model.[18] It ranged from 0.500 to 1.000, which meant from random chance to perfect discrimination.

2.6. Statistical analysis

All the data analysis was conducted by R statistical software version 3.4. We described categorical variables as frequencies and percentages. For categorical variables, we chose Pearson Chi-Squared test and Fisher exact tests to detect the statistical difference. Kaplan–Meier analysis was used to draw the survival curves. The log-rank test and Cox regression analysis were selected to sequentially distinguish independent risk factors for OS and CSS. All P values were 2-sided and $P < .05$ was considered significant.

3. Results

3.1. Baseline characteristics

As shown in Figure 1, according to the inclusion criteria and exclusion criteria, we finally included 1550 eligible patients with resected stage IV TSCC. They were randomly divided into 1085 patients in the training set and 465 patients in the validation set. Table 1 showed the baseline demographic and clinicopathological information of these patients. There were no significant differences between the training and validation sets for all the characteristics ($P > .05$). As a whole, most patients are male (1,132, 73.0%), married (900, 58.1%), and white (1,305, 84.2%), respectively. A majority of patients were between 18 and 53 years old (529, 34.1%). Most patients were diagnosed with T2 (526, 33.9%), N2 (1,264, 81.5%), M0 (1,501, 96.8%) for the AJCC TNM status. For these stage IV TSCC patients after surgery, a majority of them received radiotherapy (1322, 85.3%) as well as chemotherapy (998, 64.4%).

3.2. Univariate survival analysis

Kaplan–Meier analysis was used to evaluate univariate prognostic factors of OS and CSS in resected stage IV TSCC patients. As Table 2 showed, gender, age, marital status, race, tumor site, histological grade, AJCC T status, AJCC N status, AJCC M

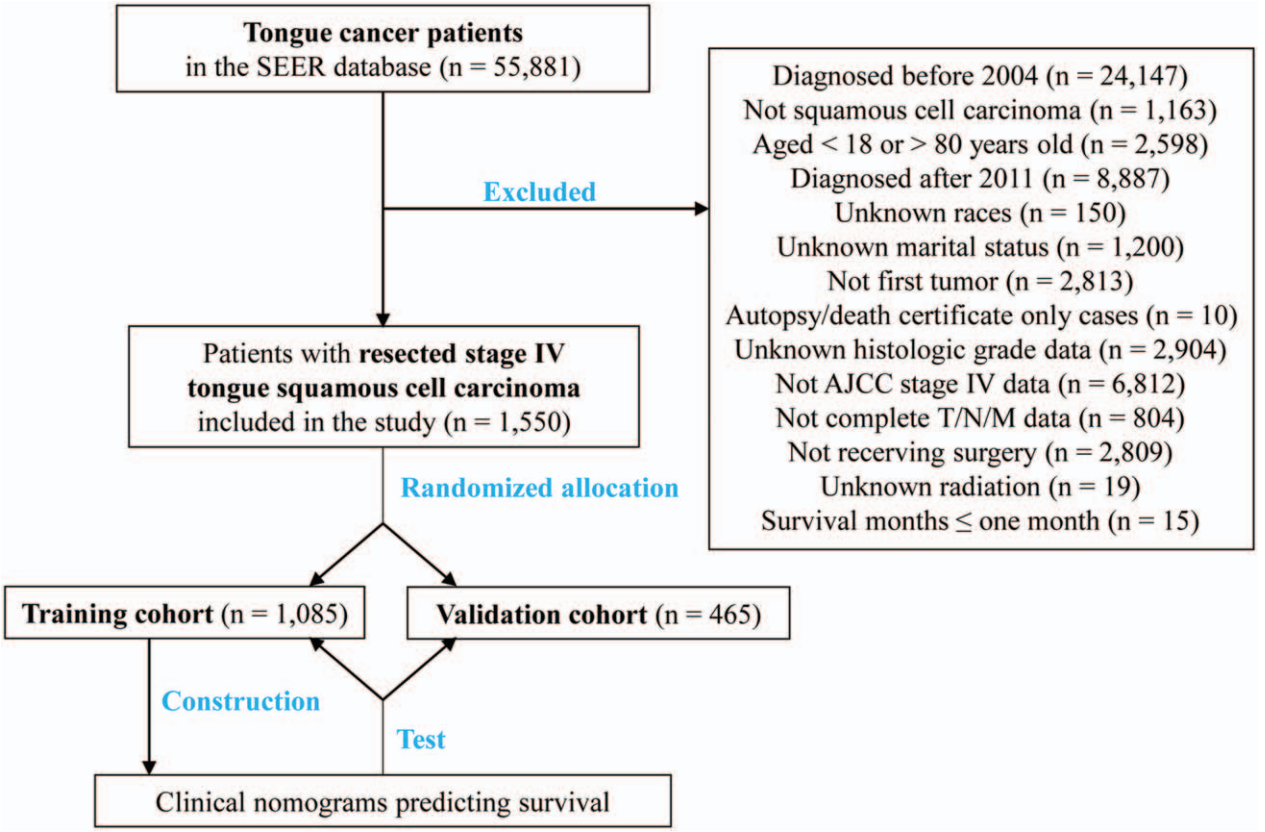

Figure 1. Flowchart of patient inclusion and exclusion. AJCC = American Joint Committee on Cancer, n = number, SEER = Surveillance, Epidemiology, and End Results.

status, radiotherapy and chemotherapy were found to be significantly associated with OS by univariate analysis. Similarly, all the above-mentioned variables were also found to be significantly associated with CSS. The 3-year and 5-year subgroup survival rates for OS and CSS were shown in Table 2. All the statistically significant variables were next analyzed by the forward method in multivariate analysis. Figure 2 displayed the Kaplan–Meier survival curves of OS and CSS for some representative variables. Kaplan–Meier survival curves for other variables were shown as Figure S1, http://links.lww.com/MD/D63.

3.3. Multivariate survival analysis

After adjustment in the multivariate Cox analysis, independent prognostic factors were discovered. As Table 3 showed, age group, marital status, race, tumor site, AJCC T status, AJCC N status, AJCC M status, and radiotherapy were found to be independent prognostic factors associated with OS ($P < .05$). Table 4 demonstrated that all these variables except marriage also acted as independent predictive factors associated with CSS ($P < .05$). When it came to therapies, patients receiving radiotherapy had better OS and CSS than those without radiotherapy (receiving vs not, HR [hazard ratio] 0.612, 95% CI [confidence interval] 0.496–0.756, $P < .001$ for OS; HR 0.610, 95% CI 0.485–0.768, $P < .001$ for CSS). To visualize the impact of radiotherapy on OS and CSS in different subgroups, forest plots were shown in Figure S2, http://links.lww.com/MD/D63. These predictive variables were subsequently included to construct the nomogram models for resected stage IV TSCC.

3.4. Construction of nomogram

Based on the training set, nomograms predicting 3-year and 5-year probabilities for OS and CSS were constructed using statistically significant variables from multivariate Cox analysis, as shown in Figure 3. Table S1, http://links.lww.com/MD/D63 displayed the numeric score of each variable for the 2 nomograms. The nomograms for both OS and CSS displayed that the AJCC N status contributed most to the survival outcomes, followed by T status and M status. Radiotherapy played an important role in the prognosis of OS and CSS. Each variable pointed to a score, and we could get a total score for an individual patient by summing up all scores. The predictive probabilities of OS and CSS at 3-year and 5-year were calculated by the total score according to the bottom scale. In general, the OS and CSS rates were better for patients with males, married status and tongue base. Patients with earlier AJCC T, N and N status survived better. Additionally, survival outcomes were superior for those receiving radiotherapy.

3.5. Validation of nomogram

Internal validation of the nomograms for OS and CSS were performed in the training sets. Similarly, external validation was performed in the validation sets. As Figure 4 showed, no matter in

Table 1

Baseline characteristic of included patients with resected stage IV tongue squamous cell carcinoma.

Characteristic	Total n = 1550	Training set n = 1085	Validation set n = 465	*P* value
Gender				.70
Male	1132 (73.0)	796 (73.4)	336 (72.3)	
Female	418 (27.0)	289 (26.6)	129 (27.7)	
Age group				.75
1st_quartile	264 (17.0)	180 (16.6)	84 (18.1)	
2nd_quartile	337 (21.7)	235 (21.7)	102 (21.9)	
3rd_quartile	420 (27.1)	302 (27.8)	118 (25.4)	
4th_quartile	529 (34.1)	368 (33.9)	161 (34.6)	
Marriage				.13
Married	900 (58.1)	616 (56.8)	284 (61.1)	
Unmarried	650 (41.9)	469 (43.2)	181 (38.9)	
Race				.48
White	1305 (84.2)	906 (83.5)	399 (85.8)	
Black	132 (8.5)	98 (9.0)	34 (7.3)	
Other	113 (7.3)	81 (7.5)	32 (6.9)	
Site				.64
Other sites	851 (54.9)	591 (54.5)	260 (55.9)	
Base of tongue	699 (45.1)	494 (45.5)	205 (44.1)	
Grade				.52
Grade I/II	886 (57.2)	614 (56.6)	272 (58.5)	
Grade III/IV	664 (42.8)	471 (43.4)	193 (41.5)	
AJCC-T				.77
T1	346 (22.3)	246 (22.7)	100 (21.5)	
T2	526 (33.9)	374 (34.5)	152 (32.7)	
T3	229 (14.8)	157 (14.5)	72 (15.5)	
T4	449 (29.0)	308 (28.4)	141 (30.3)	
AJCC-N				.44
N0	110 (7.1)	75 (6.9)	35 (7.5)	
N1	107 (6.9)	69 (6.4)	38 (8.2)	
N2	1264 (81.5)	889 (81.9)	375 (80.6)	
N3	69 (4.5)	52 (4.8)	17 (3.7)	
AJCC-M				.31
M0	1501 (96.8)	1047 (96.5)	454 (97.6)	
M1	49 (3.2)	38 (3.5)	11 (2.4)	
Chemotherapy				.83
Yes	998 (64.4)	701 (64.6)	297 (63.9)	
No/Unknown	552 (35.6)	384 (35.4)	168 (36.1)	
Radiotherapy				.65
Yes	1322 (85.3)	922 (85.0)	400 (86.0)	
No	228 (14.7)	163 (15.0)	65 (14.0)	

Notes: 1st quartile, 68 to 80 years old; 2nd quartile, 61 to 67 years old; 3rd quartile, 53 to 60 years old; 4th quartile, 18 to 52 years old.

AJCC = the American Joint Committee on Cancer, M = metastasis, N = node, n = number, T = tumor.

the internal or external validation, all the calibration curves moved towards the standard curves. It displayed a good agreement between the predicted and actual values of 3-year and 5-year probabilities for OS and CSS. In detail, the C-index for the nomogram predicting OS was 0.713 (95% CI, 0.691–0.734) corrected as 0.705 during internal validation. While in external validation, the C-index predicting OS was 0.664 (95% CI, 0.630–0.700) corrected as 0.664.

Likewise, when it came to CSS, the C-index was 0.715 (95% CI, 0.691–0.738) corrected as 0.708 in internal validation. And in external validation, the C-index for CSS was 0.663 (95% CI, 0.662–0.702) corrected as 0.664. It demonstrated that the nomogram models were generally accurate after validation.

To compare the predictive ability of the established nomograms with that of T, N, M status, we also performed both internal and external validation of T, N, M status for OS and CSS, shown in Supplemental Table S2, http://links.lww.com/MD/D63. Consequently, we found that all the C-indices as well as the corrected C-indices of T, N, M status were less than 0.650, which meant that it was not good for T, N, M status to predict survival prognosis.

4. Discussion

Tongue cancer has caused great harm all over the world. In 2017, there were 16,400 estimated new cases diagnosed with tongue cancer and 2400 estimated deaths caused by it in the United States.[19] For stage IV tongue cancer, surgery is necessary and a combination of radiotherapy is recommended for most patients. However, the current treatment strategies of stage IV advanced TSCC are decided mainly according to the AJCC TNM staging system, but the TNM staging system can not accurately predict the prognosis of advanced TSCC patients especially for those receiving surgical treatment. As rare studies developed clinical nomograms to predict survival of resected stage IV TSCC patients, here we constructed and validated nomogram models for these patients.

In this study, we took advantage of more than 1500 cases with stage IV TSCC after surgery from the SEER database. Then we selected the independent prognostic factors based on the Kaplan–Meier analysis and multivariate Cox regression analysis to visually construct OS and CSS nomograms. Internal and external validation with bootstrap resampling and cross-validation method were performed, and we used calibration curves and C-indices to estimate the predictive accuracy of 3-year and 5-year probabilities for OS and CSS. Consequently, almost all the C-indices were nearly 0.700, and the calibration curves performed well, which verified the effectiveness of clinical nomograms of stage IV TSCC patients after surgery.

Nomograms have been extensively used in cancer patients, and exhibit more accuracies of prognosis than the conventional staging system. Adibi et al developed a nomogram to predict the individualized risk 3-year and 5-year lung metastasis-free survival for patients who underwent nephrectomy for localized advanced renal cell carcinoma.[20] In order to predict the survival of adenocarcinoma of the appendix, Xie et al even constructed superior derived nomogram stages compared with traditional AJCC TNM staging system.[21] When it came to TSCC patients, Li et al developed nomograms to estimate long-term overall survival and cancer-specific survival based on 12,674 patients, which provided more personalized and reliable prognostic information, and improved clinical decision-making.[22] Compared with early stage I/II TSCC patients, the clinical diagnosis and treatment strategies of advanced stage III/IV TSCC patients are more complex, and the corresponding prognosis is more difficult to predict. So we explored the application of nomogram models on the prediction of survival outcomes for resected stage IV TSCC patients.

Here, we found that some demographic and clinicopathological characteristics acted as independent prognostic factors for OS and CSS, which is in accordance with previous studies.[23] Advanced age and black race were found to be associated with poor survival in patients with head and neck squamous cell carcinoma (HNSCC), and this effect persisted even after adjustment.[24] Another study emphasized the racial differences

Table 2

Univariate analysis for overall survival and cancer-specific survival.

Characteristic	Overall survival				Cancer-specific survival			
	3-year	5-year	Log Rank χ^2 test	*P* value	3-year	5-year	Log Rank χ^2 test	*P* value
Gender								
Female	46.0%	39.8%	7.7	.005	50.3%	45.7%	9.1	.003
Male	56.6%	49.9%			60.6%	56.4%		
Age group								
1st_quartile	42.4%	32.0%	37.1	<.001	48.0%	39.0%	26.5	<.001
2nd_quartile	50.0%	41.3%			55.7%	50.1%		
3rd_quartile	59.7%	54.9%			63.4%	61.2%		
4th_quartile	57.0%	52.1%			59.6%	56.2%		
Marriage								
Married	58.7%	54.5%	25.5	<.001	61.7%	58.5%	13.0	<.001
Unmarried	47.3%	37.7%			52.8%	46.7%		
Race								
Black	37.1%	32.1%	12.6	.002	40.6%	37.7%	12.7	.002
Other	42.8%	39.7%			46.8%	45.2%		
White	56.6%	49.5%			60.7%	55.9%		
Site								
Base of tongue	68.0%	60.4%	73.4	<.001	72.2%	68.0%	81.2	<.001
Other sites	42.0%	36.3%			45.9%	41.4%		
Grade								
Grade I/II	47.8%	41.4%	17.9	<.001	52.1%	47.6%	20.2	<.001
Grade III/IV	61.6%	54.9%			65.5%	61.3%		
AJCC-T								
T1	73.7%	66.8%	109.0	<.001	75.1%	70.8%	94.0	<.001
T2	61.5%	53.3%			65.0%	60.3%		
T3	34.3%	29.0%			38.9%	35.4%		
T4	38.5%	33.5%			44.6%	40.2%		
AJCC-N								
N0	61.8%	54.0%	7.7	.05	70.5%	63.6%	11.5	.009
N1	42.0%	37.2%			44.0%	40.8%		
N2	54.1%	47.2%			57.9%	53.5%		
N3	53.8%	51.9%			59.1%	57.0%		
AJCC-M								
M0	54.9%	48.3%	29.7	<.001	59.0%	54.6%	30.8	<.001
M1	23.0%	17.2%			27.1%	23.7%		
Chemotherapy								
No/Unknown	50.1%	40.0%	14.6	<.001	54.4%	47.8%	10.1	.001
Yes	55.9%	51.3%			59.8%	56.7%		
Radiotherapy								
No	37.8%	30.1%	35.6	<.001	43.8%	38.6%	29.2	<.001
Yes	56.7%	50.3%			60.3%	56.1%		

Notes: 1st quartile, 68 to 80 years old; 2nd quartile, 61 to 67 years old; 3rd quartile, 53 to 60 years old; 4th quartile, 18 to 52 years old.
AJCC = the American Joint Committee on Cancer, M = metastasis, N = node, T = tumor.

in male patients with HNSCC, and found black patients have a high incidence of aggressive and advanced HNSCC, leading to poorer survival in black.[25] In our studies focusing on stage IV TSCC after surgery, the impact of these demographic variables on survival outcomes was still statistically significant. It has been demonstrated that marital status acts as an independent prognostic factor in several cancers, such as breast cancer and gastric cancer.[26,27] Our previous study also found that married patients had better OS and CSS compared to other unmarried groups in TSCC, and subgroup survival analysis confirmed it.[28] Our study also proved the important role of marriage in the overall prognosis of resected stage IV TSCC. As for clinicopathological characteristics, both OS and CSS became worse along with more advanced AJCC T status, N status and M status, which was consistent with other studies.[22,24,29] Surgery is an essential routine treatment for advanced TSCC patients, and postoperative radiotherapy or chemoradiotherapy should also be considered.[3] As for treatment, radiotherapy and chemotherapy were independent prognostic factors for prognosis of HNSCC including TSCC.[30,31] However, in our study, we found that only the radiotherapy improved OS and CSS outcomes, and radiotherapy had a great impact on prognosis even after subgroup adjustment.

Compared with the established nomograms in the previous study, our nomograms show more advantages.[22] In addition to the common demographic and clinicopathological factors, we also consider the variables of tumor site and chemotherapy. The tongue is mainly divided into 2 parts, the oral tongue and the base of tongue. These 2 parts have different embryological origins, and the resulting different tumor classifications, the oral cavity cancer

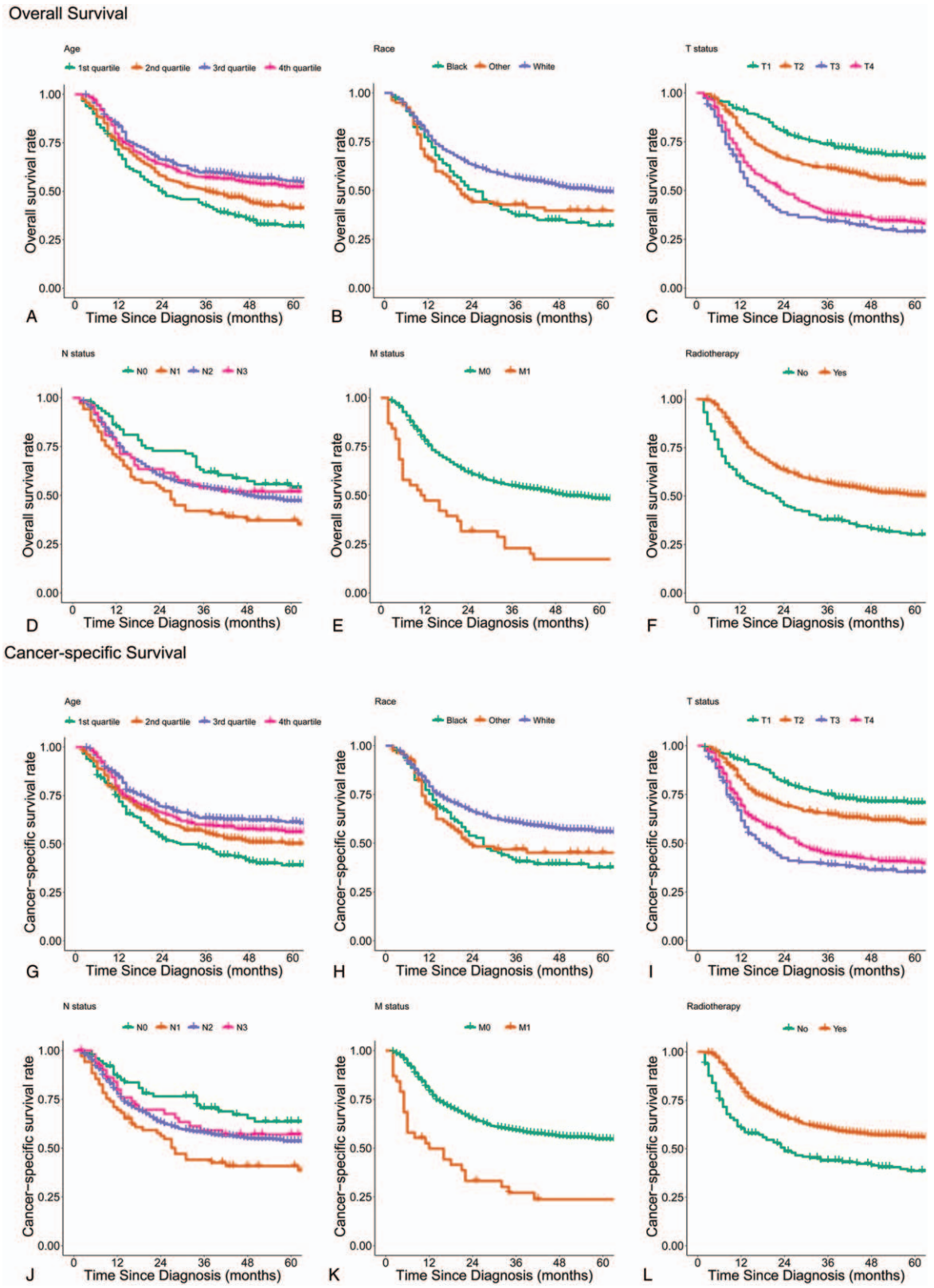

Figure 2. Kaplan–Meier curves of representative variables for OS and CSS. Notes: (A) age, (B) race, (C) T status, (D) N status, (E) M status, and (F) radiotherapy for OS; (G) age, (H) race, (I) T status, (J) N status, (K) M status, and (L) radiotherapy for CSS; 1st quartile, 68 to 80 years old; 2nd quartile, 61 to 67 years old; 3rd quartile, 53 to 60 years old; 4th quartile, 18 to 52 years old; the x-axis represents survival times, and the y-axis represents survival rates. CSS = cancer-specific survival, OS = overall survival, SEER = the Surveillance, Epidemiology and End Results.

Table 3

Multivariate Cox analysis for overall survival.

Characteristics	Coefficient	HR	95% CI	*P* value
Age group				
1st_quartile	Reference			
2nd_quartile	−0.261	0.770	0.604–0.982	.035
3rd_quartile	−0.626	0.535	0.419–0.682	<.001
4th_quartile	−0.673	0.510	0.404–0.645	<.001
Marriage				
Married	Reference			
Unmarried	0.207	1.230	1.041–1.453	.015
Race				
Black	Reference			
Other	0.019	1.020	0.697–1.493	.92
White	−0.275	0.760	0.585–0.987	.039
Site				
Base of tongue	Reference			
Other sites	0.622	1.863	1.560–2.225	<.001
AJCC-T				
T1	Reference			
T2	0.451	1.570	1.212–2.034	<.001
T3	1.071	2.917	2.191–3.883	<.001
T4	1.286	3.617	2.742–4.771	<.001
AJCC-N				
N0	Reference			
N1	0.886	2.424	1.563–3.760	<.001
N2	1.272	3.568	2.462–5.172	<.001
N3	1.375	3.956	2.287–6.840	<.001
AJCC-M				
M0	Reference			
M1	0.996	2.706	1.876–3.904	<.001
Radiotherapy				
No	Reference			
Yes	−0.491	0.612	0.496–0.756	<.001

Notes: 1st quartile, 68 to 80 years old; 2nd quartile, 61 to 67 years old; 3rd quartile, 53 to 60 years old; 4th quartile, 18 to 52 years old.
AJCC = the American Joint Committee on Cancer, CI = confidence interval, HR = hazard ratio, M = metastasis, N = node, T = tumor.

Table 4

Multivariate Cox analysis for cancer-specific survival.

Characteristics	Coefficient	HR	95% CI	*P* value
Age group				
1st_quartile	Reference			
2nd_quartile	−0.340	0.712	0.545–0.930	.013
3rd_quartile	−0.637	0.529	0.405–0.691	<.001
4th_quartile	−0.638	0.528	0.411–0.680	<.001
Race				
Black	Reference			
Other	−0.046	0.955	0.637–1.431	.82
White	−0.330	0.719	0.543–0.951	.021
Site				
Base of tongue	Reference			
Other sites	0.780	2.181	1.791–2.656	<.001
AJCC-T				
T1	Reference			
T2	0.406	1.501	1.129–1.995	.005
T3	1.075	2.929	2.149–3.992	<.001
T4	1.259	3.523	2.608–4.760	<.001
AJCC-N				
N0	Reference			
N1	1.186	3.274	2.001–5.358	<.001
N2	1.463	4.318	2.809–6.637	<.001
N3	1.648	5.196	2.817–9.584	<.001
AJCC-M				
M0	Reference			
M1	1.089	2.970	2.020–4.367	<.001
Radiotherapy				
No	Reference			
Yes	−0.494	0.610	0.485–0.768	<.001

Notes: 1st quartile, 68 to 80 years old; 2nd quartile, 61 to 67 years old; 3rd quartile, 53 to 60 years old; 4th quartile, 18 to 52 years old.
AJCC = the American Joint Committee on Cancer, CI = confidence interval, HR = hazard ratio, M = metastasis, N = node, T = tumor.

and oropharyngeal cancer. So the variable of tumor site should be taken into consideration. Besides surgery and radiotherapy, chemotherapy is another important prognostic factor for TSCC patients, which is just updated by the SEER database in recent years.[30] More importantly, we focus on the stage IV TSCC patients after surgery in this study. It is a particular group that shares diverse patterns from the early stage TSCC patients. Therefore, it is necessary for us to build specific nomograms for these patients.

The established nomograms are easily applicable to clinical practice because of visibility and utility. For 1 patient, each variable corresponds to a score, and the sum of all scores maps a linear predictor value, as well as the predictive 3-year and 5-year probabilities for OS and CSS. When we come across a new patient with resected advanced stage IV TSCC, we can predict his prognosis based on the demographic and clinicopathological information. For instance, the 62-year-old black patient was diagnosed with T3N1M0. The tumor located in other tongue sites and he was married. She received both surgery and radiotherapy. In line with our nomograms, the predicted 3-year and 5-year OS rates are 40% and 35% respectively, and 3-year and 5-year CSS rates are 35% and 30% respectively.

The nomograms in our study are significant for decision-making by patients. Modern medical models are increasingly emphasizing the patient's role during the doctor-patient communication.[32] However, until now most clinical decisions are still led by doctors. Medical terms have become an invisible barrier between doctors and patients. Based on our study, the nomogram provides patients a visualizing tool to evaluate outcomes of different clinical decisions, which could improve clinical decision-making by patients. Furthermore, the variables utilized in our nomograms are easy to understand for patients in clinical practice. So, the application of nomograms helps optimize the patient-physician interaction and promote patient-centered care.

This is an analysis based on a large population of about 1550 patients with a follow-up period of about 10 years, which diminishes biases and increases the reliability of the results. However, there are several potential limitations. Firstly, the SEER database lacks critical information, such as detailed chemotherapy, comorbidities, and complications.[33] There are important missing variables, such as p16 status and tobacco exposure. These data may affect survival outcomes. Secondly, this is a retrospective study instead of a prospective study. It inevitably brings about selection bias. So, more cohort studies are required to further verify the results. Thirdly, there are small sample sizes of patients in some subgroups, such as 35 patients with AJCC N1 status and 11 patients with AJCC M1 status in the validation set. Fourthly, when we perform OS

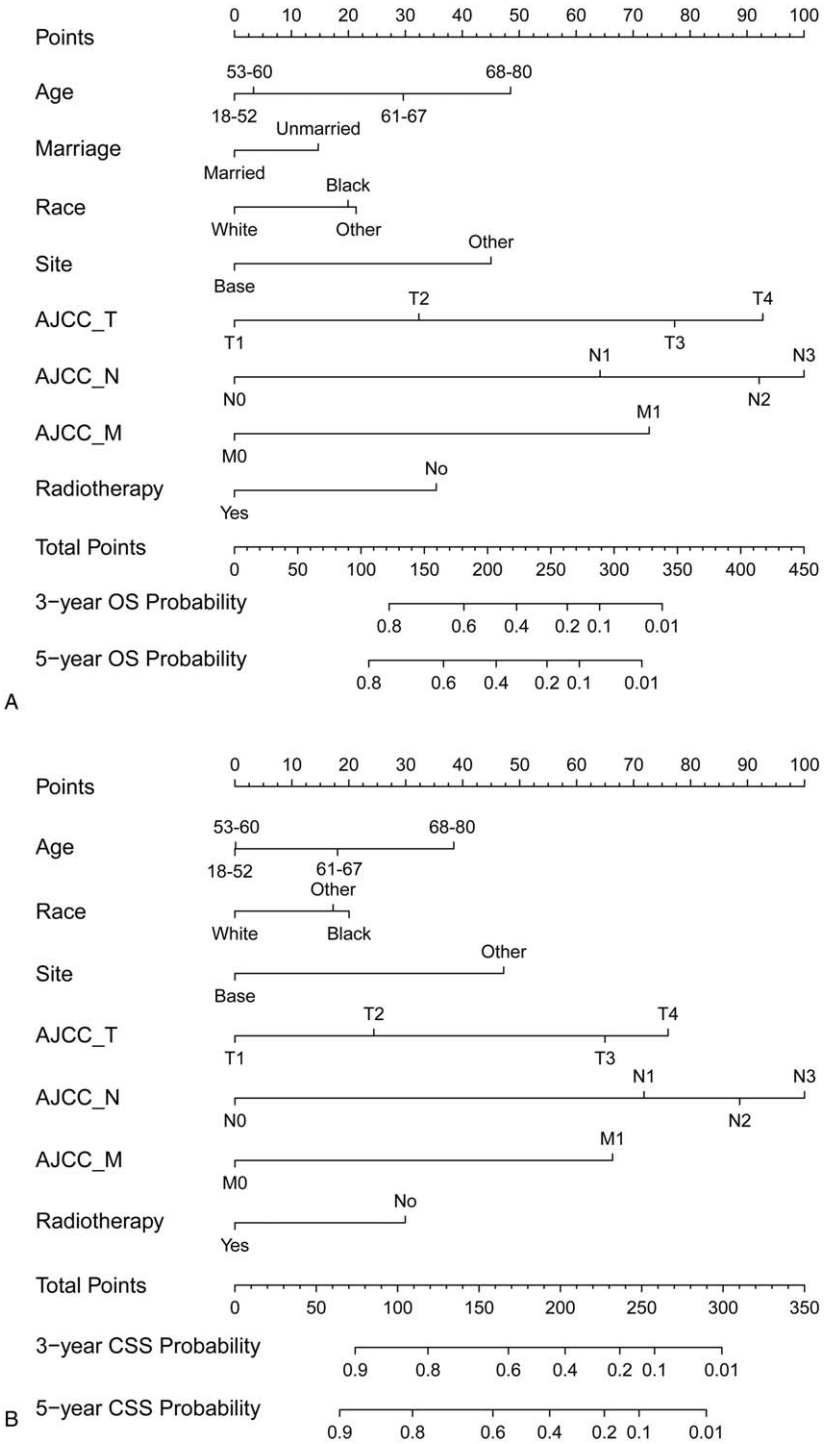

Figure 3. Nomograms predicting 3-year and 5-year probabilities for OS and CSS in patients with resected stage IV TSCC. AJCC = the American Joint Committee on Cancer, CSS = cancer-specific survival, OS = overall survival, TSCC = tongue squamous cell carcinoma.

analysis, death from other causes unrelated to cancer may differ among subgroups. It may affect the stability of the nomogram model for OS. Competing risk analysis is a better statistical method to reduce the impact of death from other causes, once all the death cause data are available from the SEER database.[34]

5. Conclusion

In conclusion, we constructed and validated clinical nomogram models to predict OS and CSS in patients with stage IV TSCC after surgery based on the SEER database. It exhibited good accuracy and effectiveness to identify those with high risks of mortality. The nomogram models act as useful tools for clinicians

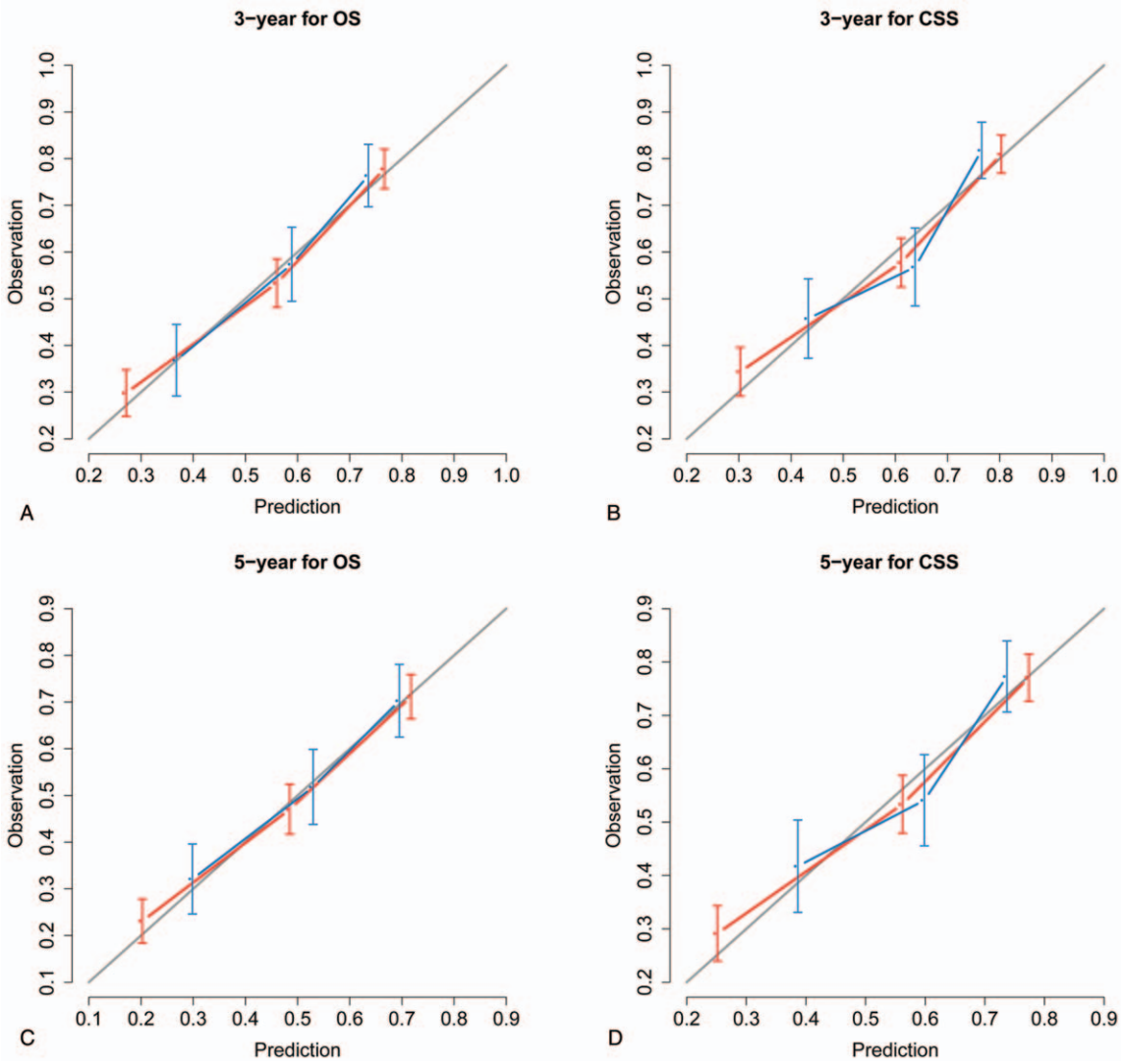

Figure 4. Calibration curves for 3-year and 5-year prediction of OS and CSS. Notes: (A) 3-year and (C) 5-year for OS; (B) 3-year and (D) 5-year for CSS; predicted survival rates are on the x-axis, and actual survival rates are on the y-axis; the red line is the calibration curve in the training set, the blue line is the calibration curve in the validation set, and the gray line is the standard curve. CSS = cancer-specific survival, OS = overall survival.

to evaluate survival outcomes and to choose appropriate treatment strategies.

Author contributions

SW contributed to study design, data analyses, preparation of figures and writing the manuscript. CMH contributed to study design, data analyses, preparation of tables, and writing the manuscript. ZSH contributed to data analyses, preparation of figures, and writing the manuscript. CHM contributed to data analyses, preparation of figures, and tables. YSH contributed to manuscript revision. QZT contributed to study design, data analyses, writing, and revising the manuscript. All authors reviewed and agreed to the manuscript.

Conceptualization: Wei Sun, Minghua Cheng, Huimin Chen, Zeting Qiu.
Data curation: Wei Sun, Zeting Qiu.
Formal analysis: Wei Sun, Zeting Qiu.
Funding acquisition: Wei Sun, Minghua Cheng.
Investigation: Wei Sun, Minghua Cheng, Shaohui Yang.
Methodology: Wei Sun, Minghua Cheng, Shaohui Zhuang, Shaohui Yang, Zeting Qiu.
Project administration: Minghua Cheng, Shaohui Zhuang, Shaohui Yang, Zeting Qiu.
Resources: Minghua Cheng, Shaohui Zhuang, Shaohui Yang, Zeting Qiu.
Software: Minghua Cheng, Shaohui Yang, Zeting Qiu.
Supervision: Shaohui Zhuang, Shaohui Yang, Zeting Qiu.
Validation: Shaohui Zhuang, Shaohui Yang, Zeting Qiu.
Visualization: Zeting Qiu.
Writing – original draft: Wei Sun, Minghua Cheng, Zeting Qiu.
Writing – review & editing: Huimin Chen, Zeting Qiu.
Zeting Qiu orcid: 0000-0003-0182-2244.

References

[1] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.

[2] Cuccurullo V, Mansi L. AJCC cancer staging handbook: from the ajcc cancer staging manual (7th edition). Eur J Nuclear Med Mol Imag 2011;38:408–1408.

[3] Sessions DG, Spector GJ, Lenox J, et al. Analysis of treatment results for oral tongue cancer. Laryngoscope 2002;112:616–25.

[4] Fein DA, Mendenhall WM, Parsons JT, et al. Carcinoma of the oral tongue: a comparison of results and complications of treatment with radiotherapy and/or surgery. Head Neck 1994;16:358–65.

[5] Sessions DG, Lenox J, Spector GJ, et al. Analysis of treatment results for base of tongue cancer. Laryngoscope 2003;113:1252–61.

[6] Nyman J, Mercke C, Lindström J. Prognostic factors for local control and survival of cancer of the oral tongue. A retrospective analysis of 230 cases in western Sweden. Acta Oncologica 1993;32:667–73.

[7] Kantola S, Parikka M, Jokinen K, et al. Prognostic factors in tongue cancer - relative importance of demographic, clinical and histopathological factors. Br J Cancer 2000;83:614–9.

[8] Aksu G, Karadeniz A, Saynak M, et al. Treatment results and prognostic factors in oral tongue cancer: analysis of 80 patients. Int J Oral Maxillofac Surg 2006;35:506–13.

[9] Hirabayashi S, Kosugi S, Isobe Y, et al. Development and external validation of a nomogram for overall survival after curative resection in serosa-negative, locally advanced gastric cancer. Ann Oncol 2014;25: 1179–84.

[10] Liang W, Zhang L, Jiang G, et al. Development and validation of a nomogram for predicting survival in patients with resected non-small-cell lung cancer. J Clin Oncol Offic J Am Soc Clin Oncol 2015;33:861–9.

[11] Kim JH, Kim HS, Seo WY, et al. External validation of nomogram for the prediction of recurrence after curative resection in early gastric cancer. Ann Oncol 2012;23:361.

[12] Keam B, Im SA, Park S, et al. P310 Nomogram predicting clinical outcomes in breast cancer patients treated with neoadjuvant chemotherapy. J Cancer Res Clin Oncol 2011;137:1301–8.

[13] Kawai K, Ishihara S, Yamaguchi H, et al. Nomogram prediction of metachronous colorectal neoplasms in patients with colorectal cancer. Ann Surg 2014;261:926–32.

[14] Paris PL, Weinberg V, Albo G, et al. A group of genome-based biomarkers that add to a Kattan nomogram for predicting progression in men with high-risk prostate cancer. Clin Cancer Res 2010;16:195–202.

[15] Shen L, Van SJ, Wang J, et al. Validation of a rectal cancer outcome prediction model with a cohort of Chinese patients. Oncotarget 2011;6:38327–35.

[16] Hayat MJ, Howlader N, Reichman ME, et al. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. Oncologist 2007;12:20–37.

[17] Hankey BF, Ries LA, Edwards BK. The surveillance, epidemiology, and end results program: a national resource. Cancer Epidemiol Biomark Prevent 1999;8:1117–21.

[18] Gerds TA, Kattan MW, Schumacher M, et al. Estimating a time-dependent concordance index for survival prediction models with covariate dependent censoring. Stat Med 2013;32:2173–84.

[19] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7–30.

[20] Adibi M, Kenney PA, Thomas AZ, et al. Prediction of pulmonary metastasis in renal cell carcinoma patients with indeterminate pulmonary nodules. Eur Urol 2015;69:352–60.

[21] Xie X, Zhou Z, Song Y, et al. The management and prognostic prediction of adenocarcinoma of appendix. Sci Rep 2016;6:39027.

[22] Li Y, Zhao Z, Liu X, et al. Nomograms to estimate long-term overall survival and tongue cancer-specific survival of patients with tongue squamous cell carcinoma. Cancer Med 2017.

[23] Sun W, Cao M, Huang W, et al. Comparative survival outcomes of different treatments for oral tongue squamous cell carcinoma in elderly patients aged 65 years and older: a propensity score matched analysis. Int J Clin Exp Med 2019;12:2549–58.

[24] Ju J, Wang J, Ma C, et al. Nomograms predicting long-term overall survival and cancer-specific survival in head and neck squamous cell carcinoma patients. Oncotarget 2016;7:51059–68.

[25] Peterson CE, Khosla S, Chen LF, et al. Racial differences in head and neck squamous cell carcinomas among non-Hispanic black and white males identified through the National Cancer Database (1998-2012). J Cancer Res Clin Oncol 2016;142:1715.

[26] Shi RL, Chen Q, Yang Z, et al. Marital status independently predicts gastric cancer survival after surgical resection–an analysis of the SEER database. Oncotarget 2016;7:13228–35.

[27] Osborne C, Ostir GV, Du X, et al. The influence of marital status on the stage at diagnosis, treatment, and survival of older women with breast cancer. Breast Cancer Res Treat 2005;93:41–7.

[28] Sun W, Qiu Z, Tan W, et al. The influence of marital status on survival in patients with oral tongue squamous cell carcinoma. Oncotarget 2017;8:82092–102.

[29] Tsai MS, Lai CH, Lee CP, et al. Mortality in tongue cancer patients treated by curative surgery: a retrospective cohort study from CGRD. PeerJ 2016;4:e2794.

[30] Spiotto MT, Koshy M. Impact of fraction size on locally advanced oropharyngeal and nasopharyngeal cancers treated with chemoradiation. Oral Oncol 2017;68:27.

[31] Shaikh T, Handorf EA, Murphy CT, et al. The impact of radiation treatment time on survival in patients with head and neck cancer. Int J Radiat Oncol Biol Phys 2016;96:967.

[32] Sun J, Liu S, Liu Q, et al. Impact of adverse media reporting on public perceptions of the doctor-patient relationship in China: an analysis with propensity score matching method. BMJ Open 2018;8:e022455.

[33] Sun W, Cheng M, Zhuang S, et al. Impact of insurance status on stage, treatment, and survival in patients with colorectal cancer: a population-based analysis. Medical Sci Monit 2019;25:2397–418.

[34] Sun W, Cheng M, Zhou H, et al. Nomogram predicting cause-specific mortality in nonmetastatic male breast cancer: a competing risk analysis. J Cancer 2019;10:583–93.