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Original Article

A prognostic scoring model based on the HPV status of oropharyngeal carcinoma patients treated with postoperative radiotherapy in China

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Abstract: Objectives: Prognostic models that can predict prognosis and guide postoperative radiotherapy (PRT) and that are based on the human papillomavirus (HPV) status of patients with oropharyngeal carcinoma (OPSCC) in China are rare. Methods: Survival was analyzed by performing a Kaplan-Meier analysis and log-rank test. A Cox regression analysis was performed for the multivariate analyses. A prognostic scoring model was constructed according to the regression coefficient obtained from the Cox regression model. Results: A prognostic model that included gender, clinical stage, histologic stage, metastasis, and HPV status was created and used to divide patients into high-risk (PI ≥ -0.008) and low-risk (PI < -0.008) groups. The results showed that the patients who received PRT had a longer overall survival time than those who did not receive PRT (47.31 months vs. 28.31 months). Furthermore, the patients who received PRT in the high-risk group had a longer survival time when the survival was greater than 20 months (P = 0.024), and PRT may indicate a worse prognosis in the low-risk group (P = 0.071). Conclusion: This model will contribute to the formulation of individualized treatment programs for OPSCC patients. PRT should be administered to high-risk patients.

Keywords: Oropharyngeal squamous cell carcinoma, human papillomavirus, prognostic model, postoperative radiotherapy

Introduction

Human papillomavirus (HPV) infection is a major risk factor responsible for a large subset of oropharyngeal squamous cell carcinomas (OPSCCs). HPV infection has been observed in 20% to 90% of OPSCC patients in the United States and Europe. HPV-associated OPSCC was identified as a solid tumor distinct from HPV-negative OPSCC due to its unique epidemiological characteristics, biologic behaviors, and clinical features [1-4]. However, the prevalence of HPV in OPSCC ranges only from 0%-34% in Asia [5-9].

The prognosis of OPSCC depends on the tumor stage and HPV status [10], and HPV status has been shown to be an independent prognostic factor [11, 12]. In particular, in all stages, nonsmoking patients with HPV-associated OPSCC have the best prognosis, while smoking patients with HPV-associated OPSCC have a moderate risk of tumor progression, invasion, and metastasis and smoking patients with HPV-negative OPSCC have the highest risk [13]. Gender, age, TNM stage and smoking status also likely play important roles in the development of OPSCC [14, 15]. Several studies have established prognostic models of OPSCC based on clinical and laboratory indices [16, 17]. Unsurprisingly, combining the most important prognostic factors, including the HPV status and TNM stage, in a multivariate model results in a more comprehensive and highly predictive model than a univariate survival analysis.

Although several prognostic models have been validated in OPSCC patients in specific regions, due to different racial and epidemiological characteristics, applying only one prognostic model to all OPSCC patients to predict survival

is not practical [16, 17]. The current prognostic models for OPSCC, particularly those for HPV-associated OPSCC, are all based on data from Europe and the United States. Epidemiological investigations have shown that low HPV detection rates and tobacco use are common among Chinese OPSCC HPV-positive patients [9, 18, 19]. However, a prognostic model based on clinicopathologic characteristics and HPV status in China has not been published to date. Furthermore, the therapeutic strategies used differ between western countries and China. In China, early-stage OPSCC is typically managed with surgery with or without adjuvant radiotherapy (RT), and advanced-stage OPSCC is treated with RT or chemoradiotherapy. In western countries, early-stage and HPV-related OPSCC have been treated with curative RT or chemoradiotherapy alone for many years [16, 20]. HPV-associated OPSCC patients are more sensitive to RT and chemotherapy and typically exhibit a lower recurrence rate, longer survival time, and better prognosis than those with HPV-negative OPSCC [11, 21-23]. However, the risks of RT complications that can have a significant impact on the patient's quality of life, such as xerostomia, osteoradionecrosis of the mandible, trismus, ischemic stroke and dysphagia, may be underestimated [13, 24, 25].

Therefore, a multi-factorial, comprehensive prognostic model for OPSCC may have a significant impact on predicting prognosis and individualizing postoperative RT protocols in Chinese patients with OPSCC.

Methods

Clinical specimens and patient information

In total, 188 primary OPSCC patients diagnosed between January 2008 and April 2014 at the Department of Oral Pathology of the Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine were enrolled, and all postoperative tumor specimens were collected. The primary location of the tumor was determined according to the clinical diagnosis, imaging results, and pathologic examination.

Prognostic factors and HPV testing

The demographic data, including sex, age, diagnosis, and tumor site, were obtained from the medical records and operative and pathology reports. The tumor stage was assigned based on either the clinical or pathologic staging according to the 2005 WHO TNM (Tumor, Nodal, Metastasis) Classification. All patients were followed prospectively by a head and neck surgeon from the date of the original diagnosis. The clinical status of the patients including information about the surgery, chemotherapy and RT, were recorded at each follow-up visit, which occurred at approximately 3-month intervals from the time of diagnosis.

The following prognostic factors were recorded at baseline: age, gender, histologic grade, T stage, N stage, smoking status, alcohol use, site of the primary tumor and HPV16/18 status, which was defined as both HPV DNA PCR and p16INK4A positivity (positive cells in ≥ 70% of the tumor).

Radiotherapy

All patients received primary tumor resection. The patients with advanced OPSCC underwent cervical lymph node dissection and postoperative RT (PRT) at a total dose of 50-60 Gy (2 Gy per fraction) depending on whether more than 2 regional lymph nodes, extracapsular spread, or positive margins on microscopic mucosal resection were observed.

Statistical analysis

All statistical analyses were performed using SPSS 22.0 (SPSS, Chicago, IL). All figures were created using GraphPad Prism 6.0 (GraphPad Software Inc., La Jolla, CA). The endpoint of this study was overall survival (OS), which was defined as the time between the date of the first OPSCC surgery and the date of death. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. A Cox regression analysis was performed for the multivariate analyses. A prognostic scoring model was constructed according to the regression coefficient obtained from the Cox regression model. As the expression of the COX model is $h(t) = h_0(t) \exp(\beta_1X_1 + \beta_2X_2 + ... + \beta_3X_3)$, we regarded $(\beta_1X_1 + \beta_2X_2 + ... + \beta_3X_3)$ as the prognostic index (PI). The area under the curve (AUC) of the receiver operating characteristics (ROC) curve was used to measure the prognostic utility of the PI and the Youden index was used to select the most

Table 1. Distribution of clinicopathologic features in 188 primary OPSCC cases

Characteristic	Overall	Percentage (%)
Age		
< 60	113	60.11
≥ 60	75	39.89
Gender		
Male	168	89.36
Female	20	10.64
Tumor Site		
Tonsil	10	5.32
Soft palate	50	26.60
Base of tongue	74	39.36
Pharyngeal wall	54	28.72
Smoking		
Non-smoker	62	32.98
Smoker	116	61.70
Unknown	10	5.32
Alcohol Consumption		
Non-drinker	89	47.34
Drinker	89	47.34
Unknown	10	5.32
Clinical Stage		
I-II	96	51.06
III-IV	92	48.94
Histologic Grade		
I	19	10.11
II	131	69.68
III	38	20.21
T Stage		
I-II	167	88.83
III-IV	21	11.17
Nodal Stage		
Negative	103	54.79
Positive	85	45.21
Metastasis		
Negative	184	97.87
Positive	4	2.13
Chemotherapy		
No	149	79.26
Received	39	20.74
Radiation		
No	88	46.81
Received	100	53.19

appropriate PI cutoff point, which was used to divide the patients into the high-risk and low-risk groups. To minimize bias and approximate a randomized trial, propensity score-based methods were used to balance the characteristics (chemotherapy treatment) between the RT-treated and non-treated patients and evaluate the effect of RT treatment on OS [26]. Finally, we included 177 of the initial 188 patients in this analysis. All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

As shown in **Table 1**, of the 188 OPSCC patients, 60.11% (113/188) of the patients were younger than 60 years, and 39.89% (75/188) of the patients were 60 years or older. In total, 89.36% (168/188) of the patients were men, and 10.64% (20/188) of the patients were women. The tumors were rarely located on the tonsils (5.32%, 10/188) and were mainly located at the base of the tongue (39.36%, 74/188), the pharyngeal wall (28.72%, 54/188), and the soft palate (26.60%, 50/188). Information regarding the smoking and drinking habits were missing in 10 of the patients; therefore, based on data from 178 OPSCC patients, smokers accounted for the majority of patients (61.70%, 116/188), and drinkers and non-drinkers each accounted for 47% (89/188). In total, 51.06% (96/188) of the OPSCC cases were in the early clinical stages (I-II), and 48.94% (92/188) of the patients were in the late clinical stages (III-IV). According to the pathologic examination, 10.11% (19/188) of the cases were classified as histologic grade I, 69.68% (131/188) of the cases were classified as histologic grade II, and 20.21% (38/188) of the cases were classified as histologic grade III. Most patients (88.83%, 167/188) were categorized as TNM stages T1-T2, 45.21% (85/188) of the cases had cervical lymph node involvement and most patients (97.87%, 184/188) did not have metastasis. In addition, only 20.74% (39/188) of the patients received chemotherapy; however, 53.19% (100/188) of the patients received PRT.

HPV status

According to the HPV16/18 E6/E7 PCR analysis, only 11.70% (22/188) of the patients were infected with HPV16, whereas no patients with HPV18 infection were identified. In addition, only 21.28% (40/188) of the patients were

Table 2. Relationship between the HPV and p16INK4A status in 188 primary OPSCC cases

	p16INK4A		Overall	Statistically significant
	Negative	Positive		
HPV				
Negative	148	18	166	< 0.001
Positive	0	22	22	

HPV, human papillomavirus; OPSCC, oropharyngeal squamous cell carcinoma.

Table 3. Kaplan-Meier and Cox regression analyses of 188 primary OPSCC cases

Variable	Kaplan-Meier	Cox Regression		
	p-value	*p*-value	Hazard Ratio	95% Confidential Interval
Age	0.833			
Gender	0.003	0.081	0.281	0.067-1.171
Tumor Site	0.378			
Smoking	0.048			
Alcohol	0.499			
Clinical Stage	0.003	0.022	1.797	1.087-2.970
Histologic Grade I	0.009			
Histologic Grade II		0.041	2.973	1.046-8.453
Histologic Grade III		0.004	5.178	1.671-16.043
T Stage	0.183			
Nodal Stage	0.004			
Metastasis	0.072	0.019	4.196	1.271-13.850
HPV16	0.009	0.011	0.158	0.038-0.658
P16INK4A	0.43			

Table 4. Multivariate analysis of independent prognostic factors in 188 primary OPSCC cases

Variable	OS	
	HR (95% CI)	*p*-value
Gender	0.281 (0.067-1.171)	0.081
HPV16	0.158 (0.038-0.658)	0.011
Clinical Stage III~IV	1.797 (1.087-2.970)	0.022
Histologic Grade II	2.973 (1.046-8.453)	0.041
Histologic Grade III	5.178 (1.671-16.043)	0.004
Metastasis	4.196 (1.271-13.850)	0.019

p16INK4A positive, and the p16INK4A positivity was significantly associated with HPV positivity (P < 0.001) [9] (**Table 2**).

Survival analysis and establishment of the OPSCC prognostic model

As shown in **Table 3**, the following factors were associated with a better OS among the 188 OPSCC patients: female sex, non-smoking status, clinical stage I-II, histologic grade I, N0 stage and HPV16 positivity (P = 0.003, 0.048, 0.003, 0.009, 0.004, 0.009, respectively). According to the multivariate analysis, the clinical stage (P = 0.022), histologic grade II, histologic grade III (P = 0.041, P = 0.004), metastasis (P = 0.011), and HPV16 positivity (P = 0.011) were independent prognostic factors (**Table 4**). The regression coefficients of each factor were as follows (**Table 3**): PI = -1.270 (if female) + 0.586 (if clinical stage III-IV) + 1.090 (if histologic grade II) + 1.644 (if histologic grade III) + 1.434 (metastasis) - 1.843 (if HPV16 positive).

Model validation

The above model was used to calculate the prognostic index for each patient. In total, 21 values were obtained for the PI (range from -3.74 to 2.84). The AUC of the ROC curve was 0.74 (95% Confidence interval (CI): 0.67-0.81) (**Figure 1**), and the Youden index was the highest at PI = -0.008 (**Figure 2**). In addition, we classified the patients into 2 risk groups according to the above cut-off value. Patients with a PI < -0.008 were assigned to the low-risk group, and patients with a PI ≥ -0.008 were assigned to the high-risk group. In total, 107 and 81 patients were assigned to the low- and high-risk groups, respectively. The patients in the high-risk group had a significantly higher risk of death, with a hazard ratio (HR) of 4.60 (95% CI: 2.21-9.58) (**Figure 2**).

Significance of the PI model for PRT

The necessity of PRT for OPSCC is controversial, and significant acute and late toxicities of RT can occur; therefore, evaluation of PRT as

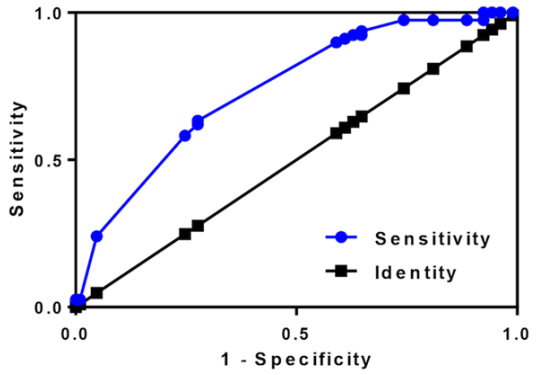

Figure 1. ROC curve of the PI in primary OPSCC patients. The value of PI ranges from -3.74 to 2.84, and the area under the curve is 0.74 (95% CI: 0.67-0.81).

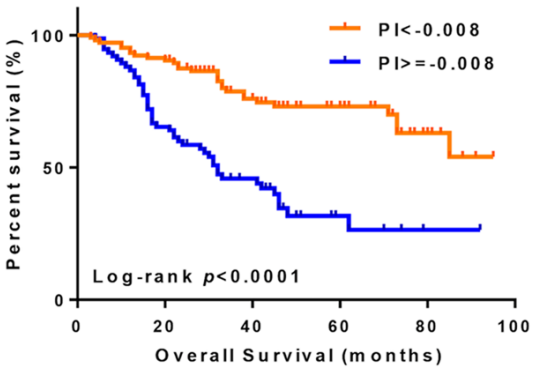

Figure 2. Survival curves of patients based on the PI. The Youden index divided into high-risk (PI ≥ -0.008) and low-risk (PI < -0.008) group. Patients had a higher risk in high-risk group with a hazard ratio of 4.60 (95% CI: 2.21-9.58).

an optional treatment strategy based on the prognostic scoring model was particularly important. To exclude the effect of chemotherapy on prognosis, we included the propensity scores of 177 patients in this analysis. As shown in **Figure 3A**, among the 177 selected patients, no significant difference was observed in the OS between patients who received PRT (N = 100) and those who did not receive PRT (N = 77) (P = 0.938), suggesting that PRT does not prolong the OS. Similarly, as shown in **Figure 3B**, among the low-risk patients (PI < -0.008, N = 101), no difference was observed in the OS between the patients who received PRT (N = 54) and those who did not receive PRT (N = 47) (P = 0.38). However, a significant difference was observed in the high-risk patient group (PI ≥ -0.008, N = 76) (**Figure 3C**, P = 0.096); the median OS time was 28.31 months (95% CI: 10.69-35.31) in the patients who did not receive PRT (N = 30) and 47.31 months (95% CI: 18.34-47.62) in the patients who received PRT (N = 30). Furthermore, we compared the OS time of patients who received PRT and those who did not receive PRT with survival times longer than 20 months. Interestingly, in the low-risk patient subgroup (PI < -0.008), PRT was associated with a worse survival time (**Figure 3D**, P = 0.071). In the high-risk patient subgroup (PI ≥ -0.008), when the OS time was longer than 20 months, the patients who received PRT had a longer survival time than the patients who did not receive PRT (**Figure 3E**, P = 0.024). These results suggest that PRT is not beneficial for all patients. Therefore, our prognostic index should be used to guide treatment protocols regarding whether PRT is necessary. PRT should not be recommended for low-risk patients, while high-risk patients should receive postoperative adjuvant RT.

Discussion

Because HPV infection is the underlying cause of a significant proportion of OPSCCs, these infections have played an important role in the recent epidemiological changes observed among OPSCC cases. HPV-associated OPSCC is more sensitive to RT, and HPV-associated OPSCC patients who receive PRT have better survival rates than patients with HPV-negative OPSCC [23, 27, 28]. However, some studies suggest that PRT might not be suitable as an alternative therapy for all high-risk OPSCC patients, such as for patients with certain clinical or pathological characteristics and because of the higher incidence rates of acute and late toxicity due to RT; such patients should consider other therapeutic options [29, 30]. These findings drew our attention and prompted the current study. In China, there is a low detection rate of HPV infection and high smoking and drinking rates in OPSCC patients, as shown in our previous study [9]. Furthermore, clinical stage, histologic grade, metastasis and HPV16 positive status were independent prognostic factors for Chinese OPSCC patients. Therefore, the distinguishing feature of Chinese OPSCC patients is that HPV-positive status was not the main prognostic factor; clinicopathologic features should receive more attention in Chinese OPSCC patients. A prognostic scoring model based on gender, clinical stage, histo-

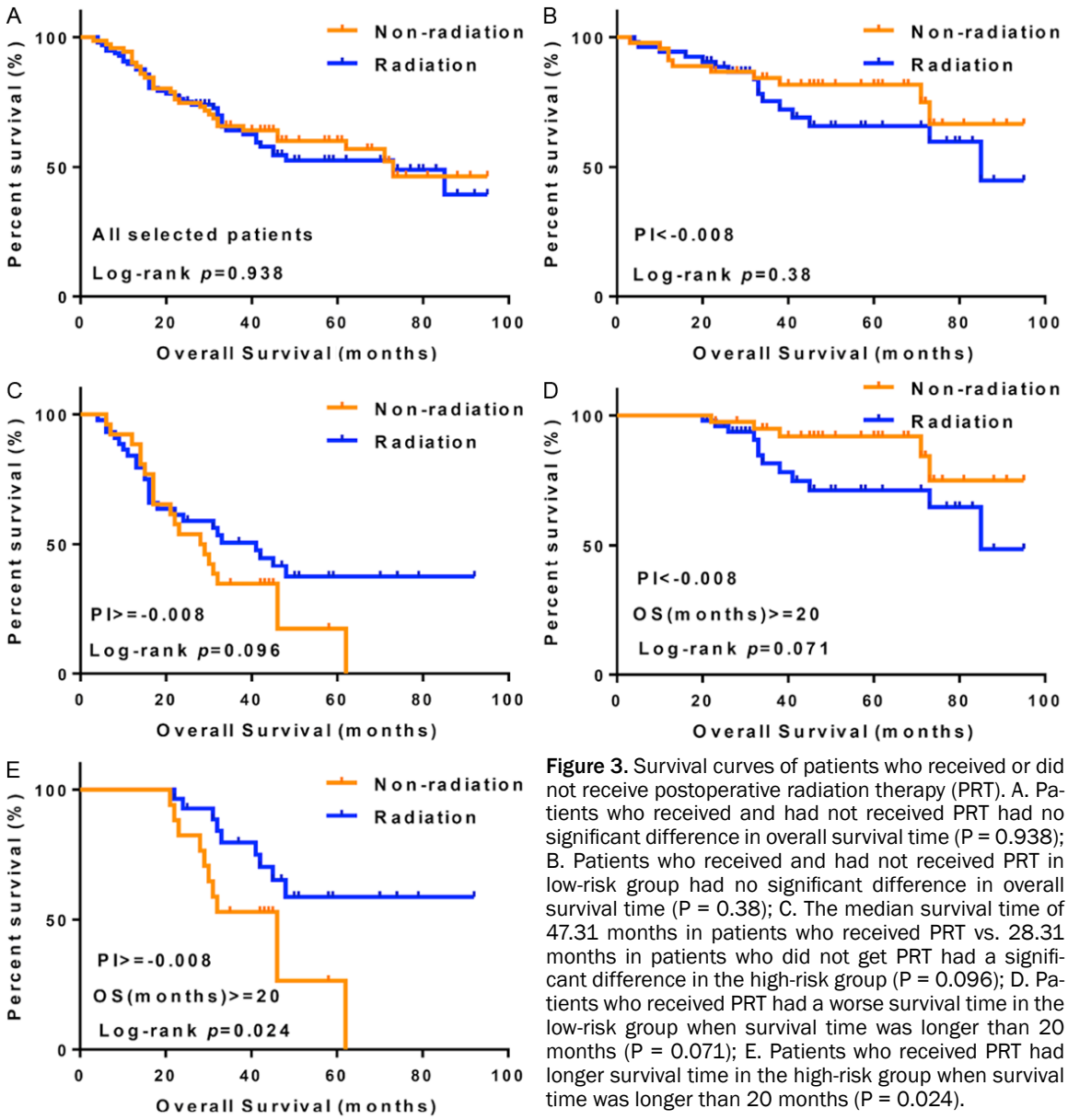

Figure 3. Survival curves of patients who received or did not receive postoperative radiation therapy (PRT). A. Patients who received and had not received PRT had no significant difference in overall survival time (P = 0.938); B. Patients who received and had not received PRT in low-risk group had no significant difference in overall survival time (P = 0.38); C. The median survival time of 47.31 months in patients who received PRT vs. 28.31 months in patients who did not get PRT had a significant difference in the high-risk group (P = 0.096); D. Patients who received PRT had a worse survival time in the low-risk group when survival time was longer than 20 months (P = 0.071); E. Patients who received PRT had longer survival time in the high-risk group when survival time was longer than 20 months (P = 0.024).

logical grade, metastasis and HPV status was established and was used to classify patients into high- and low-risk groups. The results showed that female patients of clinical stage I-II, histologic grade I, N0 metastasis and HPV16 positive showed better OS and prognosis. A significantly higher mortality risk was observed in the high-risk group than in the low-risk group of OPSCC patients, with a HR of 4.60. According to our findings, this propensity score model is a reasonable model for individualizing postoperative OPSCC radiation protocols. Interestingly, the patients who received PRT (47.31 months) had a better OS than the patients who did not receive PRT (28.31 months) in the high-risk group, particularly when the survival time was longer than 20 months (P = 0.024). However, PRT may be a risk factor for decreased survival time in the low-risk group (P = 0.071). Therefore, according to this prognostic model, we recommend postoperative adjuvant RT for high-risk OPSCC patients only.

Postoperative radiation is a standard treatment option for patients with OPSCC in China. Radiation therapy can kill or inhibit tumor cells, reduce or delay the chance of local recurrence or metastasis, and improve prognosis. However, in the current study, we found that PRT was not generally effective and may even worsen the

prognosis of low-risk patients. RT can cause permanent and severe morbidity, such as dysphagia and secretory dysfunction of the salivary glands [31, 32]. Therefore, identifying patients who are truly suitable for RT is critical.

Recently, RT has been shown to be more effective for HPV-related OPSCC than HPV-negative OPSCC [22]. Using the propensity scores to compare the groups in our study population, the high-risk group, in which the majority of the cases were HPV negative, achieved a better survival time with PRT, while PRT had little or even negative effects in the low-risk group. This prognostic model has the advantage of comprehensively evaluating individual clinicopathologic characteristics and HPV status to determine whether the patients are candidates for PRT.

To the best of our knowledge, this is the first postoperative prognostic scoring model for patient prognosis and choice of individual treatment schedule in China. However, this study has limitations, such as the lack of OPSCC patients who received RT alone. More data should be collected and validated in the future to improve the utility of this OPSCC prognostic scoring model.

In conclusion, we established an OPSCC postoperative prognostic scoring model with high accuracy that includes the following 5 risk factors: gender, clinical stage, histologic grade, metastasis and HPV status. This scoring model can supplement the TNM staging and can be applied for prognostic assessments to provide guidance regarding the formulation of individualized therapeutic strategies for PRT in Chinese OPSCC patients.

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Disclosure of conflict of interest

None.

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